Investigating emotional lability in adults with Attention Deficit Hyperactivity Disorder an integrative approach

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Investigating emotional lability in adults with Attention Deficit Hyperactivity Disorder: an integrative approach

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Abstract

Adults with Attention-Deficit Hyperactivity Disorder (ADHD) frequently report emotional lability (EL: irritable moods with volatile and changeable emotions). Little is known about the clinical and behavioural features, or neurobiological correlates of EL in ADHD. The current thesis takes an integrative approach, using a diversity of methodologies to characterise EL, and examine the nature of its association with ADHD.

All analyses are based on data from the MIRIAD project, a case-control study of 88 adult males: 47 controls, and 41 with ADHD without comorbidity, medication or current substance abuse. The study incorporated reassessment after treatment with methylphenidate in ADHD participants, with matched follow-up for controls.

The first part of this thesis examined the clinical and behavioural features of EL using self-report measures and ambulatory monitoring. Results indicated significantly elevated EL in adults with ADHD, characterized by higher intensity and instability of negative emotions. Enhanced EL was not accounted for by antisocial behaviour, subthreshold comorbid symptomatology, and adverse life events. ADHD symptoms and EL were moderately correlated, and EL independently predicted a host of daily life impairments.

The second part of this thesis focused on identifying aetiological factors which may underpin both EL and ADHD, by exploring cognitive and neurophysiological deficits associated with ADHD and self-reported EL, and examining shared treatment response. Swift emotional changes were predicted by within-subject variability in reaction time, whilst EL characterized by negative emotions was associated with behavioural and neurophysiological indices of inhibitory function. Although ADHD symptoms and EL correlated moderately in their treatment response, treatment response of cognitive measures and EL were not correlated.

The research presented here has implications for the identification and treatment of ADHD in adulthood in the context of elevated EL and mood symptoms. Results from cognitive and neurophysiological investigations present some promising avenues for further examining shared neurobiology of EL and ADHD.

Statement of work

The MIRIAD project was generated in discussions between myself and my supervisor Professor Philip Asherson, with expert advice from Dr Grainne McLoughlin and Dr Jonna Kuntsi. I was involved in designing the study, including identifying research questions, generating research hypotheses and selecting research instruments. Professor Asherson and I co-wrote the successful funding application submitted to the National Institute of Health Research and the application for ethical approval.

I was involved in the recruitment, supervision and training of research staff working on the project, and was responsible for sourcing and preparing all the equipment and tasks used in this project. I carried out day-to-day project coordination over approximately 2 years, and was a key contributor to selection of participants, organising and carrying out assessments and management of the data.

I am indebted to Jadwiga Mika, Tessa Mellow, Sarah Bates and Peter Reid, as well as my supervisor Professor Asherson, who continued work on this project during my maternity leave.

All analyses presented in this thesis were conducted by myself and were supervised by Professor Asherson. The analyses in chapter 4 were additionally supervised by Professor Ulrich Ebner-Priemer, whilst the analyses in chapters 5 and 6 were additionally supervised by Dr Jonna Kuntsi and Dr Grainne McLoughlin.

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Table of Contents

List of figures

List of tables

Chapter one: an introduction to ADHD and emotional lability

The past decade has witnessed a return of interest to emotional lability (EL) associated with attention deficit hyperactivity disorder (ADHD), including the emergence of a number of recent review articles on the topic (Barkley, 2010; Martel, 2009; Skirrow, McLoughlin, Kuntsi, & Asherson, 2009). Published clinical observations of EL in adults with ADHD describe "feelings of irritability" (Reimherr, et al., 2005, p.125), "lability of mood antedating adolescence with both "highs" and "lows" persisting for periods of hours to at most days with shifts occurring both spontaneously and reactively" (Wender, Reimherr, Wood, & Ward, 1985, p. 551), a "hot temper", "short fuse" and "low boiling point" (Wender, Wolf, & Wasserstein, 2001) and mood which is "highly volatile" (Asherson, 2005, p.530). Similar features are also described in children and adolescents with ADHD (Anastopoulos, et al., 2011; Sobanski, et al., 2010).

Emotional lability (EL) may therefore be characterised by irritability and hot-temperedness alongside highly volatile and changeable emotions. Recent studies have reported EL in a large proportion of individuals with ADHD; as many as 50-76% of children and adolescents (Anastopoulos, et al., 2011; Mick, Spencer, Wozniak, & Biederman, 2005), and 72-90% of adults (Asherson, 2005; Reimherr, et al., 2010). Moreover, EL has been revealed as independently predictive of a range of social, occupational and educational impairments in adults with ADHD, often beyond the influence of core ADHD symptoms (Barkley & Fischer, 2010; Barkley & Murphy, 2010).

There is considerable theoretical overlap between EL and the construct of neuroticism. As defined by Eysenck (1978), neurosis is a term often used for "behaviour which associated with strong emotions, which is is maladaptive, and which the person giving rise to it realises is nonsensical, absurd or irrelevant, but which he is powerless to change." However, neuroticism is also characterised by anxiety and worry, shyness, psycho-somatic symptomatology, guilt and low self-esteem, not all of which are necessarily associated with emotional lability (Francis, 1993). A study by Eid and Deiner (1999) investigating emotional variability and change as assessed by ambulatory assessment in relation to neuroticism found only small to moderate correlation coefficients between these variables (correlation coefficient range: -0.08 to .49), with larger correlation coefficients for negative emotions (e.g. sadness and fear). These findings indicate that whilst EL and neuroticism are associated constructs they cannot necessarily be considered equivalent.

However, the most recent diagnostic formulation of ADHD in the Diagnostic and Statistical Manual for Mental Disorders (DSM-IV; American Psychiatric Association, 1994, 2000) specifies EL only as an 'associated feature' of the disorder. This may contribute to a lack of awareness of ADHD as a potential differential diagnosis for clinicians encountering patients with emotional lability. This issue has raised a number of nosological contentions, as it has been noted that adults with unrecognised ADHD are frequently misdiagnosed and treated for anxiety, depression, mixed affective disorder, cyclothymia, and borderline and unstable personality disorders (Asherson, 2005; Wender, et al., 2001). Furthermore, in children and adolescents, there is some debate regarding the differentiation of ADHD with co-occurring EL from bipolar spectrum disorders (Skirrow, Hosang, Farmer, & Asherson, 2012), and from oppositional defiant disorder (ODD; Barkley, 2010), both of which heavily feature emotional symptoms in their diagnostic formulations.

It has been suggested by some (Barkley, 2010; Reimherr, et al., 2010) that EL may best be conceptualised as one of the core dimensions of ADHD. A body of evidence is accruing to suggest that this may well be true. Research indicates behavioural and neurocognitive associations between core ADHD symptoms and EL, and a correlated improvement in EL and ADHD symptoms during treatment response. However research on EL in ADHD is currently in its infancy and much further evidence is required.

The overarching aim of this thesis is to investigate the association between EL and ADHD in adulthood. The first part of this thesis takes a behavioural approach to EL in ADHD, incorporating different research techniques to characterise EL and to test the validity of the association between EL and ADHD, whilst controlling for a number of important confounders. The second part then attempts to identify causal pathways via key neurophysiological processes impacting on both ADHD symptoms and EL, with the aim of enhancing our understanding of potential shared cognitive-biological bases. This is achieved first by investigating the relationship between EL and key cognitive-electrophysiological markers which are considered sensitive to the ADHD diagnosis, and then by investigating their response to treatment.

This first chapter provides a broad introduction to this topic. It will first outline the clinical and behavioural features of ADHD, followed by a definition of EL. Discussion will then shift

to the association between ADHD and EL, first by summarising studies investigating behavioural overlap, findings from family studies, evidence from treatment response, and finally neurocognitive links between ADHD and EL. The chapter concludes by presenting the specific research questions of this thesis. Although the primary focus of this thesis is on ADHD in adulthood, evidence from the child and adolescent literature will also be discussed. To promote consistency, this thesis focuses on ADHD criteria from the DSM-IV (American Psychiatric Association, 1994, 2000).

1.1 An introduction to ADHD

1.1.1 Historical context

Features of hyperactive, impulsive and inattentive behaviours, and their association with emotional problems have been documented for centuries (Barkley, 2010, 2011). Palmer and Finger (2001) highlight one of the earliest medical references to inattentive problems in the 1798 publication by Scottish physician Alexander Chrichton, describing "mental restlessness", in children who are "incapable of attending with constancy to any one object of education". Also described are their reactions to the myriad of distractions "with a degree of anger that borders on insanity" (cited in Barkley, 2010). Another early report of ADHD-like symptoms was presented by English paediatrician George Still (1902), who presented a series of case studies on children without general intellectual impairments, manifesting deficits in "volitional inhibition", "moral control" and a "lack of attention", as well as a "noticeably weak" ability to "control of the expressions of the emotions" (p.1011).

The concept of 'minimal brain damage' was born after the 1918 influenza lethargica pandemic, which was followed by an increased number of children presenting with antisocial behaviour, irritability, impulsiveness, emotional lability and hyperactivity, in the absence of major cognitive impairment or significant brain injury (Strother, 1973). Due to lack of evidence of abnormal neurological signs in many such children, the term 'minimal brain dysfunction' was adopted in the 1960s, although the pattern of symptoms remained similar, including inability to concentrate, and lack of self-control, and frequent temper outbursts (Clements & Peters, 1962). However, over time these terminologies came under criticism again for the lack of evidence of a neurological basis, and for their lack of specificity (Herbert, 1964; Rutter, 1975).

Numerous diagnostic formulations for ADHD-like behaviours were incorporated in the Diagnostic and Statistical Manual for Mental Disorders from 1968. The first, 'hyperkinetic reaction of childhood', was accompanied by a shift in focus towards identifying and measuring behavioural features of the disorder (DSM-II; American Psychiatric Association, 1968). The second, heavily influenced by work on the central role of attention in the syndrome (Douglas, 1972), was codified 'attention deficit disorder' (DSM-III; American Psychiatric Association, 1980). With emphasis returning to hyperactivity symptoms, 'attention deficit hyperactivity disorder' (or ADHD) was introduced in the DSM-III-R (American Psychiatric Association, 1987). This diagnostic label continues to be used today, although instead of a unitary disorder, three ADHD subtypes have been introduced (DSM-IV and DSM-IV-R; American Psychiatric Association, 1994, 2000). From the second revision of the DSM-II, diagnostic formulations no longer included emotional problems previously associated with minimal brain dysfunction (Barkley, 2011). From the DSM-III these were reassigned to 'associated features', where they remain today (Reimherr, et al., 2005).

1.1.2 Diagnostic classification

As with other mental health conditions, there is no objective test for ADHD. Decisions to diagnose and treat rest on subjective (self and informant report) and more objective (observation) factors, assessed and interpreted by the clinician in light of diagnostic cut-offs (Okie, 2006).

The current DSM-IV operational criteria for ADHD (Table 1; American Psychiatric Association, 2000) comprise two primary symptom dimensions, inattention and hyperactivity-impulsivity. To fulfil diagnostic criteria, an individual must meet a minimum 6 of 9 inattentive symptoms (inattentive subtype), 6 of 9 hyperactive-impulsive symptoms (hyperactive-impulsive subtype), or 6 of 9 symptoms in both inattentive and hyperactive-impulsive dimensions (combined subtype). Some symptoms must be present and cause impairment before the age of 7 years. Furthermore, symptoms must persist for at least 6 months and cause impairment in more than one setting, for example in school or work and at home.

Table 1: Diagnostic Criteria for Attention Deficit–Hyperactivity Disorder from the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision, 2000

(A1) **Inattention**: six (or more) of the following symptoms of inattention have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

(a) often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities
(b) often has difficulty sustaining attention in tasks or play activities
(c) often does not seem to listen when spoken to directly
(d) often does not follow through on instructions and fails to finish school work, chores, or duties in the workplace (not due to oppositional behavior or failure to understand instructions)
(e) often has difficulty organizing tasks and activities
(f) often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework)
(g) often loses things necessary for tasks or activities (e.g., toys, school assignments, pencils, books, or tools)
(h) is often easily distracted by extraneous stimuli
(i) is often forgetful in daily activities

(A2) **Hyperactivity–impulsivity**: six (or more) of the following symptoms of hyperactivity–impulsivity have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

Hyperactivity

(a) often fidgets with hands or feet or squirms in seat
(b) often leaves seat in classroom or in other situations in which remaining seated is expected
(c) often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness)
(d) often has difficulty playing or engaging in leisure activities quietly
(e) is often "on the go" or often acts as if "driven by a motor"
(f) often talks excessively

Impulsivity

(g) often blurts out answers before questions have been completed
(h) often has difficulty awaiting turn
(i) often interrupts or intrudes on others (e.g., butts into conversations or games)

Additional criteria:

(B) Some hyperactive–impulsive or inattentive symptoms that caused impairment were present before age 7 years.
(C) Some impairment from the symptoms is present in two or more settings (e.g., at school [or work] and at home).
(D) There must be clear evidence of clinically significant impairment in social, academic, or occupational functioning.
(E) The symptoms do not occur exclusively during the course of a pervasive developmental disorder, schizophrenia, or other psychotic disorder and are not better accounted for by another mental disorder (e.g., mood disorder, anxiety disorder, dissociative disorders, or a personality disorder).

Attention deficit hyperactivity disorder subtypes:

Combined: If both criteria A1 and A2 are met for the past 6 months
Predominantly inattentive: If criterion A1 is met but criterion A2 is not met for the past 6 months
Predominantly hyperactive-impulsive: If criterion A2 is met but criterion A1 is not met for the past 6 months

Equivalent diagnostic criteria for ADHD are applied to both children and adults. However, there are additional concerns regarding the assessment of ADHD in adulthood where a diagnosis in childhood was not established, since onset of symptoms and impairment before age 7 years need to be determined retrospectively. A study investigating retrospective diagnoses by semi-structured clinical interviews (without informants), showed a high rate of positive diagnosis in a large sample of adults with ADHD who had previously been diagnosed with ADHD as children (78%), however the rate of false positive classifications in control participants was also relatively high (11%, Mannuzza, Klein, Klein, Bessler, & Shrout, 2002). This indicated that while some individuals may not be able to recall their childhood symptoms, false positive rates may also be a problem. The inclusion of informants, wherever possible, such as parents or siblings who may have known the patients during their childhood and can corroborate any described symptoms may therefore be considered extremely important and is a key recommendation that will be proposed for the new 5th edition of the DSM (www.dsm5.org).

1.1.3 Developmental trajectory

The developmental decline in ADHD symptoms is well documented, with most research to date suggesting a higher level of persistence of inattention symptoms, alongside a greater decline in hyperactive-impulsive symptoms (Biederman, Mick, & Faraone, 2000; Hart, Lahey, Loeber, Applegate, & Frick, 1995; Larsson, Larsson, & Lichtenstein, 2004). Using DSM-III criteria, meta-analytic regression analysis of longitudinal studies identified approximately 15% who would continue to meet full diagnostic criteria by age 25, but confirmed continuity of ADHD symptoms and impairment into adulthood in around two-thirds of cases (Faraone, Biederman, & Mick, 2006). A recent 10-year follow-up of a large sample of boys with ADHD, identified 35% who continued to meet full DSM-IV criteria for ADHD at age 22, although high rates of impairment and symptoms remained in those who no longer met full criteria (Biederman, Petty, Evans, Small, & Faraone, 2010). These observations have led to the proposal that persistence of 4 or more symptoms may be sufficient for the full diagnosis in adults under DSM-V (www.dsm5.org).

Children, adolescents and adults diagnosed with ADHD show similar diagnostic and clinical features, cognitive profiles, and problems in education or employment (Biederman, et al.,

1998; Hervey, Epstein, & Curry, 2004; Seidman, 2006). Furthermore they show a comparable response to stimulant treatment (Faraone, Spencer, Aleardi, Pagano, & Biederman, 2004). It is therefore widely believed that the adult form of disorder represents a continuation of childhood ADHD. In a second report of the 10-year follow-up study by Biederman and colleagues (Biederman, Petty, Clarke, Lomedico, & Faraone, 2011), persistence of ADHD into adulthood was found to be associated with higher levels of impairment, and more frequent diagnoses of ODD, conduct disorder (CD) and anxiety disorders during childhood. This suggests that persistent ADHD might represent a more severe and comorbid form of the disorder. However, it has also been suggested that chronic and remitting forms of ADHD may represent distinct subtypes of the disorder with different risk factors and prognosis (Biederman, et al., 1996). For example, an increased rate of ADHD was seen among the first-degree relatives of persistent compared to remitting cases, suggesting that persistent ADHD may represent a more highly familial form of the disorder (Faraone, Biederman, Feighner, & Monuteaux, 2000). Other research suggests that there may be systematic cognitive differences between individuals with remitting and persisting ADHD (Halperin, Trampush, Miller, Marks, & Newcorn, 2008), perhaps reflecting the development of compensatory processes in remitting cases. Such findings caution the use of cross-sectional analysis comparing ADHD populations across different ages, and suggest that a longitudinal approach may be more appropriate.

1.1.4 Prevalence and gender ratio: evidence from population studies

ADHD is considered one of the most highly prevalent childhood psychiatric illnesses. Estimates of prevalence in children and adolescents from meta-regression analysis stand at 5.29% (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007). However, rates in individual studies of prevalence are highly variable, which is almost certainly attributable to variations in the diagnostic methods employed (diagnostic criteria, application of impairment and pervasiveness criteria, and source of information on which diagnosis is based). Epidemiological studies support evidence of a maturational decline in ADHD, showing lower prevalence in adolescents (around 3%) compared to younger children (around 7%; Polanczyk, et al., 2007). Furthermore, estimates of the prevalence of DSM-IV ADHD in adults, again derived from a recent meta analytic study stand at 2.5% (Simon, Czobor, Balint, Meszaros, & Bitter, 2009) with a higher rate of ADHD seen in younger than in older adults.

In the largest transnational epidemiological study of ADHD in adults to date, carried out in 10 countries in the Americas, the Middle East and Europe (sample size = 11,422), Fayyad and colleagues (2007) reported a prevalence rate of 3.4%. Furthermore, ADHD rates were found to be higher among those that were less educated and living in higher income countries. However, this study had some severe limitations, since the diagnostic measures for ADHD were somewhat limited, and diagnosis was only verified by clinical reappraisal in 154 individuals from the USA. Further details of this study, alongside rates of reported ADHD in adults in recent epidemiological studies can be seen in table 2.

ADHD is more prevalent in boys than girls, with male to female ratios generally ranging from 2:1 to 4:1 (Ford, Goodman, & Meltzer, 2003; Polanczyk, et al., 2007). In a meta-analysis of epidemiological studies of ADHD in adults, Simon and colleagues (2009) identified an age by gender interaction, with younger adults with ADHD being characterised by a much larger male preponderance. A reduced gender imbalance in adults has been supported in recent epidemiological studies (detailed in table 2).

Table 2: Prevalence, gender ratio and comorbidity rates associated with elevated ADHD symptoms in adulthood in some recent population studies

Authors , Date (country)	Additional information/criteria	Measures used	Age range (yrs)	Sample size	Rate of ADHD proxy identified	Gender ratio M-F	Most common comorbidities with ADHD (%)
(Kessler, et al., 2006) (USA)	12 month comorbidity prevalence reported. Prevalence calculated by multiple imputation after clinical reappraisal of subsample. ADHD proxy: fewer ADHD symptoms required than in DSM-IV stipulations.	ADHD: DIS DSM-IV, clinical reappraisal using AACDS version 1.2 BD: WHO CIDI 3.0, clinical reappraisal using SCID	18-44	3,199	4.4%	1.6-1	47% Anxiety disorders 20% Intermittent explosive disorder 19% Bipolar disorder 19% MDD 15% Substance use disorders
(Fayyad, et al., 2007) 10 countries: (Americas, Europe and Middle East)	Prevalence of psychiatric illnesses calculated by multiple imputation after clinical reappraisal of subsample. ADHD proxy: ADHD in childhood plus interview confirming at least 1 symptom from childhood	WHO CIDI, clinical reappraisal of ADHD in 154 respondents from the USA with AACDS, Reappraisal of comorbidities with SCID	18-44	11,422	3.4%	1.5-1	25% Mood disorders 38% Anxiety disorders 11% Substance use disorders
(Park, et al., 2011) (Korea)	ADHD proxy: ASRS score of 4 and above required plus interview confirming at least 1 symptom from childhood	ASRS self-report scale of 18 DSM-IV ADHD items K-CIDI 2.1 interview	18-59	6,081	1.1%	1-1	17% Alcohol abuse/dependence 6% Anxiety disorders 6% MDD
(Bernardi, et al., 2011) (USA)	Ethnic minorities and age 18–24 oversampled. Data adjusted for oversampling and non-response ADHD proxy: symptom onset by age 18 years.	AUDADIS-IV	≥18 upper age not defined	34,653	2.5% *	1.4-1	71% Substance use disorders 74% Anxiety disorders 33% Bipolar disorder 26% MDD 20% Conduct disorder

*Note: M-F, male-to-female; ADHD Proxy, modifications to standard ADHD diagnostic practice or ADHD measured by rating scales; MDD, Major Depressive Disorder; DIS DSM-IV, Diagnostic Interview Schedule for DSM-IV; AACDS, Adult ADHD Clinical Diagnostic Scale, version 1.2; WHO CIDI, World Health Organisation Composite International Diagnostic Interview; SCID, Structured Clinical Interview for DSM-IV; ASRS, Adult ADHD Self-Report Scale; K-CIDI, Korean Composite International Diagnostic Interview; AUDADIS-IV, Alcohol Use Disorder and Associated Disabilities Interview Schedule–DSM-IV version. * Combined subtype only*

1.1.5 Comorbidity

High comorbidity rates are a widespread phenomenon in psychiatric research, even in non-referred community samples (Kessler, Chiu, Demler, & Walters, 2005; Weich, et al., 2011). Similarly, comorbidity in ADHD is common, and it appears that many more children and adults with ADHD have a comorbid condition than do not (Gillberg, et al., 2004; Sobanski, 2006).

In children with ADHD comorbid disorders are seen in around 60-100% of cases, with rates of ODD being particularly high (50-60%), but elevated rates also being reported for depressive disorders (16-26%) and reading disorders (25-40%, reviewed in Gillberg, et al., 2004). Furthermore, there is a widely variable literature on the prevalence of bipolar spectrum disorders in children with ADHD, with rates ranging from 0.5% to 21%, depending largely on the diagnostic criteria applied for bipolar disorder (Skirrow, et al., 2012).

Common lifetime comorbid conditions in clinical and population samples of adults with ADHD include depression (35-50%), anxiety disorders (40-60%), and substance use disorders (up to 50%, see literature review by Sobanski, 2006). The high rate of substance use disorders identified in adulthood is in line with a recent meta analytic study showing the children with ADHD are at increased risk for developing abuse or dependence on nicotine, alcohol, marijuana, cocaine, and other substances (Lee, Humphreys, Flory, Liu, & Glass, 2011). Rates of comorbidity in adults with ADHD are similar in large population studies (table 2), which have the benefit of being free from referral biases, but commonly rely on survey procedures or other forms of data capture that provide a less in-depth evaluation of psychopathology than is possible in clinical settings.

Comorbidity is an important confound in research on emotional lability. Stringaris (2011) notes that irritability "cuts across a range of psychiatric disorders". This is certainly the case, since irritability or temper problems are included in the diagnostic criteria for borderline personality disorder, bipolar disorder, ODD and paediatric depression (American Psychiatric Association, 2000). In studies where comorbidity is not taken into account, it is possible that it is the relationship between emotional lability and comorbidity, rather than ADHD, that is actually being studied. However, since comorbidity rates are commonly high, a compromise is often required between sample size and the inclusion of comorbid cases.

1.1.6 Overview and conclusions

The diagnostic labels used to define problems of inattention, hyperactivity and impulsivity have changed markedly over the years, although the symptom profiles underlying these diagnostic labels have shown relatively little change. Emotional problems featured highly in early definitions of ADHD-related psychopathology, but were relegated to 'associated features' of the disorder in more recent diagnostic formulations of the DSM. In the DSM-IV ADHD is defined as high levels of symptoms on one or both dimensions of hyperactivity-impulsivity and inattention, accompanied by significant impairment. This means that two individuals with entirely different symptoms could both be diagnosed with ADHD, albeit different subtypes, and diagnostic criteria can be met by individuals with as few as six and as many as eighteen symptoms. This provides an indication of the heterogeneity seen not only in the symptomatology but also the severity of the disorder. Prevalence rates indicate that ADHD is one of the most common childhood psychiatric conditions and longitudinal studies suggest that a notable proportion of children with ADHD will continue to be impaired by the condition in adulthood. Evidence to date suggests both similarities and differences in the childhood and adult forms of the disorder, indicating that cross-sectional comparisons must be treated with some degree of caution. Across the lifespan, ADHD is frequently comorbid with other psychiatric conditions, again adding to the heterogeneity of clinical presentations of ADHD. Furthermore the frequent association of emotional lability with other diagnostic constructs indicates that comorbidity is an important area for consideration when interpreting findings of EL in ADHD.

1.2 Why emotional lability? Key concepts and definitions

1.2.1 A question of semantics: moods, emotions and affect

Ketal (1975) states that moods, emotions and affect refer to distinct psychological phenomena, and that confusion regarding the application of these distinct terms results in muddled communication and conceptual uncertainties.

Mood, emotion and affect are believed to be differentiated by their temporal quality, intensity and specificity, as well as the involvement of conscious evaluative processes. It is generally accepted that mood is a long-lasting and diffuse state. According to Larsen (2000),

mood states can become chronic and maladaptive, and completely dissociated from objective life circumstances, as in depressive or anxious states. Affect is described as the feeling tone associated with mood and emotion, felt as good or bad, as pleasant or unpleasant, and as a tendency to approach or to avoid (Larsen, 2000). Emotions are shorter lived, more intense experiences than moods, with a distinct onset and offset in time and a peak in between (Larsen, 2000). Moreover, emotions are thought to entail a conscious judgement or appraisal (Russell, 2003; Stringaris, 2009) culminating in the subjective conscious experience of emotion, including meta-cognitive experiences (i.e., labelling the emotion; Russell, 2003).

When evaluating the experiences of individuals with ADHD, the described irritability, hot-temperedness and volatility are best captured by the term 'emotion', since most are shorter lived, and are reported by patients themselves, thereby being subject to conscious experience. The one exception may be the case of irritability, which has been described as a longer-lasting experience, more akin to a mood state (Stringaris, 2011). However, Stringaris (2009, p. 278) also argues for the potential of emotions to last longer, and argues for emotional reactions showing both interindividual differences and intraindividual stability, proposing that short-lived emotions are embedded within enduring emotions.

1.2.2 To regulate, or not to regulate, that is the question

There is considerable variation in the terms used to describe emotional experience and expression in ADHD, with different terms being applied interchangeably. Two main classes of broad descriptors can be identified in the literature which are outlined below. Importantly the many differing terms used tend to refer to overlapping emotional features.

1.2.2.1 A problem with the regulation of emotions

The most commonly used term for EL in ADHD is *emotional dysregulation* (Herrmann, Biehl, Jacob, & Deckert, 2010; Melnick & Hinshaw, 2000; Reimherr, et al., 2007; Retz, et al., 2010; Walcott & Landau, 2004; Waxmonsky, et al., 2008; Whalen, Jamner, Henker, Delfino, & Lozano, 2002). Related terms include: *deficient emotional self-regulation* (Biederman, et al., 2012; Surman, et al., 2011), while others describe problems with *self-regulation of emotion* (Anastopoulos, et al., 2011) or *self-regulation of affect* (Braaten & Rosen, 2000). Work by

Barkley employs the terms *emotional impulsiveness* with *deficient emotional self-regulation* (Barkley, 2010; Barkley & Fischer, 2010; Barkley & Murphy, 2010), emphasising both the regulatory failures purportedly associated with emotional problems in ADHD and their purported association with impulsivity.

1.2.2.2 A descriptive approach

In other writings of emotional problems in ADHD, a descriptive approach is favoured, including terms such as *mood instability* (Asherson, Chen, Craddock, & Taylor, 2007; Asherson, Kuntsi, & Taylor, 2005; Skirrow, et al., 2009), *emotional lability* (Sobanski, et al., 2010), *emotional reactivity* (Graziano, McNamara, Geffken, & Reid, 2012) and *emotional instability* (Hesslinger, et al., 2002).

These terms are sometimes favoured because they do not posit any particular deficits or underlying causes (Skirrow, et al., 2009; Sobanski, et al., 2010), providing a more neutral platform for the investigation of the underlying dysfunctions associated with emotional problems in ADHD. As Hinshaw (2003) highlights, the key problem with theories of emotion regulation is that it is not possible to behaviourally differentiate an overabundance of emotional reactivity, a deficit in emotional regulation, or a combination of both.

1.2.3 What is emotional lability in the context of emotion and emotion regulation?

It has been noted that change over time is a fundamental characteristic of emotional experiences, influenced by changes in the environment, as well as being influenced by past and influencing future experiences (Kupens, Oravecz & Tuerlinckx, 2010; Ebner-Priemer & Trull, 2011). Emotions which are stagnant and unchanging would lose their adaptive benefits of being contextually sensitive markers of, for example, threat or opportunity. The dynamic nature of emotions is therefore not only characteristic of emotional experiences but also important for optimal environmental adaptation (Kuppens et al., 2010). However, in the case of emotional lability, whereby emotional changes appear extreme and uncontrolled, it is also clear emotional dynamics can also be maladaptive.

It has been noted that emotions are regulating as well as regulated. Emotions are believed to aid in preparing and guiding responses to important events, which may threaten or pose

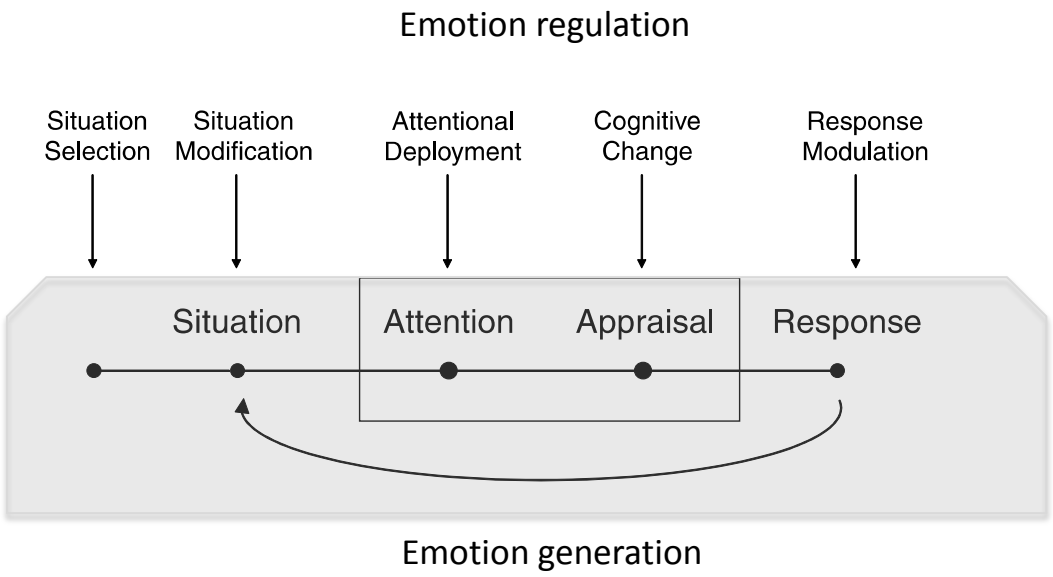
opportunities for improving wellbeing, thereby steering people towards certain things and away from others (Kuppens, et al., 2010; Frederickson, 2000). Simultaneously, there is a burgeoning literature on 'emotion regulation', involving control over, and modification of emotional experiences and expressions. There is some considerable discussion on whether emotion generation and emotion regulation can meaningfully be distinguished (Gross & Barrett, 2011; Gross, Sheppes & Urry, 2011; Thompson, 2011), with certain theories hypothesising greater distinction between emergent emotions and their control, positing competing brain networks for emotion generation and regulation, and others proposing a more unitary emotional response continually constructed by distributed networks in the brain (Gross & Barrett, 2011).

Emotion self-regulation is traditionally defined as when an individual initiates new, or alters ongoing emotional responses through the engagement of regulatory processes in the service of attaining social or personal goals. This can include changes in valence, duration or intensity of emotion (Thompson, 1994). The goal of this process is often to force the state of the emotional system in a preferred direction (Hoeksma, Oosterlaan, & Schipper, 2004): including in assisting to dampen or inhibit negative emotions, which are the least socially acceptable and produce the most detrimental effects on social outcome (Barkley, 1997; Thompson, 1994), and in generating a socially adaptive neutral or positive responses despite events that provoke negative emotions. It is this form of emotional regulation that is most frequently posited as being deficient in ADHD, resulting in behavioural features of emotional labilility (e.g. Barkley, 2010).

Gross and Thompson (2007) propose five cognitive components of emotion regulation strategies which are overlaid on processes which encompass emotional experience. This is shown in fig. 1. According to this model emotions are generated by situations, which are attended to by the person, appraised and followed by a response. As indicated by the pathway between response and situation, the emotional response often changes the situation which gives rise to the emotion in the first place. Importantly, emotions arise only when a situation is construed as being relevant to one or more of an individual's active goals (Gross et al., 2011). Overlaid on these emotion-generative processes (in grey) is emotion regulation (denoted by the downward arrows), which involve the motivated recruitment of one or more processes to influence or modify emotion generation. These include, situation

selection and situation modification, (involving the selection or modification of situations which give rise to emotions), attentional deployment (influencing emotional responding by redirecting attention within a given situation), cognitive change (changing one's appraisals in a way that alters the situation's emotional significance), and response modulation (influencing experiential, behavioural or physiological responses after response tendencies have been initiated, including the inhibition of emotional behaviours which typically accompany an emotion).

Figure 1: A process model of emotion regulation highlighting five families of emotion regulation strategies (denoted by downward arrows). Adapted from Gross & Thompson, 2007



However, most emotions observed in ourselves and others are likely to be the result of a complex interplay between emotion-generative and regulatory processes. The challenge lies in determining whether the goal to modify an emotion was activated or not (Gross et al., 2011).

As will be discussed in detail in section 1.7, studies of injury to brain regions implicated in the generation and modification of emotional responses can result in emotionally labile emotional features. Recent evidence suggests mutually regulatory influences of 'top-down' regulatory control (such as influences from the prefrontal cortex to the amygdala), and 'bottom up regulatory influences from the limbic system to higher cortical regions (Thompson, 2011), indicative that emotional regulation should not simply be regarded as a

supervisory or inhibitory control by cortical areas. However, it is this function that is traditionally emphasised in the research literature and which has been the main target of research on EL in ADHD.

1.2.3 Overview and conclusions

A variety of terms have been utilised to describe the pattern of irritability, hot-temperedness and volatility reported in ADHD, including terms describing problems with affect, mood and emotion. The term 'emotion' appears more complementary to the short lived changes and volatility described in individuals with ADHD. Furthermore, although terms such as emotional dysregulation are the most commonly used in this area of research, these posit that the emotional dynamics described in ADHD are related to regulatory or executive failures. In this thesis, which sets out to test the associations between various cognitive dysfunctions (including top-down control processes, and bottom-up indices of arousal and activation) and emotional problems in ADHD, a descriptive approach is favoured. The term e*motional lability* (EL) for the emotional features described above will therefore be adopted throughout this thesis.

1.3 Behavioural association between emotional lability and ADHD

1.3.1 Capturing emotional lability in ADHD

Research in children with ADHD has used a variety of methods for capturing EL, all yielding complementary findings. Two particular research designs do not rely on retrospective reporting, measuring emotional responses in real time. Observational studies of behaviour in frustration-inducing tasks have shown children with ADHD to respond with heightened emotional reactions and more frustration than their non-ADHD peers (Maedgen & Carlson, 2000; Melnick & Hinshaw, 2000; Walcott & Landau, 2004). Ambulatory assessment methods, in which multiple reports are logged during the day or week on a hand-held electronic device, have shown that children with ADHD report increased anger and sadness when getting ready for activities (Whalen, Henker, Ishikawa, et al., 2006).

However, the most widely used approaches include self- and other reported EL on questionnaires and in interviews. Interview-based studies have established the presence of

irritability in 72-76% of children with ADHD (Geller, et al., 2002; Mick, et al., 2005). Parents of children of ADHD report enhanced levels of sadness, anger and guilt in their children (Braaten & Rosen, 2000) and a greater reactivity to negative events than seen in peers (Jensen & Rosen, 2004), as well as enhanced features of EL (comprising unpredictable mood changes, temper tantrums and tearfulness) in comparison with their non-affected siblings (Anastopoulos, et al., 2011).

In support of the involvement of emotion regulatory failures, parents report also that their children have greater difficulty in self-regulating these negative emotions (e.g., how well the child can calm themselves down after getting angry; Berlin, Bohlin, Nyberg, & Janols, 2004); and children with ADHD also rate themselves as engaging less in strategies to regulate their own emotions than non-ADHD controls (e.g.," If I find myself getting mad, I try to calm down"; Schmitt, Gold, & Rauch, 2012; Scime & Norvilitis, 2006).

Research contrasting EL in adults with ADHD and control groups is sparser and more methodologically limited; only questionnaire measures have been utilised. However, unlike research in children, these measures tend not to focus on self-reported emotional control, but rather the pattern of emotional problems which are characteristic of EL. A recent study identified 54% of adults with ADHD as having greater self-reported EL than 95% of a healthy comparison group; (Surman, et al., 2011). Another study also showed elevated EL in adults with ADHD, beyond the rates reported in both community control populations and in comparison to a clinical control sample (evaluated for ADHD but not diagnosed with the condition; Barkley & Murphy, 2010). Moreover the ADHD group reported features of EL as frequently as symptoms of inattention, and more frequently than they did symptoms of hyperactivity-impulsivity. A study following up children with ADHD into adulthood, again reported elevated EL in those with a previous diagnosis of ADHD (Barkley & Fischer, 2010). In those with continuing ADHD into adulthood, EL features were again reported as frequently as symptoms of inattention and hyperactivity-impulsivity.

1.3.2 Developmental trajectory

No work to date has been carried out to characterise the longitudinal trajectory of EL in ADHD throughout the lifespan. Clinical descriptions of EL in children and adults with ADHD are very similar, indicating that the pattern of emotional problems may remain the same. For example Wender (1975, p. 49; 2001, p.6) describes a "short fuse" and "low boiling point" in both children and adults. Children are described as having "temper tantrums" and "short term lability", whilst adults have a "hot temper" and "affective lability".

Systematic differences in research methodology between children and adults make it difficult to comment on any continuity of specific emotional symptoms, or the longitudinal nature of their relationship to ADHD symptoms. In adult literature self-report measures are the mainstay, whilst parental reports are more common in children. Such differences may impact on the relationship revealed between ADHD symptoms and EL. For example, in a study comparing parental and self-report of EL in childhood, parental reported EL was more strongly linked to externalising problems (ADHD, oppositional and conduct disorders), whereas in self-report showed stronger links to internalising problems (depression and anxiety; Stringaris & Goodman, 2009).

Recent research in adults has shown that EL is elevated in individuals with persistent compared to remitting ADHD (Barkley & Fischer, 2010), which may indicate either that that problems with EL might diminish alongside ADHD symptoms during development (accounting for the reduced EL in remitting cases), or that elevated EL from childhood predicts poorer prognosis for remission of ADHD symptoms (contributing to the high ADHD symptoms and EL in persistent cases). Further work using longitudinal study designs is required to clarify the role of EL in the persistence of ADHD symptoms into adulthood.

1.3.3 Relationship to inattention, hyperactivity-impulsivity and impairment

A differential association between ADHD symptom dimensions and EL has been noted, with research on clinical samples placing EL alongside externalising and aggressive behaviours, and being more strongly associated with hyperactive-impulsive rather than inattentive symptoms of ADHD. Higher levels of EL have been identified in both children and adults with the combined subtype of ADHD (Anastopoulos, et al., 2011; Maedgen & Carlson, 2000;

Reimherr, et al., 2010) and other research in children and adults has shown that EL in ADHD clinic cases is more strongly associated with hyperactivity-impulsivity than inattention, with comparative analyses of ADHD subtypes revealing higher levels of EL in individuals with combined type ADHD than those with inattentive symptoms alone, and regression analyses showing a stronger association between EL and hyperactive-impulsive symptoms than inattentive symptoms (Barkley & Fischer, 2010; Marc & Crundwell, 2005; Sobanski, et al., 2010). Other research has shown strong associations between EL and aggressive, ODD and/or CD behaviours in children (Anastopoulos, et al., 2011; Graziano, et al., 2012; Melnick & Hinshaw, 2000; Sobanski, et al., 2010). Although equivalent evidence is lacking in adults with ADHD, some research has linked EL to criminal offences (Barkley & Fischer, 2010; Barkley & Murphy, 2010).

EL also has shown a strong association with impairment in individuals with ADHD. In children with ADHD, EL was found to partially mediate the effects on ADHD symptoms on indices of impairment (social skills, daily living), as well as on comorbid symptoms (Anastopoulos, et al., 2011). Studies in adults show a much stronger association with impairment, with EL contributing uniquely to numerous impairments in occupational, educational, criminal, driving, and financial outcomes beyond ADHD symptoms (Barkley & Fischer, 2010; Barkley & Murphy, 2010).

1.3.4 Confounds I: adversity

Risk for ADHD is elevated in individuals who experience greater environmental adversity in childhood, such as family conflict and parent psychopathology (Biederman, Faraone, & Monuteaux, 2002; Biederman, et al., 1995). Adults with ADHD are noted as more likely to experience interpersonal and relationship difficulties, problems due to lateness, absenteeism, and inability to accomplish expected workloads, and are more likely to be dismissed from employment (Harpin, 2005). Adverse life events have been shown to correlate with ADHD symptom severity (Muller, et al., 2008), and symptoms of ADHD have been associated with increased risk for financial loss, family problems and sick leave (Friedrichs, Igl, Larsson, & Larsson, 2012).

Research has also shown that EL may contribute to the experience of greater adversity in the everyday life of adults with ADHD, causing greater impairment in a variety of daily life

functions and being associated with a number of adverse events and outcomes (Barkley & Fischer, 2010; Barkley & Murphy, 2010). However, it is also possible that individuals with ADHD may simply experience more emotional instability, as well as increased feelings of irritability, frustration and anger due to more frequent experiences of negative events. To date, no research has investigated whether increased adversity associated with ADHD may play a contributing role to EL.

1.3.5 Confounds II: social and emotional processing deficits

Zeman et al. (2006) describes a vast array of components which require organisation and management for an emotion to be regulated: an internal component (neurophysiological, cognitive and subjective evaluations), a behavioural component (facial expression, behavioural actions) and an external/social component (cultural values, social contextual significance). Success is often indexed by how closely an individual meets social conventions including matching expected emotions (Kopp, 1989). However, difficulties in reacting appropriately to a social situation may stem from a number of different underlying problems, such as an impaired understanding of emotional information (e.g. facial expressions), a lack of empathic experience for others, inattentiveness to social cues, or a lack of understanding of social norms. Many of these functions have been found to be impaired in ADHD (Braaten & Rosen, 2000; Friedman, et al., 2003; Rapport, Friedman, Tzelepis, & Van Voorhis, 2002; Williams, et al., 2008) and may contribute directly to social and emotional problems.

However, there is evidence to suggest that individuals with ADHD may suffer problems with emotional self-regulation even after aspects of social function are taken into account. Friedman et al. (2003) found that while ADHD adults showed deficits in social functioning, they viewed themselves as more sensitive to violations of social norms than controls and less able to control their emotional responses. Scime and Norvilitis (2006) found that children with ADHD perceived themselves as less able to regulate their own emotions than their peers, but did not find differences in the children's ratings of their ability to understand, or attend to, their own emotions. Walcott and Landau (2004) found that boys with ADHD were unable to regulate their displays of emotion during a frustrating task, even when they were instructed to do so. These studies suggest that even when individuals with

ADHD understand and are aware of the need to modulate their emotional responses, they have difficulty in successfully doing so.

1.3.6 Confounds III: comorbidity

As mentioned previously, comorbidity is the norm rather than the exception in ADHD. Additionally, features of EL are diagnostically non-specific. This can cause serious problems for the interpretability of findings showing elevated EL in ADHD when the effects of comorbidity are not accounted for.

Irritability or temper problems are included in the diagnostic criteria for borderline personality disorder, bipolar disorder, ODD and paediatric depression (American Psychiatric Association, 2000). A large population study of children and adolescents, found emotional changes that were noteworthy because of their amplitude, frequency or rapidity, to be associated with a variety of psychiatric illnesses: ADHD, ODD, conduct disorder (CD), anxiety disorder and depression (Stringaris & Goodman, 2009). 'Severe mood dysregulation' (SMD; severe and chronic irritability, alongside hypoarousal symptoms: e.g. insomnia, distractibility, physical restlessness) was most strongly associated with ADHD (26.9%) closely followed by CD (25.9%) and ODD (24.5%), in a population sample of children and adolescents (Brotman, et al., 2006). In adolescence, irritability, as assessed by a single question (''is your child irritable?'') was reported by parents in 21% of a large population sample (Pickles, et al., 2010), providing an indication of its ubiquity. Furthermore, in adulthood self-reported irritability has been associated with anxiety and depression (Pickles, et al., 2010) .

Research in children and adolescents has reported that EL seemed to be more closely related to ODD than to ADHD (Sobanski, et al., 2010). However, the scale used for EL in this particular study was very short (4 items) and included one item overlapping with ODD (temper tantrums), potentially inflating the relationship between these two constructs. Anastopoulos and colleagues (2010) report correlations of EL with quantitative measures of comorbid symptomatology in children with ADHD, with correlation coefficients ranging from 0.29 (anxiety), through to 0.71 (depression), with intermediate coefficients for conduct problems (0.52). In a study investigating relatives of adults with ADHD, comorbidity was common in siblings of individuals with ADHD and co-occurring EL (51% depression, 24%

ODD, 30% alcohol dependence, 27% social phobia, 13% bipolar disorder). These findings indicate that caution is required in the interpretation of the high rates of EL in ADHD, for studies where comorbid conditions and symptoms have not been taken into account.

In most studies on EL to date, comorbidity has not been considered in any depth. Most studies in children report on small samples, and even when controlling for other comorbid conditions frequently include children with ODD and with CD. Studies of EL in adults with ADHD tend not to report on rates of comorbidity, although evidence would suggest that comorbid conditions are likely to be common. One exception is the study by Barkley and Fisher (2010), where analysis was carried out before and after covariation for anxiety and depression only, with results continuing to show enhanced EL in the adult ADHD group.

1.3.7 Overview and conclusions

There is now a considerable literature on features of EL in children with ADHD, with the literature in adults playing a rapid catch-up. Findings in children and adults appear complementary, although methodological differences and a lack of longitudinal studies prohibit an understanding of the potential developmental changes in EL alongside ADHD symptoms. Whilst the childhood literature has been inventive in measuring EL in a variety of complementary ways, the adult literature has been limited to self-report measures, which are frequently subject to a variety of recall biases (Ebner-Priemer, et al., 2006). Moreover, findings of elevated EL in ADHD may be confounded by comorbidity, adversity and social and emotional processing deficits. Further research must be carried out to investigate EL in ADHD after controlling for these potential confounds.

1.4 Familial co-transmission of emotional lability in ADHD?

Recent studies of EL in ADHD have turned to familial designs to test the aetiology behind the relationship between ADHD and EL. Family studies compare the prevalence of a trait or disorder within relatives of individuals affected with a disorder (probands) to relatives of unaffected individuals. However, since the differential effects of genetics and familial environment cannot be quantified, both may be influencing the co-occurrence of the trait in family members.

Some evidence to date suggests that EL is transmitted in families. However, whether it is co-transmitted with ADHD remains uncertain. A recent report by Barkley and Murphy (2010) investigated the association between ADHD and EL in adults, with symptoms of ADHD in their children (as measured by parental report), it was shown that proband EL predicted offspring severity of hyperactive-impulsive symptoms. In a converse study design by Epstein and colleagues (2000), EL with impulsivity was assessed by self- and other-report in parents of children with combined type ADHD. Reports of EL/impulsivity made by others were significantly elevated in the biological parents of ADHD children compared to non-biological parents and control parents.

Other studies have carried full diagnostic assessments in probands and family members and can better test whether EL is familial and co-segregates with ADHD. Sobanski and colleagues (2010) did not find evidence for co-transmission of ADHD and EL, showing that EL was elevated in siblings of children and adolescents with ADHD and high EL compared to those with low EL. Similarly, a smaller sibling study in adults by Surman and colleagues (2011) showed that ADHD was transmitted at a similar rate among siblings of ADHD probands irrespective of the presence or absence of EL, but EL was only elevated amongst siblings of probands who also had EL. These studies suggest that EL shows a distinct familial basis from ADHD.

There is consistent evidence that ADHD is a highly heritable disorder, with a meta-analysis of 20 twin studies indicating an average heritability of around 0.76 (Faraone, et al., 2005). Twin studies have explored the relationship between ADHD and its comorbidities, finding a considerable degree of shared genetic influences, for example with depressive symptoms (Cole, Ball, Martin, Scourfield, & McGuffin, 2009), autistic symptoms (Ronald, Simonoff, Kuntsi, Asherson, & Plomin, 2008), and conduct problems (Thapar, Harrington, & McGuffin, 2001). Work is now underway using similar methodologies to investigate genetic overlap of ADHD and EL (Merwood, et al., 2011); although no studies have been published to date the preliminary findings indicate both overlapping and unique genetic influences on ADHD and EL.

1.4.1 Overview and conclusions

There have been too few studies to date investigating familial and genetic factors on the co-occurrence of EL and ADHD to draw any firm conclusions. The available studies support a strong association between ADHD and EL, but the studies in which co-transmission is specifically tested, suggest that EL shows a distinct familial basis from ADHD. Future avenues for research include designs such as the twin design which would more effectively tease out genetic and environmental factors associated with overlap between ADHD and EL.

1.5 Response to treatment of ADHD and emotional lability

Emotional lability and ADHD symptoms in adults with ADHD have been found to show a shared response to treatment across a variety of treatment paradigms. Findings in children are much less clear.

Methylphenidate is the stimulant medication that is most commonly used to treat ADHD in the United Kingdom. It is a noradrenaline and dopamine reuptake inhibitor and in the UK is currently considered the first line treatment for childhood ADHD associated with severe levels of impairment and in all cases of ADHD in adults (NICE 2008, www.nice.org.uk).

A number of double-blind, placebo-controlled medication trials have now shown the beneficial effects of methylphenidate on EL in adult ADHD. In a small study of adults with continuing ADHD symptoms into adulthood, patients reported feeling happier, less angry and with a cooler temper, as part of the treatment response (Wender, et al., 1985). Two studies by Reimherr and colleagues (Reimherr, et al., 2010; 2007), reported large effect sizes for EL response (0.7-0.83), and a concurrent improvement in ADHD symptoms with EL during treatment, with high correlation between response in EL and in attention/distractibility (r=0.88) and in hyperactivity/impulsivity (r=0.81) in their earlier study, and with attention/disorganisation (r=0.89) and hyperactivity/impulsivity (r=0.88) in their later study. In a larger study in which almost all participants were free from current axis I comorbidity, Retz and colleagues (2010) reported a significant improvement in some aspects of EL with treatment. In the largest study to date, Rösler and colleagues (2010), investigated EL in 363 patients with ADHD as they underwent 24 week treatment trial. Improvements in EL were seen after treatment with a small to moderate effect size for EL

(0.37), which was comparable to effects sizes seen for symptoms of inattention, hyperactivity and impulsivity. Interestingly, no improvements were seen for depression, anxiety, anger and hostility. The smaller effect sizes seen in this study as compared to those by Reimherr and colleagues (2010; 2007) were attributed to the more modest treatment regimen in this sample and a relatively high placebo response rate. However it is notable that in the Rösler et al (2010) study, all patients also received psychoeducation during the course of the treatment trial, which may have led to a higher response rate in the placebo-treated group.

Improvement in EL has also been found with other pharmacotherapy for ADHD, most notably atomoxetine (a noradrenaline re-uptake inhibitor, and the most commonly used non-stimulant treatment for ADHD). Two double-blind placebo-controlled trials of atomoxetine in adults, again showed significant improvements of EL with treatment, with the greatest improvements seen in individuals with ADHD and co-occurring EL (Marchant, et al., 2011; Reimherr, et al., 2005).

There are fewer double-blind placebo-controlled treatment trials investigating EL in children and adolescents with ADHD, and findings are less consistent. In a meta-analysis of 62 randomised trials of short acting methylphenidate, Schachter et al. (2001) identified only two studies which reported on treatment response of EL, and treatment effects were non-significant. One study showed that teacher reported 'crabbiness' decreased during treatment with methylphenidate (Galanter, et al., 2003). Another study in a small group of preschool children showed equivalent reductions in reporting of irritability on methylphenidate as on placebo (Short, Manos, Findling, & Schubel, 2004).

Much more work in the child literature focuses on EL as a potential side effect from treatment (e.g. Kratochvil, et al., 2007; Wilens, et al., 2003), generally only acquiring data on this measure after treatment has started. A recent review article has highlighted this problem, and has called for more research in children in which EL and other emotional problems measured prospectively, to identify change in these measures (Manos, et al., 2011). However, it is notable that in adults similarly, EL has been noted as one of the more common side effects of stimulant treatment (Ramos-Quiroga, et al., 2008). Even in studies where successful treatment generally results in improved mood regulation, increased

irritability and EL have been noted in patients under higher doses of methylphenidate (Reimherr, et al., 2007).

While the treatment effects are noted as being striking in a number of medication trials, behavioural treatment with group therapy has also been shown to be beneficial in treating both mood and ADHD symptoms in adulthood; although it is not clear whether the mood symptoms that respond reflect EL rather than low self-esteem and dysthymia that also frequently accompany ADHD. Reductions in symptoms of depression were found after group therapy using (Philipsen, et al., 2007), a cognitive remediation programme was found to be helpful in reducing anger (Stevenson, Whitmont, Bornholt, Livesey, & Stevenson, 2002), and cognitive behaviour therapy for ADHD has also been found to reduce symptoms of anxiety and depression (Bramham, et al., 2009; Safren, et al., 2005).

1.5.1 Overview and conclusions

Overall research reviewed here suggests that many treatments commonly used to improve symptoms of ADHD concurrently have beneficial effects on emotional problems, particularly in adults. The striking findings in methylphenidate treatment response in adults contrasted with the mixed results from similar research in children, raises the potential of developmental effects on EL in treatment response. However, this is tempered by the limited data from the child literature. The shared treatment response observed in adults makes a strong indication for a shared neurochemistry between EL and ADHD which warrants further investigation.

1.6 Cognitive function

Although a wealth of research now documents neurocognitive deficits in ADHD, a clear model for the neuropsychological basis of the disorder remains elusive. Key issues are the heterogeneity of cognitive deficits associated with ADHD and the lack of data clarifying which cognitive deficits play a causal role in the disorder. This makes it difficult to test the association between EL and ADHD in terms of cognitive function, since the broad literature presents a myriad of cognitive targets for investigation.

Widespread cognitive impairments have been associated with ADHD (Hervey, et al., 2004; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005), and recent studies suggest the presence of a variety of independent cognitive deficits, which show separable familial transmission, and differential longitudinal relationships with ADHD (Halperin, et al., 2008; Kuntsi, et al., 2010; Sonuga-Barke, Bitsakou, & Thompson, 2010). As a result, neurocognitive models of ADHD now frequently include multiple causal pathways, each mediated by diverse constellations of cognitive dysfunction (Sonuga-Barke, 2010). These often include deficits in executive functions alongside impairments in motivational, state regulation or timing processes (Halperin & Schulz, 2006; Kuntsi, et al., 2010; Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005; Sonuga-Barke, 2003; Sonuga-Barke, et al., 2010).

However, even where specific associations between cognitive deficits and ADHD have been demonstrated, it has not yet been possible to identify whether these show a causal link to ADHD symptoms by mediating the effects of genetic and/or environmental risk factors on behavioural symptoms (intermediate phenotypes), or merely reflect one of multiple parallel outcomes of shared risk factors (pleiotropic effects; Kendler & Neale, 2010).

The bulk of evidence in relation to EL in ADHD and cognitive processes can be divided roughly into two categories, first, 'top-down' executive functions (specifically inhibitory and attentional functions) and second, 'bottom-up' arousal or emotional processing functions. It is possible that deficits in one cognitive domain may be primarily associated with EL in ADHD, although research to date, much like research on the ADHD itself, suggests EL may be associated with a variety of cognitive dysfunctions.

1.6.1 Top-down: emotional lability and executive function

Historically, research has emphasised the association between ADHD and deficits in executive function (EF; Barkley, 1997), the importance of which have been confirmed in several meta-analytic studies (Boonstra, Oosterlaan, Sergeant, & Buitelaar, 2005; Hervey, et al., 2004; Willcutt, et al., 2005). EF is a broad term used to describe a diverse set of interrelated processes that maintain an appropriate problem solving set and facilitate purposeful, goal directed activity. EF includes cognitive processes such as inhibition, shifting or maintaining attention, planning, initiating tasks, detecting and correcting errors, and working memory (Berger, Kofman, Livneh, & Henik, 2007; Riggs, Jahromi, Razza, Dillworth-

Bart, & Mueller, 2006; Sonuga-Barke, 2003; Willcutt, et al., 2005). However, not all individuals with ADHD display deficits in EF, which therefore appear to be neither necessary nor sufficient to account for the presence of the disorder (Nigg, et al., 2005; Saboya, Coutinho, Segenreich, Ayrao, & Mattos, 2009; Sonuga-Barke, et al., 2010; Willcutt, et al., 2005; Woods, Lovejoy, Stutts, Ball, & Fals-Stewart, 2002).

Eisenberg and Spinrad (2004, p. 338) summarise emotional self-regulation as "the process of initiating, avoiding, inhibiting, maintaining, or modulating the occurrence, form, intensity, or duration of internal feeling states, emotion-related physiological, attentional processes, motivational states and/or behavioural concomitants in the service of accomplishing affect-related biological or social adaptation or achieving individual goals". There is some overlap between this definition and cognitive processes classified as EF. Indeed, some researchers have proposed that a set of general self-regulatory functions may underlie the regulation of cognition, behaviour and emotion (Berger, et al., 2007; Hoeksma, et al., 2004; Posner & Rothbart, 1998).

An influential hypothesis posited by Barkley (1997, 2010) is based on this premise, and proposes a key inhibitory deficit underpinning both behavioural and emotional features of ADHD, including EL. This inhibitory deficit is postulated to render individuals with ADHD unable to delay or inhibit prepotent or dominant responses to an emotional event (*emotional impulsivity)*. Where an emotional response is successfully inhibited, this then allows for second stage of regulatory process which involves the effortful regulation or moderation of emotions (by the deployment of attention and working memory functions) to be more socially appropriate and consistent with long-term goals. Failures in this second stage have been termed *deficient emotional self-regulation*, also deemed impaired in ADHD. This framework firmly associates EL in ADHD with deficits in executive function. However, there has been limited testing of this theoretical model.

1.6.1.1 Emotional lability and inhibitory function in ADHD

There is some evidence to suggest that EL in ADHD may be related to performance on inhibitory function tasks, although to date only studies in children with ADHD have investigated this association.

In preschool children with ADHD, parental ratings of emotional control have been found to be highly correlated with ratings of inhibition, working memory, attentional shift and general executive control (Mahone & Hoffman, 2007). In school-age children with ADHD, those with higher self-reported EL performed worse on timed tasks of EF, including a measure of inhibition (Graziano, et al., 2012). In a study of highly hyperactive-impulsive boys, expressed frustration during a frustration inducing task was strongly associated with the Stop Signal Reaction Time (SSRT) on the Stop Task (Wallcott & Landau, 2004). The SSRT measures the latency of time needed to stop an ongoing response and is often used to index behavioural inhibition, however it may also be modulated by general attentional or state regulation deficits (Banaschewski, et al., 2004; Bekker, et al., 2005; Hervey, et al., 2004; Lijffijt, Kenemans, Verbaten, & van Leeuwen, 2005).

1.6.1.2 Emotional lability and attention in ADHD

The concept of 'attention deficit' in diagnostic formulations of Attention Deficit Hyperactivity Disorder is not defined in terms of cognitive function, but rather from behavioural ratings from patients, their parents and teachers. Behaviour that appears as 'inattentive', therefore may or may not be directly linked to dysfunctions in cognitive or neural networks that subserve attentional control per se (Huang-Pollock & Nigg, 2003).

Moreover, the cognitive construct of attention is widely recognised as being multifaceted, encompassing a diversity of functions. Three anatomically distinct attentional networks serving different functions are distinguished by Posner and Peterson (1990). These include, (1) alerting or vigilance: the ability to achieve and maintain a state of sensitivity to incoming stimuli; (2) automatic orienting: the automatic orientation of attention to changes in the perceptual field; and (3) voluntary orienting and executive attention: a supervisory system which enables the selection relevant information, and the voluntary shifting of attention.

Links between attentional functions and emotions have long been reported in the literature. Emotional stimuli, particularly those that are unpleasant or threat-relevant, attract attention (Pinkham et al., 2010). Moreover, as outlined previously, attentional deployment or distraction is considered a core component of emotion regulation. This involves shifting attention from one aspect of a situation to another aspect of the situation or entirely away from the situation altogether (Gross, 1998). The inverse of this can be considered

rumination, which involves directing attention selectively inward toward feelings and the consequences of certain feelings (Gross, 1998). Shifting attention away from negative stimuli may therefore help to attenuate or contain negative emotion, which may make individuals with a greater control over attention at a greater advantage in optimizing emotion (Derryberry & Rothbart, 1988).

In terms of the ADHD literature, there has been little research on EL and attentional functions. However, there is a growing literature suggesting that inhibitory deficits, which have been linked to EL both theoretically (e.g. Barkley, 1997, 2010) and in studies involving cognitive testing, may be secondary to attentional deficits. Moreover, some work to date suggests potential links between attentional orienting and EL in ADHD, as well as deficits in executive attention in the context of task performance in the presence of emotionally salient distractor stimuli.

To investigate the primacy of inhibitory deficits, attention has turned to electro-encephalographic (EEG) measures, in particular event-related potentials (ERPs). ERPs are small voltage fluctuations recorded on the scalp resulting from evoked brain activity, reflecting the average neural activation to a repeated event such as the presentation of a stimulus (Albrecht, Banaschewski, Brandeis, Heinrich, & Rothenberger, 2005; McLoughlin, Kuntsi, Brandeis, & Banaschewski, 2005). ERPs provide a direct, precise temporal measure of brain activity, which facilitates the identification of processes occurring in the absence of overt behaviour, such as preparation and attentional orienting, which may precede other deficits (McLoughlin, Kuntsi, & Asherson, 2011).

An ERP study of the SSRT suggested that deficits in attentional switching may precede inhibitory control problems in adults with ADHD (Bekker, et al., 2005). Similarly, ERP investigations of a cued Continuous Performance Test (CPT-OX) revealed impairments in covert attentional orienting and preparation which preceded inhibitory processing abnormalities in children and adults with ADHD (Banaschewski, et al., 2004; Doehnert, Brandeis, Imhof, Drechsler, & Steinhausen, 2010; McLoughlin, et al., 2010; van Leeuwen, et al., 1998). This has led researchers to question the primacy of inhibitory deficits seen in ADHD (Banaschewski, et al., 2004), and may likewise indicate some ambiguity in the relationship seen between EL and inhibitory function noted in ADHD.

In an ERP study, self-reported EL was associated with attentional function as shown by a reduction in passive auditory P3 potentials in adolescents with comorbid ADHD and conduct disorder (Du, et al., 2006). In a study by Rich and colleagues (2007) investigating children with 'severe mood dysregulation', attenuated N100 and P100 amplitudes were seen during the Emotional Posner task, indicative of impaired attentional orienting and initial attentional processing deficits. While the Rich study did not set out to investigate emotional regulation in ADHD they reported that over 80% of participants in their sample with 'severe mood dysregulation' had comorbid ADHD, which might indicate that the processes identified as impaired might also be associated with ADHD in the context of EL.

In a more recent study participants were asked to engage in a working memory task during the presentation of negative visual images which they were instructed to ignore. Adults with ADHD showed enhanced distractibility to emotionally salient stimuli (Marx, et al., 2011). The authors suggest that their findings support the hypothesis that problems with EL in ADHD might in part result from difficulties in ignoring task-irrelevant emotional stimulation, as a result of deficient executive control. It is interesting that the interpretation made here echoes the observations made by Chrichton over 200 years earlier (see section 1.1.1).

1.6.2 Bottom up: Emotional Lability and arousal, activation and emotional processing

Considerable controversy remains regarding whether underlying deficits in ADHD comprise one or more deficits in executive functions or deficiencies in more general processes that impact on both executive and nonexecutive processes (Kuntsi, Oosterlaan, & Stevenson, 2001; Rommelse, et al., 2007). In addition to established (although not universal) deficits in executive functions, impairments in ADHD have been also found across a wide range of non-executive tasks. The lack of specificity to any one task or process and the co-occurrence of both executive and non-executive deficits within individuals with ADHD has led some authors to propose earlier and more general deficits which 'cascade upwards' in ADHD, resulting in secondary executive function deficits. In relation to emotional function in ADHD, this fits into a growing literature identifying abnormalities in early stages of emotion processing, linking non-executive dysfunctions to features of EL.

1.6.2.1 Intra-individual variability in ADHD

Research has shown that individuals with ADHD are dependably inconsistent (Kuntsi, Wood, van der Meere, & Asherson, 2009). Moment-to-moment variability has been described as the one ubiquitous finding in ADHD (Castellanos & Tannock, 2002), replicated across a multitude of tasks and in a variety of cultures. The fluctuating cognitive performance seen in ADHD may be considered incompatible with theories suggesting stable cognitive impairments in executive functions.

As an example, research investigating a large sample of ADHD children and their siblings found high correlations both within and between a set of executive tasks and simple motor function tasks (Rommelse, Altink, Martin, et al., 2008; Rommelse, Arias-Vasquez, et al., 2008). In this study a single major factor was identified that best explained the co-variation between the various tasks and was characterised as a 'variability factor'. In a similar vein, in analysis of behavioural response measures on a variety of reaction time tasks (continuous performance test, a go/no-go task, a stop signal task and N-back task), Klein and colleagues (2006) reported that indices of intra-individual variability in reaction time, such as the within-subject standard deviation of reaction time, discriminated best between ADHD and control groups. More recent work has investigated cognitive factors associated with ADHD in a sibling design study (Kuntsi, et al., 2010), it was shown that reaction time variability reflected the majority of familial variance for ADHD (85%), while an error factor (comprising commission and omission errors on a go/no-go task) reflected a smaller proportion of the variance (13%).

Kuntsi and Klein (2012) outline a broad literature in which increased intra-individual variability has been described in ADHD, for example in measurement of activity, attention and interference and motor timing. Interestingly they include mood as one of the measures showing enhanced intra-individual variability. Given previous findings that within-subject variability across a variety of motor tasks loads onto a single principle component (Klein, et al., 2006), this raises the question whether variability across domains (such as reaction time and emotion) may also be associated.

1.6.2.2 Sub-optimal arousal and energetic state regulation

One prominent hypothesis of the pathophysiology of ADHD argues that sub-optimal arousal and a failure to optimise energetic state accounts for the variable response pattern seen in individuals with ADHD (Andreou, et al., 2007; Kuntsi, et al., 2010; Russell, et al., 2006; Sergeant, 2005; Todd & Botteron, 2001), with research showing that individuals with ADHD perform more poorly in task conditions which are slower and less rewarding.

However, it is worth noting that cognitive-energic models of ADHD do not tend to specify potential biological substrates for under-arousal. For example, whilst Sergeant (2000), proposes three separable state factors (arousal, effort and activation) associated with task performance in ADHD, and provides details on the function of these state factors at a descriptive level, little detail on the neurobiology underlying these three separable state factors is provided. Much of the research on arousal in ADHD is based on behavioural measures such as response rates, response variability and their manipulation with task-specific changes.

More specific neurobiological hypotheses of arousal are presented by Aston-Jones and Cohen (2005), who propose phasic locus coeruleus (LC)-norepinephrine system activity as facilitating task performance, whilst tonic LC activity is associated with task disengagement and exploration. Direct inputs from the anterior cingulate and orbitofrontal cortex to the LC are thought to monitor task-related utility. Another proposed neurobiological mechanism for behavioural markers of under-arousal (intra-individual variability especially in activities requiring sustained speeded responses and complex information processes), is proposed by Russell and colleagues (2006). They hypothesise insufficient astrocyte function in terms of the formation and supply of lactate, resulting in a slowed restoration of ionic gradients across neuronal membranes and delayed neuronal firing. However, the relationship between these neurobiological functions and task performance measures frequently associated with arousal and cognitive-energic mechanisms remains to be explored in detail.

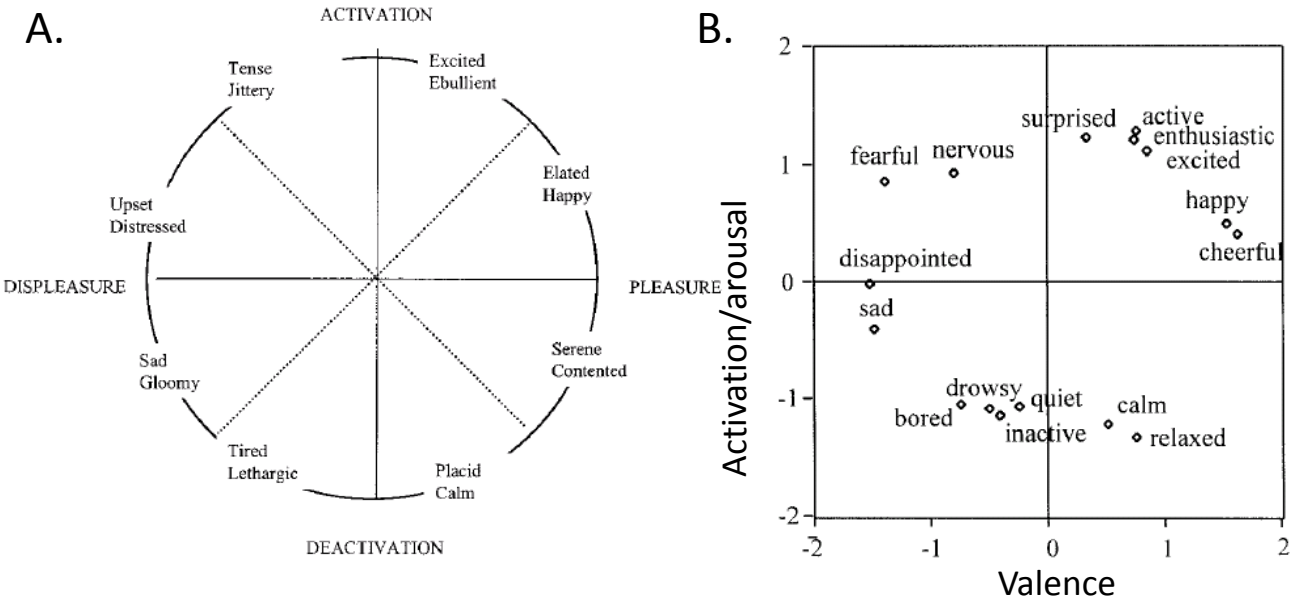
It has been proposed that arousal or state regulation deficits could give rise to impairments that span the range of executive and non-executive impairments seen in ADHD (Kuntsi, et al., 2001; Van der Meere & Sandberg, 1996). Quantitative electroencephalographic (EEG) methods (in which electrophysiological recordings are quantified in frequency ranges

believed to be pertinent to certain functional processes or states), provide data in support of the state regulation hypothesis, frequently revealing reduced power in fast wave cortical activity (mainly beta) and elevated power in slow frequency bands (predominantly theta) in children with ADHD during resting conditions (Barry, Clarke, & Johnstone, 2003; Snyder & Hall, 2006), frequently interpreted as a marker of cortical under-arousal. However, studies in adults with ADHD are fewer and results more ambiguous (van Dongen-Boomsma, et al., 2010).

It is widely argued that arousal is a core component of emotions (Bradley & Lang, 1994; Davidson, Jackson, & Kalin, 2000; Lang, 1995; Russell, 2003). According to the circumplex model of affect (Russell, 2003), core affect is built up of two components; arousal (activation and de-activation) and valence (pleasure and displeasure). The conscious feeling experience is described as a blend of these two dimensions, as a single point in two dimensional space (see fig. 2). Highly consistent judgements of emotions within this space have been seen between healthy individuals and schizophrenia patients (Kring, Barrett, & Gard, 2003), and change in emotional experiences over time have been successfully modelled using this two dimensional approach (Kuppens, Van Mechelen, Nezlek, Dossche, & Timmermans, 2007).

Although no studies have investigated the links between arousal indices and EL in ADHD to date, the relationship between arousal and mood was supported in a study of school age children by Shea and Fisher (1996), showing high correlations in self-ratings of arousal with measures of mood ($r>0.7$), with high arousal associated with more positive mood ratings. Low arousal and more variable arousal were associated with more variable mood. In addition, variability of arousal and mood were found to be strongly correlated with teacher ratings of hyperactivity in girls, and ratings of impulsivity in boys.

Figure 2: The circumplex model of core affect



Legend: A. From Russell (2004) the theoretical affect space, and B. from Kring et al. (2003) the average placement of emotions within this affect space in 7 healthy adult participants

Research has shown that strong positive and negative emotions (e.g. intense anxiety, excitement, fear and anger) are associated with increased physiological arousal levels, evidenced by increased heart rate, skin conductance and changes in pupil dilation (Bradley, Miccoli, Escrig, & Lang, 2008; Cuthbert, Schupp, Bradley, Birbaumer, & Lang, 2000; Lane, Chua, & Dolan, 1999). However, how these are related to indices of cortical arousal such as is measured in EEG is unclear.

1.6.2.3 Emotional processing deficits

A number of studies point to early emotional processing deficits which may impact on EL. There is now consistent evidence showing that children with ADHD are significantly poorer at identifying emotional expressions, especially negative expressions of fear, anger and sadness (reviewed in Herrmann, et al., 2010). However, how these processing differences related to EL in ADHD is presently unclear. The only study addressing this question was carried out by Williams et al. (2008), who showed that self-ratings of EL were strongly correlated with P120 and N170 amplitudes in response to emotional face stimuli, thought to reflect early automatic and early facial processing, respectively. These results indicate that early emotion processing deficits may also be associated with EL. Importantly these deficits were also found to respond alongside EL during the treatment with methylphenidate.

1.6.3 Overview and conclusions

EL in ADHD appears to be linked to a number of different aspects of cognitive dysfunction that have been identified as associated with the disorder. However, the literature is also limited by a clear lack of studies in adults with ADHD. Although there are potential associations between many cognitive deficits associated with ADHD and EL, the limited research carried out restricts the clear identification of any cognitive dysfunctions which may be common to both.

Although most research on cognitive function in ADHD and EL has been carried out in the domain of executive function, the nature of the relationship between EL and executive function remains unclear. The association between EL and ADHD may be due to common deficits in executive function, specifically inhibitory or attentional processing. Alternatively, bottom-up deficits such as state regulation deficits could directly influence executive functions also, and concurrently rise to greater variability in experienced emotion, much like is postulated for variability on performance measures.

1.7 Overlap of brain structure and function between ADHD and EL

1.7.1 Top down: frontal lobe dysfunction

Neuroimaging and brain injury research has shown overlapping brain structures and networks to be implicated in the control of behaviour and emotion. Specifically, the role of the frontal lobes has been emphasised (Zelazo, Cunningham, & Gross, 2007). The frontal lobes have been termed the 'final collection point for information related to both the external sensory and internal (feeling) world' (Stuss, Gow, & Hetherington, 1992), and owing to their enhanced connectivity, they are considered the ideal region for the collection, organisation and integration of information.

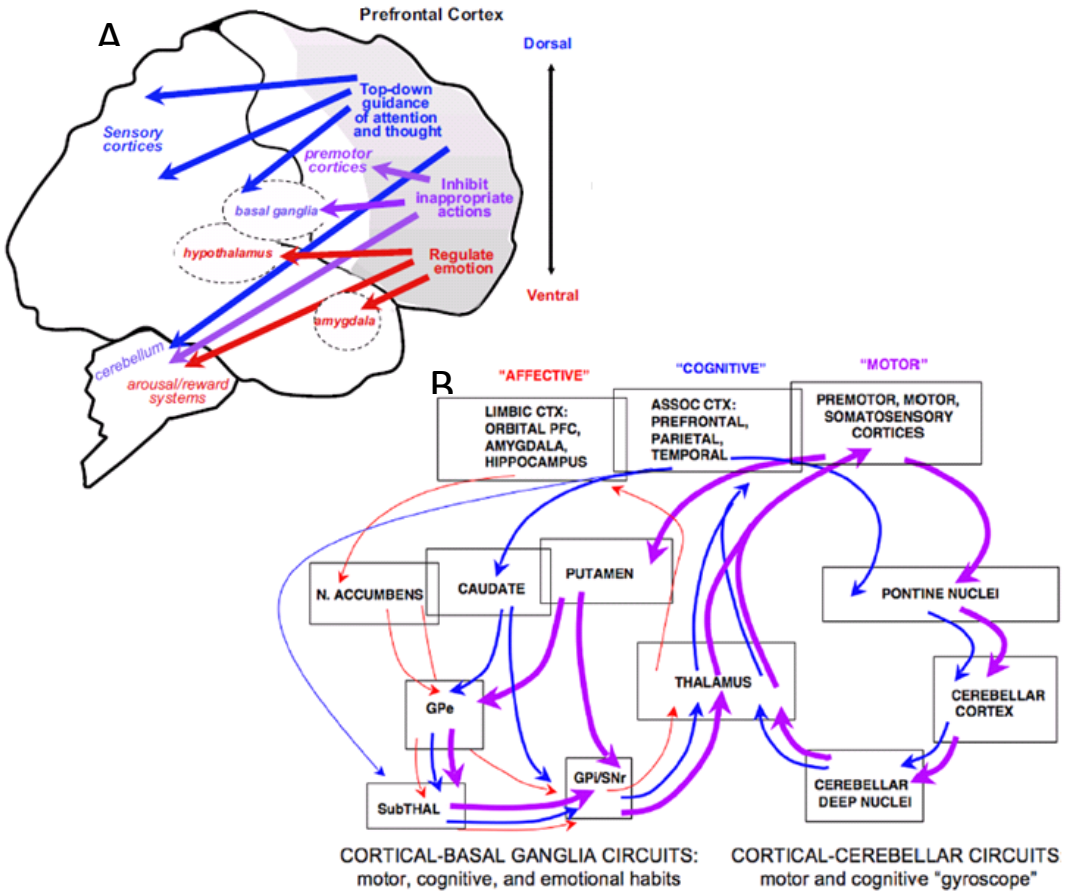
Symptoms such as failure to concentrate, distractibility, short attention span, impulsivity and altered reward processing, as well as EL and aggression are common in individuals with injury to the frontal lobes (Bush, Luu, & Posner, 2000; Grafman, Vance, Weingartner, Salazar, & Amin, 1986; Stuss, et al., 1992). This has led some to conclude that frontal lobe function may be compromised in children with hyperactivity, impulsivity and inattention

(Barkley, 1997; Mattes, 1980). Indeed the neuroimaging literature has corroborated the involvement of frontal structures in the condition, although functional and structural differences in subcortical brain regions have also been identified; altered functional activation and reduced structural volumes have consistently been identified in the prefrontal cortex, alongside basal ganglia (particularly the caudate and striatum) and the cerebellum (Dickstein, Bannon, Castellanos, & Milham, 2006; Paloyelis, Mehta, Kuntsi, & Asherson, 2007; Valera, Faraone, Murray, & Seidman, 2007).

Furthermore, research has shown that a disruption in the organisation or development of prefrontal cortex circuits leads to dysregulation in cognition and emotion, and symptoms of common psychiatric disorders (Arnsten & Rubia, 2012). However, a partitioning of emotive and non-emotive function within the prefrontal cortex has been suggested (Arnsten & Rubia, 2012; Rubia, 2011; Zelazo, et al., 2007). The proposed partitioning asserts that 'cool' functions subserved by the dorsolateral prefrontal cortex and implicated in non-emotive, abstract and decontextualised problem solving as well as motor inhibition. By comparison, 'hot' functions are proposed to be subserved by the ventromedial prefrontal cortex and implicated in the regulation of emotion.

A recent review by Arnsten and Rubia (2012) maps out three parallel prefrontal control pathways, each with subtly different connections and underlying functions. As shown in fig. 3, these three control pathways (the 'hot' control of emotion and the 'cool' control pathways of cognition and motor activity) share partially distinct and partially overlapping circuitry with the cerebellum and basal ganglia. The "hot" orbital and medial prefrontal cortices have strong connections to the amygdala, making this particular circuit anatomically well suited for the integration of emotion-related information and the regulation of approach and withdrawal responses (Zelazo, et al., 2007). By comparison, the 'cool' cognitive dorsolateral prefrontal pathway shows stronger connections with the striatal and cerebellar circuits, and primary and secondary association areas, which are thought to make this circuit well suited for the integration of sensory and mnemonic information that allow the regulation of intellectual function and action (Arnsten & Rubia, 2012; Zelazo, et al., 2007).

Figure 3: Three neurobiological circuits for prefrontal cortex regulation of emotion (red), motor behaviour (purple) and cognition (blue; from Arnsten & Rubia, 2012)



Note: ASSOC, association; CTX, cortex; GPe, globus pallidus external segment; GPi, globus pallidus internal segment; N. ACCUMBENS, nucleus accumbens; SNr, substantia nigra pars reticulata; SubTHAL, subthalamic nucleus.

Subdivisions in regulatory pathways may account for heterogeneity of cognitive deficits and EL in ADHD subtypes. Castellanos and colleagues (2006) propose an association of inattention with deficits in 'cool' executive functioning, and hyperactivity-impulsivity with 'hot' executive functioning deficits. This view provides a working hypothesis for the heightened association seen between EL and hyperactive-impulsive symptoms. Hinshaw (2003) speculates that executive dysfunctions pertinent to ADHD may lie within the 'cool' fronto-striatal pathways, but that emotionally dysregulated and aggressive individuals with ADHD show dysfunction in the 'hot' limbic pathways and interconnections. This view is in accordance with behavioural findings of increased EL in aggressive children with ADHD, and

is also in line with findings by Rubia and colleagues (reviewed in Rubia, 2011) showing that ADHD is characterised predominantly by abnormalities in 'cool' cognitive pathways, whilst conduct disorder is more strongly associated with abnormalities in 'hot cognitive pathways. However, while aggression and hyperactivity may co-occur at a higher rate than expected by chance (Biederman, Newcorn, & Sprich, 1991), they cannot be considered equivalent (Schachar & Tannock, 1995).

1.7.1 Bottom up: Influence of arousal and subcortical dysfunction

Arnsten and Rubia (2012) also highlight the importance of arousal pathways, which can markedly alter activity of the abovementioned circuits, by modulating the levels of neurotransmitters in each pathway. As discussed by Arnsten (2009), optimal levels of catecholamine release (e.g. epinephrenine, norepinephrine and dopamine) enhance prefrontal cortex regulation. However, this is reversed under conditions of psychological stress which evoke the release of high levels of noradrenaline and dopamine. Stress is believed to impair higher order prefrontal cortex ability such as attention regulation and working memory. During stress prefrontal cortex networks disconnect and cell firing is suppressed (Arnsten & Rubia, 2012), leading from a switch from thoughtful 'top-down' control by the PFC to the reflexive and rapid emotional responses of the amygdala and related subcortical structures (Arnsten, 2009).

This is in line with studies of brain injury, which have highlighted that subcortical structures are likely to be instrumental in the expression of features of EL. Damage to the amygdala can lead to apathy, increased aggression, emotional lability, and impaired reward processing (Bechara, Damasio, Damasio, & Lee, 1999; Beer & Lombardo, 2007). Damage to the basal ganglia can lead to apathy, impaired regulation of facial expression, and inappropriate and pathological crying or laughing as well as under- or over-activity (Beer & Lombardo, 2007; Bhatia & Marsden, 1994; Laplane & Dubois, 2001; Wichmann & DeLong, 1996). Both the amygdala and the basal ganglia have been implicated in motivational and appetitive functioning (Brown, Bullock, & Grossberg, 1999; Quirk & Gehlert, 2003; Tanaka, et al., 2004) and are therefore known to influence approach and avoidance behaviours. Modulation from these subcortical regions is thought to provide mechanisms through which emotion might influence learning and cognition (Derryberry & Tucker, 1992).

1.7.3 A combination of both?

Some theories of emotion self-regulation have attempted to integrate bottom-up motivational approaches and top-down executive approaches (Derryberry & Tucker, 1992; Ochsner & Gross, 2008). Cole et al. (2004) state that emotions can be understood in two ways: emotions as regulating and emotions as regulated. It has been noted that bi-directional influences in emotional processing are likely (Carlson & Wang, 2007). Emotions can help to organise an individual's thinking, learning and actions, thereby regulating behaviour in the individual. At the same time executive processes can play a role in regulating emotions, by modifying or inhibiting the emotional responses of the individual. For example, the amygdala is well known for its ability to detect fear-evoking responses and organise responses to natural dangers (LeDoux, 1998). However, in times when the intrinsic or preconditioned response is not the most adaptive (e.g. watching a frightening film), top down processes can step in to regulate behaviour and elicited emotions by inhibitory and executive processes. Abnormalities in either the generation of emotion, or the control of emotion are likely to result in aberrant emotional behaviour that may be considered unstable, and therefore viewed as dysregulated. EL may therefore be attributable to either irregular or ineffective 'top-down' or 'bottom-up' processes.

Executive functions, reward, emotional self-regulation and motivation all involve closely related neuroanatomical circuits and neurochemistry (Nigg & Casey, 2005). It has also been noted that the relationship between executive function, activation, arousal, motivational and reward responses are likely to be dynamic and reciprocal in real world behaviour (Nigg, 2005). Overlap amongst these domains could account for the behavioural and cognitive overlap between executive processes (inattention, inhibition), reward, motivation and emotion self-regulatory processes. This overlap may eventually be attributed to functional and structural overlap in neuroanatomy or neurochemistry. However, because of the lack of studies investigating ADHD, EL and functional and structural brain correlates simultaneously, it is not possible to definitively ascertain the underlying structural and functional commonalities between ADHD behaviours and EL and how these are likely to be manifested.

1.7.4 Overview and conclusions

Research to date points to three separate but parallel neurobiological circuits underpinning the regulation of emotion, cognition and motor behaviour. Clear links have been established between conduct disorder and the 'hot' pathway associated with the control of emotions (Arnsten & Rubia, 2012; Rubia, 2011). Although links have been posited between this pathway and hyperactive-impulsive and aggressive behaviours in ADHD, these have not yet been formally tested.

Important also is the potential for contribution from arousal processes and the described limbic over-ride of the prefrontal control system after the release of high levels of dopamine and noradrenaline. This may be particularly pertinent in ADHD due to the nature of medications used during treatment. Dopamine is perhaps considered the most important neurotransmitter in ADHD research, since stimulant medications, such as methylphenidate, are known to work primarily on the dopamine neurotransmitter system. Additionally, Atomoxetine (the second-line treatment for adult ADHD in the UK), is a noradrenaline reuptake inhibitor which blocks the reuptake of both NA and DA in the prefrontal cortex. Arnsten and Rubia (2012) describe the function of the dorsolateral prefrontal cortex as exhibiting an "inverted U" dose-response to both of these neurotransmitters. This brain region therefore functions sub-optimally when levels of noradrenaline and/or dopamine are either too high or too low.

Overall, the reviewed literature suggests a dynamic interplay between cortical, subcortical, and arousal mechanisms that influence the expression of emotion. How alterations in these different mechanisms relate to EL in ADHD remains to be investigated.

1.8 Overview of research questions

This chapter reviewed the clinical and behavioural profile of ADHD and associated features of emotional lability. Moreover, it presented a breadth of research showing behavioural, treatment and neurocognitive overlap between ADHD and EL, highlighting a number of areas in which further research is warranted. Although not all of these can be addressed within this thesis an attempt will be made to shed light on a number of the issues raised.

The overall aim of this thesis is to further our understanding of the association between ADHD and EL in adulthood, using a case-control design. A detailed description of the sample and methodology used in this thesis is provided in the next chapter (Chapter 2). The following four chapters (Chapters 3-6) present results from the study, which can be organised into five primary aims:

Aim 1: To Investigate the clinical concomitants of EL in adults with ADHD

This thesis aims to investigate the relationship between EL and ADHD in relation to inattention, hyperactivity-impulsivity, antisocial behaviour and impairment in a non-comorbid and untreated sample of adults with ADHD (Chapter 3).

Aim 2: To characterise the nature of EL in adults with ADHD in the context of everyday life

Using a novel methodology, this thesis sets out to investigate the characteristics of EL including the stability and instability of positive and negative emotions in adults with ADHD using real-time data capture from ambulatory assessment (Chapter 4)

Aim 3: To examine EL in adults with ADHD after controlling for a number of methodological confounds outlined in section 1.3 in this chapter.

By investigating a sample of adults with no comorbid psychopathology and by accounting for subsyndromal comorbid symptoms, this thesis aims to examine the relationship between ADHD and EL in the absence of the confounds of comorbidity (Chapter 3). Furthermore, measuring everyday adversity during ambulatory monitoring, enables examination of the relationship between the volatile emotions reported and ADHD after controlling for adverse events reported in daily life (Chapter 4).

Aim 4: To investigate cognitive correlates of EL in ADHD using electrophysiology

This thesis aims to investigate cognitive and neurophysiological deficits associated with EL in ADHD. This is done by first investigating behavioural and electro-encephalographic measures during a resting condition and in two response inhibition tasks in comparisons between ADHD and control participants. The identified cognitive deficits are then investigated in relation to self-reported EL (Chapter 5).

Aim 5: To study the treatment response to methylphenidate of behavioural concomitants of EL in ADHD (see aim 1), as well as neurophysiological processes identified as associated with EL in Chapter 5.

By following up a subset of participants with equivalent measures after treatment initiation, this thesis aims to investigate the treatment response of self-reported EL and behavioural and neurophysiological concomitants, to identify shared or disparate treatment response patterns (Chapter 6)

Chapter two: Methods

2.1 Aims

All data presented in this thesis is drawn from the MIRIAD study (Mood Instability Research in ADHD). Specific aims of this chapter are to provide background information on the study and methodology, including an overview of:

- Study background and design
- recruitment procedures involved in identifying and enlisting the research participants,
- research assessment tools,
- testing procedure,
- preparatory work: power calculations and piloting,
- practical problems encountered, and observations from running the study.

Although most measures used in the study are outlined in this chapter, these are not exhaustive, but are limited to those which are relevant to upcoming chapters. Additional questionnaire data (not reported here) have been incorporated into Masters, and undergraduate projects of students who have contributed to the project.

2.2 Study overview

2.2.3 Preliminaries: location of study, funding and ethical approval

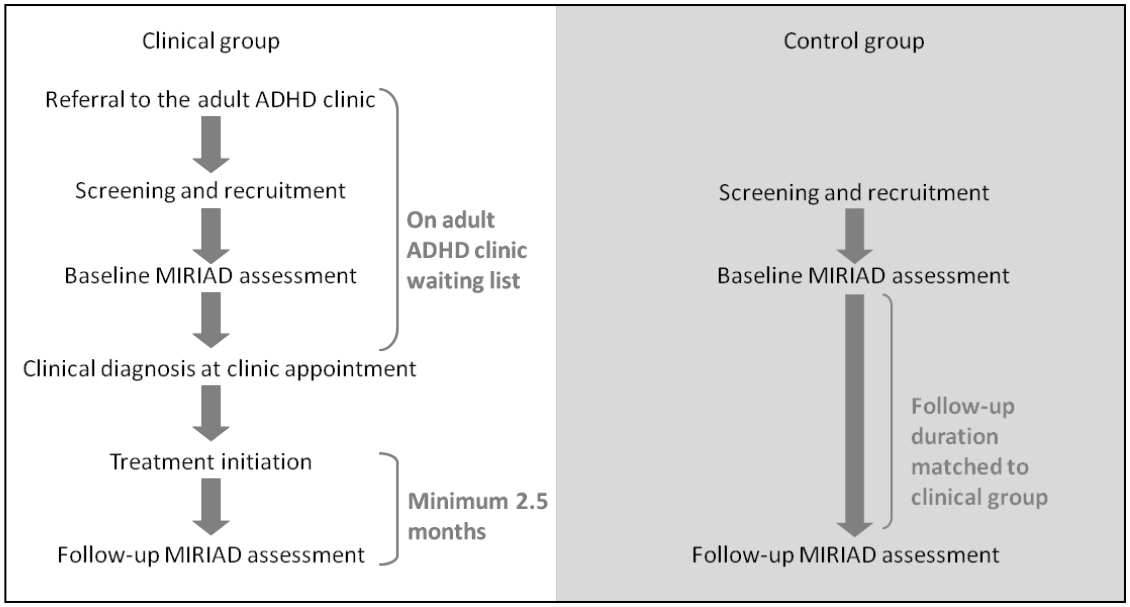
The MIRIAD study was conducted at the MRC Social Genetic and Developmental Psychiatry Centre at the Institute of Psychiatry in conjunction with the adult Attention Deficit Hyperactivity Disorder (ADHD) clinic at the South London and Maudsley Hospital NHS Trust. The study was supported by the Research for Innovation, Speculation and Creativity (RISC) funding scheme (reference: RC-PG-0308-10245) from the National Institute for Health Research; awarded to Prof Philip Asherson (Primary Investigator), Prof Declan Murphy and Caroline Skirrow. Research ethics approval for study procedures was granted by the Joint South London and Maudsley and Institute of Psychiatry Research Ethics Committee (reference: 08/H0807/93). Full informed consent was given by all subjects participating in the study.

2.2.3 Design

As shown in fig. 4, this study employed a longitudinal case-control design, comparing adults with ADHD, before and after treatment with methylphenidate was initiated, to a group of psychiatrically healthy control subjects. The clinical group was enlisted into the study whilst on the waiting list at the adult ADHD clinic at the Maudsley Hospital, London, which allowed for a more extensive period of assessment where individuals with ADHD were not on medication. Although this study investigated the effects of treatment in individuals where a diagnosis of ADHD was confirmed, it did not interfere with the nature or quality of the treatment that they obtained, but rather was a naturalistic follow-up study of patients in whom treatment was managed by community health services with support from specialists at the Maudsley hospital adult ADHD clinic.

Where psycho-pharmacological treatment for ADHD was initiated by treating practitioners, follow-up appointments were scheduled after treatment was maintained for a minimum of 2.5 months, to allow adequate time for treatment optimization in the community setting. A similar duration of follow-up was employed if patients did not undergo psycho-pharmacological treatment. Control participants provided normative data for initial assessments and at a follow-up duration matched to ADHD subjects.

Figure 4: Study design



2.3 Recruitment

Since the main aim of this study was to investigate emotional lability and cognitive function in ADHD, care was taken to ensure that confounding psychopathologies and medical conditions would not compromise the interpretability of results. Strict exclusion criteria were applied to both study groups to ensure that differences between participants with and without ADHD would not reflect co-occurring psychiatric illness, psychoactive medication, neurological conditions or substance abuse problems.

Exclusion criteria were equivalent for both groups: female gender, the presence of current Axis I or II co-morbid psychiatric diagnosis, past history of axis I psychiatric disorders (with the exception of major depressive disorder, where only those with recurrent depression or those in a depressive episode at time of contact were excluded), current or previous substance abuse, or frequent substance use (more than 8 units of alcohol consumed weekly or recreational drug use more than twice weekly), head injury or neurological conditions, IQ under 70, and any current or recent exposure to psychoactive medication: 1 month minimum period without exposure to stimulant medications (with the exception of one patient who took a one-off dose of stimulant medication 3 days before his initial assessment), 6 months for other psychoactive medication).

2.3.1 Recruitment of control participants

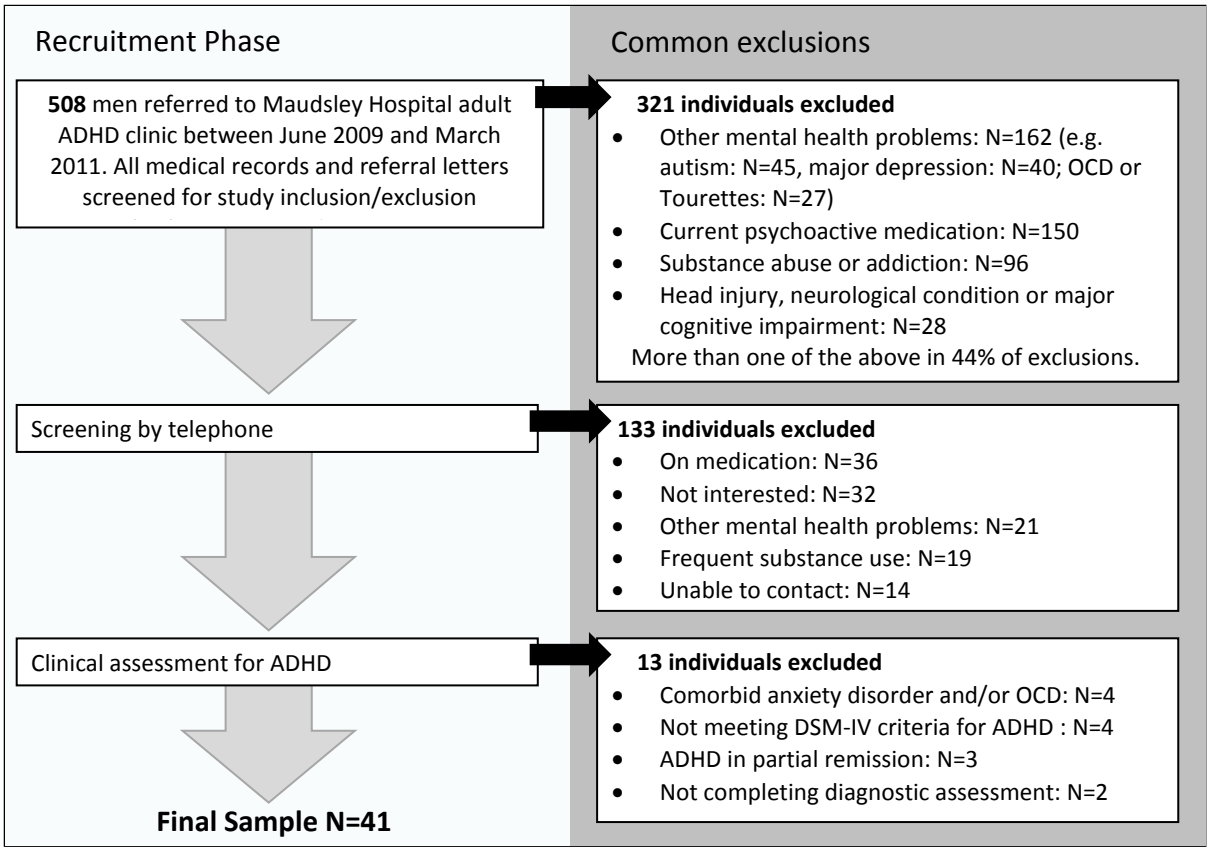
Control subjects were recruited from volunteer databases held at the Institute of Psychiatry, Kings College London, and through advertising around the university and within the local community. Initial contact was made by post, email, or telephone. Individuals who were interested in participating were asked to complete the Barkley Adult ADHD rating scales (further detailed in 2.5.1.1; Barkley, 1998) in the form of an online questionnaire, to ensure they scored below screening threshold for ADHD. Furthermore, all subjects underwent structured screening of exclusionary criteria by telephone, which involved detailed questions assessing any previous or current neurological problems, mental health problems (including presence, treatment for or diagnosis of anxious, depressive and manic/hypomanic symptoms), and drinking and drug habits.

2.3.2 Recruitment of participants with ADHD

As shown in fig. 5, the medical records for all male individuals referred to the Adult ADHD Clinic from June 2009 until March 2011 were examined for the above exclusion criteria before contact was made. Individuals who were not excluded during the initial screening phase were sent study information sheets, along with a response slip and a postage paid envelope. Where no response slip was returned, contact by telephone was initiated to determine interest in participating.

All who expressed an interest in participating in the study were then screened during a telephone conversation, in the same way as control participants (detailed in 2.3.1). Those not excluded after telephone screening were invited for an initial assessment. As seen in fig. 4 (section 2.2.3), research assessment was carried out whilst clinical subjects were on the ADHD clinic waiting list, before a formal diagnostic assessment for ADHD was completed.

Figure 5: Flow diagram of recruitment and exclusions



Note: ADHD, attention deficit hyperactivity disorder; OCD, obsessive compulsive disorder; N, number of individuals; DSM-IV, Diagnostic and Statistical Manual, fourth edition

2.3.2.1 Exclusions

As shown in fig. 5, only a very small proportion of individuals screened during the recruitment period (around 8%) met the study criteria and were interested in participating in the project. Referrals to the clinic were most frequently excluded from the study due to the presence of one or more mental health problems (apart from ADHD), current psychoactive medication, and substance abuse or frequent substance use.

Data from screening for this project suggests that mental health conditions (other than ADHD) are common in individuals referred for assessment for ADHD in adulthood. However, screening most often relied only on reports contained in medical files at the clinic. Many of these files held limited information, and frequently exclusions were made based on referral letters, potentially only reflecting the medical conditions deemed relevant by the referring practitioner. Additionally, a small proportion of referrals, who chose not to participate (6.3%) or could not be contacted (2.8%), and were not screened for exclusionary criteria. This suggests that the exclusionary rates reported here are likely to be an underestimation of mental health conditions in adults referred to the ADHD clinic.

However, it is also noteworthy that many individuals screened for the study met more than one of the stated exclusion criteria. For example, during screening of medical records, out of 162 individuals excluded due to mental health problems, substance abuse problems or psychoactive medication were frequently also reported (27% and 39%, respectively). Many excluded individuals could be considered complex cases, due to having a number of mental health conditions concurrently. This heightened level of mental health symptoms may be the result of clinical referral biases, which increase the likelihood of referral and treatment in more symptomatic and more impaired individuals (Caron & Rutter, 1991).

It is notable that the elevated rates of mental health problems identified during screening do appear to reflect some characteristics of individuals with ADHD. Population studies have revealed high rates of co-occurring mental health conditions (including mood disorders and anxiety disorders) and increased substance and alcohol abuse problems in adults with elevated levels of ADHD symptoms (Kessler, et al., 2006; Park, et al., 2011). For this project, mental health problems and substance abuse in combination contributed to the exclusion of

214 individuals during the screening of medical records alone (42% of all individuals referred during the sampling period).

The rate of Autism Spectrum Disorders (ASD) reported in medical records also appears to be high in this sample, noted in around 9% of men referred to the clinic, compared to the reported prevalence of around 2% in male adults in the UK (Brugha, et al., 2011). This is also at odds with current DSM-IV diagnostic stipulations, which preclude the co-diagnosis of ADHD and ASD; although not with NICE guidelines (NICE, 2008) or the proposed revision of the ADHD criteria for DSM-V (www.dsm5.org). The rate of ASD appears to be high even in contrast to other psychiatric outpatient clinics. Nylander and Gillberg (2001) report an ASD prevalence of 2.6% in men from a psychiatric outpatient clinic for patients afflicted by psychopathology other than ADHD (e.g. schizophrenia or psychosis, depressive disorders, eating disorders and personality disorders). However, the high co-occurrence of ASD and ADHD noted here is in line with two studies of adults from ASD clinics, showing comorbidity with ADHD in 35-43% of patients (Anckarsater, et al., 2006; Hofvander, et al., 2009). The referral patterns revealed here suggest that further work to investigate the prevalence of ASD in adult samples of ADHD patients is warranted.

A large proportion (37%) of all individuals screened for this study, were excluded on the basis of current psychoactive medication. This again is likely to be characteristic of adult ADHD samples. Treatment with psychoactive medication was mainly reported as related to either the presence of other mental health problems (e.g. depression, anxiety), or the treatment of ADHD symptoms themselves. Stimulants are currently considered the first line treatment for adults with ADHD in the UK (NICE, 2008) and many individuals with ADHD are referred to the adult ADHD clinic for reassessment during transition periods on their healthcare (from one health service to another, and from child and adolescent to adult mental health services), during which time their treatment regimen is continued.

Overall, the pattern of exclusions outlined above suggest that the population from which participants in this study are sampled show some similarities to characteristics of samples of adults with ADHD reported in the research literature. Most importantly, this highlights the selected nature of the sample for this study, which constitutes only a very small proportion of the initial sampling pool. Although this small and relatively 'pure' group of adults with

ADHD fulfils the aims of aiding in investigating emotional lability and cognitive function in the absence of confounding psychopathologies and medical conditions, this also suggests that results from this study may not readily generalise to many adults with ADHD, where the clinical presentation is more complex.

2.3.2.2 Disorganisation, no shows and cancellations

Some problems with recruitment may be considered issues inherent to the disorganised nature of the ADHD condition. Despite a reminder system being in place where all participants were telephoned the day before their appointment to confirm their attendance, many participants did not show up to their scheduled appointments. It is a reasonable estimate that only half of the scheduled appointments for the clinical group were attended.

11 individuals never showed up to their scheduled research assessments, despite being given multiple appointments. In other cases, during the scheduling of a research appointment, the research team was asked by the patient to contact a parent or spouse who organised their attendance and accompanied them to the research session. In most such cases, appointments for research were successfully attended.

These issues also may present some potential problems for the interpretation of the study results, suggesting that individuals worst affected by ADHD, and therefore unable to organise their attendance to a research appointment, were not included in the study. Furthermore, they highlight the importance of a support network for individuals with ADHD, who are likely to rely on the support of others to aid in their organisation.

2.3.2.3 Clinical Diagnosis

Participants recruited from the clinic underwent an in-depth psychiatric evaluation from a consultant adult psychiatrist specialising in ADHD. Diagnostic Criteria for DSM-IV ADHD were applied using a structured clinical interview for the 18 ADHD symptoms in childhood and adulthood, establishing symptom onset and chronicity before age 7, and confirming the presence of a minimum of 6 symptoms of hyperactivity-impulsivity and/or inattention in adulthood (Conners Adult ADHD Diagnostic Interview for DSM-IV, CAADID; Conners, Epstein,

& Johnson, 2001). Furthermore, during clinical assessment, an unstructured clinical interview was carried out for each patient to establish the presence of any other comorbid psychiatric conditions.

Individuals who were not excluded in the screening process but who were diagnosed with ADHD and a comorbid psychiatric disorder during their clinical assessment, those not meeting criteria for ADHD, those with ADHD in partial remission, and those failing to attend diagnostic assessment were excluded from the study (as shown in fig. 4, section 2.3.2).

2.4 Participants

41 adults meeting DSM-IV criteria for ADHD participated in the study. 16 (39%) had previously been diagnosed with ADHD in childhood while the rest were first time diagnoses in adulthood. Most of the participants with ADHD had a combination of inattentive and hyperactive-impulsive symptoms (N=33) with a minimum of 3 symptoms in both symptom domains as adults, as measured by the CAADID. The remainder of the participants (N=8) had primarily inattentive symptoms, with very few (≤2) hyperactive-impulsive symptoms. 47 healthy control male participants, matched roughly in age and IQ also took part.

2.5 Research assessment tools

2.5.1. Rating scale measures

All participants completed a number of self-reported ratings of everyday symptoms and problems at their initial and follow-up appointments.

2.5.1.1 ADHD

Measures of ADHD symptoms were collected using the Barkley Adult ADHD Rating Scale (BRS; Barkley, 1998), a brief and widely used self-report measure for current ADHD symptoms in adulthood, consisting of the 18 DSM-IV ADHD items for inattention and hyperactivity-impulsivity (Appendix 1).

2.5.1.2 Emotional lability

Two self-rated questionnaires were used to measure emotional lability (EL). The Affective Lability Scale-Short Form (ALS-SF; Oliver & Simons, 2004) measures swift changes from normal (euthymic) mood to other emotional modalities including elation, depression, and anger (Appendix 2). Previous factor analysis confirmed good fit for three domains in the ALS-SF: Anxiety-Depression, Depression-elation and Anger. The second measure was the auxiliary subscale of the Centre for Neurologic Study – Lability Scale (CNS-LS; Moore, Gresham, Bromberg, Kasarkis, & Smith, 1997), measuring EL with a stronger focus on negative emotions (feeling frustrated, nervous, angry and upset; Appendix 3).

2.5.1.3 Functional impairment

Impairment in major life domains was assessed using the Weiss Functional Impairment Rating Scale-Self-Report (WFIRS-S), which measures impairments in a number of everyday situations not overlapping directly with ADHD symptoms. These include impairments in the areas of family, work, education, social function, life skills (including managing money, hygiene, appearance, sleep and health), self-concept (feeling bad, incompetent, frustrated and discouraged) and risk taking behaviours (e.g. drug taking, drinking, aggressive behaviour, illegal actions, and sexually risky behaviours).

A copy or the WFIRS-S is available at:

http://www.caddra.ca/cms4/pdfs/caddraGuidelines2011WFIRS_S.pdf

2.5.2 Intellectual function

Intellectual function (IQ) was assessed using the Wechsler Abbreviated Scale of Intelligence (Psychological Corporation, 1999).

2.5.3 Cognitive function measured by electroencephalography

2.5.3.1 Rationale

Electrophysiology (event related potentials: ERP, and quantitative electroencephalography: EEG), provides a direct measure of brain activity, in the form of voltage fluctuations

recorded on the scalp. ERPs reflect the average neural activation to a repeated event such as the presentation of a stimulus (Albrecht, Banaschewski, Brandeis, Heinrich, & Rothenberger, 2005; McLoughlin, Kuntsi, Brandeis, & Banaschewski, 2005), whilst in quantitative EEG, electrode recordings are quantified into frequency ranges of interest, believed to be pertinent to certain functional processes or states. Electrophysiology enables the measurement of neural activation with millisecond resolution, posing a significant advantage over other brain imaging techniques such as PET and fMRI, which have a temporal resolution in the order of seconds. However, electrophysiological methods have poor spatial resolution, since electrical brain activity is diffused during its passage through the scalp, skull and other tissues, and since several distinct source distributions can give rise to an observed scalp distribution (McLoughlin et al., 2005).

Although behavioural cognitive tasks are frequently used in ADHD research, there has been a move towards investigating more direct indices of brain function. The benefits of electroencephalographic measures in particular are two-fold.

First, due to the superior temporal resolution of electrophysiological measures, it is possible to break down cognitively complex behavioural measures into patterns of neuronal activity relating to different cognitive processes, such as covert information processing, attention and response selection (McLoughlin et al., 2005). The most notable example of this in the ADHD research is for studies of inhibitory task performance. ERP studies have shown that the stimulus stop reaction time (SSRT) on the stop task, often utilised to index inhibitory function, may also be modulated by general attentional or state regulation deficits (Banaschewski, et al., 2004; Hervey, et al., 2004; Lijffijt, Kenemans, Verbaten, & van Leeuwen, 2005), or attentional switching (Bekker et al., 2005) in individuals with ADHD. Similarly, in ERP investigations of a cued Continuous Performance Test (CPT-OX), inhibitory processing abnormalities in children and adults with ADHD were preceded by impairments in covert attentional orienting and preparation (Banaschewski, et al., 2004; Doehnert, Brandeis, Imhof, Drechsler, & Steinhausen, 2010; McLoughlin, et al., 2010; van Leeuwen, et al., 1998). The use of ERPs therefore allows for clearer inferences of cognitive and brain function to be made, than are enabled from behavioural performance data alone. Such cognitive indices are likely to be important in the evaluation of the primacy of the

hypothesised inhibitory deficits underlying emotional lability (EL) in ADHD (e.g. Barkley, 1997, 2010).

Second, there is now a bulk of literature using quantitative EEG methods, which reveal reduced power in fast wave cortical activity (mainly beta) and elevated power in slow frequency bands (predominantly theta) in children with ADHD during resting conditions (Barry et al., 2003; Snyder & Hall, 2006). These patterns of quantitative EEG activity are frequently interpreted as a marker of cortical under-arousal. In the context of a literature associating arousal functions with emotion, quantitative EEG can provide a direct measure of cortical arousal that may be linked to EL. Previous research has linked excess beta activity in boys with ADHD with moody behaviour and temper tantrums (Clarke, Barry, McCarthy & Selikowitz, 2001a), which suggests a potential link between indices of cortical activity and EL.

2.5.3.2 Methods

An electroencephalography (EEG) recording session lasting approximately one hour was carried out during each research appointment. Conditions or tasks implemented during EEG recording are outlined below, and were administered in the order in which they are described. All tasks were administered using the Presentation software package (www.neurobs.com). A brief description of each task is provided below, more detailed descriptions of tasks and EEG recording parameters are provided in the relevant chapters (Chapters 5 and 6).

Two resting state conditions (first eyes open, then eyes closed), lasting 3 minutes each were carried out at the beginning and end of each recording session. Measures of attentional orienting, preparatory and inhibitory processing were obtained using a Cued Continuous Performance Test (CPT-OX) with flankers (Doehnert, Brandeis, Straub, Steinhausen, & Drechsler, 2008; McLoughlin, et al., 2010; Tye, Rijsdijk, et al., 2012; Valko, et al., 2009). Duration of the task was 11 minutes. The Sustained Attention to Response Test (SART) was employed to obtain measures of response inhibition, and measures of reaction time and errors (commission and omission). The test was identical to the random SART described by O'Connell and colleagues (2009). Task duration was 15 minutes

2.5.4 Structured clinical interview for comorbid conditions

Assessment of subclinical comorbid symptoms was assessed using the Clinical Interview Schedule – Revised (CIS-R; Lewis, Pelosi, Araya, & Dunn, 1992), a brief, fully structured lay interview, which has previously been used in a large general population survey of comorbidity in the UK (Meltzer, Gill, Petticrew, Hinds, & Office of Population, 1995). It assesses common psychopathology including depressive, obsessive compulsive, anxious and phobic symptoms; and consists of the following sections: somatic symptoms, fatigue, concentration and forgetfulness, sleep problems, irritability, worry about physical health, depression, depressive ideas, worry, anxiety, phobias, panic, compulsions, obsessions and overall effects.

2.5.5 Ambulatory monitoring

2.5.5.1 Rationale

Although rating scale and interview measures are frequently used in psychiatry research to investigate emotional problems, a bulk of research has now highlighted limitations of retrospective recall. Of particular note is research which identifies different recall biases in operation in psychiatrically ill and healthy populations (Ebner-Priemer, et al., 2006; Taylor & Brown, 1988). These methodological problems can be overcome by observational studies, in which emotional behaviour is elicited and coded, or prospective longitudinal data collection measures, such as in ambulatory monitoring. Ambulatory monitoring involves repeated assessments over time, and the series of immediate reports can be statistically summarised to obtain indices of daily experience without relying on participant's memory (Trull, et al., 2008), resulting in reduced systematic and random sources of measurement error, increased validity and reliability (Bolger, et al., 2003), enhanced generalizability of findings (Ebner-Priemer & Trull, 2009). Specifically, this methodology lends itself to the investigation of instability or change in emotions, which can be measured directly from one moment to another.

Although there are few studies that have investigated cognitive and brain function in conjunction with ambulatory assessment measures within the same sample, there is some research that suggests that meaningful links can be made between the two. A recent study

employed ambulatory assessment concurrently with fMRI scanning during performance of the SART, and revealed greater activation in the default mode network during trials where participants reported greater mind wandering (Christoff et al., 2009). Another study investigating EEG activity during a resting condition, reported that lower bilateral prefrontal alpha activity predicted higher rumination, and lower right prefrontal activation predicted higher self-esteem in depressed patients during seven days of ambulatory assessment (Putnam and McSweeney, 2008). In research relating specifically to emotional change and cognitive function, Hoeksma, Oosterlaan and Skipper (2004) investigated variability in anger in a sample of children over 3-4 days, showing moderate correlations (r=.41) with Stimulus Stop Reaction Time (SSRT) on the Stop Task (i.e., the time required to successfully inhibit a motor response), often presented as a measure of behavioural inhibition. Although, research therefore does not commonly link cognitive function and measures obtained in ambulatory assessment (possibly due to the already intensive nature of data collection required by this method and the statistical issues in the analysis of this data), this previous work suggests that meaningful links between cognition and brain function and on-line daily life experiences can be made.

2.5.5.2 Methodology

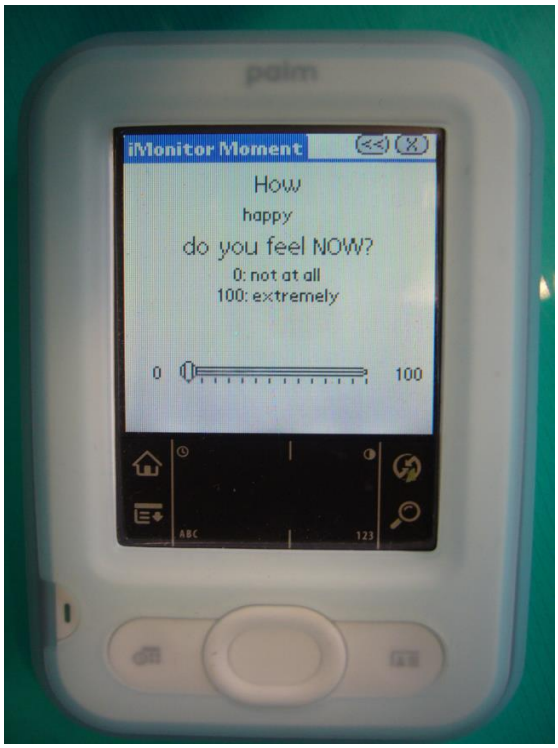
Ambulatory monitoring of emotions was carried out using a custom electronic diary programme (iMonitor Moment: http://myimonitor.com), adapted from the Maudsley Bipolar eMonitoring Project (Malliaris, Ferrier, & Scott, 2006), and uploaded onto Palm Zire 22 devices. Ambulatory monitoring was scheduled across 5 consecutive days (Monday-Friday). Signals for the onset of each monitoring period was provided by Vibralite 8 wristwatches which were synchronised with palm devices and gave silent vibration signals eight times a day, at the onset of onset of each rating period. Signals occurred on a pseudorandomised schedule, with a minimum inter-rating interval of 65 minutes and a maximum interval of 195 minutes (10 hours of data collection each day). Start and end times were the same each day and were programmed to fit with each participants' sleep schedules.

It is notable that in ambulatory monitoring research other response schedules are also widely used, such as fixed response schedules (e.g. Ebner Priemer et al., 2006), schedules

which include a fixed number of random prompts within specific time periods of a day (e.g. Solhan et al., 2009), and schedules which include a fixed period of reassessment with a shorter random interval (e.g. every hour, with a 5-minute random interval (Hoeksma, Oosterlaan & Schipper, 2004). Since the equipment used in this study did not allow for the programming of a randomised response schedule, a pseudorandomised, fixed schedule was adopted. This was to facilitate data collection that would not be anticipated by the participants, and to enable to capture of data whilst participants were engaging in their normal everyday activities. A 5-day assessment schedule was adopted (Monday-Friday) to obtain a clear impression of participant's emotional states for the majority of time during an average week. 'Weekend effects', a change in reported emotional experiences on weekends, have been previously described in the literature (Reis, Sheldon, Gable, Roscoe, & Ryan, 2000; Stone, et al., 2000).

The iMonitor employed a simple question-answer visual analogue scale dialogue format, with questions regarding the participant's current emotion (e.g. "how *angry* do you feel NOW?"), to which the participants responded using the palm stylus on a numerical analogue scales, with ratings from 0 (not at all) to 100 (extremely). Other emotion items included emotions frequently associated with ADHD in the research literature (*irritable*, *frustrated*), as well as positive emotional items (*excited*, *happy*) in an identical question format (see fig. 6 below). Additionally, participants were asked to first to report if good experiences and then if any bad experiences had occurred during the hour preceding each monitoring period (e.g. "Did any good things happen to you in the PAST HOUR?"), and how strongly these experiences had affected them overall (e.g. "How much are you affected by them NOW?", again on a numerical analogue scale rated from 0 (not at all) to 100 (extremely).

Figure 6: The iMonitor Moment on Palm Zire 22 device



2.6 Testing procedure

All participants were sent a letter by post, confirming their agreed appointment time and date. Letters included the questionnaire measures (outlined in section 2.5.1) to be completed and brought along for appointments. Participants were also asked to refrain from drinking caffeine or smoking the day of each study session, and from consuming alcohol on the day of the study session or during the preceding evening. Instructions to this effect were included in the appointment confirmation letter, and were also given by telephone during appointment reminders on the day before each research appointment.

During the initial appointment participants first underwent IQ testing (section 2.5.2), then cognitive-electrophysiological testing (section 2.5.3), and finally, the clinical screening interview (CIS-R, section 2.5.4). At the end of the testing session, participants were provided with the ambulatory monitoring equipment (palm device, vibrating wristwatch, as described in section 2.5.5, and an instruction leaflet,) and were given full instructions and training for use. A postage paid envelope was provided for participants to return the equipment after completing their ambulatory monitoring period.

Equivalent measures (administered in the same order) were included in follow-up appointments, with the exception of IQ testing, which was not repeated. For individuals on stimulant medication, follow-up research sessions were scheduled for EEG recordings to be carried out within 1 hour of taking immediate release medication (e.g. Ritalin, Equasym) and within 3 hours of extended release medication (e.g. Concerta XL, Equasym XL).

All participants were compensated for their travel and postage costs. In addition, all were given a monetary incentive on completion of their monitoring and the return of ambulatory monitoring equipment; £25 after the baseline assessment, and £50 after the follow-up assessment.

2.7 Preparatory work

2.7.1 Power calculations

The statistical software G*Power 3.0 (Faul, Erdfelder, Lang, & Buchner, 2007) was used to identify sample sizes required to replicate previous findings on which the aims and hypotheses in this thesis are based. Power was set at 80% at a one-tailed alpha of .05.

Expected effect sizes were determined from previously published findings relating to the hypotheses under investigation. Where these vary between studies, power calculations were based on the lowest reported effect sizes, unless stated otherwise. Where not explicitly reported in research studies, Cohen's d effect sizes for between-groups effects were calculated from published means (M), standard deviations (SD) and sample sizes (N) for contrasted samples (1 and 2), using the following equation:

Cohen's d = Mean1 - Mean2/ SDpooled

$$\text{where} \qquad SD_{pooled} = \sqrt{\frac{(N_1 - 1)SD_1^{\,2} + (N_2 - 1)SD_2^{\,2}}{N_1 + N_2}}$$

2.7.1.1 Self-rated severity of EL and relationship with core ADHD symptoms

Previous studies report large effect sizes for comparisons of self-reported EL between adults with ADHD and community comparison samples (Cohen's d= 1.4-2.66; Barkley & Fischer, 2010; Barkley & Murphy, 2010), suggesting that these findings could be adequately replicated with 8 participants in each group. In analyses exploring correlations between self-rated EL with ADHD symptom dimensions, moderately high correlations (r=0.46-0.62) were

identified (Barkley & Fischer, 2010). Slightly lower correlations were reported for similar measures ascertained by interview (r=0.38-0.46; Reimherr et al., 2010), suggesting a required sample of 39 participants.

2.7.1.2 Ambulatory monitoring and relationship to cognitive measures

No previous work has been carried out to investigate emotional variability in an ADHD sample using ambulatory monitoring. Research in individuals with borderline personality disorder, using some similar statistical methods to those employed in this thesis found medium effect sizes (Cohen's d=0.65) in comparisons between the clinical sample and a control population (Ebner-Priemer, Kuo, et al., 2007). Identifying a similar effect size in our study would require 30 subjects in each group.

2.7.1.3 Response to treatment

Effect sizes for treatment response of EL reported in placebo-controlled double-blinded trials of extended release psychostimulant medication have been variable (Cohen's d=0.31-0.83 (interview) and 0.30 (questionnaire); Reimherr, et al., 2007; Retz, et al., 2010; Rosler, et al., 2010). It is not possible to equate these effect sizes to the current study design in which no placebo crossover design is used and analyses are simply repeated within group after treatment initiation. Moreover, although open-label treatment studies investigating treatment response of EL, electrophysiological measures and cognitive task performance measures frequently report means and standard deviations of dependent variables before and after treatment, they do not report the correlation between repeated measures, which is required to calculate the effect sizes of analyses of paired samples (Faul, et al., 2007).

However, analysis of treatment co-variation of ADHD symptoms and EL in previous treatment studies have shown high correlations in treatment response (r=.81-.89) (Reimherr, et al., 2010; Reimherr, et al., 2007), indicating that only very small sample of 7 participants are required to replicate this effect. A previous study of co-variation of treatment response of EL with event related potential (ERP) components in relation to facial processing task, showed moderate effect sizes of P120 and N170 components for predicting EL in multiple regression analysis (R^2=0.38-.46, minimum of 11 predictor variables used) in children with ADHD (Williams, et al., 2008), indicative that a sample of 55 participants would be required to replicate a similar effect.

2.7.1.4 Cognitive electrophysiology

Medium to large effect sizes are also reported in contrasts of cognitive and electrophysiological measures in ADHD and control participants. Meta-analysis of quantitative electroencephalography in children and adults showed a pooled effect size of -.51 for beta, 1.31 for theta, and 3.08 for theta/beta ratios (Snyder & Hall, 2006). Based on the smallest effect sizes, the identification of such case control differences at 80% power would therefore require a sample of 49 subjects in each group.

Furthermore, studies of event related potentials in ADHD and control subjects similarly identify medium effect sizes. For example, a recent meta-analysis of P3 deficits in adults with ADHD on go/no go tasks found a medium effect size (Cohen's d=-0.55; Szuromi, Czobor, Komlosi, & Bitter, 2011), suggesting a sample of 42 subjects in each group would provide adequate power for replication.

2.7.1.5 Overview

Overall, power calculations suggested a target sample of approximately 40-50 subjects in each group would be appropriate for addressing the primary aims of this thesis.

However, there are a number of limitations worth bearing in mind for the power calculations outlined above. First, due to a lack of data from ADHD samples, power calculations for ambulatory assessment measures are based on a borderline personality disorder population, which may be characterised by greater EL. Second, due to the naturalistic follow-up design of this study (and resulting lack of blinding, placebo-control, and standard optimisation of treatment), it was not possible to estimate power for treatment response analyses; Third, effect sizes reported above stem primarily for EEG and ERP studies in children and adolescents, and it is unclear whether the effect sizes in children generalise to adults with ADHD also.

2.7.2 Ambulatory assessment piloting

Piloting of ambulatory assessment equipment was carried out to identify programming problems, common difficulties experienced by patients and controls, and to obtain an indication of the effectiveness of the methodology.

2.7.2.1 Participants and measures

Five adults with a diagnosis of DSM-IV ADHD (diagnostic methods equivalent to those outlined in section 2.3.2.3), 1 female and 4 male, with a mean age of 39.8 years (range 32-49) were recruited from the adult ADHD clinic. Most were free from psychoactive medication (minimum exposure free period of 3 months) during their participation, with the exception of one participant who was taking amitriptyline for depression. Comorbidities in the ADHD participant group included depression (n=1), and substance abuse (n=1). Ten control participants (5 female, 5 male), with a mean age of 26 years (Range 23-31) also took part in piloting. Control participants were primarily PhD students at the Social Genetic and Developmental Psychiatry Department of Kings College London.

Ambulatory assessment equipment and data collection methods were equivalent to the details outlined in section 2.5.5, with the exception of the phrasing of two question items, which during piloting included more than one related emotion descriptors (irritable/grumpy and excited/exciteable), based on the original style of phrasing of items from the Maudsley Bipolar eMonitoring Project (Malliaris, et al., 2006). Feedback from pilot participants later resulted in a change of this phrasing structure after completion of piloting, as participants reported finding it less confusing to rate themselves relative only to one specific emotion item. After piloting was completed, these items were modified to contain only one emotion term (irritable and excited, respectively). Participants also completed the ALS-SF (see 2.5.1.2).

2.7.2.2 Troubleshooting: compliance rates and programming issues

To reduce the likelihood of participant bias from self-selection of monitoring instances, all reports not completed within 15 minutes after the vibration signal were excluded from analysis. Allowing a choice in the self-selection of monitoring instances runs the risk of introducing each participant's bias in selecting some instances and overlooking others (Bolger, Davis, & Rafaeli, 2003). Furthermore, previous work (Delespaul, 1995) has shown that reports completed after this interval are less reliable and consequently less valid. Compliance rates for each participant were obtained by identifying the proportion of monitoring instances completed within the 15 minute window.

Compliance for participants with ADHD was on average 64.8% (Range 30%-85.7%), and for controls was 72.5% (range 50%-92.5%). The lowest compliance in participants with ADHD

(30%) was due to a programming error resulting in equipment failure and data loss. The programming was rectified to ensure that this would not re-occur.

Piloting revealed some variability in compliance, which was identified as a potential issue for this study. A number of steps were implemented to promote compliance and were incorporated into the testing protocol, including telephone calls to prompt participants when they were required to start monitoring moods, and a follow-up call in the middle of the monitoring week, opening channels for contact (providing email addresses and a 'mood monitoring hotline' telephone number), and providing an instruction leaflet as a reminder of the instructions given during assessments.

2.7.2.3 statistical analysis and results

Data for emotion items *angry*, *happy* and *frustrated* were analysed. These items included only single emotional terms rather than multiple related emotion descriptors during piloting, were reported as less confusing by participants. These items were carried forward for assessment in the remainder of the research study. Rudimentary analysis of ambulatory assessment data was carried out using mean ratings of emotion and emotional variability (standard deviation of emotion ratings). Pilot data did not deviate significantly from normal, with the exception of the item *angry* which was natural log transformed.

Group comparisons were carried out with Mann-Whitney U and independent samples t-tests. ADHD participants were significantly older than control participants ($z=-3.1$, $p=.001$), but did not differ with respect to compliance rates ($z=-.49$, $p=.68$). No significant differences between mean ratings and variability of emotion between ADHD patients and controls were found (t range-.33 to -1.63, p range=.74 to .16) with the greatest t-value for the standard deviation (SD) of *happy* (Cohen's d=1.0).

Pearson's correlations of mean ratings and variability of emotion with scores obtained from the ALS-SF across both groups showed significant correlations across the board for variability (SD) of emotion ratings (*frustrated*: R=.53; *angry*: R=.69, *happy*: R=.58, minimum p=.05), and a significant correlation with mean ratings of *frustrated* (R=.664, p=.01).

2.7.2.4 Discussion

The initial results suggested that EL measured in the form of the standard deviation of ratings from ambulatory monitoring could be reasonably sensitive for identifying differences

between individuals with ADHD and healthy control participants. Power analysis (carried out in G*Power 3.0) based on the most significant case-control contrasts from piloting (SD of *happy*) suggested that samples of approximately 13 in each group would provide power at 80% (one-tailed alpha at .05). Furthermore, the moderate correlations to high correlations with the ALS-SF scale suggested that EL as measured by ambulatory assessment and self-rated questionnaire measures may be measuring related constructs.

2.8 Practical problems and observations

Some unforeseen problems were noted during data collection, some relating to clinical characteristics of the patient sample, others to inconsistencies in clinical procedures at the adult ADHD clinic and within community practice. Furthermore, the follow-up component of this study exposed some issues associated with the referral process of patients with ADHD, resulting in difficulties in obtaining treatment for individuals who were newly diagnosed.

2.8.1 Gender

Initially, the intention was to recruit both male and female subjects into the project. However, during recruitment it became apparent that whilst female individuals with ADHD were being screened, none were being successfully recruited.

During recruitment, the gender of 100 successive referrals to the clinic were documented, identifying only 25 females, suggesting a 3-1 male to female ratio in clinical referrals. The imbalanced gender ratio is roughly in line with findings reported by Kessler and colleagues (2006) in a large adult epidemiological sample, where a positive screen for ADHD was seen 1.6 times more frequently in male than in female adults. However, other epidemiological studies in adults have shown more balance gender distributions, or even samples characterised by greater prevalence of ADHD in women (summarised in Simon, et al., 2009).

The higher ratio of male referrals for ADHD compared to rates noted in the population may suggest that some referral biases related to gender may be in play. This is similar to studies in children where discrepancies in gender ratios in clinic samples (10-1) and community samples (3-1) have been noted, with girls showing less comorbid externalising and internalising conditions, lower rates of substance use disorders and higher rates of the DSM-IV inattentive ADHD subtype (Biederman, Mick, et al., 2002). Lower rates of co-occurring

psychiatric conditions, and lower levels of hyperactivity may be instrumental in the imbalanced referral patterns seen.

In female individuals who were screened for this study, depression, bipolar disorder and use of psychoactive medication were the most common exclusionary criteria. Recruitment of female participants was abandoned at the point where 20 subjects had been recruited into the study, and not one was female. This suggests that women are rarely referred for assessments for ADHD, and that those who are referred may be more likely to be diagnosed with another mental health condition. How this relates to EL in the context of ADHD is unclear, and suggests that further investigation of EL in women with ADHD, perhaps derived from a population study may be helpful in clarifying this issue.

2.8.2 Diagnostic issues

In this study, diagnosis of ADHD was confirmed by psychiatrists in the Adult ADHD Clinic after the application of the CAADID (see 2.3.2.3). This measure provides a specification of the number of ADHD symptoms present in each individual, allowing the differentiation of DSM-IV ADHD subtypes (inattentive, hyperactive-Impulsive and combined). Although at the adult ADHD clinic the CAADID is used as standard for the purpose of diagnostic formulations, some clinicians do not formally document their scoring of the CAADID, thereby providing incomplete data for the purpose of research diagnoses and clinical subtyping.

In many cases where diagnostic data was incomplete, the CAADID was re-administered during follow-up appointments or by telephone, by Professor Philip Asherson (PA; consultant psychiatrist at the adult ADHD clinic) or a research assistant under his supervision. For the remaining patients where this was not possible (N=9), clinical reports produced by the adult ADHD clinic, describing ADHD symptoms of each patient in detail, were reviewed and scored against the CAADID by PA. CAADID scores generated in this fashion showed good consistency with clinical diagnostic formulations (including DSM-IV subtypes) and confirmed above threshold ADHD symptoms in all cases (minimum of 6 inattentive and/or hyperactive-impulsive symptoms). However, these scores are likely to be conservative, since symptoms not described in reports cannot be directly queried with the individual patients.

Table 3 shows data from 5 participants with ADHD for whom complete diagnostic data were available, and CAADID scoring from clinical reports was also completed by PA, confirming that retrospective scoring from clinical reports tends to under-count ADHD symptom scores (average difference= 2). Diagnostic subtyping, which rely on traditional cut-offs of six or more symptoms of hyperactivity-impulsivity or inattention are therefore unlikely to be wholly accurate based on this methodology.

In great part due to these variations in the quality of diagnostic data, analyses carried out as a part of this thesis do not explore differences between traditional DSM-IV ADHD subtypes. However, it is worthwhile to note that the validity of these subtype delimitations has been questioned in the research literature. For example, previous research has shown that DSM-IV ADHD subtypes do not appear to correspond to distinct familial conditions (Faraone, Biederman, & Friedman, 2000). Moreover, studies in twins have shown that ADHD symptoms can be better described by a larger range of latent classes, characterised by a combination of severity of symptom profiles, and ADHD symptom patterns along the dimensions of inattentive, hyperactive, impulsive and combined symptoms (Rasmussen, et al., 2002; Todd, et al., 2001). One study of latent class categorisations to DSM-IV subtypes, showed more than one third of individuals with a DSM-IV Inattentive type ADHD were re-assigned to severe or mild combined ADHD symptoms in latent class analysis (Todd, et al., 2001). Furthermore, the subtypes of ADHD are developmentally unstable (Lahey, Pelham, Loney, Lee, & Willcutt, 2005) and have been found to show large variation depending on assessment method and methods of information aggregation across informants (Valo & Tannock, 2010). This suggests that DSM-IV ADHD subtypes may not be especially aetiologically informative; and for this reason in the upcoming DSM-V revision they will be referred to as clinical presentations of ADHD, and no longer be considered to reflect meaningful subtypes (www.dsm5.org).

Future studies carried out in conjunction with the adult ADHD clinic cannot rely on consistent documentation of assessments carried out in the clinic, and must consider including standardised research diagnostic assessments within the research protocol, to promote clarity of findings and consistency of clinical and diagnostic data.

Table 3: Comparison of CAADID scored directly by clinician and from clinical report

Subject	CAADID Score		CAADID from clinical report		Overall difference in score
	Inattention	Hyperactivity-impulsivity	Inattention	Hyperactivity-impulsivity	
1	5	8	5	6	-2
2	7	5	6	4	-2
3	4	6	7	7	+3
4	9	4	6	0	-7
5	8	7	7	6	-2

2.8.3 Treatment issues

A number of individuals who received a diagnosis of ADHD from the adult ADHD clinic at the South London and Maudsley Hospital reported significant difficulties in receiving the treatment which was recommended by their diagnosing clinician, accounting for some of the long follow-ups reported in this thesis.

Problems with obtaining treatment are likely to be the result of a number of contributing factors which are outlined in turn below.

Funding restrictions from local NHS authorities stand in the way of many patients from receiving more specialised support for ADHD. Assessment and treatment for ADHD at the adult ADHD clinic is funded by primary care trusts. There are 151 primary care trusts in the UK associated with the National Health Service (NHS). Primary care trusts are local organisations in charge of providing healthcare services, controlling over 80% of the national budget. Although the adult ADHD clinic provides a specialised treatment initiation and patient follow-up service, the majority of referred individuals only receive funding for an ADHD assessment. After a diagnosis of ADHD is confirmed, these individuals are referred back to community health care teams, primarily to the general medical practice, for treatment initiation and management.

Many patients with ADHD taking part in the study reported a resistance by their general healthcare providers to intiate treatment for ADHD. This may be due to unfamiliarity with the diagnosis of ADHD in adulthood and concerns regarding its treatment, as well as local

resource issues. Compared with other common psychopathology, such as mood and anxiety disorders, ADHD in adulthood is relatively poorly recognised, and misdiagnosis of and treatment for other conditions, including atypical depression, mixed affective disorder, cyclothymia and borderline and unstable emotional personality disorders, have been noted as not being uncommon (Asherson, 2005). More importantly, although methylphenidate is currently recommended as the first-line treatment of ADHD in adulthood in the UK (www.NICE.org.uk), methylphenidate preparations currently available in the UK are not licensed for use in adults. This is likely to compound the concerns that general practitioners are may have when faced with following treatment recommendations received from the adult ADHD clinic.

Further issues with obtaining treatment relate to the complexity of the referral system in which a chaotic and disorganised person is required to exhibit organisational skills to obtain the treatment they need. After patients obtain a confirmation of their diagnosis of ADHD and are referred back to community healthcare teams, many are unaware that they are required to make an appointment with their general practitioner to finalise their treatment. All individuals with ADHD were contacted by the research team approximately one month after reports confirming their diagnosis had been sent out to obtain an indication of treatment progression. In many cases the patients were confused that there had been no progress and were unaware that they were required to discuss their treatment with their community healthcare team, and were urged by the research team to do so. Other problems relate to the difficulties in attending appointments (also discussed in 2.3.2.2). Two subjects who attended their research appointment failed repeatedly to attend clinical appointments, and were discharged from the clinic before completing their assessments. However, clinical interview carried out by telephone by PA confirmed the diagnosis of ADHD in these individuals. This suggests that more flexible diagnostic methods and better support networks are required for some individuals with ADHD with extreme organisational problems.

Chapter three: Emotional lability, comorbidity and impairment in adults with Attention-Deficit Hyperactivity Disorder

3.1 Summary

Adults with Attention-Deficit Hyperactivity Disorder (ADHD) frequently report emotional lability (EL). However, it is not known whether EL may be accounted for by comorbid psychiatric conditions or symptoms. This study evaluates the influence of comorbid clinical symptoms on EL, and investigates the relationship between EL and impairment. The study employed a case-control comparison of 88 adult males: 47 controls, and 41 with ADHD without comorbidity, medication or current substance abuse. Measures included IQ, clinical interview, and self-reported symptoms of ADHD, EL, impairment and antisocial behaviour. Results confirmed that ADHD participants reported elevated EL, showing good case-control differentiation in receiver operating curve analysis. EL was most strongly predicted by hyperactivity-impulsivity rather than inattentive or comorbid symptoms, and contributed independently to impairment in daily life. Results indicate that EL in ADHD appears to be primarily associated with ADHD itself rather than comorbid conditions, and helps to explain some of the impairments not accounted for by classical features of the disorder.

3.2 Introduction

Attention-Deficit Hyperactivity Disorder (ADHD) is a common developmental psychiatric disorder, that frequently persists into adulthood (Faraone, et al., 2006), with adult prevalence estimated at 2.5-3.4% (Fayyad, et al., 2007; Simon, et al., 2009). ADHD is typified by impairing symptoms of overactivity, impulsivity and inattention. Emotional lability (EL), characterised by irritable moods with volatile and changeable emotions, is a common co-occurring feature of ADHD (American Psychiatric Association, 2000; Asherson, 2005; Reimherr, et al., 2010).

Emerging evidence shows that EL frequently co-occurs with ADHD (Anastopoulos, et al., 2011; Barkley & Fischer, 2010; Barkley & Murphy, 2010; Sobanski, et al., 2010); is present at an increased rate in family members of individuals with ADHD (Epstein, et al., 2000; Surman, et al., 2011); responds to treatment within the same time-frame as core ADHD symptoms in adults (Reimherr, et al., 2010; Rosler, et al., 2010; Williams, et al., 2008); and is associated with a wide range of social, occupational and educational impairments (Anastopoulos, et al., 2011; Barkley & Fischer, 2010). Such evidence has led to the suggestion that it may be helpful to consider EL as an additional core dimension of ADHD, rather than a separate co-

occurring condition (Barkley, 2010; Reimherr, et al., 2010). However, features of EL are also frequently seen in other psychiatric conditions. For example, irritability or temper problems are included in the diagnostic criteria for borderline personality disorder, bipolar disorder, oppositional defiant disorder (ODD) and paediatric depression (American Psychiatric Association, 2000); and previous studies have also shown that comorbidity is associated with severity of EL in ADHD children and adolescents (Anastopoulos, et al., 2011; Sobanski, et al., 2010). In children strong associations have been reported between EL and antisocial behaviour, including aggressive, ODD and/or CD behaviours (Anastopoulos, et al., 2011; Graziano, et al., 2012; Melnick & Hinshaw, 2000; Sobanski, et al., 2010), and EL in adults has been linked to criminal offences (Barkley & Fischer, 2010; Barkley & Murphy, 2010). Furthermore, internalising and externalising psychiatric conditions frequently co-occur with ADHD; comorbidity with depression, for example, is noted as frequently as 50% in adults (Sobanski, 2006) and comorbidity with ODD is seen in as many as 60% of children (Kadesjo & Gillberg, 2001). High incidence of comorbidity makes it unclear whether EL may be attributable to the comorbid conditions or accompanying antisocial behaviours, rather than ADHD.

To address this issue, the current study reports data from an unmedicated sample of male adults with ADHD, with no axis I or II comorbidity or substance abuse, contrasted with a well-matched control group. Participants are tested using validated rating scales of EL, a clinical screening interview for comorbid symptoms, and self-rated impairment and antisocial behaviour. To test the premise that EL is an additional core dimension of ADHD, the following hypotheses are tested: (1) that EL will be elevated in participants with ADHD compared to controls; (2) that ADHD symptoms will be associated with EL independently from measured comorbid symptoms and antisocial behaviour; and (3) that EL will independently contribute to impairment in daily life.

3.3 Methods

3.3.1 Participants

41 male adults meeting DSM-IV criteria for ADHD participated in the study. 16 (39%) had previously been diagnosed with ADHD in childhood while the rest were first time diagnoses in adulthood. Patients were recruited from the waiting list of the National Adult ADHD Clinic

at the South London and Maudsley Hospital and were free of medication at the time of the research assessment. A comparison sample of 47 control male participants was recruited from volunteer databases held at the Institute of Psychiatry, Kings College London, and through advertising around the university and within the local community. Recruitments is detailed in Chapter 2 (section 2.3.2)

3.3.2 Measures

Emotional lability: Two self-rated questionnaires were used to measure EL. The Affective Lability Scale-Short Form (ALS-SF; Oliver & Simons, 2004) measures swift changes from normal (euthymic) mood to other emotional modalities including elation, depression, and anger. Previous factor analysis confirmed good fit for three domains in the ALS-SF: Anxiety-Depression, Depression-elation and Anger.

The second measure of EL was the auxiliary subscale of the Centre for Neurologic Study - Lability Scale (CNS-LS; Moore, et al., 1997). This scale measures EL with a stronger focus on negative emotions (feeling frustrated, nervous, angry and upset). Two items relating to impatience were dropped from the CNS-LS due to clear overlap with the impulsive dimension of ADHD.

ADHD: Measures of ADHD symptoms were collected using the self-rated Barkley Adult ADHD rating Scale (BRS; Barkley, 1998), which consists of the 18 DSM-IV ADHD items for inattention and hyperactivity-impulsivity.

Impairment and antisocial behaviour: Impairment in major life domains was assessed using the Weiss Functional Impairment Rating Scale-Self-Report (WFIRS-S; www.caddra.ca), measuring impairments in a number of everyday situations not overlapping directly with ADHD symptoms. These include impairments in the areas of family, work, education, social function, life skills (including managing money, hygiene, appearance, sleep and health), self-concept (feeling bad, incompetent, frustrated and discouraged) and risk taking (e.g. drug taking, drinking, aggressive behaviour, illegal actions, and sexually risky behaviours).

A summary measure of antisocial behaviour was also taken from five items on the risk subscale: including breaking or damaging things, doing things that are illegal, being involved with the police, being physically aggressive and being verbally aggressive.

Structured clinical interview for comorbid conditions: The Clinical Interview Schedule - Revised (CIS-R; Lewis & Pelosi, 1990) is a brief, fully structured lay interview, which has previously been used in a large national comorbidity study in the UK (Meltzer, et al., 1995). It assesses common psychopathology including depressive, obsessive compulsive, anxious and phobic symptoms; and consists of the following sections: somatic symptoms, fatigue, concentration and forgetfulness, sleep problems, irritability, worry about physical health, depression, depressive ideas, worry, anxiety, phobias, panic, compulsions, obsessions and overall effects. The CIS-R provides information on sub-threshold neurotic disorders (Jenkins, et al., 1997) but does not function well as a diagnostic tool due to poor to moderate concordance with the SCAN, a well-validated diagnostic interview (Brugha, et al., 1999; Jordanova, Wickramesinghe, Gerada, & Prince, 2004). In the context of this study, since all ADHD participants were free from comorbid Axis I and II diagnoses, the CIS-R was administered with a view to identifying sub-threshold psychiatric conditions.

Intellectual ability: IQ scores were derived by administering the Wechsler Abbreviated Scale of Intelligence (Psychological Corporation, 1999).

3.3.2 Statistical analysis

ADHD participants were categorised according to the presence and frequency of antisocial behaviours to allow for comparisons of individuals reporting any antisocial behaviour (ASB) as occurring frequently to those reporting ASB as occurring sometimes or not at all.

CIS-R subscale scores and screening cut-offs were ascertained from established algorithms (Meltzer, et al., 1995). Furthermore, a single measure of comorbid symptoms (CIS-R summary score) was obtained by summing all subscale scores with the exception of irritability and concentration/memory, fatigue and sleep problems. Concentration problems are a hallmark of ADHD, irritability is one of the variables of interest and fatigue and sleep problems are associated with adult ADHD independently of comorbidity (Schredl, Alm, & Sobanski, 2007).

Mean values for each rating scale and subscale were used as summary measures. Rating scale data were normally distributed in the ADHD sample, with the exception of the WFIRS-S risk subscale, and the ASB summary measure, which were inverse transformed for parametric analyses. By comparison rating scale data were positively skewed for control

participants. Due to these distributional differences in the patient and control groups and non-normality of demographic data, all case-control comparisons were carried out using non-parametric Mann Whitney U tests. Within ADHD group comparisons were carried out using one-way ANOVA, independent samples t-test, Mann Whitney U test, or Fishers exact tests, as appropriate.

The sensitivity of EL measures for predicting ADHD diagnostic accuracy were examined by applying receiver operating characteristic (ROC) analysis to the individual data of participants, with diagnosis as the state variable and EL as the independent variable. For contrast, equivalent ROC analyses were carried out for BRS measured ADHD symptom domains.

To account for potential age-related confounds, correlations were carried out to assess the association between age and ADHD symptom dimension scores and measures of EL. Correlations were then carried out between ADHD symptom measures and EL scales. Additionally, within the ADHD group multiple linear regression was used to identify factors associated with EL. Factors entered into the regression model for EL were IQ, BRS rated hyperactivity-impulsivity and inattention, and the CIS-R summary measure. Further multiple regression analyses were carried out to identify factors associated with ASB and impairment on the WFIRS-S. Factors entered included IQ, BRS rated hyperactivity-impulsivity and inattention, the CIS-R summary score and ALS-SF and CNS-LS summary measures. Individuals with missing data were excluded from regression analyses. Diagnostic analyses included examination of influential points (including examination of outliers outside of 2 standard deviations, leverage values and mahalanobis distances), normality of residuals and multicollinearity.

For all analyses alpha was held at .05, with Bonferroni correction implemented where multiple comparisons were carried out.

3.4 Results

3.4.1 Participants

Group demographics are listed in Table 4. All participants were 18-65 years of age with no significant difference between groups in age, IQ and years spent in education. ADHD

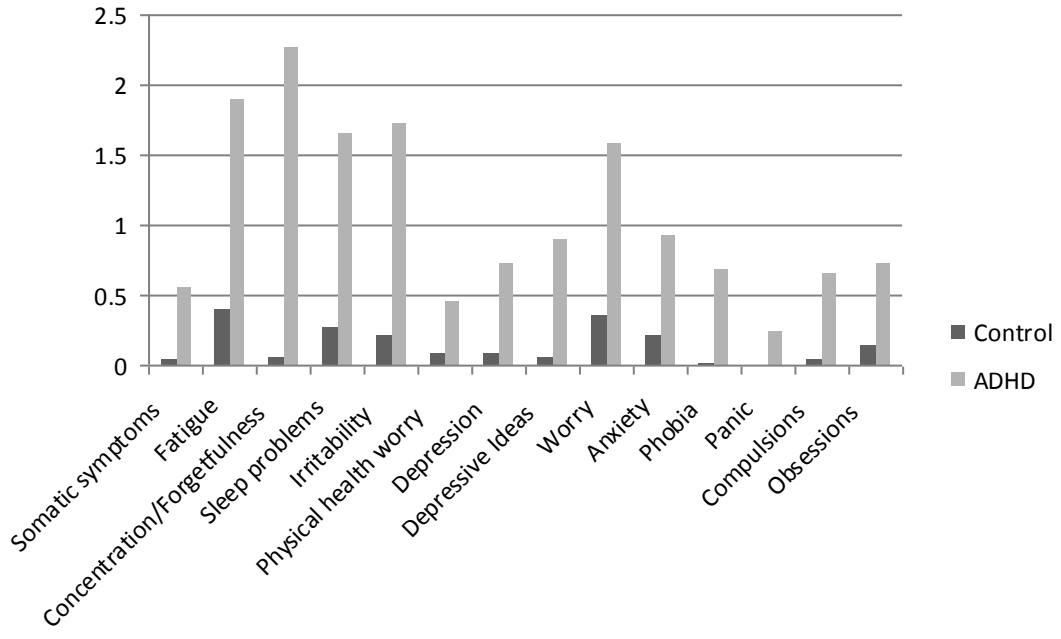
participants with a prior diagnosis of ADHD did not differ from those newly diagnosed in adulthood in current self-reported symptoms of inattention or hyperactivity-impulsivity on the BRS (inattention: z=-.89, p=.39; hyperactivity impulsivity: t=.32, p=.75)

Table 4: Group demographic data, mean (SD) and test statistics from Mann Whitney U

	ADHD	Control	Z statistic	p value
Age	28.5 (9.5)	29.0 (10.4)	-.12	.91
IQ	109.0 (15.1)	113.2 (13.4)	-1.49	.14
Years in education	15.7 (3.8)	15.7 (2.3)	-.57	.57

3.4.2 Comorbid symptoms (fig. 7)

Figure 7: Case-control differences in mean subscale scores on the CIS-R



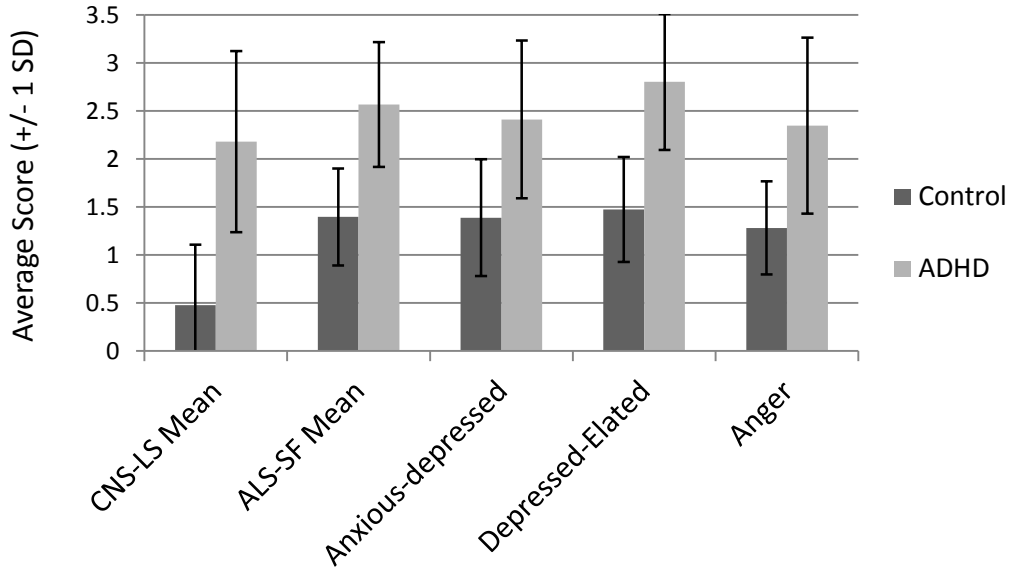
Participants with ADHD describe significantly more symptoms than control participants on many subscales of the CIS-R. Using a significance level of alpha adjusted by Bonferroni correction (p=.0036), with the exception of panic, obsession and worry about physical health scales (panic: p=.03; obsessions: p=.008; physical health worry: p=.005), all scales showed significant group differences (p<.001 and z=3.23-7.35 for fatigue, concentration/memory, sleep problems, irritability, depression, depressive ideas, worry,

anxiety, phobia and compulsions). Furthermore, ADHD participants more frequently screened positive for psychiatric domains investigated by the CIS-R (Fisher's Exact p<.001). Only one individual in the control sample screened positive for any co-occurring psychiatric problem (depressive disorder) compared to 16 individuals in the ADHD sample (most commonly depressive and anxiety disorders).

3.4.3 Emotional lability (fig. 8)

Between-group comparisons revealed elevated ratings of EL in individuals with ADHD (z=-6.97 p<.0001 for CNS-LS and z=-6.65 p<.001 for ALS-SF) as well as all the ALS-SF subscales (for anxiety-depression: z=-5.74 p<.001, depression-elation: z=-6.79, P<.001), and anger (z=-5.90, p<.001). To assess whether the increased EL scores were driven primarily by the presence of subthreshold comorbid symptoms in the ADHD group, analyses were re-run after excluding 16 individuals with ADHD and 1 control who screened above threshold for psychiatric conditions on the CIS-R. All differences remained highly significant (z range=-4.68—-5.80 all p<.001).

Figure 8: Case-control differences in EL scales (ADHD N=41, Controls N=47)



Participants with ADHD scoring below CIS-R diagnostic thresholds continue to present with significantly elevated CIS-R subscale scores compared to controls (CIS-R summary score: z=-4.44, p<.0001). Further analysis was therefore carried for participants with the fewest

psychiatric symptoms (individuals scoring zero for subscales of depression, depressive ideas, anxiety, phobia, panic, compulsions and obsessions; ADHD= 9 participants, Control= 37 participants). After Bonferroni adjustment (p=.01) individuals with ADHD continued to report elevated EL in all measures, with the exception of the ALS-SF subscale of anxiety-depression (p=.015) (z range=-2.02—-3.66 minimum p=.006).

3.4.4 Prediction of clinical status

Receiver operating characteristic (ROC) analysis for prediction of ADHD diagnosis by EL rating scales showed good predictive ability. For ALS-SF (area under the curve (AUC) =.91, 95% confidence Intervals (CI) = .88-.98) a mean score of 1.86 corresponded to a sensitivity of .85 and a specificity of .81. Similar results were found for the CNS-LS (AUC =.93, C I=.85-.97) with a mean score of 1.06 corresponding to a sensitivity of .88 and a specificity of .83. A further ROC analysis excluding individuals with a positive screen on the CIS-R showed little change in the results (ALS-SF: AUC =.90, CI= .81-=.98; CNS-LS: AUC =.92, CI =.85-.98). ROC analysis of ADHD symptom domains as measured by the BRS showed higher predictive ability of ADHD diagnosis (inattention: AUC=.99, CI=.97-1.00; hyperactivity-impulsivity: AUC=.96, CI=.91-1.00).

3.4.5 Predicting EL

Correlations of ADHD symptom scales, and EL scale and subscales with participant age were non-significant (miximum rho=-.247, minimum p=.19). In participants with ADHD, EL measures were correlated with all the ADHD subscales (ALS-SF with hyperactivity-impulsivity r=.56, p<.001, with inattention rho=.40, p=.01; CNS-LS with hyperactivity-impulsivity r=.59, p<.001, with inattention rho=.39, p=.01). Likewise, correlation coefficients within BRS inattention and hyperactivity-impulsivity subscales showed a similar magnitude of association (rho=.64, p<001). The same comparisons between ASB and ADHD subscales showed only hyperactivity-impulsivity to be significantly correlated with antisocial behaviour (rho=.50, p<.001).

Within the ADHD group multiple linear regression analyses with stepwise entry was used to determine the relative contributions of BRS rated inattention, hyperactivity-impulsivity and CIS-R symptoms and IQ on EL measures. For the ALS-SF mean score only two positive predictors were identified ($F_{2,40}$=14.30 p<.001, R^2=.43): hyperactivity-impulsivity (ß=.45), and

the CIS-R summary score (ß=.35). These two variables were subsequently included in a hierarchical regression, first entering CIS-R summary score, then hyperactivity-impulsivity, to identify whether ADHD symptoms account for variance in the ALS-SF that is not explained by comorbidity. Both CIS-R summary score (ß=.35) and hyperactivity-impulsivity (ß=.45) were predictive of EL ($F_{2,40}$=13.94 p<.001, R^2=.42). For the mean scores on the CNS-LS ($F_{1,40}$=21.52 p<.001, R^2=.35), only hyperactivity-impulsivity significantly predicted EL (ß=.59). Again, including the CIS-R summary score as the primary predictor before hyperactivity-impulsivity in a hierarchical regression indicated that although CIS-R summary score was predictive of CNS-LS mean score (ß=.25), hyperactivity-impulsivity was more strongly influential ((ß=.50) in the regression analysis ($F_{2,40}$=12.28 p<.001, R^2=.39).

When carrying out the equivalent analysis of the individual ALS-SF subscales, a differential pattern of associations emerged. For the anxiety-depression subscale, after the removal of one influential point with elevated leverage values (=.23), only CIS-R summary score was significantly predictive ($F_{1,39}$=11.61 p=.002, R^2=.23, ß=.48). Stepwise regression analysis for of the depression-elation subscale including all predictor variables, revealed significant effects only for hyperactivity-impulsivity ($F_{1,40}$=8.95 p=.005, R^2=.19, ß=.43). Hierarchical regression of the depression-elation subscale, entering CIS-R summary score as primary and hyperactivity-impulsivity as secondary predictor, revealed that CIS-R summary score alone did not significantly predict depression-elation ($F_{1,40}$=3.50 p=.07, R^2=.08, ß=.29), But continued to show a greater effect of hyperactivity-impulsivity (ß=.37) than CIS-R summary score (ß=.17), where both variables were entered ($F_{2,40}$=4.91 p=.01, R^2=.16) For the anger subscale ($F_{3,40}$=15.14 p<.001, R^2=.55), for stepwise analysis including all predictors hyperactivity-impulsivity (ß=.43) and CIS-R summary score (ß=.39) emerged as positive predictors, whilst IQ emerged as a negative predictor (ß=-.34). Reanalysis with hierarchical regression, including CIS-R summary score as primary predictor, and hyperactivity-impulsivity and IQ as secondary predictors indicated a significant influence of CIS-R summary score (ß=.38), hyperactivity-impulsivity (ß=.46) and IQ (ß=.-29) in the model ($F_{3,40}$=14.66 p<.001, R^2=.54).

3.4.6 Age at diagnosis

No differences were found for EL measures between individuals with a previously confirmed diagnosis of ADHD in childhood and those diagnosed for the first time in adulthood (ALS-SF:

t=.83 p=.41; CNS-LS: t= 1.42 p=.17). Similarly, for the ALS-SF subscales, no differences were identified between these two subgroups (anxiety-depression: t=1.92 p=.06; depression-elation: t=.43 p=.67; anger: t=.12 p=.90). ADHD participants diagnosed for the first time in adulthood did however have a greater number of subthreshold comorbid symptoms (z=-2.12 p=.035), whereas, adults with ADHD diagnosed in childhood reported more antisocial behaviours (z=-2.03 p=.046). However, none of these findings were significant after correction for multiple testing (Bonferroni adjusted p=.007).

3.4.7 Antisocial behaviour

Control participants did not report any form of antisocial behaviour occurring more than occasionally. In contrast, a number of participants with ADHD reported frequently being involved with the police (N=3), being involved in illegal activities (N=4), breaking or damaging things (N=12), and being verbally aggressive (N=12) or physically aggressive (N=4). 16 participants with ADHD reported engaging in at least one of the above antisocial behaviours often or very often. In the ADHD group, participants with antisocial behaviour did not have significantly more comorbid symptoms as measured by CIS-R summary scores compared to individuals without antisocial behaviour (z=-1.84 p=.07).

To investigate the relationship between antisocial behaviour and EL, further contrasts of EL measures were carried out between the 16 individuals who reported engaging in antisocial behaviour often or very often and the remainder of the ADHD group. No differences were present for ALS-SF mean scores (t=-1.64 p=.11), anxiety-depression (t=0.07 p=.95) and depression-elation subscales (t=-.30 p=.77). By comparison, increased ALS-SF Anger subscale and CNS-LS mean scores were identified in individuals with ADHD and antisocial behaviour (Anger: z=-3.90 p<.001; CNS-LS: t=-3.19 p=.003, robust to Bonferroni correction). However, in addition, all EL measures remained significantly different between ADHD participants without antisocial behaviour and control participants (z range=-4.18—-5.82 p<.001).

Multiple linear regression analyses with stepwise entry was carried out to determine the relative contributions of ALS-SF and CNS-LS mean scores, BRS rated inattention, hyperactivity-impulsivity, and CIS-R symptoms and IQ on antisocial behaviour. For inverse transformed mean antisocial behaviour ratings, hyperactivity-impulsivity was revealed as a negative predictor (ß=-.46) and IQ a positive predictor (ß=.37) ($F_{2,40}$=11.09 p<.001, R^2=.335),

with no independent effects of EL. These results show that antisocial behaviour is associated with higher levels of hyperactivity-impulsivity and lower intellectual function.

3.4.8 Functional impairment

ADHD participants reported significantly greater impairment in all domains assessed on the WFIRS-S (z range=-5.07—-6.84 p<.0001 for impairment in family life, work, school, life skills, self concept, social problems and risk taking). A series of multiple linear regression analyses with stepwise entry were used to determine the relative contributions of overall CNS-LS and ALS-SF scores, inattention, hyperactivity-impulsivity, CIS-R symptoms and IQ to domains of functional impairment (Table 5), with the exception of the WFIRS-S work dimension where interpretation of results was not possible due to heteroscedasticity in the data. EL as measured by the CNS-LS frequently independently predicted impairments in major life domains, including schooling, family life and social problems.

Table 5: Regression-based predictors of WFIRS-S Impairment subscales

Impairment/predictors	Beta	R	R^2	$R^2\Delta$	F	p-value
Family						
CNS-LS	.59	.59	.35		21.26	<.001
School						
CNS-LS	.44	.44	.19		5.60	.013
Life Skills						
CNS-LS	.61	.61	.38		22.84	<.001
Self concept						
CIS-R summary score	.55	.55	.30		16.53	<.001
Social problems						
CNS-LS	.35	.56	.32	.32	17.94	<.001
BRS hyperactivity-impulsivity	.35	.68	.40	.08	12.38	<.001
Risk (inverse transformed)						
BRS hyperactivity-impulsivity	-.48	.48	.23		11.78	.001

Note: all comparisons with the exception of school are robust to Bonferroni correction (adjusted p=.008)

3.5 Discussion

This study replicates research showing that adults with ADHD report heighted emotional lability (EL), which contributes to impairments in their daily life. However, in previous research the extent to which this finding was accounted for by comorbid psychiatric syndromes or symptoms was unclear. By investigating the association between EL and

ADHD in a sample of adults with ADHD and no comorbidities, and controlling for the presence of sub-threshold psychiatric symptoms in our analyses, this study reveals that heightened EL in ADHD cannot be accounted for by other psychiatric disorders or sub-threshold syndromes co-occurring with ADHD. Furthermore, this study shows that EL remains an important contributor to impairment in major life domains.

Although all the participants with ADHD were carefully selected for the absence of co-occurring axis I and II disorders, they showed a high level of common mental health symptoms across a wide range of clinical domains. This fits the clinical impression that in ADHD patients, comorbid symptoms are not all accounted for by co-occurring axis I or II disorders, but reflect a wider range of common psychopathologies associated with ADHD (Asherson, 2005).

The differential pattern of findings within ALS-SF subscales suggest that EL in ADHD is heterogeneous with some aspects related more strongly to core ADHD symptoms than others. In line with previous research, sub-threshold comorbidities were associated with severity of some domains of EL. However, hyperactive-impulsive symptoms were most strongly associated with many of the EL measures. The most complex EL construct studied here appears to be the ALS-SF anger subscale, where analyses indicated that individuals with low intellectual function and high levels of hyperactivity-impulsivity and clinical symptoms were most likely to be affected by the sudden temper and anger outbursts assessed by this measure.

Individuals with ADHD who frequently engaged in antisocial behaviour (ASB) reported greater EL on the CNS-LS and the ALS-SF anger subscale. However, EL did not predict ASB in subjects with ADHD. Much like the ALS-SF anger subscale, ASB was predicted by higher levels of hyperactivity-impulsivity and lower intellectual function. Furthermore, EL remained elevated in individuals with ADHD who reported infrequently engaging in ASB.

3.5.1 Specificity of EL

EL, measured by either scale implemented in this study, was found to be a strong predictor of ADHD diagnostic status, predicted only slightly better by self-rated inattention or hyperactivity-impulsivity. These results are in agreement with previous reports of high rates of EL in individuals with ADHD; as many as 50-76% of children and adolescents

(Anastopoulos, et al., 2011; Mick, et al., 2005) and 72-90% of adults (Asherson, 2005; Reimherr, et al., 2010). Recent work by Barkley and Murphy (2010) showed adults with ADHD reported being 'easily frustrated' and 'quick to anger' as frequently as symptoms of inattention and more frequently than symptoms of hyperactivity-impulsivity. Furthermore, adults with ADHD reported these problems more frequently than both clinical (including individuals with anxiety, drug use and mood disorders) and community control groups.

Although these studies support our finding that EL is a strong predictor of ADHD, this does not suggest that measures of EL be used to identify ADHD participants routinely. As shown here, ADHD symptoms themselves are better predictors of the disorder, and as outlined previously, EL is also present in a variety of other psychiatric disorders and is likely to lack specificity for ADHD when screening general adult populations. Instead, this study shows that even in the absence of comorbid conditions, ADHD participants are well differentiated from control participants on the basis of EL. This suggests that clinicians should consider ADHD as an important differential diagnosis when encountering patients with unstable emotional symptoms; particularly in light of research that shows a good clinical response of EL to methylphenidate and atomoxetine when treating adults with ADHD (Reimherr, et al., 2010; Reimherr, et al., 2005; Rosler, et al., 2010).

3.5.2 Longitudinal considerations

In children with ADHD, EL has been linked more specifically to hyperactivity-impulsivity rather than inattention, and the combined rather than inattentive ADHD subtype (Sobanski, et al., 2010). Similarly, EL appears to be more prevalent in adults with the combined ADHD subtype (Reimherr, et al., 2010). The specificity of the relationship between EL and hyperactivity-impulsivity is also evident in regression analyses carried out here.

Previous longitudinal research has revealed a greater developmental decline in hyperactive-impulsive than inattentive symptoms (Biederman, Mick, & Faraone, 2000; Larsson, Lichtenstein, & Larsson, 2006). The association between EL and hyperactivity-impulsivity reported in this study may indicate that problems with EL will diminish alongside hyperactivity-impulsivity during development and be less problematic in adults. One recent study potentially supporting this view, reported greater EL in adults with persistent than in those with remitting ADHD (Barkley & Fischer, 2010). However, it has been shown that

individuals with ADHD and EL tend to have more severe and complex symptoms (Reimherr, et al., 2010), and an alternative interpretation is that elevated EL in childhood predicts poorer prognosis for remission of ADHD symptoms. Further longitudinal research is required to clarify the role of EL in the persistence of ADHD symptoms into adulthood.

3.5.3 Impairment

In this study individuals with ADHD reported marked functional impairment, which for a number of subscales was independently predicted by EL, beyond the influence of core ADHD symptoms. This suggests that EL may aid in explaining a variety of problems not easily accounted for by the core features of inattention and hyperactivity-impulsivity, and should not be considered redundant alongside core ADHD dimensions. EL was particularly associated with impairment in areas of life requiring successful social interaction (home, social functioning, and in education). This is in line with the work by Barkley and colleagues (Barkley & Fischer, 2010; Barkley & Murphy, 2010), showing that EL predicted school/college problems, impairment in community activities, marital satisfaction and stress in parent-child relationships. In addition to supporting these previous findings, the current study shows that functional impairments related to EL were not accounted for by sub-threshold clinical comorbid symptoms.

However, in contrast to previous findings by Barkley and colleagues (Barkley & Fischer, 2010; Barkley & Murphy, 2010), inattentive symptoms were not as strongly associated with impairment, nor was it shown that antisocial behaviour was associated only with EL. The current study identifies EL as the leading predictor for impairment and only hyperactivity-impulsivity predicts antisocial behaviours. This may be due to the selected nature of the participant sample, or differences in the measurement of impairment in this study. More research is required to clarify whether hyperactivity-impulsivity is the main clinical variable linked to antisocial outcomes in adults with ADHD and if so, whether targeted treatment of hyperactivity-impulsivity would lead to reductions in adult antisocial behaviour.

3.5.4 Limitations

From the sampling procedure it can be seen that due to stringent exclusion criteria the vast majority of adults referred to the Adult ADHD Clinic were not eligible to participate in this study. These results may therefore not generalise to many adults with ADHD, who are

frequently affected by comorbid psychiatric conditions and substance use disorders (our most common exclusionary conditions). The drawback of including such individuals in a study with a primary purpose of investigating EL is that it then becomes unclear whether EL is associated with ADHD or the conditions which so commonly co-occur with it. Given previous studies reporting elevated EL in more clinically complex samples of individuals with ADHD, the current study fills an important gap in current research.

A more extensive clinical measure of subthreshold comorbidity, incorporating personality disorders, and oppositional and conduct problems may have been helpful, especially given previously reported associations between EL in ADHD, ODD and personality disorders (Reimherr, et al., 2010; Sobanski, et al., 2010). However, this study shows that whilst EL is elevated in individuals with ADHD and antisocial behaviour, this increase appears to be limited to emotions relating to anger and frustration. Moreover, antisocial behaviours do not fully account for the elevated EL seen in this sample.

The most important limitation of the study is its cross-sectional nature, so that the relationship between ADHD symptoms and EL over development is also not clear. A prospective longitudinal study would be better placed to measure the long-term stability and impact of EL symptoms over development, and clarify the developmental association of EL with hyperactivity-impulsivity.

3.5.5 Clinical implications

In summary, this study finds a strong association between EL in adults with ADHD that cannot be accounted for by co-occurring mental health disorders or sub-threshold psychopathologies. Furthermore, EL is independently associated with significant functional impairments. The clinical implications are important, since they indicate a potentially treatable form of emotional lability. Findings from this study indicate that adults presenting with long term problems with emotional lability should routinely be screened for the presence of ADHD.

Chapter Four: ADHD in adulthood and the dynamic nature of emotions in the context of everyday life

4.1 Summary

Emotional lability (EL) has been described as frequently co-occurring with attention deficit hyperactivity disorder (ADHD). Chapter 3 reported elevated EL as measured by retrospective self-report in a non-comorbid, untreated sample of male adults with ADHD as compared to matched healthy controls. The current study uses ambulatory monitoring within this same sample, carrying out repeated longitudinal assessment of negative and positive emotions (*irritable*, *frustrated*, *angry*, *happy* and *excited*) and the occurrence and impact of bad and good events during a working week. Individuals with ADHD reported more generalised irritability, frustration and anger, as well as greater instability in irritability and frustration. Results for positive emotion items were either equivocal or negative. Neither the increased intensity nor instability in emotions in the ADHD group could be accounted for by increased frequency or impact of bad events reported in the sampling period. Results indicate that although there is an interplay between EL and daily adversity in ADHD, EL does not arise as a result of everyday adversity. In line with previous studies of ambulatory assessment in psychiatric populations, small to moderate correlations were found between indices of EL from ambulatory assessment and those from questionnaire measures in the ADHD group. Findings suggest that ambulatory monitoring can provide findings which are complementary to rating scale measures, and can offer an independent contribution to the understanding of the dynamics of emotions and their response to daily events.

4.2 Introduction

Adults with attention deficit hyperactivity disorder (ADHD) have been described as experiencing “feelings of irritability” with “definite shifts from normal mood to depression or mild excitement” (Reimherr, et al., 2005, p.125), “lability of mood antedating adolescence with both “highs” and “lows” persisting for periods of hours to at most days with shifts occurring both spontaneously and reactively ” (Wender, et al., 1985, p. 551), and mood which is “highly volatile” and “changing around four- to five-times a day” (Asherson, 2005, p.530). In children with ADHD, similar descriptions can be seen: “low frustration tolerance, and sudden unpredictable shifts towards negative emotions such as anger, dysphoria and sadness” (Sobanski, et al., 2010, p. 916). Clinical descriptors of emotional lability (EL) in ADHD therefore describe a combination of long-lasting negative emotional

traits (such as generalised irritability), alongside emotional instability (a more highly dynamic quality of emotional experience).

Most studies of EL in ADHD report data from questionnaire measures, and in line with the observations above, many of these focus on the frequency and severity of negative emotions (irritability, frustration and anger), and emotional instability (rapid fluctuations or changes in emotions; e.g. Sobanski, et al., 2010). Although these may elicit similar behavioural expressions they do not necessarily have the same underlying cause. Individuals who report themselves as angering easily may experience greater fluctuations in their experiences of anger, or may simply experience more generalised anger in everyday life: as noted by Stringaris (2009, p. 278) "it is the angry man who is more likely to react angrily in a given situation".

Moreover, self-report measures are subject to a variety of recall biases. People tend to draw on selected moments in an almost rule-like fashion (Fredrickson, 2000): frequently ignoring the duration of an experience (Fredrickson, 2000; Fredrickson & Kahneman, 1993); and giving more weight to peak and most recent levels of experience (Hedges, Jandorf, & Stone, 1985; Redelmeier & Kahneman, 1996; Stone, Broderick, Kaell, DelesPaul, & Porter, 2000), experiences associated with positive affect (Kihlstrom, Eich, Sandbrand, & Tobias, 2000), and those that are consistent with their current state (Bower, 1981; Mayer, Mccormick, & Strong, 1995). Limitations in the accuracy of retrospective recall of emotions are also likely to influence the accuracy of assessments of emotional fluctuations across time (Trull, et al., 2008). Even more important, perhaps, is that recall biases may operate differently depending on clinical status (Ebner-Priemer, et al., 2006; Taylor & Brown, 1988), suggesting that additional caution may be required in the interpretation of such data.

Prospective longitudinal data collection methods, such as ambulatory monitoring, can help to circumvent a number of the abovementioned problems. This methodology, also known as *ecological momentary assessment* (Stone, Shiffman, Schwartz, Broderick, & Hufford, 2002), *experience sampling* (Csikszentmihalyi & Larson, 1987), or *diary methods* (Bolger, et al., 2003), is characterised by repeated assessments in real time in the natural context of individuals' daily lives. A series of immediate reports can be statistically summarised to obtain indices of daily experience without relying on participant's memory (Trull, et al.,

2008), resulting in reduced systematic and random sources of measurement error, increased validity and reliability (Bolger, et al., 2003), enhanced generalisability of findings (Ebner-Priemer & Trull, 2009), and a more proximal assessment of an individual's general behavioural tendencies or personality traits (Solhan, Trull, Jahng, & Wood, 2009). Moreover, the longitudinal nature of the data allows for a direct measure of instability, through the examination of within-individual change over time (Solhan, et al., 2009).

This methodology has shown that people can be meaningfully characterised in terms of their average reported emotions as well as how much their emotions change, and that these measures can be well dissociated. For example, Eaton and Funder (2001) reported that average reported emotion and emotional change as assessed by ambulatory monitoring were not significantly correlated. Moreover, they showed differential correlation with different personality traits, with average reported emotion correlating with extraversion, whilst emotional variability correlated with hostility, fearfulness and repression. Yet another study showed that less than 10% of the variance of intra-individual variability in positive emotions could be accounted for by mean affect levels (Eid & Diener, 1999). Furthermore, emotional variability (the standard deviation of reported emotions) shows stability over time (Eid & Diener, 1999; McConville & Cooper, 1997). Links have been drawn between personality and variability in reporting (Larsen, 1987). Indeed, indices of emotional variability derived from ambulatory monitoring have been associated with more fearful and hostile behaviour (Eaton & Funder, 2001), greater levels of neuroticism and lower self esteem (Eid & Diener, 1999; Kuppens, et al., 2007).

The capacity of ambulatory monitoring to capture aspects of everyday functioning which are related to personality and individual trait characteristics, may make this methodology specifically applicable to ADHD, where symptoms of inattention, impulsivity and hyperactivity have been described as chronic and trait-like, rather than showing symptomatic increases and declines commonly seen in other psychiatric disorders (Asherson, et al., 2007). Similarly, problems with EL have been described as chronic trait-like characteristics which frequently accompany ADHD in adulthood (Skirrow, et al., 2009).

Ambulatory monitoring has also been shown to be effective in the capture of emotional dynamics in psychiatric illness. Research using this methodology has identified variable or

instable emotions and a variety of clinical conditions and symptoms, including distress in borderline personality disorder (Ebner-Priemer, Kuo, et al., 2007), negative affect in depressive disorders of old age (Chepenik, et al., 2006), symptoms of depression in youth and young adulthood (Bauer, et al., 2007; Kuppens, et al., 2007; Larson, Raffaelli, Richards, Ham, & Jewell, 1990), and depressive symptoms in bipolar disorder (Bauer, et al., 2007). This methodology is particularly applicable where the dynamic nature of emotions can reach pathological levels, as in the case of bipolar spectrum disorders or borderline personality disorder, which are explicitly defined by the DSM-IV as characterised by uncontrolled change in emotion over time (American Psychiatric Association, 1994, 2000).

To date only a limited number of ambulatory monitoring studies have been conducted in individuals with ADHD. In the only study exploring the dynamics of emotions, Rosen and Epstein (2010) compare two children, one with a diagnosis of ADHD, and the other with ADHD and oppositional defiant disorder, concurrently being evaluated for a primary diagnosis of bipolar disorder. They described a pattern of “baseline” and “irritated” states in the first child, postulating that irritated states were being evoked by stimuli which provoked negative emotion. In the second child they described greater episodicity in the emotional ratings. However, this study is limited by the unclear nature of the bipolar disorder status, and the comparison of only two patients, restricting generalisability.

Other ambulatory monitoring research of ADHD has focused primarily on the frequency of negative moods and the contexts in which they are generated, showing that children with ADHD report increased anger and sadness when getting ready for activities (Whalen, Henker, Ishikawa, et al., 2006), and elevated levels of sadness and stress, lower levels of positive mood and lower self esteem more generally in their daily lives (Whalen, Henker, Jamner, et al., 2006). In a non-clinical sample of adolescents, increased negative moods, fewer positive moods, and lower self-reported alertness were associated with high levels of ADHD symptoms (Whalen, et al., 2002). A similar study in young adults, showed that symptoms of inattention were related to decreased positive emotions and increased negative emotions, whereas hyperactivity-impulsivity was associated with fewer problems of daily functioning (Knouse, et al., 2008).

What is unclear, however, is whether increased adversity associated with ADHD may play a contributing role to EL. Risk for ADHD is elevated in children who experience greater environmental adversity, such as family conflict and parent psychopathology (Biederman, Faraone, et al., 2002; Biederman, et al., 1995). In adults adverse life events have been shown to correlate with ADHD symptom severity (Muller, et al., 2008). Moreover, adults with ADHD have been noted as more likely to experience interpersonal and relationship difficulties, problems due to lateness, absenteeism, and inability to accomplish expected workloads, and are more likely to be dismissed from employment (Harpin, 2005). Research has also shown that EL may contribute to the experience of greater adversity in the everyday life of adults with ADHD, causing greater impairment in a variety of daily life functions and being associated with a number of adverse events and outcomes (Barkley & Fischer, 2010; Barkley & Murphy, 2010). However, it is also possible that individuals with ADHD may simply experience more emotional instability, as well as increased feelings of irritability, frustration and anger due to more frequent experiences of negative events.

The present study investigates experiences of positive and negative emotions, and good and bad events, captured by ambulatory monitoring over five days in adults with ADHD, free from concurrent comorbid conditions or current treatment for ADHD, and a matched control group. The following hypotheses are tested: (1) that individuals with ADHD will be characterised by greater intensity of negative emotions; and (2) greater instability of emotions; (3) that individuals with ADHD will report more frequent bad events, and that these will be associated with change in reported emotions; and (4) that negative and unstable emotions in daily life will be correlated with EL reported in rating scales. In addition, analyses explore whether EL in ADHD may be accounted for by greater adversity (more frequent bad events) which contribute to greater emotional instability.

4.3 Methods

4.3.1 Participants

An all-male sample of 41 adults with ADHD and 47 adult control participants participated in this study. Details on participant recruitment and clinical diagnostic procedure are given in Chapter 2, and subject demographics and statistics on group matching are provided in Chapter 3.

4.3.2 Measures

The Barkley Adult ADHD rating scale (BRS; Barkley, 1998), the Affective Lability Scale – Short form (ALS-SF; Oliver & Simons, 2004) and the Centre for Neurologic Study – Lability Scale (CNS-LS; Moore, et al., 1997), were administered as detailed in Chapter 2 (section 2.5.1). In line with previous work in Chapter 3, two items relating to impatience were dropped from the CNS-LS due to clear overlap with the impulsive dimension of ADHD. Intellectual function (IQ) was assessed using the Wechsler Abbreviated Scale of Intelligence (Psychological Corporation, 1999).

4.3.3 Momentary assessment of emotions

Participants were given an electronic diary (programmed with the software iMonitor; Malliaris, et al., 2006) loaded onto a Palm® Z22 PDA (Palm, Inc., Sunnyvale, California), a vibration-alarmed wristwatch, and an instruction leaflet (equipment is described in detail in section 2.5.5). The instruction leaflet included instructions on how to use ambulatory monitoring equipment, and the telephone number for a 'mood monitoring hotline', to contact the researcher in the event of any arising problems.

Research staff demonstrated the use of the electronic diaries, including how to respond to signals, emphasising timely responding. Participants practiced completing an electronic diary report to ensure their ability to use the equipment and to understand the content of the items. All participants were instructed to begin ambulatory monitoring the Monday following their research appointment and to continue monitoring over five consecutive days. Start and end times were the same for each day and were programmed to fit with participants' sleep schedules.

To alert participants to the onset of each monitoring event, vibration signals were emitted by the wristwatch. Signals continued for up to 20 seconds, unless stopped by the user, and were emitted at 8 pre-programmed times a day at intervals of 65-195 minutes. The electronic diary was synchronised to display during each signal. Intervals were not equally spaced to ensure participants did not get into a routine of monitoring their experiences, and to ensure that they continued to go about their everyday lives during the monitoring period.

During ambulatory monitoring, contact was maintained by telephone, including the first day of monitoring, and a mid-week follow-up.

Each report included questions enquiring about the participant's current emotions (e.g. "how angry do you feel NOW?"), rated on visual analogue scales with values ranging from 0 to 100 (0=not at all, 100=extremely). Emotion items, in an identical question format, included: *happy*, *excited*, *frustrated*, *irritable* and *angry*. The list of emotions was derived from frequently noted and published clinical descriptions of emotions in adults with ADHD, with the exception of *happy* which was included for positive balance. Participants also reported any good or bad events occurring during the hour preceding each signal (e.g. "Did any good things happen to you in the PAST HOUR?", answer yes/no), and where participants logged a good or a bad event, they were then asked to rate the impact of the event ("How much are you affected by them NOW?"), again on an identical numerical analogue scale as described above. All responses were automatically time-stamped by the software program at entry.

4.3.4 Preprocessing of ambulatory monitoring data

As in previous research (Delespaul, deVries, & van Os, 2002; Simons, et al., 2009; Solhan, et al., 2009), completed reports were recorded as valid when made within 15 minutes of the signal, incomplete reports and assessments completed outside of the signal were not included in analysis. All data preprocessing and subsequent analyses were carried out only on valid reports. These criteria were applied to avoid the self-selection of monitoring instances, which runs the risk of introducing biases in selecting some instances whilst overlooking others (Bolger, et al., 2003).

Compliance rates were calculated as the percentage of all signalled reports being completed by each participant (max. of 40 possible responses). Successive responses were defined as consecutive reports, with inter-response intervals not exceeding 6 hours. All participants with a poor response rate and few data-points (<30% successive responses) were excluded from analysis, in line with previous research practice (e.g. Simons, et al., 2009).

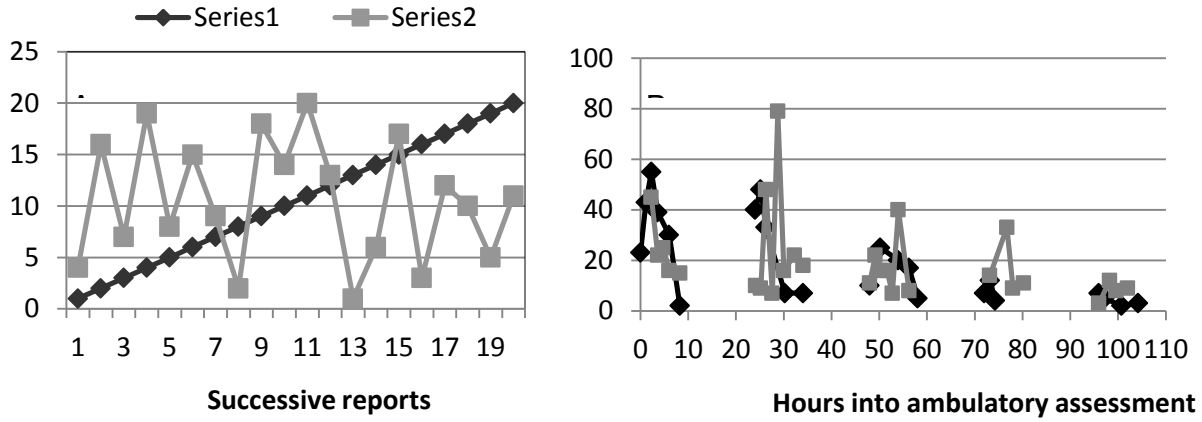
Squared successive differences (SSD) for each emotion assessed were calculated by taking the squared value of the difference between successive responses, and the Mean of

Squared Successive Differences (MSSD) was calculated by averaging the SSDs within each day and then averaging the score across all days (Solhan et al., 2009).

The Mean Squared Successive Difference (MSSD) was selected as the summary measure for instability. Unlike other commonly used indices, this measure incorporates aspects of amplitude, frequency and temporal dependency (the degree of change, the rate of change and the sequence in which reports are made, respectively; see Ebner-Priemer, Kuo, et al., 2007 for a detailed comparison of different measures of emotional change). The squaring of successive ratings results in larger changes being given more weight (Trull et al., 2008). Futhermore, the MSSD is robust to systematic time trends in time series data and does not require data to be detrended (Jahng, Wood, & Trull, 2008). Moreover, the MSSD statistic emphasises acute changes in emotion, which are of particular interest in this study.

Change in emotions has also frequently been measured using the standard deviation (SD) of reported experiences. However, the SD is an aggregate statistic which is not sensitive to the temporal ordering of reports, thereby confounding the frequency of mood changes with the extremity of changes (Larsen, 1987). Figure 9, plotted for illustrative purposes, provides a graphical representation of the benefits of the MSSD and conversely the limitations of the within-subjects SD, which does not distinguish between the two hypothetical and two real response patterns.

Figure 9: Comparison of MSSD and SD in two hypothetical and two real response patterns



Note: Two time series illustrating different statistical properties of MSSD and SDs. A) Hypothetical data illustrating the importance of temporal dependency in calculations of instability. Both series contain equivalent data, with series 2 randomly reordered (SD for both =5.91, MSSD series 1=1, MSSD series 2 =84.89). B) Comparison of irritability ratings

from two representative subjects in this study where series are matched for mean and standard deviation of ratings (series 1: mean=19.30, SD=16.62; series 2: mean=19.68, SD=16.35), but differ in MSSD (series 1=201.67, series 2=476.53).

Mean ratings for each emotion item were calculated by averaging absolute reported ratings across reporting instances for each individual. Group overall mean emotions were the mean of these individual averages within each group. The frequency of good and bad events, as well as the proportional frequency of good and bad events (e.g. number of good events/number of reports) was calculated. In individuals who logged the occurrence of more than one good and/or bad event, mean ratings of impact for each event type were extracted.

4.3.5 Statistical analysis

Analysis of data was carried out in SAS version 9.3, with the exception of F test for comparison of curves analyses which were carried out in SigmaPlot version 12.2. For all analyses alpha was held at .05 (two-tailed), and Bonferroni corrections were implemented to control for multiple comparisons, where appropriate.

Mean values for each rating scale and subscale were used as summary measures. Within and between group comparisons contrasting demographic, IQ, and rating scale data, and the frequency and impact of good and bad events were carried out using, chi-squared tests, independent samples t-test or Mann Whitney U test, as appropriate.

Since ambulatory monitoring data are characterised by an unequal number of reports from each participant (Russell, Moskowitz, Zuroff, Sookman, & Paris, 2007), and differences across the timing of reports, there is a wide consensus that they should be analysed using multilevel models (Bolger, et al., 2003; Ebner-Priemer, Kuo, et al., 2007; Knouse, et al., 2008; Trull, et al., 2008). Multilevel models account for the two-level structure of ambulatory assessment data, where correlated observations are nested within individuals (Jahng, et al., 2008), thereby controlling for non-independence of repeated measurements. Furthermore, multilevel models perform well with missing data, and can account for differences in rates of reporting (individuals with a greater number of valid reports contribute more to the estimation of group means; Jahng, et al., 2008).

Analysis of the intensity of reported emotions were assessed using two different types of multilevel models. Data distributions of all valid reports and SSDs were plotted and examined for normality. Only data for *happy* was normally distributed and was analysed using a linear mixed model with a random intercept and the default error covariance matrix in SAS (SAS command PROC MIXED). Alternative specifications of the error covariance structure, including autoregressive and an unstructured covariance structure, were explored. However, these did not improve the fit of any model as assessed by Akaike information criterion and the Bayesian information criterion, and the random effects model was therefore left unchanged. For the remainder of items, which followed a chi-squared distribution, analysis was carried out using a multilevel model with a gamma error distribution and log link (SAS command PROC GLIMMIX). All multilevel models included participant group (i.e. ADHD versus control) and duration on task (i.e. the amount of time the participant had been taking part in ambulatory monitoring, to control for fatigue, or day-of-week effects) as predictors. Additional post hoc tests to investigate duration on task effects and influences were carried out using Mann Whitney U for group comparisons, and paired samples t-tests and Wilcoxon signed ranks tests for within-group analysis.

Methods for analysis of instability using SSD data were introduced by Jahng and colleagues (2008) and Trull and colleagues (2008). Data followed a chi-squared distribution, and were again analysed using a series of multilevel models with gamma error distributions and log links, using the GLIMMIX procedure. This methodology allowed for the inclusion of covariates in the analysis, for example adjusting successive differences according to time intervals (since more proximal assessments tend to be more highly correlated; Ebner-Priemer & Sawitzki, 2007; Trull, et al., 2008).

Two different multilevel models were specified in analysis of instability using SSD data. It has been suggested that emotional instability should be assessed whilst controlling for the mean and/or squared mean emotional intensity, under the premise that this aids in identifying instability effects which are independent from mean emotion valence (Russell, et al., 2007). Less variability is possible when mean ratings are very high or very low (Eid and Diener, 1999), which can result in quadratic relationship between measures of instability and mean ratings. However, it has previously been suggested that it would be advisable to test for the effect of mean levels on instability, since research in psychiatric patients to date

has not typically controlled for mean levels (Ebner-Priemer & Trull, 2009). Here results from models which do and do not control for mean effects are presented side-by-side in order to evaluate its contribution.

The first model compared group differences, controlling for time intervals between successive reports. The second model controlled for time intervals alongside the mean (or squared mean) of emotion ratings as well as a mean (or squared mean) interaction term with group. To test the relationship between instability and mean ratings of each emotion investigated, an F test for comparison of curves was used to identify whether a quadratic relationship between MSSD and mean provided a better fit. The best predictors were then taken forward for inclusion in the second model. An interaction term between mean or squared mean covariate and participant group were specified, to control for covariates potentially having different effects in each group.

Where significant differences in instability were identified between groups which were robust to covariation for the mean (or squared mean), the contribution of reported bad and good events were investigated. Good and bad events and their reported impact were incorporated as predictors in each multilevel model. For instability analysis, since the items included in this analysis did not show a reduction in group differences from model 1 to model 2, the effects of bad and good events were assessed in model 1, which was the simpler model and included only time-interval as the covariate. Equivalent analyses were carried out where significant group differences in intensity were identified, including only duration on task as covariate.

In investigations of emotional dynamics in response to good and bad events, requiring a finer-grained analysis of emotional change, consecutive reports completed before and during the reporting of a good or bad event, with inter-response intervals not exceeding 2 hours, were investigated in a subsample of participants where this data was available. Emotional changes in response to events were calculated as the difference between the latter and earlier report.

For a more detailed analysis of emotions where a significant change was seen during reported good or bad events, data was taken from subjects who provided reports both prior

to (T-1), and after (T+1) logging a bad event, with durations between reports not exceeding 2 hours. Furthermore, available data from these participants for a further consecutive report within four hours of the reported event (T+2) was investigated. Where individual participants provided more than one such time-series, the average ratings at these time points were taken.

Finally, the relationship between data obtained by ambulatory assessment and self-report measures of EL were investigated by including mean CNS-LS and ALS ratings in models which significantly differentiated ADHD patients from controls on intensity or instability (after controlling for mean effects: model 1). Furthermore, correlational analyses were carried out between ratings scales and the MSSD for each emotion to obtain an index of the strength of the association between these measures. To control for the potential confounding effect of age, all variables which were entered into correlations were first correlated with age at assessment, and for variables where significant correlations with age were seen, partial correlations which controlled for age-effects were used.

4.4 Results

4.4.1 Participant characteristics and compliance

6 individuals with ADHD and 3 control participants were excluded due to low response rate (<30% successive responses). Individuals with ADHD who were excluded did not differ from the remainder of the ADHD group on any demographic measures (age: $z=-.44$, $p=.68$, years in education: $z=-.93$, $p=.39$, IQ: $t(39)=1.2$, $p=.23$), or on self-reported ADHD symptoms on the BRS (inattention: $t(39)=-.43$, $p=.67$; hyperactivity-impulsivity: $t(39)=1.1$, $p=.28$).

The remaining sample included 35 individuals with ADHD and 44 controls. Group demographics are provided in Table 6. All participants were 18-65 years of age with no significant difference between groups in age, IQ and years spent in education.

Table 6: Group demographic data, means (SD) and test statistics from Mann Whitney U

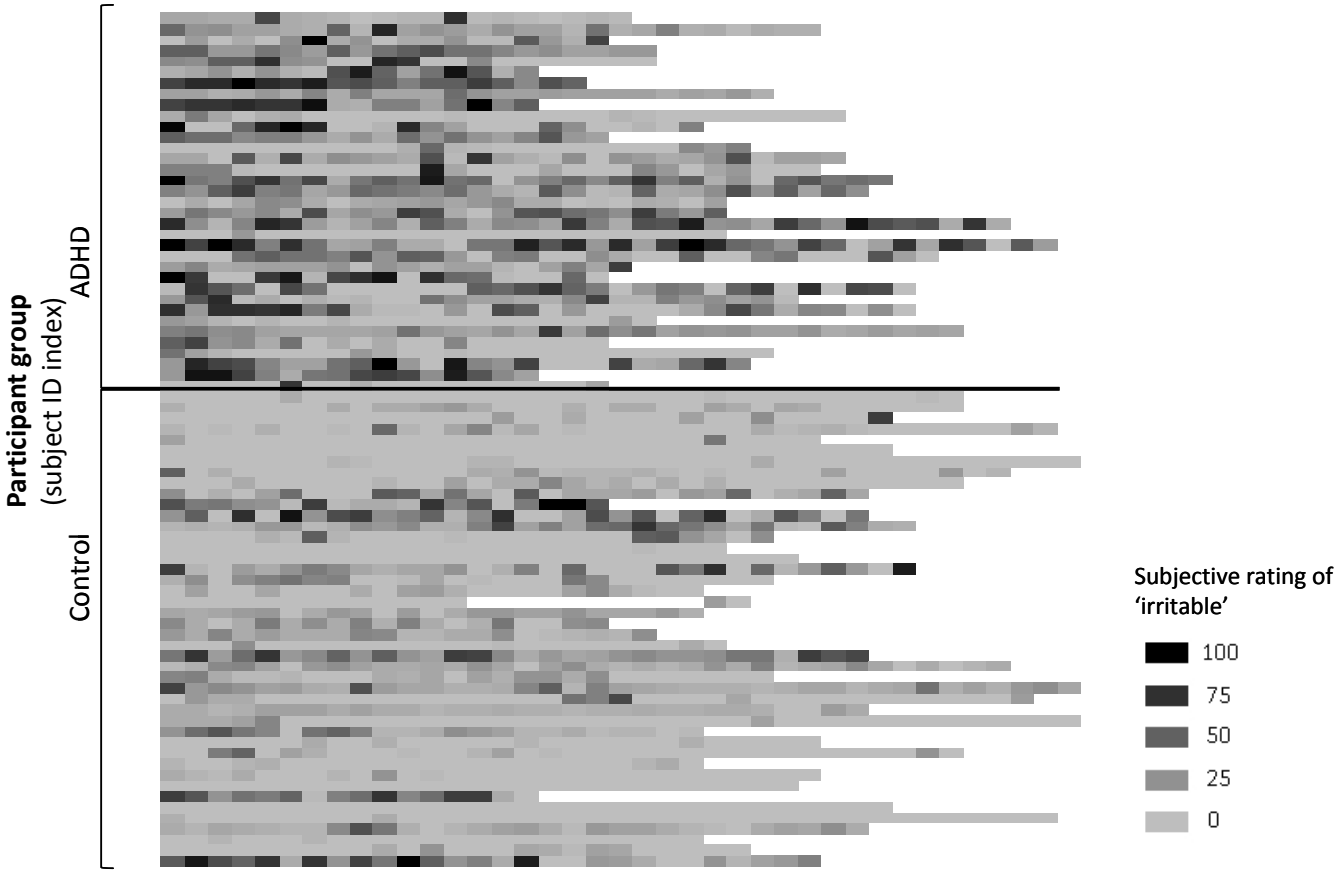
	Control (n=44)	ADHD (n=35)	Z statistic	p value
Age	29.1 (10.7)	28.5 (8.6)	-.09	.93
IQ	113.1 (13.5)	110.1 (15.6)	-.91	.36
Years in education	15.6 (2.3)	15.9 (3.9)	-.07	.95

Even after the exclusion of individuals with the lowest response rates, ADHD and control groups differed significantly for compliance rates, with ADHD subjects having an overall compliance rate of 64% and controls 72.3% (t=2.41, p=.018).

4.4.2 Visualising emotions (Fig. 10)

Figure 10 shows a three dimensional representation of the data for the emotion ratings of *irritable* over the ambulatory monitoring period. Each row represents a participant, each square corresponds to a report and the shade of grey denotes the level of *irritable* (with darker squares indicating higher ratings). Variability in the length of individual bars indicates differences in compliance. The frequency and fast changing intensity seen in the upper portion of the figure represents the within-subject variability in individuals with ADHD, and the darker shade overall suggests a greater proportion of higher ratings of *irritable.* Moreover the figure demonstrates differences in intra-individual variability within groups, with a few individuals with ADHD showing more similar patterns to those of controls, and a few controls showing more similar patterns to those seen in ADHD.

Figure 10: Irritability ratings for ADHD and control participants over five days



Note: Each row represents a participant and each square a self-report. The shade of grey denotes the level of irritability (light grey=low/no irritability, dark grey/black=high irritability)

4.4.3 Emotional intensity

Multilevel modelling was used to examine differences between the ADHD and control groups in reported emotion ratings across the monitoring week. Participant group and duration on task (i.e. the amount of time the participant had been taking part in ambulatory monitoring), were included as predictor variables. Results are shown in table 7. Significant differences between groups were seen for all negative emotion items (*irritable*, *frustrated* and *angry*) with ADHD subjects reporting significantly higher overall negative emotions, as

indexed by the significant and negative group estimate (indicating lower levels in controls). No significant group differences were seen for positive emotion items (*excited*, *happy*), although participants with ADHD showed a trend towards lower ratings of *happy* (p=.056), indexed by the positive group estimate.

Table 7: Descriptive statistics (group overall mean emotions (SD)), and between-group differences of emotion intensity as estimated by multilevel modelling.

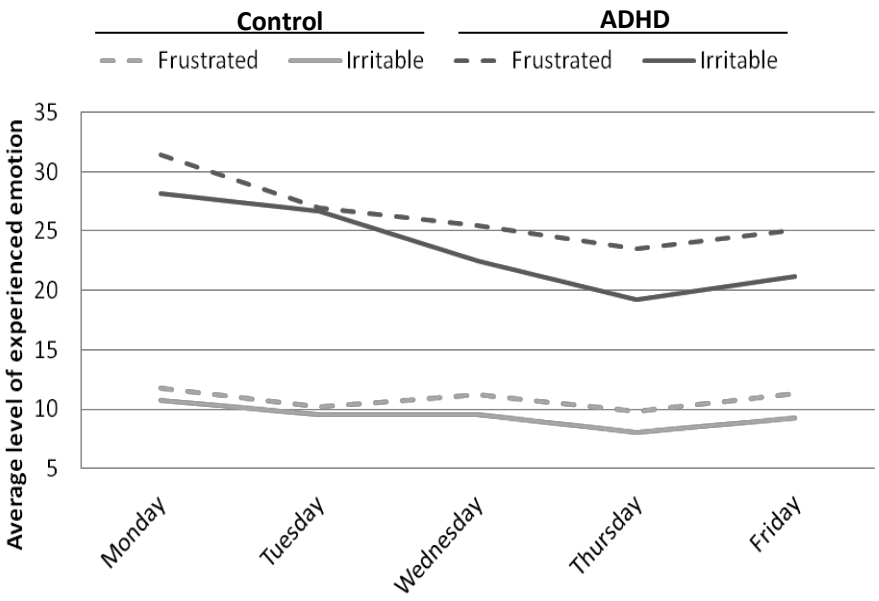
	Raw data: Mean (SD)		**Model parameters**			
	Control Group 1	**ADHD** Group 2	**Predictors**	**Estimate**	**Standard error**	**p-value**
Irritable	10.33	24.71	Intercept	3.197	0.184	
	(11.57)	(15.17)	Group	-1.131	0.238	<.0001
			Duration	0.00007	0.00001	<.0001
Frustrated	11.50	27.53	Intercept	3.197	0.190	
	(12.14)	(17.64)	Group	-1.11	0.245	<.0001
			Duration	-0.00004	0.00001	0.003
Angry	6.70	13.91	Intercept	2.332	0.203	
	(8.74)	(10.76)	Group	-0.832	0.261	0.002
			Duration	-0.00002	0.00002	0.128
Happy	49.33	40.32	Intercept	41.055	3.506	
	(19.68)	(20.54)	Group	8.910	4.591	0.056
			Duration	0.00004	0.0002	0.851
Excited	29.48	29.55	Intercept	3.118	0.140	
	(15.54)	(16.86)	Group	0.007	0.180	0.969
			Duration	0.00002	0.00001	0.028

In addition to the significant group findings, significant negative estimates for duration on task were seen for *irritable* and *frustrated*, driven by decreasing irritability and frustration during the week of monitoring, primarily in individuals with ADHD (fig. 11). This effect was not accounted for by higher compliance rates at the beginning of the week, since analysis of individuals with equivalent levels of compliance for Monday and Thursday (on average 6 reports on both days) showed a very similar reduction in ratings of *irritable* and *frustrated*

between the two days, as shown below for the entire sample. There was a positive estimate for duration on task for the item excited, which showed an small increase in ratings of intensity over the period of monitoring in the ADHD group (Monday: ADHD 26.64, control 30.42; Friday: ADHD 31.68, control 30.36).

Additional post hoc tests were carried out to test for the presence of group by duration effects. Data was selected from Monday and Thursday where ratings of *irritable* and *frustrated* were the most discrepant in both groups (see fig. 11), and average ratings were generated for these days. Analyses indicated that duration effects were significant for the ADHD group only (*irritable*: z=-4.06, p<.001; *frustrated*: z=-3.39, p=.001), no differences were seen in the control group (minimum p=.13). Differences for *excited* were maximal between Tuesday and Friday, and average ratings were compared across these days with no significant differences seen for either group individually (minimum p=.50).

Figure 11: Average reported frustration and irritability by group across weekdays



Inspection of the rates of bad events reported during the week provide a potential insight into the decrease in ratings of *frustrated* and *irritable* seen in the ADHD group in particular. Specifically, Mondays were marked by a significantly elevated frequency of bad events reported in the ADHD group (0.77 bad events reported per participant), compared to controls (0.15 bad events reported per participant, z=-3.31, p=.001). Both groups reported

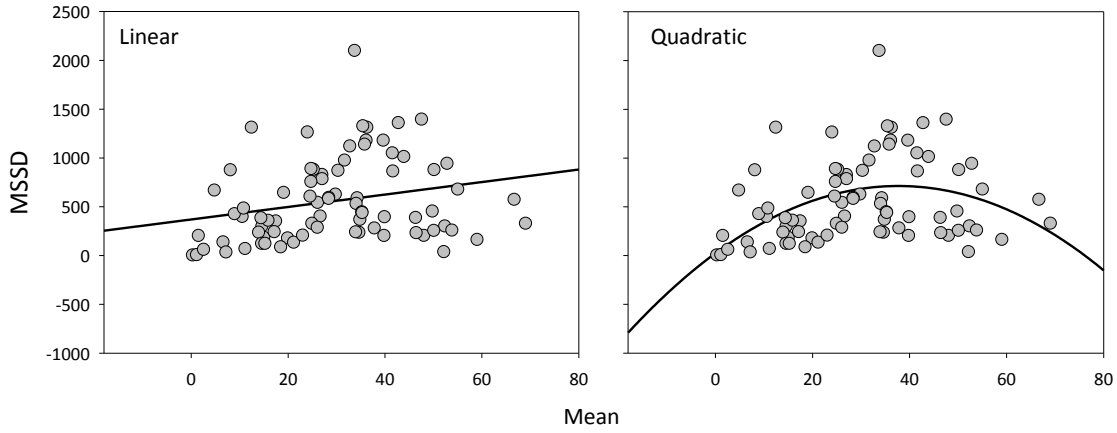
similar frequency of bad events on Tuesday through Friday (each group reporting a total of 13-19 bad events for each day), showing no significant group differences (minimum p=.15). However, analyses indicated that this may be related in better compliance earlier in the week since individuals with equivalent compliance for Monday and Thursday (as described above) reported an equivalent number of bad events on both days (ADHD: 0.73 bad events per participant, control: 0.11 bad events per participant on both days).

4.4.4 Emotional instability

4.4.4.1 Specification of Covariates

To aid in specifying whether the mean or squared mean should be included as covariate in the second multilevel model, a series of F-tests for comparison of curves were carried out contrasting fit for linear or quadratic associations between mean ratings and MSSDs. Quadratic functions provided significantly better fit for *excited* ($F(1,76)=11.24$, $p=.04$) and *frustrated* ($F(1,76)=12.12$, $p=.04$), but not for *angry* ($F(1,76)=.22$, $p=.81$) *happy* ($F(1,76)=5.66$, $p=.1$), or *irritable* ($F(1,76)=9.0$, $p=.054$). An example of a quadratic relationship providing a significantly better fit can be seen in Fig. 12. Where a quadratic function provided a significantly better fit, model 2 (which covaried for mean effects) included the squared mean rather than the mean as covariate.

Figure 12: Comparison of linear and quadratic curve fit for mean and MSSD of *excited*



4.4.4.2 Multilevel modelling of instability (table 8)

Multilevel modelling of SSDs was carried out to investigate differences between ADHD and control groups with respect to instability of emotion items. Two models were specified: model 1 included only group and the time interval between successive reports; model 2 also included the mean or squared mean level of emotion ratings (whichever relationship was found to be most appropriate), and an interaction term between mean (or squared mean) and group, since mean emotion ratings differed across groups for a number of variables.

Model 1 yielded significant group differences in emotional instability for all negative emotion items (*irritable*, *frustrated* and *angry*), with significantly higher instability reported by ADHD participants, shown by the negative estimates for group, indicating lower instability in controls (group 1). No significant group differences were seen for positive emotion items (*excited*, *happy*), although ADHD participants showed a trend towards higher instability for *happy* (p=.06). After including mean or mean squared level of emotion ratings as a predictor (as appropriate), and the interaction term with group, significantly higher instability in the ADHD group remained for *irritable* and *frustrated* (p<.0001). Group differences for *angry* were no longer significant. The loss of this effect for *angry* after covarying for the mean and the group by mean interaction was driven by the low level of variance of *angry*, as shown by the lower mean and SD for *angry* in both groups (table 8) and the higher correlation between mean and SSD, compared to the other variables (correlations between mean ratings and MSSDs: *irritable*: rho=.87, p<.0001; *frustrated*: rho=.83, p<.001; *angry*: rho=.90, p<.001; *happy* rho=.23, p<.04; *excited* rho=.31, p<.005).

Results for *happy* are more puzzling. The initial negative value for the group estimate indicates higher instability in the ADHD group. However, after controlling for the mean and the mean by group interaction this effect reverses, indicating higher instability in the control group. This variable had two notable outliers in the ADHD group (both with MSSD values more than 3 standard deviations above the remainder of the group), and differences in the strength of the correlations between the mean and the MSSD between the groups (controls rho=-.47, p=.001; ADHD subjects rho=0.08, p=.65), making the interaction term difficult to interpret. In view of the contrasting findings from models 1 and 2, I am hesitant to interpret group differences for the *happy* variable.

Table 8: Descriptive statistics (group overall MSSD (SD)), and between-groups differences in emotional instability as estimated by multilevel modelling

	MSSD (SD)		Model 1 parameters				Model 2 parameters			
	Control Group 1	**ADHD** Group 2	**Predictors**	**Estimate**	**Standard error**	**p-value**	**Predictors**	**Estimate**	**Standard error**	**p-value**
Irritable	290.58 (452.26)	714.41 (641.89)	Intercept	5.764	0.309		Intercept	4.655	0.392	
			Group	-1.867	0.389	<.0001	Group	-2.195	0.439	<.0001
			Time-interval	0.003	0.0009	0.0005	Time-interval	0.003	0.001	0.0006
							Mean	0.045	0.013	0.0009
							Mean*group	0.096	0.020	<.0001
Frustrated	361.76 (454.88)	851.90 (747.58)	Intercept	5.982	0.326		Intercept	5.547	0.374	
			Group	-1.749	0.414	<.0001	Group	-2.050	0.451	<.0001
			Time-interval	0.003	0.0009	0.006	Time-interval	0.003	0.0009	.007
							Mean^2	0.0004	0.0002	.079
							Mean^2*group	0.002	0.0006	.0001
Angry	162.95 (234.13)	546.69 (570.74)	Intercept	5.122	0.410		Intercept	2.906	0.462	
			Group	-1.812	0.527	0.001	Group	-0.917	0.537	.092
			Time-interval	0.0007	0.001	0.465	Time-interval	0.0008	0.002	.471
							Mean	0.160	0.026	<.0001
							Mean*group	0.039	0.038	.307
Happy	359.63 (311.13)	609.59 (550.59)	Intercept	5.572	0.213		Intercept	5.074	0.395	
			Group	-0.498	0.261	.060	Group	1.825	0.567	.002
			Time-interval	0.003	0.0008	0.0006	Time-interval	0.003	0.0008	.0004
							Mean	0.012	0.009	0.155
							Mean*group	-0.049	0.012	<.0001
Excited	468.62 (325.08)	672.08 (501.87)	Intercept	5.796	0.197		Intercept	5.459	0.264	
			Group	-0.194	0.232	0.406	Group	0.019	0.338	0.955
			Time-interval	0.002	0.0008	.009	Time-interval	0.002	0.0008	0.007
							Mean^2	0.0003	0.0002	0.065
							Mean^2*group	-0.0002	0.0002	0.431

Note: Mean^2, squared mean emotion; Mean*group or Mean2*group, interaction term between (squared) mean and group

Time-interval generally showed a positive association with SSD, as indexed by the positive value of the estimate and the high level of significance for most variables, confirming previous findings that emotion ratings from more proximal time periods are generally more highly correlated, with greater durations between successive reporting being associated with higher SSDs. This association was seen for all emotions investigated with the exception of the item *angry*, which shows no association between time-interval and SSD. This appeared to be driven in great part by frequency of the lowest possible value being reported (the value 0), which was most frequent for *angry* compared with other items (55.3% of responses overall for *angry*, compared to only 39% for *irritable*, 39% for *frustrated*, 6% for *happy*, 18% for *excited*). This lack of variance in the *angry* most likely resulted in strong correlations for distal time points as well as for proximal time points.

In model 2 a linear relationship with the within-subject mean was significant for items *irritable* and *angry*. The positive estimate values indicate a positive adjustment of variability in these mean emotions, in line with the observation that variability is limited when ratings are very low (Eid & Diener, 1999). This is indeed the case with these items, where overall more than 50% of ratings of *irritable*, and over 70% of ratings of *angry* were made in the 0-10 range. The positive estimate for the interactive effect for *irritable* and *frustrated* shows positive adjustment for a lower mean was applied mostly to group 1 (controls), in line with their lower overall mean emotions. The converse pattern for the item *happy* shows the opposite to be the case, whereby higher ratings of *happy* were associated with lower variability, as shown by the correlations reported above, and the adjustment is made for this converse relationship.

4.4.4.3 The influence of 'happy'

It is of interest that although the variable *happy* itself did not show clear or significant differentiation between the groups either for mean levels of emotions or for instability, it showed a negative association with instability of emotions, but only in control participants. As shown in table 9, higher within-subject mean ratings of *happy* were associated with lower instability (as measured by the MSSD) on all emotion items, with the exception of *excited* and *angry*, potentially indicating a protective effect of positive emotions on emotional instability that only operated in control subjects.

Table 9: Correlation coefficients and p-values for relationship between mean within-subject ratings of happy and MSSDs of all emotion items

(**ρ**) partial correlation with adjustment for age at assessment.

		Irritable MSSD	Frustrated MSSD	Angry MSSD	Happy MSSD	Excited MSSD
Controls	**Happy mean**	-0.56 (p<.0001)	-0.36 (**ρ**) (p=.02)	-0.26 (**ρ**) (p=.10)	-0.47 (p=.001)	-0.08 (p=.60)
ADHD	**Happy mean**	-0.06 (p=.72)	-0.18 (p=.29)	0.08 (p=.63)	-0.07 (**ρ**) (p=.70)	0.18 (**ρ**) (p=.32)

4.4.5 Good and bad events

Although mulitilevel models can show the relative contribution of specific events to emotion and their instability, they cannot show the specific emotional dynamics in relation to events. In this section a combination of approaches (time-based analysis and multilevel models) are used to investigate the effects of reported good and bad events in our two groups.

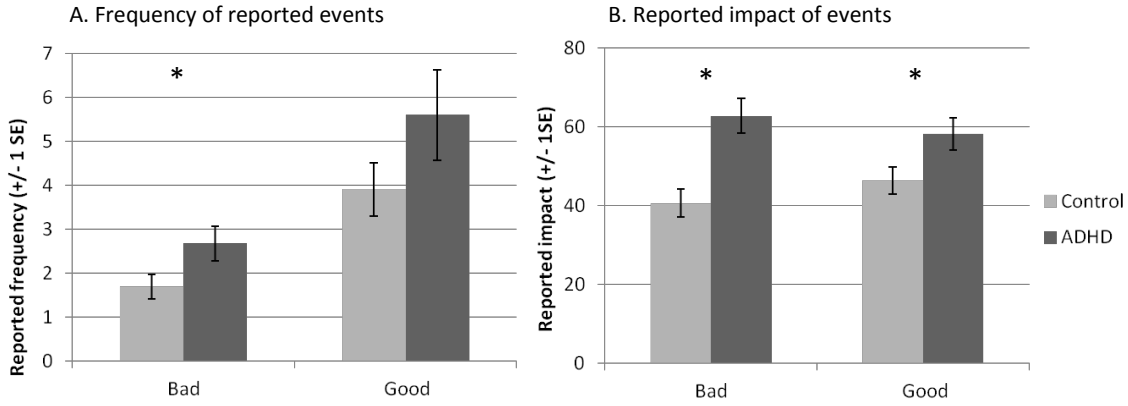
4.4.5.1 Frequency and impact of good and bad events (Fig.13)

One or more good events were logged during the assessment period by 39 controls and 28 individuals with ADHD. Both groups were equally likely to report the occurrence of at least one good event (χ^2=1.13, p=.35). Groups did not differ significantly on the frequency of reported good events (z=-.68, p=.50), or proportional frequency of good events. Where good events were logged, individuals with ADHD reported that these had a greater impact on their current state (t(65)=-2.23, p=.03). However, analysis of real-time change in emotion from reports immediately preceding and during the reporting of a good event (for consecutive reports within 2 hours), revealed no significant group differences in time-based change in any reported emotion (z range=-.07 to .73, p range= .94 to .14, sub-sample of 35 controls, 23 ADHD).

Both groups were equally likely to report the occurrence of at least one bad event (31 controls, 30 ADHD; χ^2=2.58, p=.18). However, individuals with ADHD reported a higher frequency of bad events (2.7 versus 1.7 reports per individual during the week; z=-2.12,

p=.03), and also reported that these had a stronger impact on their current state than controls (t(60)=-4.15, p<.001). This effect was reflected in the real-time change in ratings of *angry* (analysis as detailed above); revealing a significantly greater enhancement of anger ratings in individuals with ADHD during reporting of a bad event (z=2.39, p=.017 (uncorrected), sub-sample of 23 individuals in each group). No significant differences were seen for any other reported emotions (minimum p=.20).

Figure 13: Good and bad events: frequency and impact



Note: A) group comparison of frequency of reported events during monitoring period; B) Average reported impact of reported events (* significant group difference)

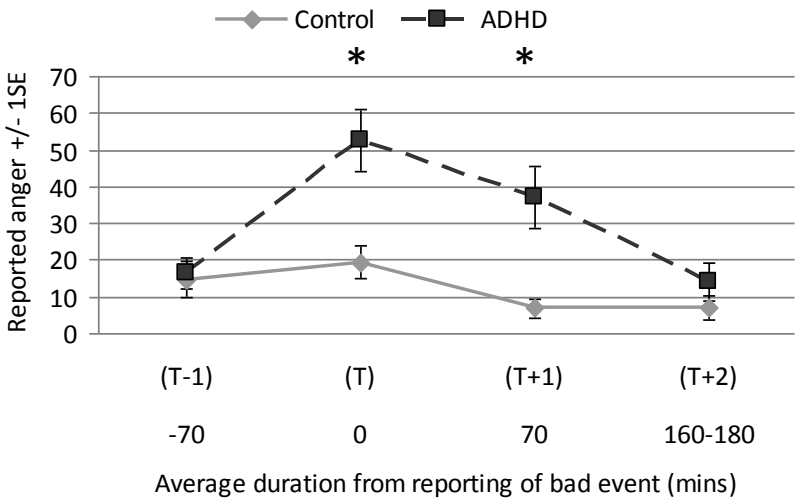
4.4.5.2 Time-based change in anger ratings after bad events (Fig. 13)

In light of the above findings, anger ratings were analysed in relation to instances where a bad event was reported (T). Analysis was limited to subjects who provided successive reports, within two hours before (T-1) and within two hours after (T+1) logging a bad event (18 ADHD, 20 controls). In addition, a further consecutive report of anger within four hours (T+2) of a reported bad event was studied in a smaller group where this data was available (15 ADHD, 18 controls).

Data comparing anger ratings before, during and after the reporting of bad events were skewed and no transformations were successful in normalising the distributions (cubic, square, identity, square root, log, 1/square root, inverse, 1/square, 1/cubic). Repeated non-parametric Mann Whitney U tests were therefore carried out, with Bonferroni corrections to control for associated inflations in type 1 errors.

Results are illustrated in Fig. 14. No group differences in anger ratings were seen at T-1 (z=-.501, p=.61). However, individuals with ADHD reported elevated anger during instances where they concurrently reported bad event as having occurred in the past hour (T: z=-2.75, p=.005), which remained significantly elevated at T+1 (z=-2.98, p=.004), but not at T+2 (z=-.92, p=.36). Differences were robust to Bonferroni correction (adjusted p value=.013), and time lags between reports were equivalent for both groups (t(36)=-.40, p=.69 for T-1; t(36)=-.54, p=.59 for T+1; z=-.46, p=.68 for T+2). Since individuals with ADHD logged a greater number of bad events occurring, analysis was repeated after the exclusion of data at T+1 which reported a concurrent bad event. Although the resulting differences between ADHD and controls was smaller, anger ratings in individuals with ADHD remained elevated (z=-.219, p=.04).

Figure 14: Time-based investigation of the impact of a reported bad event on anger



Note: Number of participants at each time point; T-1, T and T+1: 20 control, 18 ADHD, T+2: 18 control, 15 ADHD, * indicates significant group difference

4.4.5.2 The influence of good and bad events on emotional intensity and instability in multilevel analysis (table 10)

The relationship between the intensity and instability of emotions and good and bad events experienced by participants were investigated. Multilevel models for intensity of *irritable, frustrated* and *angry* as well as models of instability for *irritable* and *frustrated (*which were robustly more unstable in individuals with ADHD after controlling for means) were repeated,

after the inclusion of the presence and intensity of the experience of bad and good events as predictors. Since group differences for *irritable* and *frustrated* were not significantly moderated by the additional covariates in model 2, analyses were carried out only by including the presence and intensity of good and bad events as predictors in the simpler model (model 1). Results are presented in table 10.

Table 10: Between-group differences in intensity and instability with as estimated by multilevel modelling after the inclusion of good and bad event data

Note: significant effects denoted by *

		Model parameters		
	Predictors	**Estimate**	**Standard error**	**p-value**
Intensity				
Irritable	Intercept	2.903	0.176	
	Group	-1.123	0.233	<.0001*
	Duration	0.00003	0.00008	0.751
	Bad event	0.499	0.189	0.008*
	Bad impact	0.007	0.003	0.028*
	Good event	-0.148	0.145	0.306
	Good impact	-0.004	0.002	0.076
Frustrated	Intercept	2.957	0.185	
	Group	-1.096	0.245	<.0001*
	Duration	-0.00005	0.00008	0.530
	Bad event	0.906	0.187	<.0001*
	Bad impact	0.005	0.003	0.076
	Good event	-0.044	0.143	.0755
	Good impact	-0.008	0.002	0.001*
Angry	Intercept	2.157	0.198	
	Group	-0.763	0.255	0.004*
	Duration	-0.00003	0.00001	0.057
	Bad event	0.570	0.200	0.005*
	Bad impact	0.013	0.003	<.0001*
	Good event	-0.004	0.154	0.978
	Good impact	-0.004	0.003	0.072
Instability				
Irritable (model 1)	Intercept	5.586	0.307	
	Group	-1.792	0.384	<.0001*
	Time-interval	0.003	0.0009	0.0007*
	Bad event	0.556	0.350	0.112
	Bad impact	0.007	0.006	0.239
	Good event	0.151	0.272	0.578
	Good impact	0.0006	0.005	0.899

Frustrated (model 1)	Intercept	5.767	0.326	
	Group	-1.654	0.412	0.0001*
	Time-interval	0.002	0.0009	0.055
	Bad event	1.068	0.341	0.002*
	Bad impact	0.005	0.006	0.360
	Good event	0.366	0.265	0.167
	Good impact	-0.0009	0.004	0.830

Group differences for all models remained significant after the inclusion of good and bad event data as predictors, with models indicating increased negative emotions and increased instability in the ADHD group. For analyses of intensity the occurrence of bad events and their reported impact predicted overall greater levels of *irritable*, *frustrated* and *angry*. Reported good events did not show any significant effect on intensity in these emotions. However, the reported impact of good events was associated with lower reported frustration (as seen by the negative estimate).

The effect of task duration was abolished once data from reported good and bad events were included for both *irritable* and *frustrated*. This is in line with findings reported earlier, that the beginning of the monitoring week was associated with both higher overall ratings of *irritable* and *frustrated* accompanied by a higher number of reported bad events.

In analyses of instability, an interesting dissociation was seen between *irritable* and *frustrated*, which at face value may seem like very similar items. The item *irritable* was not found to be associated with either the presence or the impact of good or bad events. By contrast *frustrated* was associated with the occurrence of the bad event, but did not appear to be contingent on the reported impact of the bad event.

4.4.6 Relationship of ambulatory assessment data to rating scales of EL

To investigate the relationship between differences identified in emotional intensity and instability which distinguished ADHD and control groups and self-reported rating scales of emotional lability, multilevel analyses were again repeated after the inclusion of self-reported EL on the ALS-SF and the CNS-LS rating scales. As shown in table 11 the best predictor for all measures was the ALS-SF, which showed the only significant effect on both the mean emotion over the week and instability in emotion. Interestingly, once self-rated

EL was taken into account, group differences no longer presented as significant, indicating that a reasonable proportion of the variance in group differences can be accounted for by EL as measured by the ALS-SF in this specific model.

Table 11: Predicting instability and intensity of emotions from on rating scale measures

	Model parameters			
	Predictors	**Estimate**	**Standard error**	**p-value**
Intensity				
Irritable	Intercept	1.109	0.507	
	Group	-0.246	0.330	.458
	Duration	0.00002	0.00008	.823
	CNS-LS	0.101	0.183	.581
	ALS-SF	0.647	0.240	.009
Frustrated	Intercept	0.961	0.512	
	Group	-0.048	0.333	.887
	Duration	-0.00009	0.00008	.278
	CNS-LS	0.189	0.185	.309
	ALS-SF	0.689	0.2426	.007
Angry	Intercept	0.258	0.562	
	Group	0.236	0.364	.518
	Duration	-0.00002	0.00002	.117
	CNS-LS	0.2049	0.202	.313
	ALS-SF	0.648	0.265	.017
Instability				
Irritable (model 1)	Intercept	2.484	0.832	
	Group	-0.296	0.537	.583
	Time-interval	0.003	0.0010	.0004
	CNS-LS	0.151	0.297	.613
	ALS-SF	1.162	0.391	.004
Frustrated (model 1)	Intercept	2.393	0.879	
	Group	0.012	0.567	.983
	Time-interval	0.003	0.0009	.005
	CNS-LS	0.231	0.314	.465
	ALS-SF	1.217	0.413	.004

Confirming these relationships by examining the correlations between the MSSD and self-reported EL on the ALS-SF revealed a clear relationship with ALS-SF scores for all emotion measures when analysed across groups (table 12). Where variables were significantly correlated with age at assessment, age was partialled out in these analyses. Correlations remained high when investigated in control participants alone, with lower correlations seen in the ADHD group. This most likely reflects, at least in part, the generally lower level of

reported EL in both the ALS-SF and the ambulatory monitoring measures in the control group, leading to less variation in the data as a whole. Crucially, compliance rates were not correlated with any self-reported measures of EL.

Table 12: Correlation coefficients (p-values) for mean and MSSD (across all emotion items which differentiate ADHD and control subjects) with EL as measured by the ALS-SF

(**ρ**) partial correlation with adjustment for age at assessment

	ADHD & Control groups ALS-SF	**Control ALS-SF**	**ADHD ALS-SF**
Irritable mean	0.59 (p<.001)	0.40 (p=.006)	0.33 (p=.052)
Irritable MSSD	0.62 (p<.001)	0.59 (p<.001)	0.35 (p=.039)
Frustrated mean	0.64 (p<.001)	0.60 (p<.001) (**ρ**)	0.37 (p=.03) (**ρ**)
Frustrated MSSD	0.62 (p<.001)	0.55 (p<.001) (**ρ**)	0.13 (p=.45)
Angry mean	0.59 (p<.001)	0.46 (p=.002)	0.44 (p=.007)

4.5 Discussion

The current study which assesses emotional lability (EL) in adults with ADHD with ambulatory monitoring yields results which are complementary to many clinical descriptions of ADHD (e.g. Asherson, 2005; Reimherr, et al., 2005; Wender, et al., 1985). Furthermore, the results are in accordance with research carried out using traditional rating-scale measures which show elevated EL occurring alongside the disorder in adulthood (e.g. Barkley & Fischer, 2010; Barkley & Murphy, 2010; Surman, et al., 2011). The current study shows that adults with ADHD are characterised by higher levels of irritability, frustration and anger. Results are in line with previous research in children with ADHD and adolescents and adults with high levels of ADHD symptoms, who are reported to display elevated negative emotions such as increased negative moods and increased anger (Whalen, Henker, Ishikawa, et al., 2006; Whalen, et al., 2002). An important novel finding, previously unreported in ADHD populations, is that adults with ADHD experience more unstable irritability and frustration, even after controlling for mean effects.

Since data is collected by ambulatory monitoring, it is possible to establish that group differences are not related to recall bias, and are relevant in the context of events, stressors and experiences encountered in day-to-day living. Furthermore, the lack of comorbid conditions in the ADHD sample used in this study, suggests that increased and unstable negative emotions cannot be accounted for by other co-occurring clinical conditions, but are instead likely to be related to ADHD itself.

4.5.1 Good and Bad events

ADHD has also been associated with greater adversity in everyday life (Harpin, 2005; Muller, et al., 2008), which raises the question whether EL is simply a reaction to the greater number or intensity of problems in daily life. Individuals with ADHD reported a higher number of bad events compared to controls, whilst not differing in the number of reported good events. They showed an exaggerated anger response after the occurrence of a bad event, and a slower return to baseline levels, with anger ratings remaining elevated for over an hour after a bad event was reported. Frequency of bad events also accounted for some of the variance in the instability of reported frustration, but not irritability. Although no information was gathered regarding the nature of bad events, participants were asked to report how much these bad events affected them. The ADHD group reported that both bad and good events affected them more strongly than control subjects, indicating either that ADHD is associated with more extreme difficulties and successes in everyday life, or that individuals with ADHD differ in their appraisal of such events. The reported impact of bad events did not however influence instability in either frustration or irritability. Moreover, group differences in instability of both *irritable* and *frustrated* remained after covarying for the occurrence of bad and good events and their reported impact.

In relation to emotional intensity, bad events and their impact exerted a significant influence on intensity of all negative emotion items (*irritable*, *frustrated*, *angry*). Although the presence of reported good events did not influence any models, the intensity of good events were found to have a protective effect on reported frustration, with those who experienced good events which had effected them more strongly reporting lower ratings of frustration. Again, intensity differences in *irritable, frustrated* and *angry* remained after covarying for the occurrence of good and bad events and their reported impact.

Although the current findings indicate a limited contribution of experienced bad events to emotional instability and intensity of negative emotions, the design of the study is not best placed to investigate environmental effects on emotions. Whilst time-contingent recordings, such as hourly or random assessments within the day are ideal for investigating the dynamics of continuous phenomena such as emotional instability (Ebner-Priemer & Trull, 2011), a combined event-contingent (provide reports when experiencing certain environmental events) and signal-contingent (respond to random prompts) paradigm, would be required to test the environmental reactivity model of affective instability more directly (Trull, et al., 2008). This combined methodology would enable the capture of event data which would have otherwise been missed by the current sampling strategy. Furthermore, little is known about the nature of reported events (which may vary in severity across individuals and occasions), and could in some cases also be reported as having occurred as a post-hoc explanation for the experience of negative emotions. An avenue for future research would be to further characterise these events in relation to overall emotional experience, emotional change and instability.

4.5.2 Positive and negative emotions

Some clinical descriptions highlight instability in positive emotions in adults with ADHD, including “definite shifts from normal mood to depression or mild excitement” (Reimherr, et al., 2005, p. 125), and “rapid shifts into depression and excitability” (Asherson, et al., 2007, p.4). However, positive emotions tend to be under-represented in rating scales frequently used to assess EL in ADHD, which instead tend to focus on temper problems, anger and frustration (e.g. Barkley & Murphy, 2010; Conners, 2003; Conners, Sitarenios, Parker, & Epstein, 1998). This study showed no significant group differences for reported excitement, either in terms of general intensity or in instability. Results for reported happiness are more difficult to interpret, given the trending difference between groups for intensity and the unclear result for instability after controlling for mean differences. The results presented here for positive emotions therefore are inconclusive and further research investigating intensity and instability of positive emotions is required.

Replication in a study with a larger sample size, a more frequent sampling design, or a higher rate of compliance may help to identify whether the trending differences for reduced

reporting of happiness are likely to be meaningful in individuals with ADHD. Overall results from this study suggest that intensity and instability in negative emotions are more clearly able to distinguish between individuals with ADHD and controls. This may result in part from the greater range of negative emotions endorsed by ADHD subjects as compared to control subjects, which is likely to have given these items more power in analyses to detect differences in instability.

Alternatively, it may be the case that intensity and instability of negative emotions are more characteristic of ADHD populations. This would suggest that EL may not be a unitary construct and that instability in positive and negative emotions can be dissociated. Previous research has shown that self-reported positive and negative affective traits can be dissociated, with negative affective traits specifically associated with poor coping, high stress and increased frequency of unpleasant events, as well as psychiatric symptoms of depression and anxiety (reviewed in Watson, Clark & Tellegen, 1988; Watson, Clark & Carey, 1988). Since ADHD is associated with greater adversity, higher levels of comorbid symptoms and impairment, a negative affective style may well be more characteristic of the condition.

Higher ratings of happiness were associated with reduced instability in the control group, but this association did not hold for individuals with ADHD. Previous research by Kuppens and colleagues (2007) showed variability in emotions to be associated with lower self esteem and increased depression, providing some support for the pattern of association seen in control subjects here. It seems that in psychiatrically healthy individuals an overall more cheerful disposition may be protective against instability in other emotion domains, but this association is absent in individuals with ADHD.

4.5.3. Clinical implications: overlap with bipolar disorder

The generalised increased intensity of anger, irritability and frustration described here have a potential impact on the current debate of conceptualisations of bipolar disorder in relation to ADHD, where considerable symptomatological overlap between the two disorders has been highlighted (see Skirrow et al., 2012 for detailed review). The DSM-IV describes mixed episodes in bipolar disorder with features of co-occurring mania and depression, which can be characterised as an irritable mood state (American Psychiatric Association, 1994, 2000), and some researchers and clinicians believe severe and chronic

irritability to be the hallmark of mania in children and adolescents (Biederman, Mick, Faraone, et al., 2000; Wozniak, et al., 1995). It has been suggested that unlike in bipolar disorder, individuals with ADHD frequently enjoy normal moods but can become frustrated or angry with unexpected emotional challenges, and furthermore that these emotions subside relatively rapidly and do not form a distinct protracted episode of the type that would qualify for a mood disorder (Biederman, et al., 2012).

The current findings highlight the problems with making assertions about the temporal dynamics of emotional states where these have not been appropriately or systematically studied. Figure 9 demonstrates that some degree of irritability is very frequently reported by adults with ADHD, and some individuals experience some irritability across most or all reporting instances over a 5-day period, indicative of a chronically irritable mood profile. Moreover, the lack of relationship seen between instability of irritability and bad events, indicate that irritability in ADHD is not as contingent on the environment as some researchers might suggest (e.g. Biederman, et al., 2012; Rosen & Epstein, 2010). These findings indicate that protracted irritability may not differentiate well between bipolar disorder and ADHD. However, since the diagnostic contentions between ADHD and bipolar disorder are strongest in children, similar research is required in children to identify the developmental stability of these effects.

Further research implementing ambulatory assessment could be used to contrast emotional profiles in individuals with ADHD and those with other clinical conditions, including bipolar spectrum disorders, to identify patterns of emotional features and dynamics which are characteristic of each or common to both conditions. This approach has been previously successfully used to identify greater emotional instability in individuals with borderline personality disorder than patients with depression/dysthymia (Solhan, et al., 2009).

4.5.4 Duration effect on emotional intensity

The current analyses also identified differences in the reported intensity of irritability, frustration and excitement in relation to the duration on task, with earlier reports in the monitoring week being associated with increased levels of frustration and irritability and later reports being associated with increased excitement. Post hoc tests revealed reductions in intensity of *irritable* and *frustrated* to be significant only in the ADHD group,

and no group-specific effects for *excited*. Furthermore, there was some indication that more frequent bad events were experienced earlier in the week, which may have contributed to this result. However, these findings are confounded by a reduction in compliance over the monitoring period which limits the interpretability of this finding. Whilst in the current design, where all assessments were carried out from Monday to Friday, it is not possible to distinguish day-of-week, duration-on task, or habituation effects, the results do bear some resemblance to the previously identified 'weekend' effects, where more positive and less negative emotions and moods are seen on weekends and Fridays (Reis, Sheldon, Gable, Roscoe, & Ryan, 2000; Stone, et al., 2000).

4.5.6 Relationship between rating scales and ambulatory monitoring

Multilevel models showed that differences in reported EL from questionnaire measures accounted for a significant proportion of the variance in the intensity and instability of emotions which differentiated between ADHD subjects and controls. Specifically, the ALS-SF, which focuses on swift changes in emotions, was most strongly associated both with increased generalised frustration, irritability and anger and with more unstable irritability and frustration, suggesting that this particular measure is better suited than the CNS-LS to capture EL in ADHD in the context of everyday life. However, the limited association as shown by relatively low correlations between the ALS-SF and ambulatory assessment measures in the ADHD sample (with correlation coefficients between 0.13 and 0.44 for means and MSSDs) suggest only a small to moderate concordance between these two measures. These findings are in line with previous research in bulimia nervosa and personality disorders, where low correlation coefficients in such comparisons were also seen (Anestis, et al.; Links, Heisel, & Garland, 2003; Solhan, et al., 2009). Overall these results indicate that whilst these measures can be considered complementary, they cannot be considered equivalent.

4.5.7 Limitations

Minimal missing data are critical for the assessment of instability that is defined by successive scores from one occasion to the next (Ebner-Priemer & Trull, 2011; Trull, et al., 2008). The moderate compliance rate obtained here, particularly in the ADHD group is low in contrast to some previous studies in borderline personality disorder and depression

(compliance rates >90%; Ebner-Priemer, Welch, et al., 2007; Solhan, et al., 2009), but is more closely in line with studies of ambulatory assessment in outpatients with schizophrenia (69%; Granholm, Loh, & Swendsen, 2008), and healthy adolescents (71%; Hedeker, Mermelstein, Berbaum, & Campbell, 2009).

Multilevel models have become the primary method for analysis of clustered data since all available data is used for each subject, and models can effectively handle: 1) data which is correlated within subjects, 2) time effects which differ between participants, 3) binary and continuous covariates which can change over time, and 4) missing data which occurs at random in the dataset (Gueorguieva & Krystal, 2004). The assumption that data is missing for ignorable random reasons (MAR) is defined by missingness which depends on (or is explained by) the observed data (Mallinckrodt, Clark, & David, 2001). In treatment trials missingness has been defined as non-ignorable if the probability of dropping out is related to the current or future response, or to an unobserved process related to the response. In the current study, missingness was greater in ADHD subjects, but was not correlated with ADHD symptoms, self-reported EL (CNS-LS or ALS-SF), IQ or age across groups (rho=-.03 to -.16, minimum p=.16), indicating that missingness was best predicted by diagnostic categorization, which was included in all multilevel models. Future studies of emotional functions in ADHD must make further efforts to reduce data missingness, for example by including compliance contingent renumeration for participants (Anestis, et al., 2010).

Moreover, the validity of findings reported here are supported by more rudimentary analyses using mean ratings of emotions and variability indices (within-subject standard deviation) of emotions identified equivalent results to analyses carried out by multilevel modeling (mean comparisons; *irritable*: z=-4.34, p<.001, *frustrated*: z=-4.22, p<.001, *angry*: z=-3.02, p=.003; SD comparisons; *irritable*: z=-4.49, p<.001, *frustrated*: z=-4.12, p<.001). Although variability (SD) cannot be considered equivalent to the index of instability (MSSD), these measures have previously been shown to be highly correlated in some, but not all studies (Ebner-Priemer & Trull, 2009), and do show complementary results in this study.

4.5.8 Conclusions and future directions

The current study utilises ambulatory assessment to characterise the intensity and instability in emotions experienced by individuals with ADHD over the period of a working

week. Real-life assessment of emotions shows complementary findings to clinical observations of EL and studies of self-reported EL in adult patients with ADHD, in particular in relation to negative emotion domains (increased intensity of irritability, anger, frustration and increased instability in irritability and frustration). However, no clear group differences were found for positive emotion domains (*happy*, *excited*). Importantly, significant differences in intensity and instability could not be accounted for by the frequency or impact of adverse events reported by participants with ADHD. Moderate levels of compliance and the trending differences for intensity and instability of happiness obtained for this study suggest that results require replication in larger samples.

Promising avenues for future research include the investigation of the nature of good and bad events and their relationship to change in emotion and emotional instability, using data collection procedures more closely tailored to capturing such events. Most importantly, ambulatory assessment could allow the direct comparison of emotional intensity and instability across diagnostic categories, and could clarify contentious areas of psychiatric overlap, such as that seen between ADHD, bipolar disorder and the emotional instability that characterises many patients diagnosed with a personality disorder.

Chapter Five: An electro-encephalographic investigation of arousal, attentional orienting and preparation, and inhibitory functions: exploring links with emotional lability in adults with ADHD

5.1 Summary

Chapters 3 and 4 described enhanced emotional lability (EL) in a sample of untreated, non-comorbid men with ADHD compared to a matched group of healthy control participants. The current study investigates the role of cognitive function in EL within these participants, first by examining cognitive function on a variety of tasks, and then by taking results which significantly differentiated ADHD and control subjects forward to investigate the relationship with EL. The present study focuses on some 'common culprits' of cognitive dysfunction in ADHD, including measures of response variability, inhibition, attentional orienting and preparation, and arousal. Cognitive function was assessed with task performance measures and electroencephalographic measures (EEG and ERP), acquired during a resting condition and two tasks: the cued Continuous Performance Task (CPT-OX) and the Sustained Attention to Response Task (SART). ADHD subjects showed elevated within-subject variability in reaction time (SD-RT) and commission errors on the SART, and enhanced omission errors on both tasks. The CPT-OX, targeting the assessment of covert ERP indices of attentional orienting and preparatory processing, yielded no significant group differences. An inhibitory processing deficit in participants with ADHD was seen in the SART, indexed by an increased latency of the P3 on trials where a pre-potent response was withheld. Traditional indices of cortical arousal (e.g. theta-beta ratios) yielded no significant group differences during task or resting conditions. However, control subjects showed an adaptive increase in theta and beta power from rest to task conditions, which was absent in subjects with ADHD. Regression analysis revealed that EL characterised by swift changes in emotion was most strongly associated with SD-RT, whilst EL characterised by negative emotions such as frustration, nervousness and anger was associated with indices of inhibitory function, including commission errors and the latency of the inhibitory P3 on the SART.

5.2 Introduction

Although a wealth of research now documents cognitive deficits in Attention Deficit Hyperactivity Disorder (ADHD), a clear neuropsychological model for the disorder remains elusive. ADHD is associated with widespread cognitive impairments (Hervey, et al., 2004; Willcutt, et al., 2005), with research indicating the presence of a variety of deficits, which

show separable familial transmission and differential association with longitudinal clinical outcome (Halperin, et al., 2008; Kuntsi, et al., 2010; Sonuga-Barke, et al., 2010). As a result, contemporary neuropsychological models of ADHD frequently include multiple causal pathways, mediated by diverse constellations of cognitive dysfunction (Sonuga-Barke, 2010). A number of these implicated cognitive processes may also contribute to features of emotional lability (EL: irritable mood with volatile and changeable emotions), which often accompany ADHD (Asherson, 2005).

5.2.1 A role for executive function in EL?

An influential hypothesis posited by Barkley (1997, 2010) proposes a key inhibitory deficit underpinning both ADHD and EL, which renders individuals with ADHD unable to stop elicited emotional responses. Recent elaborations of this hypothesis detail a second stage of emotional dysfunction in ADHD, described as deficient emotional self-regulation. This deficit is proposed to involve the subsequent effortful regulation or moderation of emotions to be more socially appropriate and consistent with long-term goals. This framework therefore proposes that EL in ADHD is related to deficits in executive function.

Executive function (EF) is a broad term used to describe a diverse set of processes that maintain an appropriate problem solving set and facilitate purposeful, goal directed activity. These processes include cognitive processes such as inhibition, shifting or maintaining attention, planning, initiating tasks, detecting and correcting errors, and working memory (Sonuga-Barke, 2003; Willcutt, et al., 2005). It has been proposed that a set of general self-regulatory functions may underlie the regulation of cognition, behaviour and emotion (Berger, et al., 2007; Hoeksma, et al., 2004); and that executive functions can be understood as a domain-general construct, recruited by many cognitive processes, including the self-regulation of emotion in the service of goal directed behaviour (Zelazo, et al., 2007).

Research in ADHD populations has shown some support for the association of EF deficits with EL. Stop Signal Reaction Time (SSRT) on the Stop Task (i.e., the time required to successfully inhibit a motor response) was found to predict observational ratings of frustration in a group of boys with and without ADHD (R^2=.11; Walcott & Landau, 2004). Another study showed that children with ADHD with higher self-reported EL performed worse on timed tasks of EF, including a measure of inhibition (Graziano, et al., 2012). Self-

reported EL was also associated with attentional function as shown by a reduction in passive auditory P3 potentials in adolescents with ADHD and comorbid conduct disorder in an electrophysiological study using event related potentials (ERPs; Du, et al., 2006). ERPs are small voltage fluctuations recorded on the scalp resulting from evoked brain activity, reflecting the average neural activation to a repeated event such as the presentation of a stimulus (Albrecht, et al., 2005; McLoughlin, et al., 2005).

5.2.2 Influence of a more primary deficit in ADHD and EL?

Not all individuals with ADHD display deficits in executive function (Nigg, et al., 2005; Saboya, et al., 2009; Sonuga-Barke, et al., 2010; Willcutt, et al., 2005; Woods, et al., 2002). Moreover research has shown behavioural measures of EF are frequently cognitively complex. For example, SSRT, often utilised to index inhibitory function, may also be modulated by general attentional or state regulation deficits (Banaschewski, et al., 2004; Hervey, et al., 2004; Lijffijt, et al., 2005). An ERP study of the SSRT suggested that deficits in attentional switching may precede inhibitory control problems in adults with ADHD (Bekker, et al., 2005). Similarly, in ERP investigations of a cued Continuous Performance Test (CPT-OX), inhibitory processing abnormalities in children and adults with ADHD were preceded by impairments in covert attentional orienting and preparation (Banaschewski, et al., 2004; Doehnert, et al., 2010; McLoughlin, et al., 2010; van Leeuwen, et al., 1998).

Research using neuroimaging and electro-encephalographic measures in ADHD has shown general impairments in emotional processing which may precede deficits in EF. In an ERP study of children and adolescents with ADHD, Williams et al. (2008) showed that self-ratings of EL were moderately correlated with P120 and N170 amplitudes in response to emotional face stimuli, thought to reflect early automatic and early facial processing, respectively. Similarly, Herrmann and colleagues (2009), identified a general deficit in early emotional stimuli processing (indexed by the Early Posterior Negativity) in adults with ADHD. Posner and colleagues (2011) compared functional Magnetic Resonance Imaging (fMRI) brain activation on a tasks engaging cognitive control (cognitive Stroop task) and emotional processing (emotional Stroop task) in adolescents with ADHD, showing that dysfunctional emotional processing in ADHD was underpinned by neural alterations independent from those associated with impaired cognitive control, characterised by increased reactivity in

the medial prefrontal cortex during the emotional processing. The range of deficits uncovered suggest that more general impairments may underlie EL and emotional processing deficits in ADHD.

One prominent hypothesis of the pathophysiology of ADHD argues for an important role of sub-optimal arousal and a failure to optimise energetic state (Andreou, et al., 2007; Kuntsi, et al., 2010; Russell, et al., 2006; Sergeant, 2005; Todd & Botteron, 2001). Research has shown that individuals with ADHD are dependably inconsistent, with cognitive deficits having a "now you see it, now you don't" quality (Kuntsi, et al., 2009), indicative of dynamic impairments rather than stable cognitive deficits. Moment-to-moment variability has been described as the one ubiquitous finding in ADHD (Castellanos & Tannock, 2002), with heightened variability in reaction times frequently reported in reaction-time tasks (Boonstra, Oosterlaan, et al., 2005; Hervey, et al., 2004; Klein, et al., 2006; Kuntsi, McLoughlin, & Asherson, 2006; Lijffijt, et al., 2005). Quantitative EEG methods (in which electrophysiological recordings are quantified in frequency ranges believed to be pertinent to certain functional processes or states), provide data in support of the state regulation hypothesis, revealing reduced power in fast wave cortical activity (mainly beta) and elevated power in slow frequency bands (predominantly theta) in children with ADHD during resting conditions (Barry et al., 2003; Snyder & Hall, 2006); frequently interpreted as a marker of cortical under-arousal. However, not all studies support this finding, and results in adults are more ambiguous (van Dongen-Boomsma, et al., 2010).

It has been widely argued that arousal is a core component of emotions (Bradley & Lang, 1994; Lang, 1995; Russell, 2003). Strong emotions (e.g. intense anxiety, excitement, fear and anger) are associated with increased physiological arousal levels, evidenced by increased heart rate, skin conductance and changes in pupil dilation (Bradley, et al., 2008; Cuthbert, et al., 2000; Lane, et al., 1999). Emotions and arousal have also been linked in self-report. High correlations of self-ratings of arousal with measures of emotion were reported in school-age children (Shea & Fisher, 1996), with high arousal associated with more positive emotional ratings and low arousal and more variable arousal with more variable emotions. In addition, the same study reported that variability of arousal and emotion were correlated with teacher ratings of hyperactivity in girls, and ratings of impulsivity in boys.

However, the relationship between EEG indices of cortical arousal and physiological arousal or autonomic activity is not straight-forward. Most research to date investigating the relationship between these processes has contrasted measures from skin conductance with EEG measures with mixed results. Some previous studies do not show a relationship between traditional measures of cortical arousal (theta power and theta-beta ratios) and skin conductance level in children and adults with ADHD (Barry, Clarke, Johnstone, McCarthy, & Selikowitz, 2009; Barry, et al., 2004; Hermens, et al., 2004). By contrast, other studies have reported moderate correlations between theta power and frequency of non-specific skin conductance responses (Lazzaro, et al., 1999), and a correlated treatment-related change in theta power with skin conductance response amplitude in adolescents with ADHD (Hermens, Williams, et al., 2005).

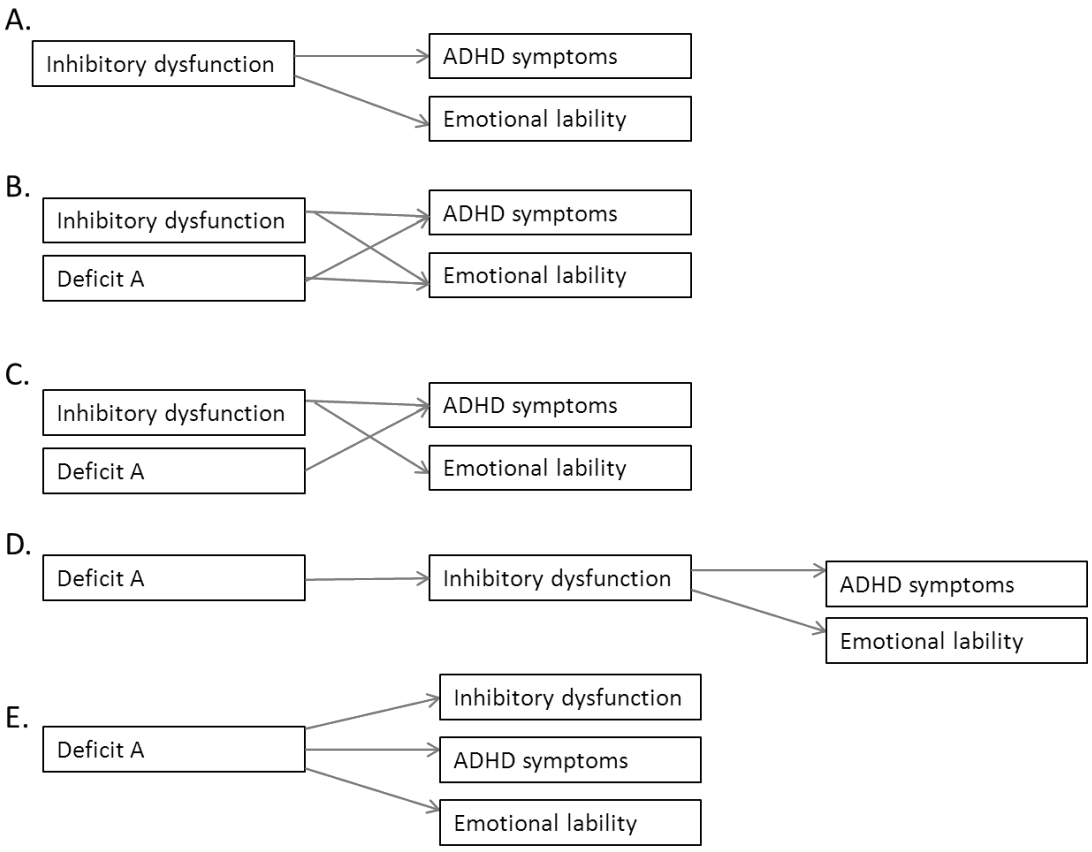
5.2.3 Investigating the influence of cognitive deficits in EL

Although there are many putative relationships between cognitive deficits, ADHD and EL, there has been limited research in this field. Many studies have examined such deficits from a single theoretical perspective, without systematically contrasting the contribution of different cognitive functions which have been found to be impaired in ADHD. By investigating cognitive and neurophysiological commonalities between EL and ADHD, this chapter aims to identify aetiological factors which may underpin both EL and ADHD. Specifically, it aims to test the hypothesis put forward by Barkley (1997, 2010), which postulates an inhibitory deficit underlying ADHD and EL. This hypothesis would suggest a primary deficit in inhibitory function being associated with greater EL. However, as previously outlined, recent work suggests that inhibitory deficits may well be secondary to arousal, preparatory or attentional deficits in ADHD, which have also been linked to EL in previous research. This chapter therefore aims to investigate the association of inhibitory deficits in ADHD alongside the influence of cognitive markers of these potentially more primary deficits.

As shown in Figure 15, below, there are many putative cognitive pathways which may culminate in the association between ADHD and EL. The potential pathways outlined in this figure are not exhaustive, but serve to present a number of viable options for the cognitive basis of ADHD and co-occurring EL. Pathway A outlines the basic premise of the hypothesis

by Barkley (1997, 2010), whereby inhibitory dysfunctions lead to ADHD symptoms and EL. In Pathway B, both inhibitory dysfunctions and an additional deficit (Deficit A), both contributed independently to ADHD symptoms and EL. An alternate option is presented in pathway C, whereby an inhibitory dysfunction contributes to ADHD symptoms and EL, and an additional deficit (Deficit A) is associated with ADHD symptoms but not EL. In pathways C and D, a more primary deficit (Deficit A) gives rise to inhibitory dysfunctions, ADHD symptoms and EL. Although the methods in the current study are not suited to identifying whether an inhibitory dysfunction does or does not mediate the effects of an additional deficit, and thereby cannot differentiate between pathways B, D and E, the study aims to identify whether EL is more strongly associated or correlated with cognitive deficits which have been robustly identified as associated with ADHD in the literature and whose influences may cascade upwards to impact on higher order cognitive functions, ADHD symptoms and EL.

Figure 15: Some potential pathways between inhibitory function, a second deficit (Deficit A) and symptoms of ADHD and EL.



5.2.4 Selection of tasks and electrophysiological indices

The current study adopts a number of EEG and ERP tasks and paradigms which are sensitive to impairments in ADHD, in indices of arousal, attentional orienting and preparation and inhibitory functions. These electrophysiological methods have the potential to isolate different interrelated cognitive processes that cannot be separated by task performance alone, as well as identifying covert functional abnormalities in the absence of task performance deficits (Banaschewski & Brandeis, 2007).

Specifically, two tasks of inhibitory function were selected (the continuous performance test with flankers – CPT-OX, and the Sustained Attention to Response Task – SART), which provided some similar electrophysiological indices, but differ in the response strategies required, and allow for the investigation of some different processes. Of specific interest in these tasks are electrophysiological measures during inhibitory trials. Both tasks produce a negative electrophysiological component at fronto-central sites between 150 and 300 ms after the inhibitory stimulus (the no-go-N2) and a later positive component between 200 and 600 ms at central sites (the no-go-P3). Both components have been linked to inhibitory mechanisms, with the earlier component potentially reflecting an early frontal inhibitory mechanism and the later component reflecting the reset or closure of the inhibition process (Falkenstein & Hohsbein, 1999).

The CPT-OX was selected with the aim to investigate the primacy of inhibitory dysfunctions in ADHD and EL. This task provides additional ERP components worthy of study in the context of potential early deficits. A recent study replicating a body of research in children, found that inhibitory deficits in adults with ADHD were preceded by deficits in attentional orienting as indexed by a decreased amplitude of the P3 component to cue stimuli, and a reduced contingent negative variation component (CNV), indicative of abnormal preparation and anticipation (McLoughlin et al., 2010). Moreover, there was a significant correlation between the cue P3 component and the inhibitory no-go-P3 component, suggestive of an association between the reduced allocation of resources to the cue stimulus and a reduced strength in inhibitory processing (McLoughlin et al., 2010).

Since it has been noted that the inhibitory load of the CPT-OX is low in comparison with other go/no-go tasks (Doehnert et al., 2010), the SART was selected to provide a clearer

measure of inhibitory processing and provide behavioural indices of inhibitory failures, which are rare in the context of the CPT-OX. If EL was primarily associated with inhibitory function deficits, it may therefore be expected that EL would correlate with electrophysiological (no-go-N2 and no-go-P3) and behavioural measures of inhibitory function. However, if EL was associated with more primary measures of resource allocation and attentional orienting, it would be expected that EL would correlated also with these measures (the cue P3 and CNV on the CPT-OX).

Quantitative EEG activity, specifically theta and beta activity, were investigated in the context of resting and task conditions, in order to examine the role of arousal in EL. As previously discussed, reduced power in beta activity and elevated power in theta has been frequently noted in children with ADHD during resting conditions, and has been replicated in some studies of adults. The pattern of enhanced theta and reduced beta power during resting conditions has frequently been interpreted as a marker of cortical underarousal, in line with work showing theta band activity to be dominant during rest, and shifting to beta band activity during task activity in healthy individual (reviewed in Barry et al., 2004). However, recent research suggests also the importance of both theta and beta activity for task performance. During task activity, theta band oscillatory dynamics in medial frontal sites have been linked to action and error monitoring, evaluation of feedback, and prediction of errors (Cavanagh, Frank, Klein, & Allen, 2010; Cohen, 2011; Cohen & Cavanagh, 2011; Luu, Tucker, & Makeig, 2004). Beta activity has been associated with successful inhibitory responding (Swann, et al., 2009). In the context of the aims of this chapter, and research linking EL to arousal, theta and beta activity were primarily investigated with an aim to investigating potential links between EL and cortical arousal.

5.2.5 Aims of the study

The present study contrasts cognitive function in a healthy control group, and a sample of adults with ADHD with high levels of EL. EEG and ERP measures are investigated during a resting condition and two ERP tasks: the CPT-OX and the SART. This study aims to replicate previously identified markers of cognitive function deficits in ADHD, such as: 1) deficits in task performance measures including more variable reaction times, increased rates of omission and commission errors; 2) quantitative EEG markers indicative of under-arousal:

abnormalities in theta, beta and theta-beta ratios during resting condition; 3) deficits in inhibitory ERPs (both the inhibition of a prepared but not yet initiated response on the CPT-OX, and the inhibition of a continuous pre-potent response on the SART), and 4) deficient covert attentional orienting and preparation as assessed with ERPs to cue stimuli in the CPT-OX (Cue P3 and contingent negative variation; CNV). By then investigating the relationship between cognitive and neurophysiological measures which differentiate between ADHD subjects and controls and two validated rating scale measures of EL, this study aims to identify cognitive deficits which may contribute to features of EL in adults with ADHD.

5.3 Methods

5.3.1 Participants

Participants included 41 adult males with ADHD and 47 healthy adult male control participants. Details on participant recruitment and clinical diagnostic procedure are given in Chapter 2, and subject demographics and statistics on group matching for the entire group are reported in Chapter 3, showing that participants did not differ for any demographic measures (IQ, age or educational level). All subjects were asked to refrain from consuming alcoholic or caffeinated beverages or smoking the day of the study session, and from consuming alcohol during the preceding evening.

5.3.2 Measures

The Barkley Adult ADHD rating scale (BRS; Barkley, 1998), the Affective Lability Scale–Short form (ALS-SF; Oliver & Simons, 2004), and the Centre for Neurologic Study–Lability Scale (CNS-LS; Moore, et al., 1997), were administered as detailed in Chapter 2 (section 2.5.1). In line with previous analysis in Chapters 3 and 4, two items relating to impatience were dropped from the CNS-LS due to overlap with impulsivity in ADHD. The Wechsler Abbreviated Scale of Intelligence (Psychological Corporation, 1999) was used to measure IQ.

5.3.3 EEG recording and tasks

EEG was recorded using a 62 channel direct-current-coupled recording system (extended 10-20 montage), with electrode impedances below 10 kΩ. The reference electrode was positioned at FCz. Vertical and horizontal electro-oculograms were simultaneously recorded

above and below the left eye and at the outer canthus of each eye. The signal was digitized at a sampling rate of 500Hz and stored for offline analysis.

Participants were seated on a height adjustable chair in a dimly lit video monitored testing cubicle. Stimuli were presented on a computer monitor at a distance of approximately 120cm, using the Presentation software package (www.neurobs.com). All participants completed a 3-minute fixed gaze eyes open resting condition, followed by the CPT-OX and the SART, in fixed order, as part of a larger test battery. Responses to tasks were made with a mouse button press with the right index finger.

Cued Continuous Performance Test with flankers (CPT-OX; Doehnert, et al., 2008; McLoughlin, et al., 2010)**:** The task consisted of 400 black letters, Including cue letter 'O', target letter 'X' and distractors 'H', 'B', 'C', 'D', 'E', 'F', 'G', 'J' and 'L'. Letters were presented centrally on the computer monitor, subtending approximately 0.5 degrees. All letters were flanked on either side by the letters 'X' or 'O', and cue and target letters (O and X) were flanked by the incompatible letter (X and O). Participants were instructed to ignore the flanking letters and respond as quickly as possible to cue-target sequences (O-X). 80 cues (O) were followed by the target letter (X) in 40 trials (go condition), and neutral distractors in the remainder of trials (no-go condition). In 40 trials, a letter X was not preceded by a cue O and had to be ignored. Letters were presented every 1.65 seconds for 150ms in a pseudo-random sequence. Ten practice trials preceded the main task blocks and were repeated, if required, to ensure participant comprehension. Task duration was 11 minutes.

Sustained Attention to Response Test (SART): The task was identical to the $SART_{random}$ previously reported by O'Connell and colleagues (2009). The task consisted of nine digits (1 through 9) presented in random order. Participants were instructed to withhold responses to the digit 3 (no-go trial) but to respond with a button press after all other digits (go trial). Subjects were instructed to time their response to the offset of each stimulus, which has been shown to reduce inter-individual variability and speed–accuracy tradeoffs (Manly, Davison, Heutink, Galloway, & Robertson, 2000; Stuss, Murphy, Binns, & Alexander, 2003). Participants completed the SART over three blocks, each with a duration of approximately 5 minutes. Individual blocks consisted of 225 digits, with each digit presented 25 times. Stimuli were presented in five digit sizes (font size 100, 120, 140, 160 and 180 in Arial text),

subtending approximately 1.7°, 2.1°, 2.4°, 2.7°, respectively in the vertical plane. Digits were presented 0.31° above a central white fixation cross on a grey background. Digits were presented for 150ms followed by an inter-stimulus interval of 1000msec.

5.3.4. Scoring performance measures

Reaction time measures were calculated across tasks with correct responses only, including mean reaction time on response trials (MRT, i.e. mean latency of responding in ms after onset of stimulus requiring response), within-subject variability in reaction time (SD-RT, i.e. within-subject standard deviation of reaction time), the coefficient of reaction time variability (CV, i.e. SD-RT/MRT). CV was calculated since previous work has shown high phenotypic correlations between SD-RT and MRT, and since previous work has shown SD-RT and MRT to load onto a single familial factor (Andreou, et al., 2007; Kuntsi, et al., 2010). CV provides an estimate of variability in reaction time that controls for individual MRT score. For the CPT-OX errors were broken down into commission errors (response to non-targets) and omission errors (non-response to targets). Similar measures were derived for the SART, with commission errors (erroneous response to the number 3), and omission errors (non-response on target trials). Two ADHD participants were excluded from analysis of the CPT-OX (including quantitative EEG and ERP analysis) due to extreme commission (N=43) or omission errors (N=31), indicative of insufficient task engagement (Tye, Rijsdijk, et al., 2012).

5.3.5 EEG data pre-processing

Analyses were carried out in Brain Vision Analyzer 2.0 (Brain Products, Munich, Germany). EEG signal was re-referenced offline to the average signal and downsampled to 256Hz. Data were filtered by applying 0.1 to 30 Hz (24dB/oct) Butterworth filters. Ocular artifacts were removed from the data using biased infomax Independent Component Analysis (ICA, Jung, et al., 2000). Independent components were manually inspected, and all components with the exception of those which contained the ocular signal were back-projected for further analysis. All trials were inspected visually to detect additional subtle artifacts, and remaining artifacts in any channel were removed from the data. Trials with remaining artifacts exceeding 200µV peak-to-peak in any channel were rejected.

Quantitative EEG was investigated for the three conditions (resting, CPT-OX and SART). Data were segmented into 2-second epochs and power spectra were computed using a Fast Fourier Transform with a 10% Hanning window. To reduce the number of statistical comparisons, these analyses focused only on the frequency bands that have been most frequently associated with arousal: namely theta (4-7.5Hz) and beta (12.5-30Hz). EEG power density ($\mu V^2/Hz$) within these frequencies was averaged across frontal (Fz, F1, F2, F3, F4, F5, F6, F7, F8), central (Cz, C1, C2, C3, C4, C5, C6), parietal (Pz, P3, P4, P7, P8) scalp electrode sites. Theta-beta ratios were calculated by dividing theta power by beta power at each site. Change in quantitative EEG between conditions was calculated by subtracting EEG power from rest and CPT from the SART (e.g. change in frontal beta from rest to SART= SART frontal beta- resting frontal beta).

CPT-OX: ERPs were determined on the basis of correct responses and correctly rejected trials, and computed separately for each participant in three conditions: (1) go trials (target Xs preceded by O) (2) no-go trials (non-target letters following O), (3) cue trials (letter O). Stimulus-locked data were segmented into epochs of 100 msec before to 1800ms after stimulus onset, and baseline corrected relative to the interval -100 to 0 ms. A minimum of 20 artifact-free trials were required per ERP per individual (mean accepted sweeps are shown in table 13). In addition to the two individuals excluded due to extreme errors, three further individuals with ADHD and three control participants were excluded due to excessive movement and data artifact.

The identification of peak ERP amplitudes were restricted to leads and time windows for which the effects were expected to be largest, based on previous research (Banaschewski, et al., 2004; McLoughlin, et al., 2010), and verified against the grand mean of each ERP component across both groups. Data from the largest peaks were extracted from the following latency windows and electrodes: The go-$P3_{CPT}$ at Pz between 200 and 500 ms; the go-$N2_{CPT}$ at Fz between 150-300 ms; no-go-$P3_{CPT}$ at Cz between 200 and 500 ms; no-go-$N2_{CPT}$ at Fz between 150 and 300 ms; the cue-$P3_{CPT}$ at Pz between 200 and 500 ms; The contingent negative variation (CNV) to the cue was the area under the curve at Cz between 1300 and 1650 ms. Maps of the topographical scalp distribution of electrical brain activity were spline interpolated between the electrode locations.

SART: ERPs were determined on the basis of correct responses, and computed separately for each participant in two conditions: (1) go trials (all numbers with the exception of 3 followed by a button press) (2) no-go trials followed by a correct withhold of response. Error trials were not analysed due to insufficient data. Data were segmented into epochs of 100 msec before to 1000ms after stimulus onset, and baseline corrected relative to the interval -100 to 0 ms. A minimum of 20 artifact-free and correct trials were required per component per individual. Two ADHD participants were excluded due to excessive movement and data artifact. The number of accepted sweeps is presented in table 13 below.

Based on previous work using this task (Zordan, Sarlo, & Stablum, 2008), and centered on the peak latency of the grand average waveform, analyses were restricted to midline electrodes, and ERP peak components were identified as the largest peak within the following time windows: 220-350ms (N2 range), 300-500ms (go-P3 range) and 300-600ms (no-go-P3 range). Peak amplitudes and latencies from components at electrodes with maximal amplitudes (across both groups) were taken forward for analysis: go-$P3_{SART}$ at CPz, go-$N2_{SART}$ at Fpz, no-go-$P3_{SART}$ at Cz and no-go-$N2_{SART}$ at FCz. Poor data from electrodes CPz in two individuals (1 ADHD, 1 control), and FPz in 6 individuals (1 ADHD, 5 controls), due to electrode saturation or excessive noise, resulted in the exclusion of the affected components from analysis for these individuals. Maps of the topographical scalp distribution of electrical brain activity were spline interpolated between the electrode locations.

Table 13: Mean (SD) trials per stimulus for each participant for CPT-OX and SART

			Mean number of trials contributing to ERP per participant		
		Number of participants	Cue	Go	No-go
CPT-OX	Controls	44	67.73 (6.2)	36.07 (4.0)	29.57 (2.8)
	ADHD	36	67.36 (5.6)	35.53 (4.4)	28.89 (3.2)
SART	Controls	47		498.85 (59.1)	51.21 (9.7)
	ADHD	39		476.38 (56.7)	43.36 (2.3)

5.3.6 Statistical analysis

Mean values for each rating scale were used as summary measures. Deviations from normality of all data were tested using the Shapiro-Wilk test. Data transformations were performed where possible, and analyses were carried out using parametric and non-parametric tests, as appropriate. Case-control comparisons, including analysis of ERP and EEG variables were carried out using independent samples t-tests, and Mann-Whitney U tests, unless specified otherwise. Significance level for all comparisons was held at .05 (two tailed). Bonferroni corrected statistics are presented alongside uncorrected p-values.

Theta-beta ratios (natural logarithm transformed), and theta power (inverse transformed), were each investigated with a 2x3x3 repeated measures analysis, including within (recording site and condition: rest vs. CPT-OX vs. SART) and between subjects contrasts. Diagnostic tests included checking for equality of error variances (Levene's test) and sphericity (Mauchly's test). Greenhouse-Geisser corrections were employed in analyses with significant departures from sphericity, and adjusted degrees of freedom were rounded to the nearest whole number. For comparisons of beta power, data could not be successfully transformed, and a series of Friedman's tests of within-subject change in beta activity were performed, with post-hoc Wilcoxon Signed Ranks test to identify significant effects.

Where significant case-control group differences in cognitive or electrophysiological measures were identified, these were correlated with self-reported EL as measured by the ALS-SF, using Spearman's or Pearson's correlations, as appropriate. First correlations with with age at assessment were carried out for all these variables to investigate the potentially confounding effect of age. Where age was significantly correlated with the variables of interest, correlations between measures of EL and cognitive and electrophysiological measures were performed after partialling out the effects of age using partial correlations. Correlational analyses were carried out across both groups, and repeated for the case and control groups separately to identify any differences in the relationship between variables, which may have been associated with clinical status.

Since data for both EL scales across both groups were highly skewed, scores were normalized using a van der Waerden transformation, whereby data were ranked and transformed into quantiles of a standard normal distribution (Lehman, 1975; van der

Waerden, 1952) in the statistical package R. This transformation has also previously been used in similar types of research (e.g., Rommelse, Altink, Martin, et al., 2008; Rommelse, Altink, Oosterlaan, et al., 2008). EL measures were then subjected to a multiple linear regression analysis, with measures significantly correlating with the ALS-SF and the CNS-LS across both groups included as predictors. Due to differences in the correlational relationship between variables in ADHD and control groups, additional multiple linear regression analysis was carried out with clinical status as one of the predictor variables, to identify whether cognitive measures predicted EL beyond the influence of diagnostic status.

Finally correlational analysis was carried out to investigate the relationship between task performance measures and neurophysiological indices. Significant findings or findings of interest are reported in the text, and a full correlational table can be seen in Appendix 4. Again, where age was significantly correlated with the variables of interest, correlations were performed after partialling out the effects of age using partial correlations.

5.4 Results

5.4.1 Participant characteristics

Participants were 18-65 years of age with no significant difference between groups in age, IQ and years spent in education. Subject demographics and statistics on group matching are reported in Chapter 3.

5.4.2 Task performance (table 14)

Task performance results show no differences for MRT on either task. Significant differences in SD-RT, CV and omission and commission errors were seen between ADHD and control subjects during the SART. Significantly increased omission errors were also seen for the CPT.

Table 14: Means (SDs) of task performance data on the CPT-OX and the SART and statistics for group differences.

	Control	ADHD	Statistic and p value
MRT *for correct responses (ms)*			
CPT-OX	428.75 (68.1)	442.05 (77.2)	t=-0.74, p=.46
SART	377.74 (66.1)	380.50 (64.7)	t=-0.20, p=.85
SD-RT *for correct responses (ms)*			
CPT-OX	91.53 (45.7)	101.23 (47.5)	t=-0.83, p=41
SART	102.51 (33.6)	125.3 (43.8)	t=-2.57, p=.01
CV			
CPT-OX	0.21 (0.09)	0.22 (0.09)	z=-0.99, p=.32
SART	0.27 (0.07)	0.34 (0.12)	z=-3.20, p=.005†
Commission Errors			
CPT-OX	2.36 (4.0)	2.47 (4.2)	z=-0.55, p=.59
SART	16.09 (8.2)	24.64 (15.0)	t=-3.37†, p=.002
Omission Errors			
CPT-OX	0.91 (2.0)	1.67 (2.5)	Z=-2.24, p=.03
SART	4.94 (7.0)	15.41 (18.3)	z=-3.11†, p=.002

Note: MRT: mean reaction time in milliseconds; SD-RT: within-subject variability in RT in milliseconds; CV: Coefficient of variation (SD-RT/MRT). † differences robust to Bonferroni correction (adjusted p=.005)

5.4.3 Quantitative electro-encephalography

Theta-beta ratios analysed with repeated measures ANOVA (within-subjects factors: location and condition), compared between the two groups. No main effects of group or group interactions with condition or recording site were seen.

Theta power was subjected to repeated measures ANOVA (within subjects factors: location and condition). No significant main effect of participant group was identified ($F(1,77)=0.12$, $p=.74$). However, analyses revealed a significant effect of condition ($F(2,121)=25.81$, $p<.001$), with differences in theta power between all conditions reaching significance, showing an increment in power from resting to CPT-OX to SART. A group-by-condition interaction was seen ($F(2,121)=7.55$, $p=.002$), shown in fig. 16, driven by a marginally non-significant greater increase in the control group in theta during the CPT-OX than resting

(p=.051, also shown in table 15) and higher theta during the SART than during resting (p=.002). Analyses also identified a significant effect of recording site, showing significantly lower theta power in central than frontal and parietal locations (F(2,154)=129.58, p<.001), theta power in frontal and parietal locations did not differ (p=.63). Condition-by-site interaction effects fell just short of significance (F(3,215)=2.33, p=.08. However a condition-by-site-by-group interaction was significant (F(3,215)=3.72, p=.02, with the interaction effect being driven by differences between the SART and resting between frontal and central electrode sites (p=.03), due to a greater increase in theta from resting to SART conditions being present on the frontal (as compared to central) site in controls.

Beta power was non-normally distributed and could not be normalized by any transformation. Cross-sectional analyses revealed no group differences for any condition (minimum p=.26). Analysis of change in beta power from resting to task conditions was investigated separately in ADHD and control groups using a series of Friedman's repeated measures tests, which revealed significant increase in frontal ($\chi2$=8.59, p=.01) and parietal beta ($\chi2$=8.59, p<.001) in controls only. Post-hoc tests revealed that significant increase in control subjects for frontal beta was seen between rest and SART conditions only (p=.03), and for parietal beta increase was seen only between rest and SART (p=.02) and CPT-OX and SART (p<.001). No significant differences were seen for central beta ($\chi2$=4.55, p=.10), nor any tests in adults with ADHD (p range=.14-.71). Condition-related change in parietal beta in control subjects were robust to Bonferroni correction (adjusted alpha level=.017).

Figure 16: Frontal theta and beta power across the three tasks.

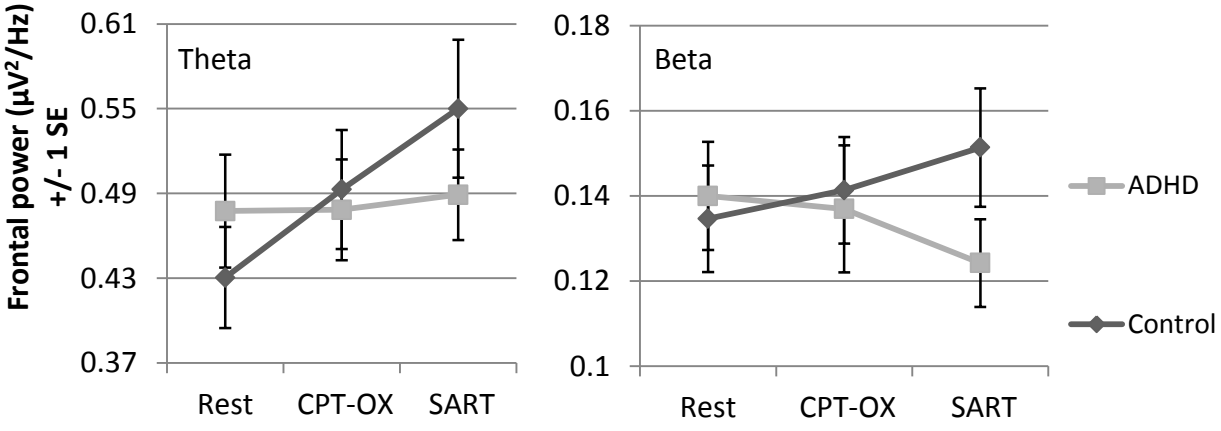


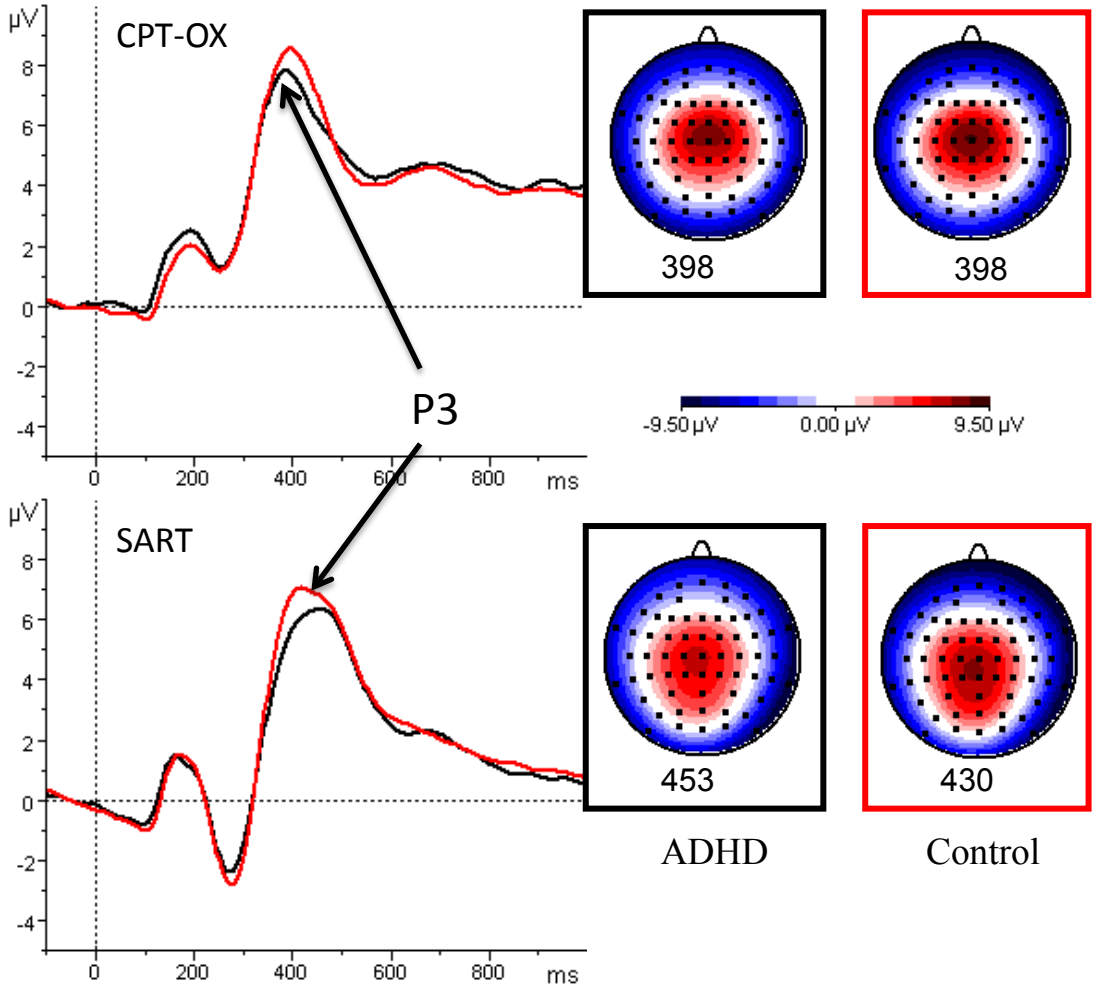
Table 15: Mean (SD), theta and beta power density (μV2/Hz) across groups and tasks (raw, untransformed data)

			Control	ADHD
Theta	**Resting**	Frontal	0.43 (0.24)	0.47 (0.24)
		Central	0.28 (0.15)	0.31 (0.15)
		Parietal	0.42 (0.30)	0.46 (0.23)
	CPT-OX	Frontal	0.49 (0.28)	0.48 (0.21)
		Central	0.31 (0.16)	0.33 (0.16)
		Parietal	0.47 (0.31)	0.46 (0.21)
	SART	Frontal	0.55 (0.33)	0.48 (0.19)
		Central	0.35 (0.18)	0.34 (0.17)
		Parietal	0.55 (0.35)	0.49 (0.23)
Beta	**Resting**	Frontal	0.135 (0.08)	0.141 (0.08)
		Central	0.083 (0.06)	0.083 (0.07)
		Parietal	0.121 (0.08)	0.114 (0.06)
	CPT-OX	Frontal	0.141 (0.08)	0.139 (0.09)
		Central	0.089 (0.07)	0.084 (0.07)
		Parietal	0.118 (0.07)	0.110 (0.06)
	SART	Frontal	0.152 (0.09)	0.127 (0.07)
		Central	0.091 (0.07)	0.085 (0.06)
		Parietal	0.129 (0.08)	0.115 (0.06)

5.4.4 Event related potentials (ERPs)

Overall latencies and amplitudes of ERP components investigated in the CPT-OX and the SART are provided in table 16, alongside statistical tests for group comparisons. In the CPT-OX no significant group differences were seen for the latency or amplitude of any component. A trending group difference was seen for the CNV area at Cz ($t(78)=1.88$, $p=.06$), with a trend for larger CNV area under the curve being seen in ADHD participants (ADHD: 1305.33, Control: -1035.33). Similarly, no amplitude differences for any components investigated were seen on the SART. A single significant group difference was seen for the latency of the no-go-$P3_{SART}$ ($p=.03$, fig. 17; uncorrected for multiple comparisons).

Figure 17: P3 to the no-go stimulus at Cz during the CPT and SART



Note: Isocontour maps derived from the grand-average at the peak latency for each group (black=ADHD, red=Controls).

Table 16: CPT-OX and SART ERP components, mean amplitude and latency (SD), with simple group comparison statistics and p-values (uncorrected for multiple comparisons)

Note: simple group comparison statistics include independent samples t-tests and Mann-Whitney U comparisons. Figures for all components can be seen in Appendix 5.

		Amplitude			Latency		
Condition	**Electrode**	**Control**	**ADHD**	**Statistic P value**	**Control**	**ADHD**	**Statistic p value**
CPT-OX							
Cue	P3 (Pz)	5.19 (2.6)	4.26 (2.3)	t=1.69 p=.10	441.85 (56.3)	424.4 (87.5)	z=-0.14 p=.88
Go	P3 (Pz)	8.20 (3.8)	7.93 (3.2)	t=0.350 p=.73	401.10 (46.8)	411.57 (61.2)	z=-0.46 p=.65
	N2 (Fz)	-0.80 (2.1)	-0.50 (2.1)	t=-0.64 P=.53	240.15 (60.8)	240.45 (57.1)	z=-0.01 p=.99
No-go	P3 (Cz)	9.46 (4.7)	8.67 (4.6)	t=.76 p=.45	399.95 (36.6)	395.40 (40.8)	z=-0.79 p=.43
	N2 (Fz)	-2.69 (2.5)	-2.10 (1.9)	t=-1.14 P=.26	314.63 (70.2)	309.14 (69.59)	z=-0.45 p=.66
SART							
Go	P3 (Cpz)	2.89 (1.9)	2.31 (1.8)	z=-0.92 p=.36	397.58 (60.8)	394.36 (63.8)	z=-0.29 p=.77
	N2 (Fpz)	-2.42 (2.1)	-1.80 (1.8)	z=-1.22 P=.22	291.67 (42.9)	275.97 (40.6)	z=-1.63 p=.10
No-go	P3 (Cz)	8.22 (3.9)	7.29 (4.8)	t=0.98 p=.33	428.44 (49.6)	453.19 (52.0)	t=-2.25 p=.03
	N2 (FCz)	-4.04 (3.4)	-2.87 (3.4)	t=-1.59 p=.11	290.81 (28.2)	288.39 (27.1)	t=0.96 p=.69

5.4.5 Correlational and regression analysis with measures of EL

Taking forward significant case-control differences identified from cognitive tasks, a series of correlational analyses were carried out to investigate the relationship between these measures and self-reported EL across and within groups. First, however, correlations between these variables of interest and age at assessment were carried out to control for the potentially confounding effect of age. No significant correlations of age with measures of EL were seen, either across or within groups (maximum rho=.10, minimum p=.53). However, significant correlations with age at assessment were seen across both groups for change in frontal, central and parietal theta from rest to SART (rho range =-.25 to -.29, minimum p=.04). No other significant correlations with age were seen for the remaining cognitive variables across both groups. In analyses repeated within groups, only omission errors on the CPT-OX correlated significantly with age in the control group (rho=.37, p=.01), no significant correlations with age at assessment were seen for any other cognitive variables under investigation in the control sample (p range .07-.89). However, in the ADHD group, SART SD-RT (rho=-.36, p=.03), commission errors (rho=-.38, p=.12), omission errors (rho=-.43, p=.01), and CV (rho=-.41, p=.01) correlated with age. No other correlations with cognitive variables were significant.

Correlational analyses between measure of EL and cognitive variables were then carried out across both groups to allow comparison with earlier studies showing relationships between cognitive variables and EL which employed a similar methodology (e.g. Walcott and Landau, 2004; Du et al., 2006). However, there are some important statistical limitations to this approach, since potential bivariate distributions driven by group differences in many of the measures of interest are likely to inflate correlation coefficients. Correlations are therefore repeated within groups to provide a clearer indication of the pattern of results presented in each group. Correlations are shown in table 17, with sections demarcated by (**ρ**) indicative of where partial correlations were carried out to control for the effects of age. Significant correlations between cognitive performance measures and both EL rating scales included indices of reaction time variability (SD-RT and CV) on the SART, as well as omission errors on both the SART and CPT-OX. Significant correlations across both groups were also seen between EL and the no-go-$P3_{SART}$.

Table 17: Correlation coefficients (p-values) for association between EL (ALS-SF and CNS-LS) with cognitive measures which significantly differ between groups.

	Self-reported EL from ALS-SF			Self-reported EL from CNS-LS		
	Both groups	Control	ADHD	Both groups	Control	ADHD
Quantitative EEG						
Change in frontal theta from rest to SART	-.17 (**ρ**) (p=.12)	.13 (p=.39)	.01 (p=.95)	-.26(**ρ**) (p=.01)	.15 (p=.32)	-.09 (p=.60)
Change in central theta from rest to SART	-.07 (**ρ**) (p=.54)	.07 (p=.64)	.16 (p=.35)	-.18(**ρ**) (p=.09)	.16 (p=.27)	-.03 (p=.84)
Change in parietal theta from rest to SART	-.14(**ρ**) (p=.21)	.11 (p=.48)	.04 (p=.83)	-.23(**ρ**) (p=.03)	.17 (p=.24)	-.04 (p=.80)
Change in frontal beta from rest to SART	-.24 (p=.03)	-.19 (p=.20)	.12 (p= .46)	-.20 (p=.06)	-.10 (p=.50)	.13 (p=.43)
Change in parietal beta from rest to SART	-.16 (p=.14)	-.04 (p=.77)	-.20 (p=.22)	-.13 (p=.25)	-.05 (p=.73)	.01 (p=.96)
Change in parietal beta from CPT to SART	-.15 (p=.20)	-.06 (p=.68)	-.03 (p=.87)	-.10 (p=.40)	.18 (p=.23)	.06 (p=.73)
ERP						
No-Go-$P3_{SART}$ latency	.30 (p=.004)	.23 (p=.11)	.13 (p=.42)	.26 (p=.02)	.09 (p=.54)	.09 (p=.60)
Task performance						
SD-RT (SART)	.35 (p=.001)	.50† (p<.001)	.08 (**ρ**) (p=.63)	.30 (p=.005)	.30 (p=.04)	.06 (**ρ**) (p=.71)
CV (SART)	.28 (p=.02)	.36 (p=.01)	.03 (**ρ**) (p=.86)	.27 (p=.01)	.27 (p=.07)	-.07 (**ρ**) (p=.68)
Commission errors (SART)	.19 (p=.08)	.002 (p=.99)	-.03 (**ρ**) (p=.88)	.26 (p=.02)	.22 (p=.15)	-.14 (**ρ**) (p=.40)
Omission errors (SART)	.37† (p<.001)	.46 (p=.001)	-.03 (**ρ**) (p=.86)	.37† (p<.001)	.26 (p=.08)	-.09 (**ρ**) (.58)
Omission errors (CPT)	.26 (p=.02)	.60 (**ρ**) † (p<.001)	-.10 (p=.58)	.30 (p=.01)	.40 (**ρ**) (p=.01)	-.04 (p=.84)

†findings significant after Bonferroni correction for 72 comparisons (adjusted p=0.0007).
(**ρ**) results from partial correlations which control for the effects of age at assessment

Most of these associations were seen when the control group was analysed alone (either at significance threshold or at trend level), with the exception of the electrophysiological measures where the relationship between the no-go-$P3_{SART}$ and change in frontal beta did not replicate in either group individually. No relationship was seen between any cognitive task measures and self-reported EL in the ADHD group when analysed separately to the control group.

Cognitive measures which were significantly correlated across both groups with the ALS-SF and CNS-LS scores, respectively, were then taken forward for inclusion in two multiple linear regression analyses with stepwise entry, to determine the relative contributions of cognitive measures on these different measures of EL. For the ALS-SF predictor variables included SART SD-RT, CV and omission errors, CPT omission errors, no-go-$P3_{SART}$ latency and change in frontal beta from rest to SART; for the CNS-LS, predictor variables included SART SD-RT, CV, omission and commission errors, CPT omission errors, no-go-$P3_{SART}$ latency, change in frontal theta from rest to SART and change in parietal theta from rest to SART. For the ALS-SF only SD-RT emerged as a significant predictor ($F_{1,78}$=11.49 p<.001, R2=.135, ß=.36). For the CNS-LS, after the removal of one influential point with extreme leverage values, no-go-$P3_{SART}$ (ß=.29) and commission errors (ß=.24) predicted EL ($F_{1,77}$=6.50 p<.002, R2=.148)

Due to differences in the correlational relationship between variables in subjects with ADHD and controls, two additional multiple linear regression analyses with stepwise entry were carried out including clinical status (i.e. controlling for ADHD versus control status) alongside the above predictor variables for each self-report measure of EL, to identify whether any cognitive measures predicted EL beyond the influence of diagnostic status. In this model both clinical status (ß=.65) and SD-RT (ß=.18) emerged as significant predictors (F1,78=41.95, p<.001, R2=.525) for the ALS-SF. However, for the CNS-LS only group emerged as significant predictor (F1,77=80.84, p<.001, R2=.515, ß=.72).

5.4.6 Correlation of task performance and electro-encephalographic measures

Correlational analyses between task performance with neurophysiological measures are described below. Analyses are not corrected for multiple testing. However, full correlational tables, with statistics for Bonferroni correction are shown in Appendix 4.

Where significant correlations were previously seen between cognitive and electrophysiological variables and age, age was partialled out from correlation coefficients.

First analyses investigated the relationship between the no-go-$P3_{SART}$ and other electrophysiological and task performance indices which differed significantly between groups. In terms of theta and beta power transition between task conditions, the latency of the no-go-$P3_{SART}$ correlated only with change in parietal beta power from CPT-OX to the SART (rho=.30, p=.01) when correlated across both groups, moreover this effect was replicated in the ADHD group alone (rho=-.49, p=.003), but not in controls alone. Significant correlations were seen between the latency of the no-go-$P3_{SART}$ and some performance measures on the SART, namely SD-RT (rho=.33, p=.002) and omission errors (rho=.25, p=.02), and omission errors on the CPT (rho=.28, p=.01). In analysis of ADHD and control groups separately the relationship between SD-RT and no-go-$P3_{SART}$ latency in controls was significant (rho=.43, p=.003), as well as the relationship between omission errors on the CPT-OX and the no-go-$P3_{SART}$ (partial r=.37, p=.01). No other relationships between task performance and no-go-$P3_{SART}$ were significant.

When looking at EEG task transition effects which significantly differentiated ADHD subjects and controls, change in frontal theta and beta from rest to SART correlated with commission errors (partial r=-.24, p=.03 and rho=-.31, p=.003, respectively) across both groups. However this was not replicated in the control and ADHD groups individually. Parietal beta change from the CPT to the SART was negatively correlated with SD-RT (rho=-.29, p=.01) and with SART omission errors (rho=-.29, p=.01). In analysis of ADHD and control groups separately, the relationship with SD-RT was significant in the ADHD group (partial r=-.40, p=.02), and was non-significant in controls (p=.18); the relationship with omission errors was non-significant (minimum p=.14).

Higher correlation coefficients were seen in comparisons carried out within task performance domains, and within EEG task transition effects. For example, a high correlation between omission errors and SD-RT on the SART was seen (rho=.77 across both groups, and rho=0.62-0.82 within groups, all p<.001). A high moderate correlation was also seen between omission errors and commission errors on the SART across both groups

(rho=.43, p<.001), driven by a high correlation in adults with ADHD (partial r=0.47, p=.003), not present in controls (rho=-0.03, p=.85).

5.5 Discussion

The present study investigated cognitive performance and electrophysiological markers of ADHD in adulthood and their association with emotional lability (EL). A number of electrophysiological and behavioural performance deficits were seen in individuals with ADHD. ADHD participants showed more within-subject variability in reaction time (SD-RT), and made more frequent omission and commission errors on the SART. Furthermore, they showed reduced task-related increases in theta and beta power, and deficient processing of an inhibitory stimulus (no-go-$P3_{SART}$ Latency). Whilst many of these measures correlated with self-reported EL, regression analysis revealed that only SD-RT independently predicted EL as measured with the ALS-SF, and only no-go-$P3_{SART}$ latency and commission errors predicted EL as measured by the CNS-LS. SD-RT continued to predict EL as measured by the ALS-SF after including clinical status within the multiple linear regression model, while a similar adjustment in the regression model for the CNS-LS removed all effects of cognitive measures.

These findings add to a body of research highlighting the heterogeneity of EL. As noted in Chapter 3, the ALS-SF and the CNS-LS measure different facets of EL. The ALS-SF measures swift changes from normal (euthymic) mood to other emotional modalities, whilst the CNS-LS measures EL with a stronger focus on negative emotions. Here, these measures show a differential association with cognitive measures, with the CNS-LS showing a more primary association with inhibitory processing deficits and commission errors (frequently taken as an index of inhibitory failures), and the ALS-SF showing a greater association with within-subject variability in reaction time (SD-RT). Furthermore, the association between ALS-SF and SD-RT is to some extent independent of the association with ADHD, suggesting that SD-RT indexes both ADHD and non-ADHD related processes on EL, whereas the association between CNS-LS and the inhibitory processing deficits can be entirely explained by processes related to ADHD.

Overall the findings provide support for both the involvement of inhibitory processing deficits in negative emotional patterns, and for more general deficits impacting on variability in response patterns and changeability in emotions.

5.5.1 Task performance measures and emotional lability

Elevated within-subject variability in reaction time and increased omission and commission errors were seen in the ADHD group on the SART, in line with previous research in adolescents with ADHD on this particular task (Braet, et al., 2011), and with the broader ADHD literature (Boonstra, Oosterlaan, et al., 2005; Klein, et al., 2006). By contrast, with the exception of elevated omission errors in the ADHD group, a lack of a group performance differences were seen in the cued Continuous Performance Test (CPT-OX). This is perhaps not surprising, since a lack of omission and commission errors on this particular task was shown in previous work in adults with ADHD (McLoughlin, et al., 2010) as well as adolescents with high levels of ADHD symptoms (Tye, Rijsdijk, et al., 2012), where differences in reaction time measures were also not seen.

Although a number of task performance measures correlated significantly with self-reported EL, only SD-RT independently predicted EL on the ALS-SF. Kuntsi and Klein (2012) recently described a broad literature of increased within-subject variability in a number of domains in ADHD; including measurement of activity, attention and interference, motor timing, and mood. This raises the question whether variability across domains (such as reaction time and emotion) may also be associated. The present study provides preliminary evidence in favour of this association, particularly since the ALS-SF was associated with real-time emotional instability in Chapter 4. However, the relationship between SD-RT and real-time change in emotions remains to be investigated.

5.5.2 Inhibitory function and emotional lability

ADHD subjects showed both longer latency of the no-go-$P3_{SART}$ during correctly inhibited trials, and a greater number of inhibitory failures as indexed by the higher rate of commission errors. The latency of the P3 component is believed to be associated with the amount of time required to evaluate a stimulus (Barry, Johnstone, & Clarke, 2003; Courchesne, Hillyard, & Courchesne, 1977), suggesting that individuals with ADHD are

slower to complete processing of inhibitory targets. However, correlational analysis indicated a lack of relationship between no-go-$P3_{SART}$ latency and errors of commission on the SART. This may indicate a dissociation between two inhibitory processes, the first of which culminates in inhibitory failures (commission errors) and the second of which indicates additional resources for successful inhibitory processing (no-go-$P3_{SART}$), or may reflect a type II error. Although these are not correlated, both are associated with EL.

Results presented here are in line with previous studies, which have also highlighted the difficulty of associating ERP derived indices of inhibitory processing with behavioural inhibitory failures, due to a lack of systematic relationship with performance measures (e.g. Falkenstein, Hoormann, & Hohnsbein, 1999). The inhibitory P3 has also been linked to attentional resource allocation, cognitive demands during task processing, reaction time, and target and non-target discrimination (Azizian, Freitas, Watson, & Squires, 2006; Courchesne, et al., 1977; Polich, 2007). In this study no-go-$P3_{SART}$ latency was correlated with within-subject variability in reaction time, and omission errors, providing support for its association with attentional processes and reaction time indices.

Both the observed no-go-$P3_{SART}$ latency differences and frequency of commission errors predicted CNS-LS scores. Findings are in line with previous research showing an association between EL and behavioural inhibition (Graziano, et al., 2012; Hoeksma, et al., 2004; Walcott & Landau, 2004), and provide some support for hypotheses formulated by Barkley (1997, 2010) which postulate a key deficit in inhibitory processing as contributing to EL. However, further research on the distinctions between inhibitory failure and deficits in inhibitory processing is required before firm conclusions can be made.

5.5.3 Quantitative EEG and task transition

Differences in resting state quantitative EEG were not seen in this sample. Although increased theta, decreased beta and increased theta-beta ratios have been reported in a number of studies of children, results from adult studies have been more ambiguous (van Dongen-Boomsma, et al., 2010). Previous research has shown an age-related decline in slow wave activity in children with ADHD (Bresnahan, Anderson, & Barry, 1999; Snyder & Hall, 2006), also seen during development in healthy children (Benninger, Matthis, &

Scheffner, 1984; Clarke, Barry, McCarthy, & Selikowitz, 2001b). This may suggest that EEG abnormalities during resting state may resolve to a certain extent during maturation.

Control participants showed a task-related increase in theta and beta activity during the SART, primarily in frontal and parietal regions, which was absent in ADHD subjects. Previous research of task-related change in EEG activity has shown mixed results in ADHD populations (El-Sayed, Larsson, Persson, & Rydelius, 2002; Loo, et al., 2009; Mann, Lubar, Zimmerman, Miller, & Muenchen, 1992), although differences may be accounted for by task-related discrepancies. The current study shows the EEG effects task transition are largest in the SART which also shows great performance differences, indicating that this is a more demanding tasks, requiring more neuronal resources, which are not allocated when needed in ADHD.

Theta band oscillatory dynamics in medial frontal sites have been linked to action monitoring, error monitoring and cognitive control, the evaluation of positive and negative feedback, and prediction of error for behavioural adjustment (Cavanagh, Frank, Klein, & Allen, 2010; Cohen, 2011; Cohen & Cavanagh, 2011; Luu, Tucker, & Makeig, 2004). Beta activity has been associated with successful inhibitory responding (Swann, et al., 2009). Findings reported here show some complementary results, with frontal theta and beta power increase from rest to SART associated with a reduction in commission errors, and increase in beta from CPT to SART being associated with greater SD-RT. Findings are in line with previous work by Loo and colleagues (2004), which showed significant correlations between performance measures on a reaction time task with beta power, and may indicate the importance of beta with concentration, and more cautious response style (Loo, et al., 2009; Loo, Teale, & Reite, 1999). Further work is required to investigate task related changes in theta and links to task performance.

Research on the Default Mode Network has identified a pattern of brain activity which is dominant when an individual is at rest, and is attenuated during task states (Broyd, et al., 2009). In relation to ADHD, it has been suggested that this pattern of brain activity, if inadequately attenuated, has the potential to interfere with cognitive processes required for goal-directed task performance (Sonuga-Barke & Castellanos, 2007). Another prominent hypothesis of the pathophysiology of ADHD argues for a failure to optimise energetic state

(Andreou, et al., 2007; Kuntsi, et al., 2010; Sergeant, 2005). In the context of the cognitive-energetic model (Sergeant, 2005), the deficits seen here may be interpreted as deficient activation, defined as a "separable tonic measure reflecting the task-related mobilization of energy needed to perform a task" (VaezMousavi, Barry, Rushby, & Clarke, 2007). The deficits reported here could support either hypothesis, reflecting either interference from the default resting mode or an inability to increase energy to perform a task in ADHD.

Alternatively, these findings may be interpreted as a reflecting a lack of task engagement. This may be unlikely since all participants were video monitored during task performance and the few who overtly displayed a drift away from the task were quickly prompted. However, this would not account for a covert drift of task, where individuals with ADHD may be appearing to remain on task, but nevertheless experience a drift of attention. Furthermore, it is not clear whether the heightened interactive difference between the SART and resting as opposed to comparisons with the CPT-OX may reflect task difficulty, the heightened response pattern required by the SART, or alternatively time on task, since the SART was always the last of the three tasks administered. Future research should consider balancing the order of tasks. More work will be required to identify factors influencing task transition abnormalities in ADHD, for example by exploring the relationship of the ratio of go to no-go trials, or the effects of response rate with change transition effects.

5.5.4 Negative findings on the CPT-OX

Although inhibitory processing deficits were identified on the SART, findings from the CPT-OX were negative. This is in contrast to previous studies, which have shown reduced no-go-P3 amplitudes in the CPT-OX in adults with a diagnosis of ADHD (Dhar, Been, Minderaa, & Althaus, 2010; McLoughlin, et al., 2010) and adults with high rates of ADHD symptoms (Valko, et al., 2009).

Task-related differences may have played a role in the differing results obtained on these two tasks. The CPT-OX requires participants to monitor a stream of stimuli for the occurrence of a rare cue stimulus during which they must prepare a response, and on half of these occasions participants are required to withhold this prepared but not yet initiated response (Albrecht et al., 2005). In the SART there is no cue stimulus and participants are required to respond to the vast majority of stimuli and correct performance is highly

dependent on the participant's ability to suppress the already initiated go response on the appearance of the no-go target (O'Connell, et al., 2009). Whilst the current results suggests that inhibitory processing deficits can only be seen under certain task conditions, it is not possible to dissociate such task differences from task difficulty, since the CPT-OX has been described as having a lower inhibitory load than other go no-go tasks (Doehnert et al., 2010).

Furthermore, in contrast to previous research, individuals with ADHD did not show significant aberrations in covert orienting and preparatory processes as indexed by the cue-$P3_{CPT}$ and CNV. A weak trend was seen in this sample (around p=0.10) but this is far from significant and our sample is larger than that used in previous studies. The reduced cue-$P3_{CPT}$ has been frequently described in electrophysiological studies of children with ADHD (Banaschewski, et al., 2004; Doehnert, et al., 2010; van Leeuwen, et al., 1998), with more mixed results in adults (Dhar, et al., 2010; Doehnert, Brandeis, Schneider, Drechsler, & Steinhausen, in press; McLoughlin, et al., 2010). The reasons for these study differences require further evaluation but could be explained by three main factors. First, our sample has a broader age-range than that used in previous studies of adults, such as McLoughlin et al (2010); and the follow-up study from Doehnert and colleagues (in press), who repeated the task at 4 different ages, suggest that case-control differences for the cue-P3 decline with increasing age. Secondly, the sample used here is unusual in being free of any major comorbidities and in addition with none or very limited prior exposure to stimulants or other drugs and medications. This could indicate that some of the previously observed effects might also be secondary to medication or comorbidity effects. Finally, the cases included in this study might reflect a less severe clinical group than that used in some of the previous studies. Nevertheless our study, using a larger sample that used previously, indicates that an attentional orienting and preparation deficit is not a reliable marker of ADHD in adults, as assessed with the CPT-OX.

5.5.5 Limitations

Although care was taken to limit the number of comparisons made in this study, the exploratory nature of the analysis, which contrasted several theories of cognitive function, resulted in a large number of comparisons. It is worth noting that none of the ERP measures

identified would stand up to corrections for multiple testing. Results here indicate that this study may well have been improved by using a more homogeneous participant sample (in terms of age and symptom severity) and a larger sample size to aid in robustly and clearly identifying case control-differences in the results which reach or are nearing significance levels.

Another limitation to conclusions that can be drawn from this study is reflected in the overall low level of significant correlations between cognitive measures and EL in the ADHD group. The significant findings presented here are most strongly driven by relationships seen in the control sample, which means that it has not been possible to delineate cognitive and neurophysiological correlates that influence levels of EL in ADHD cases. Findings could therefore reflect some of the phenotypic heterogeneity of the disorder in terms of the presence of co-occurring EL. It is not clear whether this is simply due to increased variability more generally within the ADHD group, or whether the clear relationship (between SD-RT and EL for example) breaks down at the extreme levels of EL or ADHD symptoms. For example clinical cases reflect the top 2-5% of the population in terms of ADHD symptom severity (and thereby also selection for EL), and may reflect a highly heterogeneous group with regard to different aetiologies, referral biases and the effects of different lifetime exposures to pharmacological and non-pharmacological treatments and other environmental factors. Further longitudinal research is therefore needed to fully understand the processes involved in the development of EL in adults with ADHD. Overall, the results indicate that there may well be a more complex relationship between cognitive measures and EL in individuals with ADHD than in control subjects.

5.5.6 Conclusions and future directions

Overall, this study identified further heterogeneity in self-reported constructs of EL, with swift emotional changes associated with within-subject variability, and frequent negative emotions associated indices associated with inhibitory function. The relationship of EL characterised by swift emotional changes with SD-RT withstood the inclusion of diagnostic status as concurrent predictor, suggesting that SD-RT adds additional predictive value beyond clinical status for identifying individuals with elevated EL. However, whilst these cognitive and neurophysiological measures showed a significant predictive effect on EL, the

small-to-moderate covariation of these variables suggests only a small proportion of EL can be accounted for by the SD-RT, suggesting that further research is required to identify other cognitive dysfunctions associated with EL in ADHD. An additional novel finding is the limited task-related increase in theta and beta activity in individuals with ADHD in comparison with controls. Although this measure shows a less clear relationship with EL, it provides some complementary findings to current hypotheses of the workings of the default mode network and energetic state regulation deficits. Further research is required to elucidate the causal relationships between these measures. Longitudinal studies may be well placed to investigate potential causal relationship between SD-RT, inhibitory functions and EL across time, whilst behavioural genetic studies can provide further indications of shared genetic variance contributing to cognitive dysfunctions and EL. This study provides an important first step in identifying some potential cognitive markers for such analyses.

Chapter six: Investigating response of ADHD symptoms, emotional lability, impairment and cognitive function in an open-label study of community treatment with methylphenidate in adults with ADHD

6.1 Summary

Chapter 3 documented associations between self-reported emotional lability (EL), symptoms of ADHD and functional impairment in daily life. Chapter 5 reported a number of cognitive and neurophysiological deficits in a sample of untreated adults with ADHD during a resting condition and the Sustained Attention to Response Test (SART). Cognitive heterogeneity of EL was reported, with negative emotions associated with indices of inhibitory dysfunction (commission errors and latency of the inhibitory P3 component; no-go-$P3_{SART}$), whilst swift emotional changes were associated with within-subject variability in reaction time (SD-RT). The current study investigates equivalent measures of EL, ADHD symptoms, impairment and cognitive and neurophysiological function in a subsample of the same adults with ADHD after extended treatment with methylphenidate, and a healthy control group matched for follow-up duration. EL, ADHD and impairment measures all improved after treatment. Treatment response was correlated for EL and ADHD symptoms, and improvements in functional impairment were primarily predicted by reductions in ADHD symptoms. Treatment-related changes were absent in SD-RT and the no-go-$P3_{SART}$. However, after treatment ADHD subjects showed enhanced amplitude of the inhibitory N2 component (no-go-$N2_{SART}$), reduced commission errors, slowed reaction times, reduced coefficient of reaction time variability, and a normalization of task-related increase in theta activity. Change in cognitive measures were not associated with reductions in EL, however enhancement of the no-go-$N2_{SART}$ amplitude was associated with a poorer response of inattentive symptoms, suggesting that this may be a marker for poor treatment response, or alternatively indicative of additional processing efforts in those with continuing high inattentive symptoms after treatment. Results indicate broad effects of methylphenidate across behavioural and cognitive domains, but suggest differential rather than common effects of treatment on many of these measures. Lack of a placebo-controlled design and limited power due to the small sample size indicates that these findings must be considered preliminary.

6.2 Introduction

Attention-Deficit Hyperactivity Disorder (ADHD) is a common developmental psychiatric disorder, characterised by impairing symptoms of hyperactivity, impulsivity and inattention. ADHD is frequently accompanied by emotional lability (EL: irritability and hot-temperedness with highly volatile and changeable emotions; Barkley, 2010; Skirrow, et al., 2009), as well as a variety of daily adversities and difficulties, including interpersonal and relationship difficulties, family problems, and problems in employment (Friedrichs, et al., 2012; Harpin, 2005).

Pharmacotherapy is the most common intervention for ADHD in the United States and Europe, and stimulant medications are some of the most widely prescribed (Greenhill, Pliszka, Dulcan, & the Work Group on Quality Issues, 2002). The stimulant medication methylphenidate (MPH) is a noradrenaline and dopamine reuptake inhibitor and acts by increasing levels of dopamine in the synaptic cleft by blocking the function of dopamine transporters (Volkow, Wang, Fowler, & Ding, 2005). Meta-analytic studies have confirmed the efficacy of MPH for reducing symptoms of inattention and hyperactivity-impulsivity in children, adolescents and adults with ADHD (Faraone, et al., 2004; Koesters, Becker, Kilian, Fegert, & Weinmann, 2009; Schachter, et al., 2001). In the UK, MPH is currently the recommended first line treatment for childhood ADHD associated with severe levels of impairment, and in all cases of ADHD in adults (NICE 2008, www.nice.org.uk).

Besides reductions in ADHD symptoms, pharmacological trials have shown treatment response of a number of problems and impairments associated with ADHD. Recent evidence shows that MPH is effective in reducing emotional lability in adults with ADHD (Reimherr, et al., 2010; Reimherr, et al., 2007; Retz, et al., 2010; Rosler, et al., 2010). In two controlled treatment trials, response of EL was highly correlated with the response of ADHD symptoms (correlation coefficient>0.8; Reimherr, et al., 2010; Reimherr, et al., 2007). Treatment with MPH has also been linked with improvements in quality of life and daily functioning in adults with ADHD (Buitelaar, et al., 2012). Since EL predicts a host of daily life impairments in adults with ADHD beyond the influence of core ADHD symptomatology (Barkley & Fischer, 2010; Barkley & Murphy, 2010), EL may be an important target for treatment as it may help to alleviate the everyday impairments.

The shared treatment response of EL and ADHD symptoms observed in adults raises the possibility that there may be a shared neurochemistry between EL and ADHD which warrants further investigation. Causal links have been drawn between cognitive functions, particularly inhibitory functions, and EL. An influential hypothesis posited by Barkley (1997, 2010) proposes a key inhibitory deficit underpinning both behavioural and emotional features of ADHD. This model would suggest that treatment response in inhibitory functions would likewise impact on both ADHD symptoms and EL. The results from Chapter 5 provide some support for the role of inhibitory function in EL, but also indicate an additional role for within-subject variability in reaction time in EL. This makes treatment response a potentially useful mechanism for testing the relationship between EL and cognitive processes that have been associated with it. However, there has been a dearth of research in this field.

Deficits in cognitive tasks which have been associated with ADHD frequently show a pattern of improvement after treatment with MPH. Error rates (commission and omission errors) and within-subject variability in reaction time, both commonly noted as elevated in ADHD, were reduced after treatment with MPH in both adults and children with ADHD during motor response tasks (Boonstra, Kooij, Oosterlaan, Sergeant, & Buitelaar, 2005; Castellanos, et al., 2005; DeVito, et al., 2009; Frobel Smithee, Klorman, Brumaghim, & Borgstedt, 1998; Kratz, et al., 2012; Losier, McGrath, & Klein, 1996; Spencer, et al., 2009). Quantitative electroencephalography (EEG) studies of brain activity during resting conditions have indicated that MPH may increase or 'normalise' cortical arousal in children, reducing the elevated slow wave activity and increasing the low levels of fast wave EEG oscillations associated with the disorder (Hermens, Williams, et al., 2005; Loo, Hopfer, Teale, & Reite, 2004; Loo, et al., 1999).

Effects of MPH have also been investigated using event related potentials (ERP), an average of small voltage fluctuations recorded on the scalp resulting from evoked brain activity to a repeated stimulus (Albrecht, et al., 2005; McLoughlin, et al., 2005). Two ERP components have been functionally related to motor response inhibition tasks (tapping into inhibitory processes), namely the frontal negative no-go-N2 and the more centrally located positive no-go-P3 (Banaschewski, et al., 2004), and have been the focus of much research in ADHD. Studies have revealed lower amplitudes of the no-go P3 component in children and adults

with ADHD on Continuous Performance Tests (CPT) and Stop Signal Test (SST) (Bekker, et al., 2005; Dhar, et al., 2010; Fallgatter, et al., 2005; McLoughlin, et al., 2010) and of the no-go N2 component in children on two SST studies (Albrecht, et al., 2005; Pliszka, et al., 2007), although studies investigating the no-go-N2 in cued CPT tasks in children and adults with ADHD do not show this effect (Banaschewski, et al., 2004; McLoughlin, et al., 2010).

In ERP studies investigating the effects of MPH, one the most consistent findings in children and adolescents appears to be an increase in the amplitude of the inhibitory P3 component after treatment in a variety of tasks, including CPT studies (Seifert, Scheuerpflug, Zillessen, Fallgatter, & Warnke, 2003; Verbaten, et al., 1994), and studies of go/no-go (GNG) (Groom, et al., 2010) and SST tasks (Pliszka, et al., 2007). However, it is worth noting that increased amplitude of the P3 during go-trials and of go and no-go N2 components have also been noted after treatment in a number of studies (Broyd, et al., 2005; Groom, et al., 2010; Pliszka, et al., 2007; Verbaten, et al., 1994). MPH induced reduction in the latency of the P3 component has also been reported in CPT studies, in the absence of change in amplitude (Sunohara, et al., 1999). However, findings in adults show a contradictory pattern of results, with one GNG study showing no effects of MPH (Ohlmeier, et al., 2007), and another SST study in adults showing reductions in P3 amplitudes after MPH treatment (Overtoom, et al., 2009).

Although previous studies have investigated treatment response in cognitive task variables (ERP and task performance), few have investigated potential shared treatment effects on cognitive task variables and treatment response of EL. One previous open-label treatment study of MPH in adolescents with ADHD indicated a shared treatment response of ERPs to early facial processes (N170 and P120) with EL (Williams, et al., 2008). The present study uses a similar approach with an open-label treatment design to investigate response to MPH of EL with cognitive and neurophysiological deficits identified during a response inhibition task and during a resting condition. Here we are looking at the naturalistic outcome of 'treatment as usual' on MPH in an uncontrolled treatment program; and using the effects of medication to identify behavioural (EL) and cognitive-electrophysiological outcomes that co-vary with the treatment response on ADHD, in addition to those that show treatment effects that are independent of ADHD.

Participants in this study are a subset of the subjects from whom data is reported in Chapters 3 through 5, where high levels of EL (Chapters 3 and 4) and a pattern of cognitive deficits on the Sustained Attention to Response Task (SART; Chapter 5) were reported in the ADHD group. In Chapter 5 it was shown that these ADHD subjects exhibited elevated within-subject variability and omission and commission errors, increased latency of the P3 on inhibitory response trials, and a lack of rest-to-task transition effects in EEG theta and beta activity. The current study investigates treatment response in these measures in participants from this same sample who underwent treatment with MPH (which comprised over 85% of participants on pharmacotherapy). Other forms of pharmacotherapy (dexamphetamine and atomoxetine) were infrequently in use in this sample. Analyses were therefore limited only to a sub-sample of adult patients returned for follow-up appointments after maintaining a steady treatment regimen with MPH (N=21) for a minimum of 2.5 months, and a control group matched for follow-up (N=36).

Although this open label treatment design may not be ideal for identifying medication specific effects, since medication effects will be in addition to non-specific (placebo) and practice effects, it provides an initial indication of where treatment effects are seen, and the relationship of different treatment outcome measures to one another. Furthermore, by retaining the control group at a matched follow-up duration it was possible to differentiate generalized practice effects manifesting as equivalent test-retest changes seen in both the ADHD and control groups, from differing response patterns in contrast between participant groups, which indicate that differences between assessment times are in addition to practice effects (Hood, Baird, Rankin, & Isaacs, 2005).

The following hypotheses are tested: (1) that individuals with ADHD will show improvements in ADHD symptoms, EL and impairment in daily life in response to MPH treatment; (2) that ADHD symptoms and EL will show a correlated treatment response; (3) that reductions in self-reported impairment will be predicted by improvements in EL; and (4) that cognitive deficits identified prior to treatment in this sample (Chapter 5) will show a treatment response; and (5) that those cognitive domains associated with EL prior to treatment (commission errors, no-go-$P3_{SART}$ latency and within-subject variability in reaction time) will show a correlated treatment response with EL.

6.3 Methods

6.3.1 Participants

Participants included 41 adult males with ADHD and 47 healthy adult male control participants. Details on participant recruitment and clinical diagnostic procedure are given in Chapter 2, and subject demographics and statistics on group matching for the entire group are reported in Chapter 3. All participants attended an initial assessment (time 1), prior to starting any treatment for ADHD, and were invited for reassessment (time 2), either after treatments were initiated (including non-pharmacological treatment in some cases), or at a matched duration if treatment was not sought.

Appointments at time 2 were scheduled for EEG recordings to be carried out within 1 hour of participants taking immediate release MPH and within 3 hours of extended release MPH. Participants were asked to refrain from taking alcoholic or caffeinated beverages or smoking on the day of each study session and from consuming alcohol during the preceding evening.

6.3.2 Treatment

Treatment for ADHD was managed by community health services after a diagnosis of ADHD was confirmed by specialists at the Maudsley Hospital adult ADHD clinic. Where pharmacological treatment was initiated, time 2 assessments were scheduled after treatment was maintained for at least 2.5 months, allowing an adequate duration for treatment optimisation. Participants with ADHD who did not undergo psycho-pharmacological treatment were also invited for re-assessment at a similar follow-up duration. 39 control participants provided normative data at both time 1 and time 2 at a matched follow-up duration.

31 ADHD subjects returned for reassessment at time 2: twenty-three were on steady pharmacotherapy for ADHD (21 taking methylphenidate (MPH) based medications, 1 dexamphetamine, 1 atomoxetine), two reported taking their medication inconsistently (one MPH and the other atomoxetine), and six were not taking any medication. Of those on a steady MPH regimen, 11 were prescribed extended release formulations (Equasym XL or Concerta XL) with daily doses ranging from 18mg up to 72mg; the remainder (N=10) were

taking immediate release medication (e.g. Ritalin IR, Equasym IR) with doses ranging from 10mg to 60mg daily, generally taken in three discrete doses during the day.

Analyses will focus on the 21 adults with ADHD who attended their second assessment after maintaining a steady treatment regimen with MPH (average treatment duration: 3.9 months; range 2.5-9.7 months), and 36 control subject who underwent follow-up testing within a matched time period of this ADHD sub-group (range 2.5-16.5 months). Follow-up durations were therefore matched between ADHD (mean: 8.23 months) and control (mean: 8.6 months) groups.

6.3.3 Measures

Self-report measures were identical at time 1 and time 2. Assessment of ADHD symptoms and EL included the Barkley Adult ADHD rating scale (BRS; Barkley, 1998), the Affective Lability Scale–Short form (ALS-SF; Oliver & Simons, 2004) and the Centre for Neurologic Study–Lability Scale (CNS-LS; Moore, et al., 1997). In line with previous analyses in Chapters 3, 4 and 5, two items relating to impatience were dropped from the CNS-LS due to clear overlap with the impulsive dimension of ADHD. The Weiss Functional Impairment Rating Scale-Self-Report (WFIRS-S; www.caddra.ca), was administered to assess a range of daily life impairments as detailed in Chapter 2 (section 2.5.1). Intellectual function (IQ) was measured with the Wechsler Abbreviated Scale of Intelligence (Psychological Corporation, 1999).

6.3.4 Electrophysiology: tasks, data collection methods and EEG pre-processing

EEG recording equipment and data collection methods are identical to those detailed in section 5.3.3. Current analyses are limited to tasks which yielded the bulk of case-control differences at time 1, namely EEG during a 3-minute fixed gaze eyes open resting condition, and during the Sustained Attention to Response Task (SART), which are outlined in detail in section 5.3.3. Two ADHD participants were excluded from analyses of electrophysiological data due to excessive movement and data artifact during their assessment at time 1. The number of accepted sweeps during both assessments is presented in table 18 below. A greater number of trials were available for analysis at follow-up for both go and no-go trials in the ADHD group (go: $z=-2.42$, $p=.02$; no-go: $z=-2.96$, $p=.003$), with equivalent

improvements only seen at trend level in the control group for the go-condition (go: z=-1.66, p=.10; no-go: z=-.29, p=.77).

EEG data pre-processing was carried out as detailed in section 5.3.5. To reduce the number of statistical comparisons and investigate treatment response of differences identified in Chapter 5, analyses focused only on the frequency bands that have been most frequently associated with arousal: namely theta (4-7.5Hz) and beta (12.5-30Hz). EEG power density (μV^2/Hz) within these frequencies was averaged across frontal (Fz, F1, F2, F3, F4, F5, F6, F7, F8), central (Cz, C1, C2, C3, C4, C5, C6), parietal (Pz, P3, P4, P7, P8) scalp electrode sites. Theta-beta ratios were calculated by dividing theta power by beta power at each site. Change in quantitative EEG between rest and SART conditions was calculated by subtracting EEG power from rest and CPT from the SART (e.g. Change in frontal beta from rest to SART= SART frontal beta- resting frontal beta).

ERP peak components on the SART were identified as the largest peak within the following time windows: 220-350ms (N2 range), 300-500ms (go-P3 range) and 300-600ms (no-go-P3 range) with analyses restricted to midline electrodes. In this sample, electrodes with the maximal amplitudes (across both groups) for ERP components were equivalent to those identified in the larger sample at time 1 (section 5.3.5), and peak amplitudes were extracted at following electrodes: go-$P3_{SART}$ at CPz, go-$N2_{SART}$ at Fpz, no-go-$P3_{SART}$ at Cz and no-go-$N2_{SART}$ at FCz. Poor data from electrodes CPz from one control subject at time 1 and Fpz (3 ADHD, 5 control) at either time 1 or time 2, due to electrode saturation or excessive noise, resulted in the exclusion of the affected component from analysis for these individuals.

Table 18: Mean (SD) SART trials per stimulus for each participant at time 1 and time 2

			Mean number of trials contributing to ERP per participant	
		Number of participants	Go	No-go
Time 1	Controls	36	500.81 (62.4)	52.14 (10.4)
	ADHD	19	474.11 (59.4)	39.67 (16.0)
Time 2	Controls	36	515.52 (49.7)	52.08 (11.0)
	ADHD	19	499.05 (42.1)	51.84 (12.3)

6.3.5. Scoring performance measures

Reaction time measures were calculated across tasks with correct responses only, including mean reaction time to the target (MRT, i.e. mean latency of responding in ms after target onset), within-subject variability in reaction time (SD-RT, i.e. within-subject standard deviation of reaction time), the coefficient of reaction time variability (CV, i.e. SD-RT/MRT). Errors were broken down into commission errors (response to non-targets) and omission errors (non-response to targets).

6.3.6. Statistical analysis

Mean values for each rating scale and subscale were used as summary measures. Change scores (denoted by Δ) for all measures were calculated by subtracting data at time 1 (initial assessment) from time 2 (follow-up assessment). This yielded change scores in which negative values indexed reductions and positive scores indexed increases, with the exception of the ERP N2 amplitudes, which produce a negative value if follow-up components have a higher amplitude (due to the sign of values for these components). Loss to follow-up of patient and control groups was tested using a chi-square statistic.

Deviations from normality of all continuous data were tested using the Shapiro-Wilk test. For non-normal data distributions, transformations were carried out where possible, and parametric and non-parametric comparisons and correlational analyses were carried out, as appropriate. Cross-sectional case-control comparisons, including analysis of ERP and EEG variables were carried out using independent samples t-tests, and Mann-Whitney U tests, unless specified otherwise. For longitudinal analysis of within-group change over time, paired samples t-tests and Friedman's tests were carried out, again unless specified otherwise. Significance level for all comparisons was held at .05 (two-tailed), and Bonferroni corrected statistics are presented alongside uncorrected p-values.

Analyses carried out in the ADHD group alone included the calculation of effect sizes for change in self-report measures after treatment (indexed by d_z for matched pairs), using the software G*Power. Furthermore, a series of multiple linear regression analyses with stepwise entry was used to determine the relative contributions of Δ CNS-LS, ALS-SF, and BRS rated inattention and hyperactivity-impulsivity to Δ functional impairment.

2x2 repeated measures analyses of variance (ANOVA), including within (time 1 versus time 2) and between subjects contrasts, were performed on the task performance measures SD-RT (after natural logarithm transformation) and MRT. Equivalent analyses were carried out on ERP amplitudes and latencies on the SART, including amplitudes of the go-$P3_{SART}$ (after natural logarithm transformation) and the go-$N2_{SART}$ (after sign reversal and inverse transformation) and the no-go-$N2_{SART}$ and the no-go-$P3_{SART}$, as well as for the latencies of no-go-$N2_{SART}$ and go-$P3_{SART}$ components. The remaining ERP latencies and omission error data were non-normal and could not be successfully transformed. A series of non-parametric between (Mann-Whitney U) and within-subjects (Friedman's test) comparisons were carried out. Data from commission errors violated assumptions of equality of error variances, and paired-samples t-tests adjusting for variance inequalities was carried out within each group to investigate change over time.

A repeated measures analysis was performed on theta-beta ratios (natural logarithm transformed) and theta power (inverse transformed), including within-subject (time 1 versus time 2, rest versus task, and frontal, central and parietal recording sites) and betweens subjects contrasts. Diagnostic tests included checking for equality of error variances (Levene's test) and sphericity (Mauchly's test). Beta power could not be successfully normalized through transformation and were tested in a series of non-parametric pair-wise tests for within and between subjects effects, as described above.

For all repeated measures ANOVAs, Greenhouse-Geisser corrections were employed in analyses with significant departures from sphericity, and adjusted degrees of freedom were rounded to the nearest whole number.

To limit the number of statistical comparisons in exploratory correlational analysis with ADHD symptoms and EL, summary measures of change in theta activity across assessments were calculated. Since effects of task transition in theta were not enhanced at any specific recording site, global theta activity was calculated by averaging theta activity across frontal, central and parietal recording sites. Change in global theta power was calculated by subtracting data at time 1 (initial assessment) from time 2 (follow-up assessment) separately for rest and SART conditions. Furthermore, since significant effects were driven by task transition (rest to SART) rather than in specific task conditions, an additional

measures of change in global theta task transition was calculated (e.g. Δ global theta transition from rest to SART = (global SART $theta_{time2}$- global resting $theta_{time\ 2}$)- (global SART $theta_{time1}$- global resting $theta_{time\ 1}$)).

Correlational analyses were carried out to investigate the co-variation of treatment response between cognitive measures (task performance, EEG and ERP measures which showed significant change in the ADHD sample at time 2) and behavioural symptoms of EL, inattention and hyperactivity-impulsivity. To control for the potentially confounding effect of age, age at assessment was correlated with all measures, and where significant effects of age were found for variables of interest, subsequent correlations with these variables partialled out the effects of age. Additional correlations were carried out to investigate the co-variation of treatment response of cognitive and neurophysiological measures. Spearman's, Pearson's or partial correlations were employed, as appropriate, and results are presented alongside Bonferroni corrected statistics.

6.4 Results

6.4.1 Participants

ADHD and control groups did not differ in rate of loss to follow-up (χ^2=.36, p=.55). Control participants lost to follow up did not differ significantly from those who remained in the study in terms of their IQ (z=-1.25, p=.22) or age (z=-0.72, p=.48). ADHD participants lost to follow-up showed a trend for being younger (z=1.72, p=.09), and having lower IQ (t=-1.80, p=.08). However, ADHD symptom scores as measured by the BRS did not differ between ADHD patients who remained in the study and those lost to follow-up (Inattention: t=-0.3, p=.98; Hyperactivity-Impulsivity: t=.56, p=.58).

Participants with ADHD on a steady MPH regimen at follow-up (N=21) and control participants who attended follow-up (N=36) were also matched in terms of age, IQ, educational level and follow-up duration (table 19).

Table 19: Group demographic data, follow-up duration (months), means (SD) and test statistics (from Mann Whitney U)

	ADHD N=21	Control N=36	Z/t statistic	p value
Age	30.00 (10.35)	29.44 (11.2)	z=-0.27	.79
IQ	108.33 (13.77)	112.25 (13.4)	z=-1.34	.18
Years in education	16.19 (4.2)	15.90 (2.4)	z=-1.18	.24
Follow-up duration (months)	8.23 (3.9)	8.60 (3.4)	t=0.36	.72

6.4.2 ADHD symptoms and EL (fig. 19)

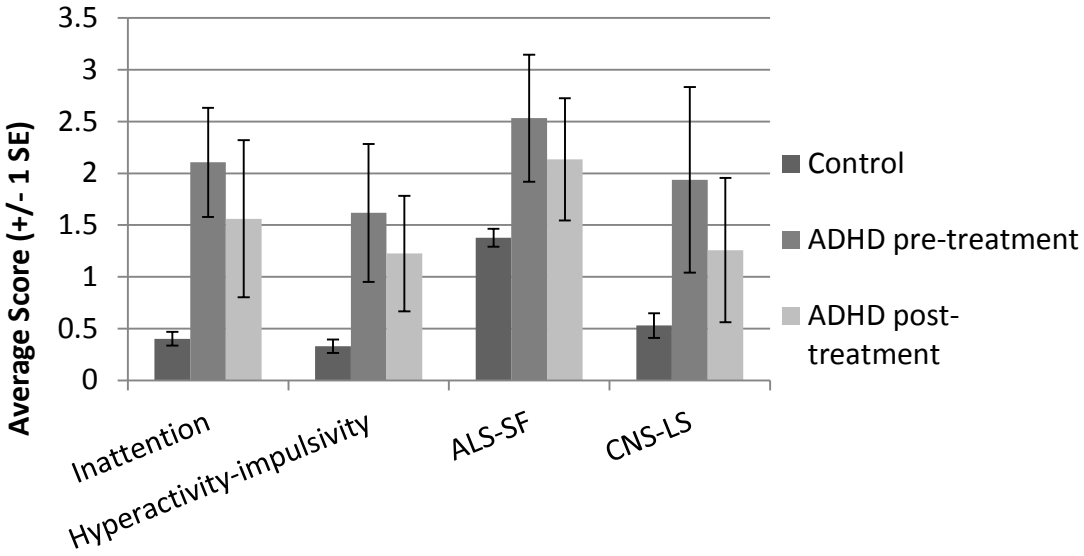
No change over from the first to second assessment was seen in self-reported ratings of ADHD symptoms (inattention or hyperactivity-impulsivity) or EL in the control group (z range=-1.29 to -0.59, p range=.20 to .56). The ADHD group exhibited a significant reduction in ADHD symptoms on the BRS (inattention: t=3.62, p=.002, d_z=1.13; hyperactivity-impulsivity: t=3.07, p=.006, d_z=1.10), and on both measures of EL (ALS-SF: z=3.18, p=.001, d_z=1.31; CNS-LS: t=3.54, p=.002; d_z=1.24) after treatment. All significant differences were robust to Bonferroni correction (adjusted p=.0063). Although a significant decrease in ADHD symptoms and EL was seen in the ADHD group, ADHD subjects continued to report significantly elevated ADHD symptoms and EL after treatment in comparison with controls (inattention: z=-5.31; hyperactivity-impulsivity: z=-5.42; ALS-SF: z=-4.34; CNS-LS: z=-3.53, all p values<.001). Figure 17 shows treatment response patterns in the ADHD group in the absence of normalization of self-reported ADHD and EL.

Change in ALS-SF scores correlated negatively with age (rho=-.51, p=.02), with older participants reporting more significantly decreased scores on the ALS-SF after treatment. No other significant correlations with age were seen for measures of ADHD symptoms and EL (minimum p=.59).

ADHD and EL showed a significant treatment co-variation in the ADHD group. For Δ ALS-SF correlations with Δ hyperactivity-impulsivity (partial correaltion=.64, p=.002) were slightly higher than those for Δ inattention (r=.52, p=.02). Correlations with Δ CNS-LS were lower, and for Δ hyperactivity-impulsivity did not reach significance despite a moderate correlation

coefficient (Δ inattention: r=.51, p=.02; Δ hyperactivity-impulsivity: r=.33, p=.15). Δ in ADHD symptom domains of inattention and hyperactivity-impulsivity were highly correlated (r=.80, p<.001).

Figure 18: Pre-and post treatment self-reported ADHD symptoms and EL (ALS-SF and CNS-LS), with average ratings from both testing occasions in controls



To investigate treatment response of different domains of EL, investigations of ALS-SF subscales were also carried out. Results revealed significant reductions for all subscales after treatment: anxiety-depression (t=2.32, p=.03, d_z=0.68); depression-elation (t=3.33, p=0.003, d_z=1.07); and anger (t=2.95, p=.008,d_z=0.50). Differences in depression-elation and anger remained significant after correction for multiple testing (adjusted p=.017). Only change in ALS-SF depression-elation was correlated with age at assessment, again with older participants showing a greater improvement in this scale (rho=.53, p=.01, all other subscale correlations with age minimum p=.48). Investigation of treatment co-variation of ALS-SF subscales with ADHD symptoms revealed no significant correlations between Δ anxiety-depression and either Δ inattention (r=.20, p=.28) or Δ hyperactivity-impulsivity (r=.21, p=.36). However, significant correlations were seen between Δ depression-elation with Δ inattention (partial correlation r=.57, p<.01), and with Δ hyperactivity-impulsivity (partial correlation=.47, p=.04). Conversely, Δ anger was most strongly associated with Δ hyperactivity-impulsivity (r-.56, p=.01), with no correlation seen with Δ inattention (r=.15,

p=.52). However, none of these correlations withstood correction or multiple testing (adjusted p=.008).

6.4.3 Functional impairment

No significant change over time in impairment ratings were reported by control subjects (z range= -.02 to -1.58, p range=.11-.98). ADHD participants reported significant reductions in impairment on the WFIRS-S after treatment initiation, with the exception of impairment in school/education (z=1.58, p=.15), for which there was only repeated data for 10 individuals, due to the low number of participants in education during both assessments. For the remainder of impairment scales, improvement after treatment was significant (family: t=3.25, p=.004; work: t=2.91, p=.009, life skills: t=4.55, p<.001; self concept: t=2.97, p=.008, Risk: t=2.51, p=.022). After Bonferroni correction for multiple testing (adjusted p=.0042), improvements in domains of family, and life-skills remained significant.

Although the ADHD group reported significant reductions in a variety of daily life impairments after treatment, impairment remained elevated in ADHD subjects compared to controls after treatment (risk: z=-2.14, p=.03, all other impairment scales: z range= -2.14 to -5.19, all p-values<.001). With the exception of the risk subscale, all group differences were robust to Bonferroni correction.

Multiple linear regression analyses with stepwise entry were used to determine the relative contributions of overall treatment response of CNS-LS and ALS-SF, inattention and hyperactivity-impulsivity to change in domains of functional impairment (Table 20). Results show a primary effect of EL limited to impairment in self-concept, all other measures were primarily predicted by ADHD core symptoms of inattention and hyperactivity-impulsivity.

Table 20: Regression-based predictors of treatment-related improvement in WFIRS-S Impairment subscales

Δ Impairment/predictors	Beta	R^2	F	p-value
Δ Family				
Δ BRS hyperactivity-impulsivity	.72	.52	19.42	<.001
Δ Work				
Δ BRS Inattention	.69	.48	14.70	.001
Δ Life Skills				
Δ BRS Inattention	.63	.29	7.19	.015
Δ Self concept				
Δ ALS-SF	.61	.34	10.18	.005
Social problems				
Δ BRS Inattention	.61	.33	10.00	.006
Risk				
Δ BRS hyperactivity-impulsivity	-.48	.23	11.78	.001

Note: Δ, Change from time 1 to time 2

6.4.4 Task performance

Task performance results are presented in table 21. To contrast the potential of treatment versus practice effects in performance data, repeated measures ANOVAs were carried out. A series of repeated measures analyses of variance for MRT revealed no significant group effect (F(1, 53)=.08 p=.77), and no significant effect of assessment time (F(1,53)=1.24, p=.27), but did reveal a significant task-by-group interaction (F(1, 53)=12.30, p=.001), driven by a decrease in MRT in control participants and an increase in MRT in ADHD participants at time 2. Repeated measures analysis of SD-RT (natural log transformed), revealed a trending difference for group (F(1, 53)=3.99, p=.054), and a significant effect of assessment time, with a reduction in SD-RT at time 2 shown in both groups (F(1,53)=9.54, p=.003), but no time-by-group interaction, indicating that change in SD-RT between time 1 and time 2 did not differ between groups (F(1,53)=0.11, p=.74).

Analysis of commission errors with paired samples t-tests revealed no significant differences for control subjects (t=-1.18, p=.25), but a significant decrease in ADHD subjects (t=4.34, p<.001). Data from omission errors and CV were subjected to non-parametric contrasts of time 1 and time 2, revealing a trending significance in change in omission errors in the ADHD

group (ADHD: z=-1.85, p=.064; controls: z=-.37, p=.71), and a significant reduction in CV in the ADHD group (ADHD: z=-2.50, p=.01; controls: z=-1.08, p=.28).

Table 21: Mean (SD) of task performance data on the SART at time 1 and time 2, with statistics for group differences.

	Time 1			Time 2		
	Control	**ADHD**	**Statistic and p-value**	**Control**	**ADHD**	**Statistic and p-value**
MRT *for correct responses (ms)*	373.28 (64.8)	350.33 (48.0)	t=-1.36 p=.18	354.24 (66.75)	387.06 (86.52)	t=-1.56 p=.12
SD-RT *for correct responses (ms)*	95.74 (32.65)	114.83 (38.7)	t=-1.95 p=.06	87.83 (31.08)	103.31 (34.5)	t=-1.78 p=.08
CV	0.25 (0.06)	0.34 (0.13)	t=-2.77 p=.010	0.25 (0.09)	0.27 (0.08)	t=.48 p=.64
Commission Errors	15.44 (8.4)	28.37 (16.8)	z=-2.79† p=.005	16.89 (11.6)	15.79 (13.0)	z=-.42 p=.68
Omission Errors	4.19 (6.4)	15.57 (19.8)	z=-2.91† p=.004	4.14 (5.9)	6.68 (12.5)	z=-.40 p=.69

Note: MRT, mean reaction time in milliseconds; SD-RT, within-subject variability in RTs in milliseconds; CV, Coefficient of variation (SD-RT/MRT).
† differences robust to Bonferroni correction (adjusted p=.005)

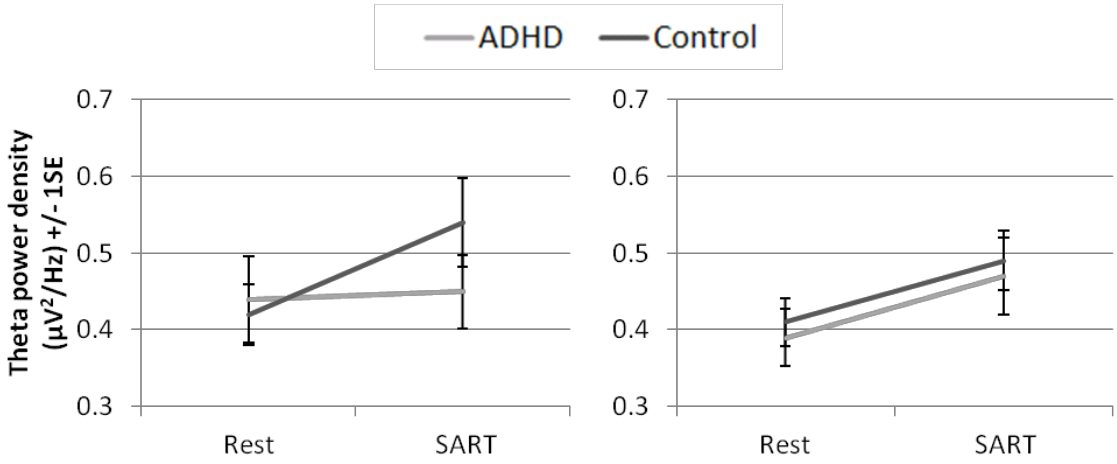
6.4.5 Quantitative electro-encephalography

Theta-beta ratios were analysed using a repeated measures ANOVA (within-subject factors: assessment at time 1 versus time 2, rest versus task, and EEG recording site; between subjects factors: group). No significant main effects of group (F(153)=0.19, p=.66) was seen, nor any interaction effects of group with recording site, task and/or time. Significant effects were only present for task (F(153)=10.93, p=.002), with increased theta-beta ratios seen in the SART across both groups and at both assessment times. Although findings are in agreement with results presented in Chapter 5, showing no group differences in theta-beta ratios, the possibility of power issues in the small sample cannot be precluded.

Theta power was inverse transformed and submitted to an equivalent repeated measures analysis. Analyses yielded no significant main effects of group (F(1,53)=.01, p=.92), nor assessment time (F(1,53)=1.74, p=.19). Significant main effects included task (F(1,53)=43.83, p<.001), corresponding to higher theta power during the SART, and

recording site, driven by significantly lower theta power in central than in frontal or parietal sites (both p<.001). Interaction effects revealed a task-by-group interaction (F(1,53)=7.03, p=.01), driven by a greater increase in theta power from rest to task conditions in the control group, and a significant three-way interactive effect between assessment time, task and group (F(1,53)=4.57, p=.04), driven by a change of the direction of task effect in the ADHD group at follow-up (seen in fig. 20). No interaction was seen with recording site, indicative of global changes in theta power.

Figure 19: Task-related change in absolute power density in frontal theta, across rest and SART conditions, plotted separately for time 1 and time 2



Beta power was non-normally distributed and could not be normalized by any transformation. Cross-sectional analyses revealed no group differences for any condition (minimum p=.28, uncorrected). Analysis of beta power transition from resting to task conditions was investigated separately in ADHD and control groups. Controls exhibited significant task transition in frontal (z=-2.31, p=.02), central (z=-2.33, p=.02), and parietal beta (z=-2.73, p=.006) beta at time 1 and parietal beta (z=-2.73, p=.006) only at time 2. In ADHD subjects no significant task transition in quantitative EEG power was seen at time 1 (min p=.38), nor time 2 (min p=.17). To investigate whether there were any medication-induced changes in resting or task-related EEG measures, identical measures collected at time 1 and time 2 were contrasted within groups. With the exception of a significant reduction in parietal beta during the SART time 1 to time 2 in control subjects (z=-1.96,

p=.05, uncorrected), no other differences were significant (p-range=.11-.52). Furthermore, no differences identified in beta withstood correction for multiple testing.

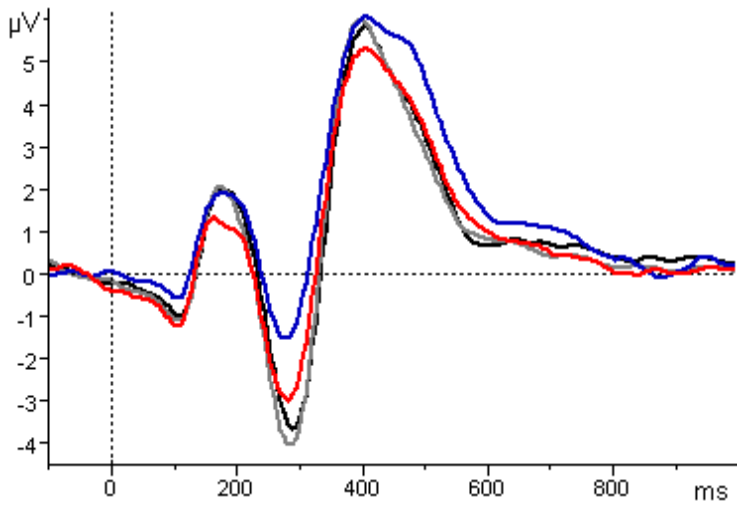
Table 22: Theta and Beta mean power density (µV2/Hz) across groups (SD) for time 1 and time 2 (raw, untransformed data)

			Theta		Beta	
			Control	ADHD	Control	ADHD
Resting	**Time 1**	Frontal	0.42 (0.24)	0.44 (0.24)	0.128 (0.08)	0.130 (0.06)
		Central	0.27 (0.13)	0.29 (0.17)	0.078 (0.06)	0.075 (0.04)
		Parietal	0.39 (0.22)	0.44 (0.27)	0.110 (0.06)	0.105 (0.05)
	Time2	Frontal	0.41 (0.19)	0.39 (0.16)	0.122 (0.07)	0.105 (0.05)
		Central	0.26 (0.14)	0.26 (0.15)	0.073 (0.05)	0.066 (0.03)
		Parietal	0.37 (0.21)	0.41 (0.21)	0.104 (0.06)	0.102 (0.05)
SART	**Time 1**	Frontal	0.54 (0.34)	0.45 (0.21)	0.150 (0.09)	0.120 (0.06)
		Central	0.34 (0.16)	0.32 (0.20)	0.088 (0.07)	0.082 (0.06)
		Parietal	0.53 (0.32)	0.46 (0.25)	0.122 (0.07)	0.113 (0.07)
	Time 2	Frontal	0.49 (0.23)	0.47 (0.22)	0.132 (0.07)	0.119 (0.06)
		Central	0.32 (0.14)	0.31 (0.18)	0.078 (0.05)	0.068 (0.03)
		Parietal	0.48 (0.25)	0.47 (0.24)	0.110 (0.06)	0.109 (0.07)

6.4.6 Event related potentials

ERP components were subjected to repeated measures ANOVA contrasting time at assessment (within-subjects variable) and group (between-subjects variable) simultaneously. There was a trending main effect of group for the no-go-$N2_{SART}$ amplitude, which was reduced in the ADHD group ($F(1,53)=3.36$, $p=.07$), and a significant group-by-time interaction ($F(1,53)=4.77$, $p=.03$), driven by a significantly greater increase in amplitude of this component in the ADHD group at time 2 (fig. 21). Equivalent analysis of no-go-$P3_{SART}$ and go-$P3_{SART}$ amplitudes, revealed no significant main effects or interactions (minimum $p=.14$). The go-$N2_{SART}$ showed only a significant main effect of time ($F(1,44)=7.19$, $p=.01$), driven by an increased amplitude in both groups at time 2. No interactive effects between group and time were seen, indicating that change in the go-$N2_{SART}$ did not differ between groups.

Figure 20: N2 to the no-go stimulus at FCz during the SART, for time 1 and time 2 in the two participant groups



Note: (control group: black=time 1, grey= time 2; ADHD group: blue: time 1, red: time 2)

In terms of latency, no significant group, time or group-by-time interaction effects were seen for no-go-$N2_{SART}$ (minimum p=.24), nor the go-$P3_{SART}$ (minimum p=.25). The remaining latencies could not successfully be normalised through transformation and were tested in a series of pair-wise tests. No group differences were seen between groups at time 1 (z=-1.28, p=.20) nor time 2 (z=-.92, p=.36) for the go-$N2_{SART}$. Similarly analysis within groups for change over time in the latency of the go-$N2_{SART}$ revealed a lack of significant change in ADHD subjects (t=-1.41, p=.18) and in controls (z=-1.27, p=.21). For the no-go-$P3_{SART}$ there was a trending group significance at time 1 (z=-1.82, p=.07), but not at follow-up (z=-1.22, p=.22). As shown in table 23, this reduction in significance was related to a slight increase in latency in the control group, with very little change seen in the ADHD group. In line with this, no change over time was seen within participant groups (Control: z=-.28, p=.78; ADHD: -.48, p=.63).

Table 23: Amplitude and latency (SD) of ERP components on the SART at time 1 and time 2

		Amplitude		Latency	
Condition	**Electrode**	**Control**	**ADHD**	**Control**	**ADHD**
			Time 1		
Go	P3 (Cpz)	2.92 (2.8)	2.79 (1.7)	395.54 (62.6)	378.08 (57.1)
	N2 (Fpz)	-2.34 (2.3)	-2.11 (2.0)	290.45 (44.2)	274.05 (40.0)
No-go	P3 (Cz)	8.40 (4.2)	7.51 (3.9)	426.32 (46.7)	450.38 (40.7)
	N2 (FCz)	-4.43 (3.4)	-2.06 (3.8)	295.68 (25.44)	285.29 (23.5)
			Time 2		
Go	P3 (Cpz)	3.27 (2.4)	2.70 (1.8)	388.24 (63.1)	385.69 (66.1)
	N2 (Fpz)	-2.98 (2.7)	-2.60 (2.3)	297.97 (42.0)	284.94 (44.3)
No-go	P3 (Cz)	8.89 (5.2)	7.27 (3.9)	431.75 (59.6)	450.04 (58.1)
	N2 (FCz)	-4.92 (3.5)	-3.75 (3.5)	295.03 (25.1)	285.56 (23.9)

6.4.7 Correlation of treatment related change of cognitive and neurophysiological measures with self-reported EL and ADHD symptoms within the ADHD group

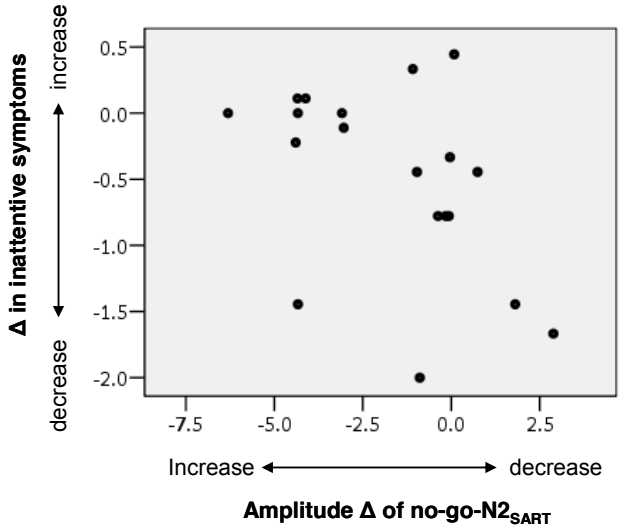
Shared treatment effects of the cognitive and neurophysiological measures with self-reported ADHD symptoms and EL were then investigated in a series of correlational analyses in the ADHD group. Cognitive and electrophysiological measures which showed a significant improvement after treatment (i.e. a change from time 1 to time 2 in the ADHD group in the absence of an equivalent change in controls) were taken forward to investigate their relationship to change in EL and ADHD symptoms. All measures were first correlated with age at assessment, to investigate potential confounding effects of age. Significant correlations with age were seen for treatment-related theta change during resting (rho=.478, p=.03), and change in theta transition from rest to SART (rho--.55, p=.01), no other correlations with age were significant. As shown in table 24, with the exception of the increase in the amplitude (negativity) of the no-go-$N2_{SART}$ during treatment with was associated with self-reported inattention, no other correlations reach significance (fig. 22).

Table 24: Correlation coefficients (p-values, uncorrected) for cognitive variables responsive to treatment with treatment-related change in EL and ADHD symptoms

(**ρ**) partial correlation with adjustment for age at assessment.

	Treatment related change in:			
	Emotional lability		**ADHD symptoms**	
Treatment related change in:	Δ ALS-SF	Δ CNS-LS	Δ Inattention	Δ Hyperactivity –impulsivity
Quantitative EEG				
Δ global theta transition from rest to SART	-.05 (**ρ**) (p=.85)	-.09 (**ρ**) (p=.70)	-.01 (**ρ**) (p=.96)	-.01 (**ρ**) (p=.97)
Δ resting global theta	-.08 (**ρ**) (p=.73)	.17 (**ρ**) (p=.48)	-.06 (**ρ**) (p=.80)	.02 (**ρ**) (p=.92)
Δ SART global theta	.10 (**ρ**) (p=.67)	.001 (p=1.00)	-.03 (p=.91)	.01 (p=.96)
ERP				
Δ No-Go-$N2_{SART}$ amplitude	-.11 (**ρ**) (p=.67)	-.11 (p=.67)	-.46 (p=.05)	-.31 (p=.20)
Task performance				
Δ MRT	-.10 (**ρ**) (p=.68)	-.26 (p=.29)	-.03 (p=.91)	-.05 (p=.84)
Δ Commission errors	-.01 (**ρ**) (p=.97)	-.06 (p=.82)	.12 (p=.62)	.16 (p=.53)
Δ CV	-.10 (**ρ**) (p=.68)	-.33 (p=.18)	-.05 (p=.83)	-.01 (p=.97)

Figure 21: Scatterplot of treatment response of no-go-$N2_{SART}$ amplitude with change in inattentive symptoms



Note: Negative values of no-go-$N2_{SART}$ denote increased amplitude, whilst negative values for change in inattentive symptoms denote decreased inattentive symptoms at time 2

6.4.8 Correlation of treatment related change in task performance and neurophysiological measures

Taking forward cognitive and electrophysiological measures which showed a significant improvement after treatment (i.e. a change from time 1 to time 2 in the ADHD group alone), a series of correlational analyses were carried out to investigate the relationship between measures which showed significant treatment response in the ADHD group. Analyses revealed high correlations within change between commission errors with coefficient of variance (rho=.78, p<.001), and with MRT (rho=.54, p=.02). Treatment related change in commission errors showed a trending association with treatment related change in theta during the SART (rho=.45, p=.052). All other comparisons were non-significant. Full correlational tables are shown in appendix 6, alongside statistics for Bonferroni correction.

6.5 Discussion

This open label study of methylphenidate (MPH) treatment replicates previous research showing that emotional lability (EL) and functional impairment exhibit a good response to MPH, and that change in EL is correlated with treatment response of ADHD symptoms in adults with ADHD. Contrary to predictions, reductions in EL had limited influence on improvements in functional impairment. Instead, response to treatment of daily life impairment was more strongly associated with improvements in the core ADHD symptom domains.

Change in a variety of neurophysiological and task performance measures during resting conditions and on the Sustained Attention to Response Task (SART) was seen after treatment in ADHD participants. ADHD participants exhibited reductions in commission errors and coefficient of variance (CV), and increases in Mean Reaction Time (MRT), theta activity during rest to task transition, and increased negativity of the no-go-$N2_{SART}$ component. Two of the three measures associated with EL in Chapter 5 did not show treatment-related change in the ADHD group, including within-subject variability in reaction time (SD-RT) and the latency of the no-go-$P3_{SART}$ component. Furthermore, none of the identified cognitive measures which were responsive to treatment were correlated with treatment response in either EL or the symptom domains of ADHD.

Whilst it is possible that the remaining high levels of EL in ADHD subjects are related, at least in part, to those cognitive functions which did not respond to treatment, the findings cast uncertainty on earlier findings reported in Chapter 5, which associated elevated EL on the CNS-LS with commission errors. In this study, ADHD subjects showed a normalisation of commission errors after returning for assessment after treatment with MPH. However, this reduction did not correlate with change in any measure of EL. However, these findings must be interpreted with caution due to the limited power to detect correlational associations in the current sample.

It may be that many case-control effects would often not be reflected in treatment effects, in some cases due to a lack of treatment response, or due to placebo or practice effects. A second interpretation of this finding relates to potential pleiotropic rather than mediating or causal effects of neurobiological correlates and behavioural symptoms. It is not clear whether these cognitive functions mediate the effects of genetic and/or environmental risk factors on behavioural symptoms (intermediate phenotypes), or rather reflect one of many parallel outcomes of such risk factors (pleiotropic effects), reflected in different underlying neuronal circuitry or neurochemistry (Kendler & Neale, 2010).

6.5.1 Emotional lability and impairment

Previous placebo-controlled MPH trials have reported comparable treatment effect sizes for ADHD symptoms (Reimherr, et al., 2007; Rosler, et al., 2010), much like the results shown here where effect sizes for EL were similar to those of inattention and hyperactivity-impulsivity symptoms. Moreover, current findings replicate previous work which reveals a correlated treatment response of EL and ADHD symptoms (Reimherr, et al., 2010; Reimherr, et al., 2007), although correlation coefficients in this study were in the moderate rather than high range reported in previous studies.

Overall the reductions in EL as measured by the ALS-SF showed highest correlations with decreases in hyperactive-impulsive symptoms, whilst change in the CNS-LS was most strongly associated with change in inattentive symptoms. In investigations of the ALS-SF subscales, no significant correlations were seen for change in anxiety-depression with change in hyperactive-impulsive or inattentive symptoms, in accordance with results

presented earlier in Chapter 3, where this subscale was most strongly predicted by subthreshold comorbid symptomatology rather than symptoms of ADHD. Whilst earlier analyses in chapter 3 associated all other subscales and overall measures of EL with symptoms of hyperactivity-impulsivity, in the current analyses reductions in depression-elation subscale was most highly correlated with change in inattentive symptoms. This indicates although at face value hyperactive-impulsive symptoms may show the strongest association with most features of EL, symptoms of inattention may also exert an important influence, and play a key role in treatment response of EL.

Current results also replicate findings from a previous double-blind MPH treatment trial which showed treatment-related improvements in quality of life and daily functioning in adults with ADHD, which was correlated with reductions in hyperactivity-impulsivity symptoms (Buitelaar, et al., 2012). The current study supports these findings in relation to major life impairments centred around family and risk activities. However, improvements in work, life skills (managing money, hygiene, appearance, sleep and health) and social problems were associated with response of inattentive symptoms. Reductions in EL only predicted change in impairments in WFIRS-S self-concept subscale (measuring a number of emotional and self-esteem related problems), which are more closely associated with emotional function.

However, although clear reductions of ADHD symptoms, EL and impairments were seen at time 2 in the ADHD group, indicative of treatment effects, none of these measures showed normalisation with treatment. High levels of symptomatology, EL and impairment remained in the ADHD group. This suggests that even after treatment with MPH, adults with ADHD remain significantly impaired, and indicate the need for further support in the form of improved optimisation of medical treatments and the additional use of non-pharmacological treatment in these individuals.

6.5.2 Task performance

Significant changes in commission errors, mean reaction time (MRT) and the coefficient of variation (CV) were seen in the ADHD group, in the absence of comparable change in controls. Individuals with ADHD showed a sharp decrease in commission errors during the second assessment, where they made fewer commission errors, on average, than control

participants. Findings are in line with previous studies of children and adults with ADHD showing MPH-related reduction in commission errors on the continuous performance test (CPT; Boonstra, Kooij, et al., 2005), and during a go/no-go (GNG) task (Broyd, et al., 2005). ADHD subjects showed an increase in MRT at follow-up assessments, whilst control subjects showed a decrease. In healthy adults, reduced reaction time across repeated tasks has been related to practice effects (Flehmig, Steinborn, Langner, Scholz, & Westhoff, 2007). Conversely, increased reaction time in adults with ADHD has been reported in two studies of MPH response (Boonstra, Kooij, et al., 2005; Ohlmeier, et al., 2007). In the ADHD group, a negative correlation between change in MRT and change in commission errors indicates that increased MRT was correlated with reduced commission errors, suggesting this may reflect a less impulsive responding style in individuals with ADHD at time 2.

Reductions in SD-RT at time 2 were seen in both ADHD and control groups, indicative of practice effects which are common to both groups. Whilst results are in line with previous research of speeded reaction time tasks in healthy and brain injured subjects which have shown task repetition related reductions in SD-RT (Flehmig, et al., 2007; Schweinberger, Buse, & Sommer, 1993), they are at odds with some previous research showing reductions in response variability after treatment (e.g. Boonstra, Kooij, et al., 2005; Castellanos, et al., 2005; DeVito, et al., 2009). This discrepancy of findings may well be related to the instructions given during the performance of the SART task, where participants were asked to time their response to the offset of the stimulus. This may have resulted in a greater homogeneity of responding across the two presentations of the task in both groups. An alternative explanation can be given in light of findings by Castellanos and colleagues (2005), who revealed that children with ADHD showed an increase, rather than decrease in reaction time oscillations during a repeated reaction time with placebo, and a reduction in reaction time oscillations when treated with MPH. This indicates that that practice effects may operate differently in ADHD and control participants. However, it is not possible to test for this effect in the current sample. Future studies must consider carrying out parallel assessments on an untreated, or placebo treated ADHD participants also.

A significant reduction in CV was seen in the ADHD group alone between time 1 and time 2. At time 2 very little difference in CV remained between ADHD subjects and controls, indicative of a normalization of this measure. However, this normalization in the ADHD

group is resultant from aberrations in the two component parts which make up CV, namely a trending differences for SD-RT (p=.08) and MRT which was enhanced at follow-up.

6.5.3 Quantitative electro-encephalography: Theta and beta activity

Analysis of quantitative electroencephalographic (EEG) indices, during resting and task activity and before and after treatment initiation yielded no significant group difference or group interactive effects in relation to theta-beta ratios, or beta activity. However, as shown graphically in fig. 18, ADHD subjects showed limited rest to task change in theta power at time 1, and a normalisation of rest to SART transition effects at time 2.

Change in theta during the SART in the ADHD group showed a trending positive correlation with change in commission errors, with decreased theta activity between time 1 and time 2 being associated with reduced commission errors. Enhanced theta in mid frontal sites has been noted during response errors, resulting in the postulation of the role of theta activity in action monitoring, error monitoring and cognitive control and the prediction of error for behavioural adjustment (Cavanagh, et al., 2010; Cohen, 2011; Cohen & Cavanagh, 2011; Luu, et al., 2004).

6.5.4 Event Related Potentials (ERPs)

Trending differences between ADHD and control groups were seen for the latency of the no-go-$P3_{SART}$ and the amplitude of no-go-$N2_{SART}$. The latency of the no-go-$P3_{SART}$ remained unchanged between assessments in participants with ADHD (time 1 latency: 450.38ms; time 2 latency: 450.04ms). Although this does not replicate some previous work in children (Sunohara, et al., 1999), which showed a latency reduction in the no-go-P3 after treatment, it is worth noting that results from this study are based on performance on a CPT task, and results may not so readily be generalised to the current study in adults investigating response to the SART. In contrast to findings in children which having showed increased no-go-P3 amplitudes after MPH treatment, findings are more in line with those previously reported in adults, which showed limited effects of MPH treatment on ERP measures (Ohlmeier, et al., 2007), although limited power due to small sample size (N=10) is likely to have been a problem in this study.

However, significant interactive effects with time at assessment were seen for the amplitude of the no-go-$N2_{SART}$, with individuals with ADHD showing increased negativity of this component after treatment with MPH. Results support previous research which identified increased negativity of no-go-N2 components during GNG and stop signal (SST) tasks in children and adolescents with ADHD after treatment with MPH (Broyd, et al., 2005; Groom, et al., 2010; Pliszka, et al., 2007). The N2 component is often described as reflecting the activity of a neural network involving prefrontal areas regulating attentional orienting and motor response preparation, with enlargement of amplitude on no-go trials being specifically associated with response inhibition processes (Banaschewski, et al., 2004; Falkenstein, et al., 1999; Pliszka, et al., 2007). However, other research has linked the no-go-N2 to the detection of response conflict (the conflict between the prepared and required response) or response monitoring, rather that inhibitory functions (Donkers & van Boxtel, 2004; Kok, Ramautar, De Ruiter, Band, & Ridderinkhof, 2004).

6.5.5 Lack of association of cognitive and neurophysiological measures with emotional lability but some association with inattentive symptoms

One of the primary aims of this study was to investigate the response of cognitive measures which were associated with EL in Chapter 5 and investigate potentially shared treatment effects with EL. Change after treatment was noted in a variety of cognitive measures investigated here. However, two of the three measures previously associated with EL in Chapter 5 (i.e. within-subject variability in reaction time (SD-RT) and no-go-$P3_{SART}$ latency) did not show any change with treatment. Of the three cognitive variables which were previously associated with EL in Chapter 5, only commission errors showed a significant and specific reduction in the ADHD group.

Although a significant reduction in EL was seen after treatment with MPH, high levels of EL remained in the ADHD group. It is possible that the remaining elevated EL in ADHD subjects are related, at least in part, to those cognitive functions (i.e. SD-RT and no-go-$P3_{SART}$) which did not respond to treatment. Furthermore, no other cognitive and neurophysiological measures which responded to treatment in this study were correlated with treatment response in EL. This suggests that treatment effects show broad benefits across symptom domains and cognitive and neurophysiological measures, but that the symptom domains do

not appear to share common treatment mechanisms with the measured cognitive and neurophysiological processes. This further raises the question that if they do not share treatment mechanisms, the cognitive-neurophysiological measures, in most cases, are unlikely to reflect mediating (causal) processes that underlie the symptoms and impairments of ADHD.

Results also raise questions regarding earlier findings in Chapter 5 associating elevated EL on the CNS-LS with commission errors. In the current study, ADHD subjects showed a normalisation of commission errors after treatment with MPH. Commission errors are often interpreted as reflecting impulsivity or an inability to inhibit a prepotent response (Boonstra, Kooij, et al., 2005; Corkum & Siegel, 1993). Specifically, the hypothesis by Barkley (Barkley, 1997, 2010), which defines EL as 'emotional impulsivity', proposes a common cognitive dysfunction in the form of a generalised inhibitory deficit underlying symptoms of EL and ADHD. The current results indicate that at least in terms of motor inhibition failures, this relationship does not hold true, since reductions in commission errors were not associated with concurrent improvements in either ADHD symptom or EL. This conclusion is also supported by previous cognitive studies in children and adults which indicate that inhibitory processing deficits may be secondary to impairments in attentional orienting and preparation impairments (Banaschewski et al., 2004; McLoughlin et al., 2010).

Associations between treatment-related cognitive change and response of ADHD symptoms were also broadly non-significant, with the exception of a moderate negative correlation ($r=-0.46$) between the no-go-$N2_{SART}$ amplitude and inattentive symptoms in the ADHD group. The direction of this effect is contrary to expectations since both variables showed significant treatment response. The results here indicate the improvements in one are at the expense of the other. This appears counter-intuitive, since as noted previously, the increased negativity of the N2 during no-go trials is believed to reflect the increased additional processing requirements of inhibitory processes, or response conflict. Other research has linked the amplitude of the no-go-N2 to more general cognitive control processes, linking amplitude differences to perceptual overlap between go and no-go stimuli, and deviance from expectation (such as a novel or rare stimulus; Folstein & Van Petten, 2008; Nieuwenhuis, Yeung, & Cohen, 2004). Whilst this may indicate a cognitive marker of resistance to treatment, it may also reflect greater processing efforts in the

context of treatment-related increases in energetic resources in individuals with persistent inattentive symptoms, as indicated by the trending correlation between change in task transitional effects and change in no-go-$N2_{SART}$ (appendix 6). Further research is required to test the robustness of the association between treatment response in the no-go-$N2_{SART}$ and inattentive symptoms, and investigate the mechanisms underlying the relationship.

6.5.6 Limitations

To determine whether an individual's cognitive abilities or symptomatic presentation have been significantly influenced by treatment, it is necessary to establish whether the observed changes from the initial assessment time are reliable and exceed those expected for comparable treatment-free subjects tested over similar intervals (Chelune, Naugle, Luders, Sedlak, & Awad, 1993). Potential practice effects cannot be discounted in this study, although they are likely to have been minimized by the longer follow-up period employed here, and by the retention of the control group at time 2, which allowed the identification of generalized practice effects across both groups (Hood, et al., 2005). However, differences across time points seen in ADHD subjects alone may be attributable to a variety of additional effects: task repetition may have a different impact on individuals with ADHD and control subjects (Aman, Roberts, & Pennington, 1998), and placebo effects, commonly seen in controlled treatment trials of ADHD (e.g., Reimherr, et al., 2007; Rosler, et al., 2010), are likely to be confounded with treatment effects.

A clear caveat to the approach used in this chapter is the correlation between difference scores (pre- to post-treatment change in variables of interest), a method which although widely used, is relatively contentious. There has been some discussion regarding the reliability of this methodology (e.g. Williams & Zimmerman, 1996). For example, it has been noted that error measurements occur independently at two different assessments and that error variances contributing to difference scores are therefore assumed to be additive, leading to a loss of reliability. However, mathematical modelling of change scores under a number of different manipulations of reliability coefficients of initial test scores, and change in variance from pre-to-post-test led authors to conclude that gain scores are sufficiently reliable for research purposes when pre-test scores themselves are reliable (Williams & Zimmerman, 1998). However, others have stated that difference scores should only be

preferred in controlled experiments with random assignment to conditions (May & Hittner, 2010), which was not carried out in this study. Despite these disputed and contentious properties of change scores, the correlation of change scores carried out here allows for the replication of previous reported work in this area of research (e.g. Reimherr et al., 2007, 2010).

The high rate of participant drop out (24% ADHD, 17% controls) in this study is another clear limitation to interpretability. ADHD patients underwent initial assessments whilst on the waiting list for a clinical assessment for ADHD, and on average remained on the waiting list for another 2 months before the clinical assessment took place (range 0-2.8 months). Community healthcare teams were also frequently slow to finalise treatment options, and treatments were started on average 2.5 months after the clinical assessment for ADHD was completed (range 0-7.8 months). The slow rate of treatment for many participants led to disillusionment and frustration in many patients, which is likely to have influenced retention rates. Moreover, the community treatment design adds further limitations, since it did not enable an equivalent treatment titration protocol for all patients. Many ADHD participants attended follow-up assessments describing an ineffective dosage, but found treatment adjustment in community healthcare teams to be difficult. It is therefore possible that the treatment response identified in the current study is an underestimate of the effects that could be seen in a more controlled trial.

Most importantly, the study is likely to have been underpowered, indicated by the lack of replication of some case-control differences seen in the larger sample in Chapter 5 (in for example SD-RT and the no-go-$P3_{SART}$). Post hoc power calculations indicate that the current study only had approximately 60% power to identify a correlation coefficient of 0.5 (two tailed), and only 40% power to identify a moderate correlation of 0.4 (two tailed). This is in line with results presented here, where correlational analyses in the ADHD group were only able to identify moderate to large effects at acceptable significance levels, which means that potentially meaningful small to moderate associations between cognitive and self-report measures may have been missed. This highlights the need to further research using this methodology, using a larger sample.

6.5.7 Conclusions and future directions

In summary, this study replicates previous controlled trials which show improvements in ADHD symptoms, EL and daily functional impairment after treatment with MPH. Moreover, EL and ADHD symptoms show a correlated response pattern, potentially indicating the importance of shared treatment mechanisms. Reductions in functional impairment in a number of daily life domains were primarily associated with decreased ADHD symptomatology rather than EL.

Although this study failed to find treatment-related change in two measures previously associated with EL in Chapter 5, a number of improvements in markers of cognitive dysfunction were identified after treatment. Treatment with MPH were associated with reduced inhibitory failures and enhanced inhibitory processing or conflict monitoring, a slowing of reaction time, and a normalization of task-related increase in theta activity in individuals with ADHD after treatment. Cognitive and neurophysiological measures which showed significant change after treatment, including commission errors (associated with EL in Chapter 5), were not associated with reductions in EL. Correlation were also not seen for treatment response in the majority of these measures with change in ADHD symptom dimensions, with the exception of enhanced no-go-$N2_{SART}$ amplitude, which was associated with a poorer response of inattentive symptoms. Results suggest that the no-go-$N2_{SART}$ may be a marker for poor treatment response, or alternatively indicative of additional processing efforts in those with continuing inattentive symptoms after treatment. Further research is required to elucidate the relationship between this ERP marker and inattentive symptoms in the context of treatment response. Overall, results indicate that although treatment shows improvements across symptom domains and cognitive and neurophysiological measures, many are unlikely to share common treatment mechanisms.

The study is limited by its open-label fixed order design and the small sample investigated. Results show no relationship between treatment-related change in cognitive function and measures of EL. However, a larger placebo-controlled study would be required to confirm these findings in the absence of additional confounds which may have increased noise in the data and masked meaningful relationships between these variables.

Chapter 7: Overall conclusions and future directions

7.1 Overview of primary findings

The overall aim of this thesis was to further our understanding of the association between ADHD and emotional lability (EL) in adults, bringing together a diversity of methodologies and approaches to investigate this association and clarify the underlying clinical, behavioural and cognitive features of EL in ADHD.

The work presented in this thesis can be separated into two broad sections, the first examining behavioural and clinical features and concomitants of EL in ADHD; and the second which focused on identifying common aetiological factors which may underpin both EL and ADHD symptoms, exploring cognitive and neurophysiological deficits common to both EL and ADHD, and examining shared treatment response of ADHD symptoms, cognitive functions and EL.

This thesis presents a number of novel findings in addition to results which are complementary to previous research. Research included in this thesis is the first to: 1) consider EL in ADHD after controlling for comorbid conditions and subthreshold comorbid symptomatology; 2) investigate EL in the context of daily adversities; 3) characterise the features and dynamics of emotional experience in daily life in ADHD patients; 4) take an approach of comparing and contrasting the contribution of a variety of cognitive deficits implicated in ADHD to EL; and 5) examine common treatment mechanisms between ADHD, EL, impairment and cognitive functions.

7.1.1 Principal findings

In table 25, the original hypotheses from each chapter are restated with a brief summary of the relevant findings and an indication of whether each hypothesis was supported. Of the 17 proposed hypotheses in this thesis, nine were supported by the evidence obtained, 6 were partially supported, and no confirmatory evidence was available for 2. The following section provides a brief overview of findings from each Chapter alongside interim conclusions made.

Table 25: Summary of findings in relation to original study hypotheses

Chapter 3 – *Investigating the clinical concomitants of EL in adults with ADHD*

Hypothesis	Supported?	Specific Results
1) EL will be significantly elevated in adults with ADHD	Yes	• All EL measures were elevated in ADHD participants compared with controls • EL predicted ADHD diagnosis by receiver operating characteristic (ROC) analysis
2) ADHD symptoms will be associated with EL independently from comorbid symptoms	Yes	• The majority of EL measures (4/5) remained elevated in ADHD participants after excluding all individuals with comorbid symptoms • EL scales were moderately correlated with symptoms of hyperactivity-impulsivity (r=.56-.59) and inattention (rho=.39-.40) • Hyperactivity-impulsivity was the primary predictor of EL, with some EL scales showing additional influence of subthreshold comorbid symptoms and intellectual function (IQ). Only one EL subscale (anxiety-depression) was predicted solely by subthreshold comorbid symptoms
3) ADHD symptoms will be associated with EL independently from antisocial behaviour	Yes	• EL remained elevated in ADHD subjects on all scales after excluding individuals with antisocial behaviour • Symptoms of hyperactivity-impulsivity and IQ were primary predictors of antisocial behaviour, with no independent effects of EL
4) EL will independently contribute to impairment in daily life	Yes	• One measure of EL (CNS-LS) predicted impairment in family, school, life skills and social problems beyond the influence of ADHD symptoms. Hyperactivity-impulsivity only predicted risk activities, and contributed to social impairments. Self-concept (feeling bad, incompetent, discouraged and frustrated) was only predicted by subthreshold comorbid symptoms

Chapter 4 – *Characterising emotions of in adults with ADHD in the context of everyday life using ambulatory monitoring*

	Hypothesis	Supported?	Specific Results
5)	Individuals with ADHD will be characterised by greater intensity of negative emotions	Yes	• Participants with ADHD showed greater intensity of all negative emotions assessed: *irritable, frustrated* and *angry* compared with control participants. • No group differences were seen for intensity of positive emotions
6)	Individuals with ADHD will be characterised by greater instability of emotions	Partially	• Greater instability of *irritable* and *frustrated* was seen in ADHD participants, robust to corrections for average emotional intensity. Instability of *angry* did not significantly differ between groups after an equivalent correction • No group differences were seen for instability of positive emotions
7)	Individuals with ADHD will report more frequent bad events and these will be associated with change in reported emotions	Yes	• Bad events were more frequently reported by ADHD participants • ADHD participants reported bad events as having a larger impact on their current state than controls • After bad events, ADHD participants showed an exaggerated anger response, and a slower return to baseline levels than controls • Bad events were significantly associated with intensity of *irritable*, *frustrated* and *angry*, as well as instability of *frustrated.* Reported impact of bad events was associated with intensity of *irritable*, and *angry*
8)	Identified negative and unstable emotions in daily life will be correlated with EL reported in rating scales	Partially	• One self-report measure of EL (ALS-SF) was significantly associated with all real-time emotional instability/intensity indices differing between groups • Correlations between the ALS-SF were moderate for summary measures of intensity and instability of negative emotions in controls (range=.40-.62) but were lower in ADHD participants (range= .13 to .44)

Chapter 5 - *investigating cognitive correlates of EL in ADHD using electrophysiology during a resting condition, the Continuous Performance Test with flankers (CPT-OX) and the Sustained Attention to Response Test (SART)*

Hypothesis	Supported?	Specific Results
9) ADHD participants will be characterised by elevated task performance deficits	Yes	• ADHD participants only showed elevated omission errors on the CPT-OX • Within-subject variability in reaction time (SD-RT), coefficient of variability (CV), commission errors and omission errors were significantly increased in ADHD participants on the SART
10) ADHD participants will exhibit quantitative EEG markers of under-arousal (reduced beta, and enhanced theta and theta-beta ratios)	Partially	• Groups did not differ in any quantitative EEG measures during rest or tasks • Control participants showing a significant increase in theta and beta activity from resting condition to the SART which was absent in ADHD participants
11) The ADHD group will exhibit covert attentional orienting and preparatory processing deficits on the CPT-OX	No	• Only trending group differences for Event Related Potential (ERP) response to the cue were seen, indicating that this is not a reliable marker of ADHD in adults
12) Inhibitory processing deficits will be seen on CPT-OX and SART tasks in ADHD participants	Partially	• No group differences were seen for any ERP measures in the CPT-OX • On the SART, ADHD participants exhibited a significant increase in the latency of the no-go-P3 component
13) The contribution of different cognitive deficits associated with ADHD in this study will be explored in relation to self-reported EL. *Exploratory analysis with no formal hypotheses, since the literature was inconclusive*	-	• Across both groups, swift emotional changes (ALS-SF) were predicted by SD-RT, significant even after including diagnostic status as predictor. Frequent negative emotions (CNS-LS) were predicted by commission errors and the SART no-go-P3 latency, but did not withstand the inclusion of diagnostic status as predictor. • No significant correlations were seen between EL and cognitive measures in the ADHD group alone

Chapter 6 – *Examining the response of behavioural concomitants of EL in ADHD as well as neurophysiological processes identified as associated with EL in Chapter 5 after treatment with methylphenidate (MPH)*

Hypothesis	Supported?	Specific Results
14) Treatment will give rise to reductions in ADHD symptoms, EL and impairment in daily life	Yes	• Reductions in ADHD symptoms, all measures of EL and impairment (with the school impairment) were seen in the ADHD sample after treatment.
15) ADHD symptoms and EL will show a correlated treatment response	Yes	• Treatment co-variation of ADHD symptom domains and EL measures were moderate (r=.33-.63) for overall EL scales (CNS-LS and ALS-SF).
16) Reductions in self-reported impairment will be predicted by improvements in EL	Partially	• EL treatment response only predicted change in self concept (emotional and self-esteem problems). For all other areas of functional impairment, improvement was predicted by reduction in ADHD symptoms.
17) Cognitive deficits identified prior to treatment in ADHD participants will respond to treatment	Partially	• ADHD participants showed significantly reduced commission errors and CV after treatment. No significant or specific treatment change was seen for omission errors or SD-RT. • Task transition deficits in theta power normalised after treatment in ADHD participants. No significant effects were seen for beta or theta-beta ratios • Latency of the SART no-go-P3 component did not change after treatment
18) Cognitive domains associated with EL prior to treatment in Chapter 5 will show a common treatment response with EL	No	• Treatment response was not seen for SD-RT nor SART inhibitory P3 latency • Commission errors normalised after treatment, but were not correlated with treatment response in EL.

Abbreviations: CNS-LS: Centre for Neurologic Studies – Lability Scale; ALS-SF: Affective Lability Scale – Short Form

Chapter 3: The first study evaluated the influence of comorbid clinical symptoms on EL, and investigated the relationship between EL and impairment. Although enhanced emotional lability was seen in the context of antisocial behavior and subsyndromal comorbid symptoms, enhanced EL in ADHD was not accounted for by these co-occurring clinical features. The primary predictor of EL was hyperactivity-impulsivity. Moreover, EL predicted a host of daily impairments in adults with ADHD beyond the influence of core ADHD symptoms of inattention and hyperactivity-impulsivity. Results indicate that EL in ADHD is primarily associated with ADHD itself rather than comorbid conditions; and that EL may be an important clinical feature, since it helps to explain some of the impairments not accounted for by classical ADHD symptoms. Since EL was highly predictive of ADHD diagnosis, it was argued that ADHD should be considered as an important differential diagnosis in patients with unstable emotional symptoms.

Chapter 4: One limitation of the first study was the reliance on retrospective self-report, as a variety of recall biases may affect results from self-report ratings, and such biases have been found to operate differently in psychiatric and healthy populations. The second study circumvented these problems by using prospective longitudinal data collection methods. Ambulatory monitoring was carried out over a period of five days, and positive and negative emotional features of ADHD and the influence of daily adversity on emotions was investigated. ADHD participants showed a pattern of increased emotional intensity and instability for negative emotions only. Furthermore, although ADHD participants reported a greater frequency of adverse events, neither elevated intensity nor instability in emotions in the ADHD group could be accounted for by adverse events or their reported impact. In line with previous studies of ambulatory assessment in psychiatric populations, small to moderate correlations were found between indices of EL from ambulatory assessment and those from questionnaire measures. It was concluded that ambulatory monitoring provides results which are complementary to rating scale measures in adults with ADHD, indicating a pattern of negative emotionality and negative emotional instability in ADHD. Moreover, results indicated that although there is interplay between EL and daily adversity in ADHD, EL does not arise as a result of everyday adversity.

Chapter 5: The third study investigated the role of cognitive function in EL. Task performance indices and electroencephalographic measures (EEG and ERP), were acquired

during a resting condition, the cued Continuous Performance Task (CPT-OX) and the Sustained Attention to Response Task (SART). Some cognitive deficits previously associated with ADHD were replicated (enhanced within-subject variability in reaction time (SD-RT), commission errors, and omission errors), and some were not (group differences were not seen on any ERP measures of the CPT-OX, nor quantitative EEG markers of under-arousal during resting conditions). Some novel results were also reported, including a slower inhibitory P3 latency on the SART, indicative of an inhibitory deficit, and lack of rest to task increase in theta and beta activity in the ADHD group. Cognitive measures which significantly differed between ADHD and control participants were then taken forward to investigate the relationship with EL across both ADHD and control groups. SD-RT predicted EL characterised by swift changes in emotion (as measured by ALS-SF), significant even after including diagnostic status as a predictor. EL as characterised by frequent negative emotions (measured by the CNS-LS) was predicted by commission errors and the latency of the SART inhibitory P3, but did not withstand the inclusion of diagnostic status as a predictor. Results were interpreted as providing support for both the involvement of inhibitory processing deficits in negative emotional patterns, and for more general deficits impacting on variability in response patterns and changeability in emotions.

Chapter 6: The final study revisited measures of EL, ADHD symptoms, impairment and cognitive and neurophysiological measures from resting condition and SART in a smaller sample of adults after treatment with methylphenidate, and a control group matched for follow-up duration. EL, ADHD and impairment measures all improved after treatment. Reductions in functional impairment were primarily predicted by decline in ADHD symptoms, and improvements in EL and ADHD symptoms were found to co-vary with treatment. Treatment-related changes were absent in two of the three measures previously associated with EL (the SD-RT and the latency of the SART inhibitory P3). However, treatment response was seen across a range of other cognitive measures: enhanced amplitude of the inhibitory N2 component, reduced commission errors, slowed reaction times, reduced coefficient of reaction time variability, and a normalization of task-related increase in theta activity. No treatment-related changes in cognitive or electrophysiological measures were associated with reductions in EL, or either of the two ADHD symptom dimensions, with one exception. The novel finding that enhancement of the

inhibitory N2 amplitude was associated with a poorer response of inattentive symptoms, suggesting that this may be a marker of the treatment response, or alternatively indicating additional processing efforts in those with continuing high inattentive symptoms after treatment. Results indicate broad effects of methylphenidate across behavioural and cognitive domains. Although ADHD symptoms, EL and impairment appear to share a common treatment response, this was not found to extend to cognitive measures. It was concluded that many cognitive measures do not share common treatment mechanisms with behavioural features of EL and ADHD.

7.2 Recurring themes

A number of recurring themes were seen across different analyses reported in this thesis. First, there is a clear congruency of the clinical descriptors of EL in ADHD with the measures used to capture EL, which concur with findings from ambulatory monitoring. These include both enhanced instability or volatility of emotions in ADHD alongside heightened negative emotions.

Elevated EL was observed in adults with ADHD across a number of measures and methodologies, and after controlling for a myriad of confounders. EL was correlated with ADHD symptoms before treatment, and during treatment response, indicative of a consistent relationship between these behavioural problems and a potential shared treatment response mechanism. Furthermore, even after significant improvements with treatment, enhanced EL remained in ADHD participants alongside elevated symptoms of inattention and hyperactivity-impulsivity. This is again suggestive of the constancy of EL, and indicates that whilst EL may be improved with treatment, it is likely to continue to remain a problem.

Another recurring theme of this thesis was heterogeneity of EL. The two self-report measures of EL used in the current study showed differential relationships to: 1) clinical features (ADHD symptoms and subthreshold comorbid symptomatology); 2) impairment; 3) EL as measured in the context of daily life by ambulatory monitoring; 4) measures of cognitive and intellectual function (inhibitory function, within-subject variability in reaction time, and IQ); and 5) relationship to clinical symptoms in treatment response. This indicates that EL is unlikely to be a unitary construct and that studies investigating the relationship

between EL and ADHD may report different results depending on the measures used. Further research is required to identify different features of EL which may show relative independence and investigate their relationship with ADHD.

Although associations between cognitive processes and EL were identified in Chapter 5, their effects were small. Cognitive measures were correlated with self-reported features of ADHD and EL across both groups. Correlations were generally replicated within control sample but were absent in the ADHD group. Moreover, treatment response was seen in a large proportion of cognitive measures which showed initial differences between ADHD participants and controls. The broad lack of co-variation in treatment response seen for these measures with EL indicates that cognitive findings which were associated with EL can only be considered preliminary and require further investigation and replication.

7.3 General discussion

Overall, this thesis fills a number of gaps in the literature and clinical understanding of the nature of the relationship between EL in ADHD.

The initial two results chapters (Chapters 3 and 4), investigate EL as measured by self-report and by ambulatory assessment. Despite using very different methodologies they report clearly complementary findings. This indicates that elevated self-reported EL in ADHD reported in chapter 3 cannot simply be considered as reflecting biases in the recall and reconstruction of emotional experiences, which are commonly reported in the literature. Moreover, the results presented in chapter 4, identify EL in the daily lives of individuals with ADHD, showing good ecological validity. The consistent finding that individuals with ADHD are more emotionally labile, characterised by greater intensity and instability of negative emotions, independent of methods by which EL is measured indicates that elevated EL reported is not likely to have arisen as the result of a methodological artifact.

This thesis aimed to investigate the relationship between EL and ADHD in relation to inattention, hyperactivity-impulsivity and impairment, as well as subthreshold comorbid symptoms and adversity. Important findings include the identification of EL in untreated individuals with ADHD who are free from comorbidity and who do not have problems with antisocial behaviour. These findings indicate the value of investigating EL as a co-occurring

feature of ADHD, rather than a feature that is simply reflective of other co-occurring psychopathology. The reported finding that EL is more strongly associated with hyperactivity-impulsivity than inattentive symptoms, and predicts daily impairment is in line with much of the published research. Moreover, the finding that adversity contributes to EL, but does not wholly account for it suggests a less reactive behavioural profile than has previously been suggested (see section 7.5 for further discussion), with the present research being more indicative of chronic problems with the intensity and instability of negative emotions. Results have clear implications for upcoming revisions to diagnostic formulations (see sections 7.5 and 7.6 for further discussion).

Although further research of a similar nature is required in children to obtain a clear indication of the specificity of these findings to adults with ADHD and their potential continuity from childhood, the current results indicate the need for the awareness of ADHD as a potential contributing condition to patterns of EL seen clinically, and indicate that further research is required to investigate the relationship between ADHD symptoms and newly proposed diagnostic conditions in the DSM-5 which primarily reflect features of EL.

This thesis also attempted to investigate common aetiological factors which may underpin both EL and ADHD symptoms. This was done by investigating the relationship between EL and cognitive and neurophysiological deficits commonly reported in ADHD, and any shared or disparate responses to treatment. The use of electrophysiological measures (ERP and EEG) allowed the direct investigation of brain function and activity during rest and task conditions, and enabled the investigation of cognitive measures and deficits (for example, inhibitory deficits in the context of correct responses, blunted task-related increases in EEG theta and beta power) in ADHD subjects which would not have been identifiable using task performance data alone. Although findings for chapters 5 and 6, which explored associations between cognitive and neurophysiological indices and EL did not yield a consistent pattern of associations between EL and cognitive measures, and the implications of the results are less clear, they indicate some valuable avenues for future research.

Firstly, findings highlight the heterogeneity of EL, shown by differential relationship between two measures of EL and different cognitive indices in chapter 5. This indicates that findings presented in the literature to date may be more strongly influenced by the measure

of EL used than previously acknowledged, and that further research into a potential fractioning of EL may be required before relationships with cognitive measures can be meaningfully explored, to allow for replicable findings in this area of research.

Secondly, although different relationships were seen between different facets of EL and measures of cognitive function, correlations across these measures (across groups) were typically only of a small effect size, and did not tend to replicate in within-group analysis. This suggests although there may be some relationship between the cognitive measures investigated here and EL, the association between these measures is likely to be weak, and the cognitive measures identified are therefore unlikely to account for much of the observed variance in EL. Therefore, although some supporting evidence was found for the hypothesised role of inhibitory functions in EL (Barkley, 1997, 2010), the current results do not suggest that a generalised inhibitory deficit underpins EL in ADHD.

Investigations of treatment response in this sample indicated that whilst ADHD and EL share a correlated treatment response, there was little covariation in the response of EL, ADHD symptoms and measures of cognitive function. Although the study was potentially underpowered, and there were a number of clear limitations to the investigation of treatment response in this sample (see section 7.4.3 for further discussion), these findings may be indicative of a shared treatment mechanism in terms of dopamine enhancement in ADHD, resulting in a wide ranging improvements in a variety of systems which are independent of one another. Treatment response may therefore be a valuable approach to teasing apart shared and non-shared systems which underpin co-occurring features of ADHD, meriting future research.

7.4 Strengths and limitations

7.4.1 Sample characteristics

7.4.1.1 Exclusion criteria

From the participant sampling procedure outlined in Chapter 2, it can be seen that due to stringent exclusion criteria the vast majority of adults referred to the Adult ADHD Clinic were not eligible to participate in this study. This gave rise to two major limitations of this

study. The first is that results may not generalise to many adults with ADHD, who are frequently affected by comorbid psychiatric conditions and substance use disorders. The second is the resulting small sample size which may have been underpowered for some investigations, most notably in the studies examining cognitive function and treatment response, where some trending results were identified and tests frequently did not withstand correction for multiple testing.

However, the restricted sampling procedure can also be considered as offering a number of benefits to the study. For example, the drawback of including individuals with ADHD alongside comorbid conditions and/or substance abuse problems in a study with a primary purpose of investigating EL is that it then becomes unclear whether EL is associated with ADHD or the co-occurring clinical conditions. As noted previously, Irritability or temper problems are included in the diagnostic criteria for borderline personality disorder, bipolar disorder, ODD and paediatric depression (American Psychiatric Association, 2000). In adulthood self-reported irritability has been associated with anxiety and depression (Pickles, et al., 2010), which were common reasons for the exclusion of individuals from this study.

Lack of replication of some of the cognitive findings previously reported in the literature (most notably covert attentional orienting, preparatory and inhibitory processing deficits on the CPT-OX, and arousal indices at rest) may be attributable to a lack of power and small sample size, although this study used a larger sample size that reported in the previous positive studies. However, the lack of association with ADHD may also indicate that some of the previously observed effects might be secondary to medication or comorbidity effects. Since the current sample was free from comorbid conditions and was not subjected to the standard practice of a brief medication washout prior to assessment, it can be argued that those effects which were identified in this study can therefore clearly be related to ADHD rather than these potential confounds.

7.4.1.2 Gender

The sample was limited to male participants, and all results and conclusions can therefore only be generalized to men with ADHD. Further studies are required to confirm these findings in females. As discussed previously in section 2.8.1, the initial aims of this study

were to include women as well as men in the study sample. However, the low rates of female referrals, alongside frequent treatment for comorbid conditions in women who underwent ADHD assessments meant that recruitment of women was simply not feasible alongside the strict exclusion criteria for the study. Studies which would aim to investigate ADHD in a more gender balanced design would require a much longer duration of study recruitment, or less restrictive exclusionary criteria.

7.4.1.3 Clinical heterogeneity

The majority of investigations to date of key neurophysiological processes in ADHD have been in the combined ADHD subtype. An additional reason for the lack of findings in some cognitive and neurophysiological domains may therefore have been related to behavioural and symptomatic heterogeneity in this sample, which included a range of symptom severity from combined ADHD symptomatology (N=14) to those with very few (≤2) symptoms of hyperactivity-impulsivity (N=8).

However, this increased heterogeneity also rendered it possible to compare the relationship between levels of ADHD symptoms and EL, which resulted in the confirmation that EL is most strongly associated with hyperactive-impulsive symptomatology. These analyses may have lacked power to discriminate between inattention and hyperactivity-impulsivity in a homogeneous combined-type ADHD sample. Moreover, findings confirmed in this thesis are relevant to ADHD patients across a range of clinical severity, which may be important considering the symptomatic heterogeneity which is common within the disorder.

7.3.1.4 Age effects

The broad age-range (18-65 years) of adults in this study may have contributed to negative findings of some neurophysiological measures. Previous studies which have successfully identified case-control differences in the CPT-OX in relation to ADHD have used much narrower age bands (e.g. 18-40 years; McLoughlin, et al., 2010). In healthy aging P3 amplitudes have been found to decrease with age, whilst peak latencies show an increase during a simple discrimination task (Polich, 1997). A longitudinal study from Doehnert and colleagues (in press), who repeated the CPT-OX at 4 different ages, suggests that case-control differences for the cue-P3 and the no-go-P3 decline with increasing age. Similarly,

research on quantitative EEG measures, indicate a developmental decrease in theta-beta ratios (Snyder & Hall, 2006) and an age-related decline in slow wave activity in children with and without ADHD (Benninger, et al., 1984; Bresnahan, et al., 1999; Clarke, et al., 2001). Other studies show a continued decrease in slower band activity (delta, theta and alpha) during healthy cognitive aging from adulthood into middle age (Cummins & Finnigan, 2007; Polich, 1997).

This suggests that even though participant groups were well matched for age, the broad age-range sampled in this study may have contributed to greater age-related variability in measures of interest, potentially masking some meaningful results. Future studies may wish to investigate more homogeneous groups.

7.4.1.5 Diagnostic issues

As described previously in section 2.8.2, the current study had issues with incomplete diagnostic data from standardised clinical interview scales completed during assessment for ADHD at the Adult ADHD Clinic at the South London and Maudsley Hospital. Diagnostic criteria are applied as specified in the DSM-IV at the Adult ADHD clinic, with a structured clinical interview for the 18 ADHD symptoms in childhood and adulthood being used as standard for diagnostic assessments, establishing symptom onset and chronicity before age 7, and confirming the presence of a minimum of 6 symptoms of hyperactivity-impulsivity and/or inattention in adulthood (Conners Adult ADHD Diagnostic Interview for DSM-IV, CAADID; Conners, et al., 2001). However, some clinicians did not formally document their scoring of the CAADID, thereby providing incomplete data for the purpose of research diagnoses and clinical subtyping. Although steps were taken to obtain as complete diagnostic data as possible (see section 2.8.2), this still prohibited diagnostic subtyping and the comparison of inattentive and combined ADHD subtypes in the current study.

This issue may have been avoided by including a standardised diagnostic assessment for ADHD in the assessment battery for the study. However, this would likely have been at the expense of other measures during an already long testing session (in most cases lasting at least 3 hours).

7.4.2 Measures of EL and ADHD

An additional limitation of this thesis is that findings are based exclusively on self-reported measures from participants. The inclusion of informant reports would have strengthened findings, and would be an important area in which to extend analyses. Additional analyses could have been made possible by clear diagnostic data provided by clinician report; however this was not available in the current study.

However, despite these methodological drawbacks, the current study showed some similar findings for EL across two very different measurement techniques (retrospective reporting and prospective longitudinal reporting), indicative of the consistency of the current results.

7.4.3 Treatment investigation

As discussed previously, interpretation of findings of treatment response in this study are limited by the lack of placebo control. Potential practice effects cannot be discounted, although they are likely to have been minimised by the longer follow-up period employed, and by the retention of the control group during the second assessment, which allowed the identification of generalised practice effects across both groups (Hood, et al., 2005). However, differences across time points seen in ADHD subjects alone may be attributable to a variety of additional effects: task repetition may have a different impact on individuals with ADHD and control subjects (Aman, et al., 1998), and placebo effects, commonly seen in controlled treatment trials of ADHD (e.g., Reimherr, et al., 2007; Rosler, et al., 2010), are likely to be confounded with treatment effects.

Although the ideal treatment design to investigate treatment response would have been an extended placebo-controlled treatment trial, this was not feasible due to limited resources for this project. The current research investigated the naturalistic outcome of 'treatment as usual' on methylphenidate in an uncontrolled treatment program. The identification of participants for the study before a diagnosis of ADHD had been confirmed allowed for an extended period of investigation (as required for ambulatory monitoring) whilst patients were not being treated for ADHD. The current study therefore did not interfere with the treatment regimen of individuals with ADHD, unlike many studies where participants are asked to undergo a medication wash-out period prior to assessment. Furthermore, since the

study investigated the effects of methylphenidate after participants had undergone treatment titration in the community over a period of months, this enabled the assessment of longer-term changes in ADHD symptoms, impairment and EL.

7.4.2.2 Problems with community treatment

The high rate of participant drop out (24% ADHD, 17% controls) in the investigation of treatment response is another clear limitation to interpretability. The average duration of follow-up for ADHD patients was 8.2 months, during which time they were being treatment for only 3.9 months. Follow-up was extended by duration on the waiting list before clinical assessment for ADHD, and the time required by community healthcare teams to finalise treatment options. However, whilst these are the statistics for individuals returning to the study, the duration may have been much longer for those who eventually dropped out. A number of problems in obtaining treatment were noted during the study (outlined in detail in section 2.8.3), which may have influenced retention rates.

The community treatment design adds further limitations, since it did not enable an equivalent treatment titration protocol for all patients. Many ADHD participants attended follow-up assessments describing an ineffective dosage, but found treatment adjustment in community healthcare teams to be difficult. It is therefore possible that the treatment response identified in the current study is an underestimate of the effects that could be seen in a more controlled trial.

7.5 Clinical and diagnostic implications

As described previously, EL is specified only as an 'associated feature' of ADHD in the current diagnostic formulation in the Diagnostic and Statistical Manual for Mental Disorders (DSM-IV; American Psychiatric Association, 1994, 2000). This potentially contributes to a lack of awareness of ADHD as a differential diagnosis for clinicians encountering patients with emotional lability. Asherson (2005) and Wender and colleagues (2001) note that adults with unrecognised ADHD are not infrequently misdiagnosed and treated for anxiety, depression, mixed affective disorder, cyclothymia, and borderline and unstable personality disorders. Furthermore, there is some debate regarding the differentiation of ADHD with co-occurring EL from bipolar spectrum disorders, where symptomatic overlap between the two

conditions includes distractibility, psychomotor agitation, talkativeness as well as features of EL (Skirrow, et al., 2012).

In the debate of the differentiation between ADHD and bipolar disorder, it has been suggested that since mood symptoms are not core features of ADHD (not appearing in DSM-IV criteria for ADHD), their presence as a major presenting problem suggests the presence of a mood disorder rather than ADHD (Wilens, et al., 2003). The current study does not support this assertion. Specifically, current results show that EL remains elevated in adults with ADHD even after controlling for subsyndromal comorbid symptoms and antisocial behavior. This fills an important gap in the literature (Skirrow, et al., 2009), since to date it has not been possible to identify whether EL was associated specifically with ADHD or with the host of comorbid conditions which often accompany the disorder.

The current findings also indicate that EL is a strong predictor of ADHD. However, this does not indicate that measures of EL should be used to identify ADHD participants routinely, since EL is also present in a variety of other psychiatric disorders, and ADHD symptoms themselves are better predictors of the disorder. Instead, findings suggest that ADHD should be considered an important differential diagnosis when encountering patients with unstable emotional symptoms; particularly in light of previous research, and work presented in this thesis showing a good clinical response of EL to methylphenidate when treating adults with ADHD (Reimherr, et al., 2010; Rosler, et al., 2010).

It has previously been assumed that individuals with ADHD show a primarily reactive emotional pattern. Biederman and colleagues (2012) describe individuals with ADHD as frequently enjoying normal moods but with a tendency to become frustrated or angry with unexpected emotional challenges. They describe emotions in ADHD as rapidly subsiding and not forming a distinct protracted episode, which would otherwise qualify for a mood disorder. Findings from ambulatory monitoring indicate that these assertions are unlikely to be correct. First, the findings show that negative emotions and emotional instability cannot wholly be explained by greater adversity experienced by individuals with ADHD. Second, ambulatory assessment showed a generalised increased intensity of anger, irritability and frustration over a 5-day period, with results indicative of a chronically irritable mood profile

in some participants with ADHD. These findings suggest that EL in ADHD is a combination of generally negative and irritable moods as well as instable and reactive emotions.

Adults with ADHD who undergo treatment with methylphenidate for ADHD showed significant improvements across ADHD symptom domains, EL and daily life impairment. However, a host of behavioural features, EL and impairments, remain elevated after treatment in individuals with ADHD. This potentially indicates the need for additional support for individuals with ADHD, either in the form of improved optimisation of medical treatments and/or the additional use of non-pharmacological treatment in these individuals. Further studies are needed to investigate the causes of poor clinical response and develop more effective treatment protocols.

7.6 Proposed revisions for the DSM-V

Proposed revisions for the DSM-V (www.dsm5.org) include a new diagnostic category defined by high levels of EL: 'disruptive mood dysregulation disorder' (renamed from 'temper dysregulation disorder'). The most current diagnostic specifications (as of June 2012) are shown in table 26 below. As can be seen a number of the described symptoms appear at face value to reflect emotional problems which have been associated with ADHD, although not enough research has been carried out on EL in ADHD to identify whether the exact specifications of frequency, duration, persistence and impairment would also be met. It has been noted that this diagnostic category is being created to provide a diagnostic 'home' for children with severe non-episodic irritability, who have previously been treated as bipolar patients (Stringaris, 2011). The high rates of antisocial and aggressive behaviour seen in the participants in this study, alongside the generalised irritability shown in ambulatory monitoring, suggests that a number of these criteria may well be met by adults with ADHD who have minimal comorbid symptoms. How this would relate to presentations of EL in children is an important area for further investigation

Table 26: Diagnostic Criteria for Disruptive Mood Dysregulation Disorder outlined in the planned revisions for the DSM-V

(A)The disorder is characterized by severe recurrent ***temper outbursts*** that are grossly out of proportion in intensity or duration to the situation.

1. The temper outbursts are manifest verbally and/or behaviorally, such as in the form of verbal rages or physical aggression towards people or property.
2. The temper outbursts are inconsistent with developmental level.

(B) **Frequency**: The temper outbursts occur, on average, three or more times per week.

(C) **Mood between temper outbursts***:*

1. Nearly every day, most of the day, the mood between temper outbursts is persistently irritable or angry.
2. The irritable or angry mood is observable by others (e.g., parents, teachers, peers).

(D) **Duration:** Criteria A-C have been present for 12 or more months. Throughout that time, the person has not had 3 or more consecutive months when they were without the symptoms of Criteria A-C.

Additional criteria:

(E) Criterion A or C is present in at least two settings (at home, at school, or with peers) and must be severe in at least in one setting.

(F) The diagnosis should not be made for the first time before age 6 or after age 18.

(G) The onset of Criteria A through E is before age 10 years.

Exclusionary criteria:

(H) There has never been a distinct period lasting more than one day during which abnormally elevated or expansive mood was present most of the day, and the abnormally elevated or expansive mood was accompanied by the onset, or worsening, of three of the "B" criteria of mania (i.e., grandiosity or inflated self-esteem, decreased need for sleep, pressured speech, flight of ideas, distractibility, increase in goal directed activity, or excessive involvement in activities with a high potential for painful consequences). Abnormally elevated mood should be differentiated from developmentally appropriate mood elevation, such as occurs in the context of a highly positive event or its anticipation.

(I) The behaviours do not occur exclusively during an episode of Major Depressive Disorder and are not better accounted for by another mental disorder (e.g., Autism Spectrum Disorder, Posttraumatic Stress Disorder, Separation Anxiety Disorder, Dysthymic Disorder). (Note: This diagnosis cannot co-exist with Oppositional Defiant Disorder or Bipolar Disorder, though it can co-exist with Attention Deficit/Hyperactivity Disorder, Conduct Disorder, and Substance Use Disorders. Individuals meeting criteria for both Disruptive Mood Dysregulation Disorder and Oppositional Defiant Disorder should only be given the diagnosis of Disruptive Mood Dysregulation Disorder. If an individual has ever experienced a manic or hypomanic episode, the diagnosis of Disruptive Mood Dysregulation Disorder should not be assigned.) The symptoms are not due to the effects of a drug or to a general medical or neurological condition.

Note: DSM-V draft currently open for final public comment

7.7 Directions for future research

7.7.1 Developmental considerations

There are a number of promising avenues for continued research on EL and ADHD. One previously unexplored approach involves investigating the longitudinal relationship between EL and ADHD. Such work could look at developmental relationships between ADHD and EL, for example investigating whether ADHD symptoms precede EL or whether these behavioural features manifest concurrently. Furthermore, longitudinal analysis could illuminate the relationship between EL and ADHD which persists and remits in adulthood. Previous longitudinal research has revealed a greater developmental decline in hyperactive-impulsive than inattentive symptoms (Biederman, Mick, & Faraone, 2000; Larsson, et al., 2006). The association that was found in this thesis between EL and hyperactivity-impulsivity indicates that problems with EL might diminish alongside hyperactivity-impulsivity during development and be less problematic in adults. However, individuals with ADHD and EL have been shown to be more likely to have more severe and complex symptoms (Reimherr, et al., 2010), and an alternative interpretation is that elevated EL in childhood predicts poorer prognosis for remission of ADHD symptoms.

Although there have been a number of studies in adults with ADHD investigating the shared treatment response of ADHD symptoms and EL, there has been a dearth of research investigating treatment response of EL in children. And despite similarities in descriptions of EL in both children and adults it is not yet clear whether ADHD in children and ADHD in adults shows a similar response to pharmacotherapy for ADHD. The bulk of research in the child literature focuses on EL as a potential side effect from treatment (e.g. Kratochvil, et al., 2007; Wilens, et al., 2003), generally only acquiring data on this measure after treatment has started. A recent review article highlighted this problem, and has called for more research in children in which EL and other emotional problems measured prospectively, to identify change in these measures (Manos, et al., 2011).

7.7.2 Cross-disorder investigations

Another promising avenue for future research is the concurrent contrasting of emotional profiles of individuals with ADHD compared with other psychiatric conditions, including bipolar spectrum disorders, to identify patterns of emotional features and dynamics which are characteristic of each or common to both conditions. This approach has been successful in identifying greater emotional instability in individuals with borderline personality disorder than patients with depression/dysthymia (Solhan, et al., 2009), and could be invaluable for further diagnostic delimitation between disorders which show overlapping symptomatology.

Neurocognitive markers may be considered an important avenue for aiding in establishing differential diagnosis. Recent work by Tye and colleagues (2012) reported on neurophysiological measures which successfully differentiated between children with ADHD, children with autism spectrum disorders, and combined comorbid group. A number of recent studies have investigated neurocogntiive similarities and differences between ADHD and bipolar disorder (reviewed in Skirrow et al., 2012). More cross-disorder studies are required to identify cognitive markers which are disorder specific, and would aid in making differential diagnoses for patients with symptoms that could relate to more than one diagnostic category.

7.7.3 Emotional processing deficits

There is now a rapidly growing literature on general impairments in emotional processing, including deficits in responses to facial and emotive stimuli in ADHD (Herrmann, et al., 2009; Posner, et al., 2011; Williams, et al., 2008). Importantly the study by Williams and colleagues (2008) showed a clear treatment co-variation between EL and alterations in ERPs in response to emotional facial expression stimuli. This indicates that the relationship between EL and emotional processing deficits may require further attention.

Research has also revealed impairments in cognitive control of emotional stimuli. For example research has shown enhanced emotional interference in working memory performance in adults with ADHD, who showed difficulty in suppressing attention towards emotionally laden stimuli (Marx, et al., 2011). Another study examining measures of

respiratory sinus arrhythmia (RSA) in an emotion regulation task, showed that whilst typically developing children showed systematic variation in RSA during positive and negative emotion and emotional suppression and induction tasks, children with ADHD displayed an inflexible and ineffective physiological response pattern across all task conditions, indicative of regulatory problems (Musser, et al., 2011). Whilst many such studies investigate emotional processing deficits, measures of EL are infrequently included.

Future research on EL in ADHD may wish to incorporate paradigms in which emotional processing and emotional regulation paradigms are used, since deficits in the processing and control of emotional stimuli in particular may be specifically pertinent to EL in ADHD.

7.7.4 Aetiology and neurobiology

Preliminary findings of cognitive and neurophysiological markers of EL in ADHD were presented here which require replication in larger studies. Moreover, the finding that SD-RT was associated with a self-report measure of EL which measured swift emotional changes indicates that an investigation between real-time emotional instability as measured by ambulatory monitoring and SD-RT would be warranted.

Whilst investigation of common treatment response provides a promising avenue for the investigation of shared and disparate treatment mechanisms, findings in the current study did not identify any promising cognitive correlates of treatment response. Indeed results only negated earlier findings that commission errors were associated with EL on the CNS-LS. This study was however limited by the small sample size and the lack of placebo control. Replication in a larger controlled treatment trial is required before any firm conclusions can be made.

Another avenue for investigating a potentially shared biology of ADHD symptom and EL lies in the investigation of familial and genetic effects of ADHD and EL. Recent studies have shown a familial component of EL, although these studies indicate that levels of EL within children and adults with ADHD increase the risk of EL but not ADHD among their siblings, and therefore seems to represent an independent familial risk from that for ADHD (Sobanski, et al., 2010; Surman, et al., 2011). Current ongoing studies include behavioural genetic analysis of ADHD symptoms and EL in several general population samples of twins

(Merwood et al., in prep), and family and twin studies of cognitive task performance data (including SD-RT and commission errors) (Merwood et al., in prep; Banaschewski, et al., Submitted). These studies will provide additional information on the shared biological and cognitive factors driving the association between ADHD and EL.

Finally, despite power issues in the current analyses of treatment co-variation, the investigation of shared treatment response provides a promising avenue for investigating causal mechanisms between clinical conditions and features, such as cognitive deficits, which have been associated with them. The current research showed a good treatment response for a variety of behavioural and cognitive measures. A clear co-variation of ADHD symptoms and EL was seen, indicative of shared treatment mechanisms for these behavioural features, but there was limited treatment co-variation with cognitive and electrophysiological measures. This may be indicative of a shared treatment mechanism in terms of dopamine enhancement, potentially acting on systems that are independent of one another.

However, as noted previously, Williams and colleagues (2008) identified a shared treatment response of ERPs in a facial processing task with EL and hyperactivity symptoms in a larger sample of adolescents with ADHD. The use of this method to investigate shared treatment response of cognitive measures such as those associated with EL here (inhibitory function and SD-RT) as well as those associated with ADHD symptoms (the inhibitory N2 component on the SART), in a larger sample and more controlled conditions would be valuable for elucidating causal relationships during the treatment response. Moreover, this approach could provide a translational outcome in terms of identifying markers of treatment response and processes to target for future treatment development.

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Appendix 1: Barkley Adult ADHD Rating Scale (BRS)

Instructions:
Please circle the number next to each item that best describes your behaviour DURING THE PAST 6 MONTHS

Items:		Never or Rarely	Sometimes	Often	Very Often
1.	Fail to give close attention to details or make careless mistakes in my work	0	1	2	3
2.	Fidget with hands or feet or squirm in seat	0	1	2	3
3.	Have difficulty sustaining my attention in tasks or fun activities	0	1	2	3
4.	Leave my seat in situations in which sitting is expected	0	1	2	3
5.	Don't listen when spoken to directly	0	1	2	3
6.	Feel restless	0	1	2	3
7.	Don't follow through on instructions and fail to finish work	0	1	2	3
8.	Have difficulty engaging in leisure activities or doing fun things quietly	0	1	2	3
9.	Have difficulty organising tasks and activities	0	1	2	3
10.	Feel "on the go" or "driven by a motor"	0	1	2	3
11.	Avoid, dislike, or am reluctant to engage in work that requires sustained mental effort	0	1	2	3
12.	Talk excessively	0	1	2	3
13.	Lose things necessary for tasks or activities	0	1	2	3
14.	Blurt out answers before questions have been completed	0	1	2	3
15.	Easily distracted	0	1	2	3
16.	Have difficulty awaiting turn	0	1	2	3
17.	Forgetful in daily activities	0	1	2	3
18.	Interrupt or intrude on others	0	1	2	3

Appendix 2: Affective Lability Scales – Short form (ALS-SF)

Please rate how generally true each statement is

1. At times I feel just as relaxed as everyone else and then within minutes I become so nervous that I feel light-headed and dizzy.

- ☐ Very undescriptive
- ☐ Rather undescriptive
- ☐ Rather descriptive
- ☐ Very descriptive

---

2. There are times when I have very little energy and then just afterwards I have about the same energy level as most people.

- ☐ Very undescriptive
- ☐ Rather undescriptive
- ☐ Rather descriptive
- ☐ Very descriptive

---

3. One minute I can be feeling OK and then the next minute I'm tense, jittery, and nervous.

- ☐ Very undescriptive
- ☐ Rather undescriptive
- ☐ Rather descriptive
- ☐ Very descriptive

---

4. I frequently switch from being able to control my temper very well to not being able to control it very well at all.

- ☐ Very undescriptive
- ☐ Rather undescriptive
- ☐ Rather descriptive
- ☐ Very descriptive

---

5. Many times I feel nervous and tense and then I suddenly feel very sad and down.

- ☐ Very undescriptive
- ☐ Rather undescriptive
- ☐ Rather descriptive
- ☐ Very descriptive

---

6. Sometimes I go from feeling extremely anxious about something to feeling very down about it.

- Very undescriptive
- Rather undescriptive
- Rather descriptive
- Very descriptive

---

7. I shift back and forth from feeling perfectly calm to feeling uptight and nervous.

- Very undescriptive
- Rather undescriptive
- Rather descriptive
- Very descriptive

---

8. There are times when I feel perfectly calm one minute and then the next minute the least little thing makes me furious.

- Very undescriptive
- Rather undescriptive
- Rather descriptive
- Very descriptive

---

9. Frequently, I will be feeling OK but then I suddenly get so mad that I could hit something.

- Very undescriptive
- Rather undescriptive
- Rather descriptive
- Very descriptive

---

10. Sometimes I can think clearly and concentrate well one minute and then the next minute I have a great deal of difficulty concentrating and thinking clearly.

- Very undescriptive
- Rather undescriptive
- Rather descriptive
- Very descriptive

---

11. There are times when I am so mad that I can barely stop yelling and other times shortly afterwards when I wouldn't think of yelling at all.

- Very undescriptive
- Rather undescriptive
- Rather descriptive
- Very descriptive

---

12. I switch back and forth between being extremely energetic and having so little energy that it's a huge effort just to get where I am going.

- Very undescriptive
- Rather undescriptive
- Rather descriptive
- Very descriptive

---

13. There are times when I feel absolutely wonderful about myself but soon afterwards I often feel that I am just about the same as everyone else.

- Very undescriptive
- Rather undescriptive
- Rather descriptive
- Very descriptive

---

14. There are times when I'm so mad that my heart starts pounding and/or I start shaking and then shortly afterwards I feel quite relaxed.

- Very undescriptive
- Rather undescriptive
- Rather descriptive
- Very descriptive

---

15. I shift back and forth between being very unproductive and being just as productive as everyone else.

- Very undescriptive
- Rather undescriptive
- Rather descriptive
- Very descriptive

---

16. Sometimes I feel extremely energetic one minute and then the next minute I might have so little energy that I can barely do a thing.

- Very undescriptive
- Rather undescriptive
- Rather descriptive
- Very descriptive

---

17. There are times when I have more energy than usual and more than most people and then soon afterwards I have about the same energy level as everyone else.

- Very undescriptive
- Rather undescriptive
- Rather descriptive
- Very descriptive

---

18. At times I feel that I'm doing everything at a very slow pace but then soon afterwards I feel that I'm no more slowed down than anyone else.

- Very undescriptive
- Rather undescriptive
- Rather descriptive
- Very descriptive

Appendix 3: Centre for Neurologic Study – Lability Scale (CNS-LS)

Directions: This questionnaire is designed to find out about people's moods. Using the scale below, select the number that best describes the frequency each item appears in your behavior in the present time - last month.

Applies Never	Rarely	Occasionally	Frequently	Most of the time
0	1	2	3	4

*** For each item, circle only one answer.**

A) People have told me at times that I seem to get upset very easily or that I get upset over little things.

Last month	0	1	2	3	4

B) I've noticed that I get upset very easily.

Last month	0	1	2	3	4

C) Others have told me that I seem to get frustrated very easily or that I seem to get frustrated over little things.

Last month	0	1	2	3	4

D) I can quickly go from feeling calm to feeling very angry over little things or for no reason at all.

Last month	0	1	2	3	4

E) At times I can be feeling no more impatient than others but then I'll suddenly become very impatient over something small or for no reason at all.

Last month	0	1	2	3	4

F) People have told me at times that I seem to get impatient very easily or that I seem to get impatient over little things.

Last month	0	1	2	3	4

G) Others have told me that I seem to get nervous very easily or that I seem to become nervous over little things.

Last month	0	1	2	3	4

H) Sometimes I can be feeling fine one minute and then I'll yell or raise my voice in an angry way the next.

Last month	0	1	2	3	4

Appendix 4: Correlational tables of EEG data and performance data

		Frontal theta Δ rest to SART	Central theta Δ rest to SART	Parietal theta Δ rest to SART	Frontal beta Δ rest to SART	Parietal beta Δ rest to SART	Parietal beta Δ CPT-OX to SART	Latency No-Go-$P3_{SART}$	SD-RT (SART)	CV (SART)	Comm-ission errors (SART)	Omission errors (SART)
Central theta Δ rest to SART	Corr.	0.72 (**ρ**)										
	Sig.	<0.001†										
Parietal theta Δ rest to SART	Corr.	0.87 (**ρ**)	0.87 (**ρ**)									
	Sig.	<0.001†	<0.001†									
Frontal beta Δ rest to SART	Corr.	0.25 (**ρ**)	0.11 (**ρ**)	0.13 (**ρ**)								
	Sig.	0.03	0.31	0.25								
Parietal beta Δ rest to SART	Corr.	0.20 (**ρ**)	0.12 (**ρ**)	0.35 (**ρ**)	0.31							
	Sig.	0.08	0.27	0.001	0.003							
Parietal beta Δ CPT-OX to SART	Corr.	0.20 (**ρ**)	0.17 (**ρ**)	0.26 (**ρ**)	0.12	0.37						
	Sig.	0.08	0.14	0.02	0.30	<0.001						
Latency No-Go-$P3_{SART}$	Corr.	-0.07 (**ρ**)	-0.07 (**ρ**)	-0.04 (**ρ**)	-0.07	0.004	-0.30					
	Sig.	0.51	0.95	0.70	0.50	0.97	0.01					
SD-RT (SART)	Corr.	-0.06 (**ρ**)	0.12 (**ρ**)	-0.02 (**ρ**)	-0.12	-0.10	-0.29	0.33				
	Sig.	0.59	0.27	0.84	0.29	0.37	0.01	0.002				
CV (SART)	Corr.	-0.12 (**ρ**)	0.10 (**ρ**)	-0.02 (**ρ**)	-0.15	-0.15	-0.17	0.13	0.89			
	Sig.	0.29	0.38	0.87	0.18	0.17	0.13	0.25	<0.001†			
Commission errors (SART)	Corr.	-0.24 (**ρ**)	-0.02 (**ρ**)	-0.13 (**ρ**)	-0.32	-0.10	-0.04	-0.03	0.32	0.59		
	Sig.	0.03	0.88	0.25	0.003	0.35	0.74	0.79	0.002	<0.001†		
Omission errors (SART)	Corr.	-0.20 (**ρ**)	-0.04 (**ρ**)	-0.13 (**ρ**)	-0.10	-0.07	-0.29	0.25	0.77	0.74	0.43	
	Sig.	0.08	0.75	0.24	0.37	0.54	0.01	0.02	<0.001†	<0.001†	<0.001†	
Omission errors (CPT-OX)	Corr.	0.02 (**ρ**)	0.05 (**ρ**)	0.09 (**ρ**)	-0.21	-0.13	-0.14	0.28	0.46	0.39	0.30	0.37
	Sig.	0.98	0.69	0.45	0.06	0.27	0.22	0.01	<0.001†	<0.001†	0.01	<0.001

Table a: Correlational analysis across ADHD and control groups for EEG and performance data

Corr.= correlation coefficient; Sig.= significance level, Δ = change; SD-RT = within-subject subject variability in RTs in milliseconds, CV: Coefficient of variation (SD-RT/mean reaction time). † differences robust to Bonferroni correction for 198 comparsisons (adjusted p =0.00025), (**ρ**) partial correlation with adjustment for age at assessment.

		Frontal theta Δ rest to SART	Central theta Δ rest to SART	Parietal theta Δ rest to SART	Frontal beta Δ rest to SART	Parietal beta Δ rest to SART	Parietal beta Δ CPT-OX to SART	Latency No-Go-P3$_{SART}$	SD-RT (SART)	CV (SART)	Comm-ission errors (SART)	Omissio n errors (SART)	Omissio n errors (CPT-OX)
Frontal theta Δ rest to SART	Corr.		0.68	0.76	0.49	0.21	0.12	0.13	0.06(**ρ**)	-0.03(**ρ**)	-0.20(**ρ**)	-0.07(**ρ**)	-0.11
	Sig.		<0.001†	<0.001†	0.001	0.21	0.48	0.44	0.74	0.85	0.24	0.69	0.54
Central theta Δ rest to SART	Corr.	0.65		0.75	0.31	0.24	-0.01	0.15	0.21(**ρ**)	0.17 (**ρ**)	-0.02(**ρ**)	0.09(**ρ**)	-0.08
	Sig.	<0.001†	.	<0.001†	0.06	0.15	0.97	0.36	0.20	0.33	0.89	0.58	0.67
Parietal theta Δ rest to SART	Corr.	0.90	0.67		0.35	0.49	0.04	0.04	0.18(**ρ**)	0.09 (**ρ**)	-0.14(**ρ**)	-0.01(**ρ**)	-0.08
	Sig.	<0.001†	<0.001†	.	0.03	0.002	0.83	0.8	0.28	0.32	0.42	0.99	0.67
Frontal beta Δ rest to SART	Corr.	-0.12	-0.03	-0.15		0.37	0.32	-0.07	-0.18(**ρ**)	-0.19(**ρ**)	-0.21(**ρ**)	-0.18(**ρ**)	-0.11
	Sig.	0.41	0.85	0.33	.	0.02	0.06	0.66	0.29	0.28	0.22	0.29	0.54
Parietal beta Δ rest to SART	Corr.	0.25	0.08	0.21	0.20		0.25	-0.25	-0.28(**ρ**)	-0.17(**ρ**)	-0.04(**ρ**)	-0.15(**ρ**)	-0.03
	Sig.	0.09	0.60	0.17	0.17	.	0.15	0.13	0.09	0.34	0.84	0.39	0.86
Parietal beta Δ CPT-OX to SART	Corr.	0.44	0.35	0.44	-0.14	0.43		-0.49	-0.40(**ρ**)	-0.30(**ρ**)	-0.20(**ρ**)	-0.32(**ρ**)	-0.17
	Sig.	0.003	0.02	0.003	0.36	0.004	.	0.003	0.02	0.09	0.27	0.07	0.33
Latency No-Go-P3$_{SART}$	Corr.	0.03	0.03	-0.08	0.04	0.21	-0.09		0.23(**ρ**)	0.10(**ρ**)	-0.05(**ρ**)	0.27(**ρ**)	0.23
	Sig.	0.84	0.85	0.62	0.78	0.15	0.55	.	0.17	0.57	0.76	0.12	0.19
SD-RT (SART)	Corr.	-0.05	0.13	-0.07	0.07	0.08	-0.20	0.43		0.88 (**ρ**)	0.29(**ρ**)	0.82 (**ρ**)	0.50 (**ρ**)
	Sig.	0.75	0.40	0.62	0.62	0.61	0.18	0.003	.	<0.001†	0.09	<0.001	0.003
CV (SART)	Corr.	-0.05	0.13	-0.08	0.03	-0.02	-0.08	0.200	0.86		0.59(**ρ**)	0.88(**ρ**)	0.48(**ρ**)
	Sig.	0.75	0.40	0.58	0.84	0.90	0.59	0.19	<0.001†	.	<0.001†	<0.001†	0.004
Commission errors (SART)	Corr.	0.05	0.12	0.11	-0.15	-0.07	0.07	-0.12	0.05	0.33		0.47(**ρ**)	0.19(**ρ**)
	Sig.	0.72	0.41	0.46	0.31	0.66	0.66	0.41	0.74	0.03	.	0.003	0.28
Omission errors (SART)	Corr.	-0.28	-0.09	-0.23	0.10	0.09	-0.20	0.18	0.62	0.49	-0.03		0.64(**ρ**)
	Sig.	0.06	0.55	0.12	0.50	0.54	0.19	0.22	<0.001†	0.001	0.85	.	<0.001†
Omission errors (CPT-OX)	Corr.	-0.19(**ρ**)	0.25(**ρ**)	-0.33(**ρ**)	-0.10(**ρ**)	-0.21(**ρ**)	-0.23(**ρ**)	0.37(**ρ**)	0.33(**ρ**)	0.24(**ρ**)	0.18(**ρ**)	0.19(**ρ**)	
	Sig.	0.22	0.11	0.03	0.52	0.17	0.14	0.01	0.03	0.13	0.25	0.22	.

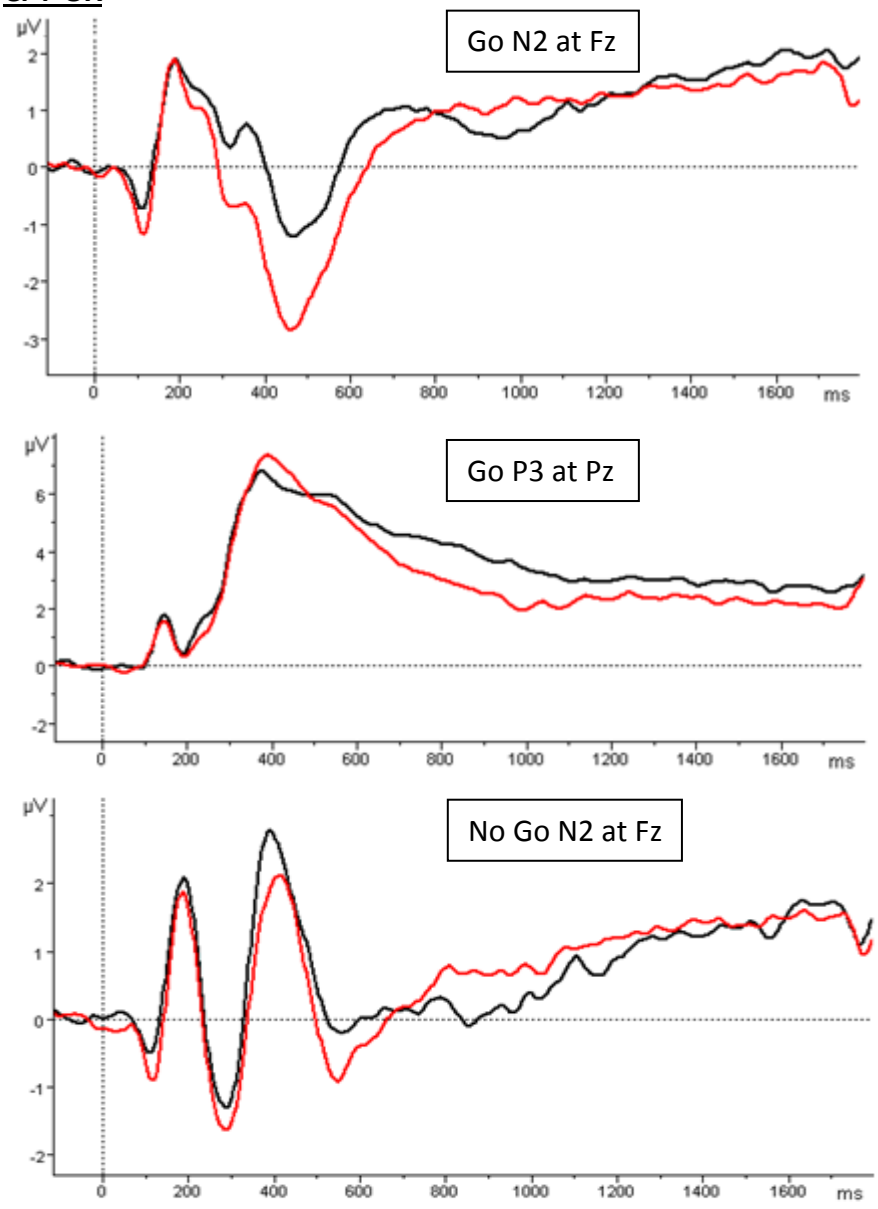
Table 2: Correlational analysis carried out separately for ADHD and control subjects for EEG and performance data. Upper section (pale grey) correlation coefficients and significance level for ADHD subject, lower section (clear) equivalent analyses for controls

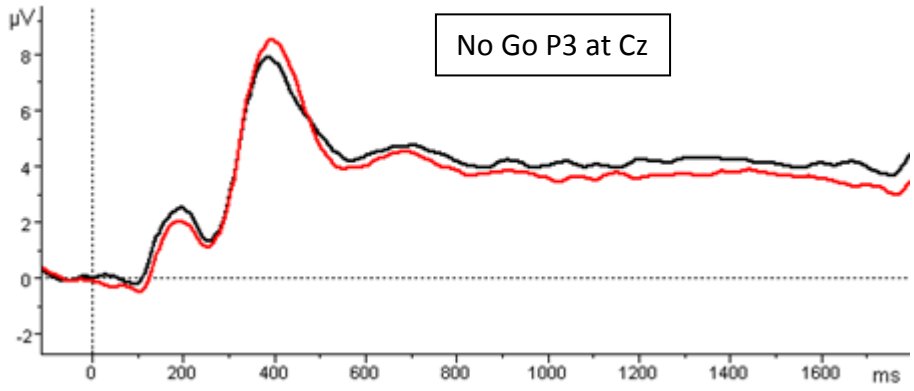
Corr.= correlation coefficient; Sig.= significance level, Δ = change; SD-RT = within-subject subject variability in RTs in milliseconds, CV: Coefficient of variation (SD-RT/mean reaction time). † differences robust to Bonferroni correction for 198 comparsisons (adjusted p =0.00025), (**ρ**) partial correlation with adjustment for age at assessment.

Appendix 5: Figures for EPR components presented in chapter 5

Note ADHD group is presented in black and control group in red for all figures.

CPT-OX

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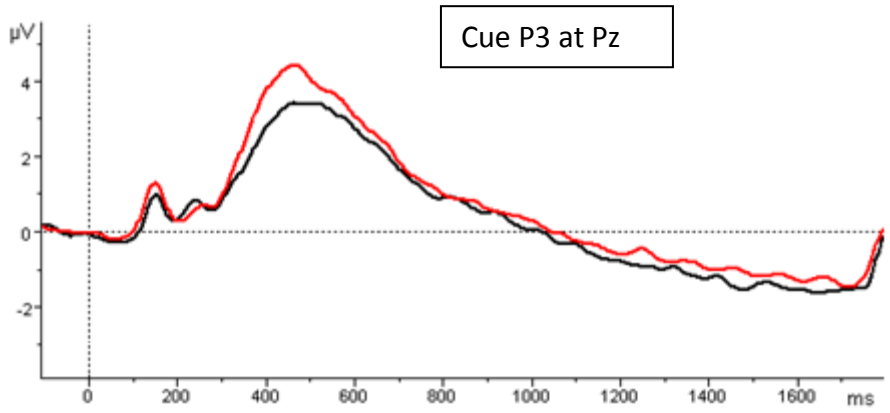
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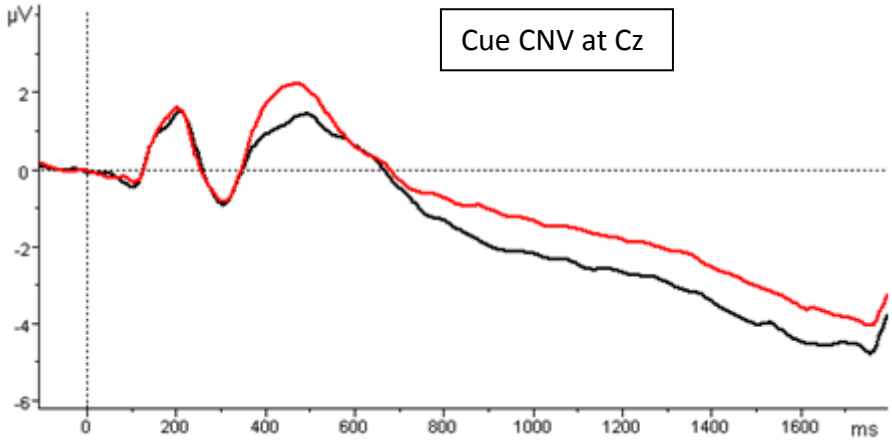
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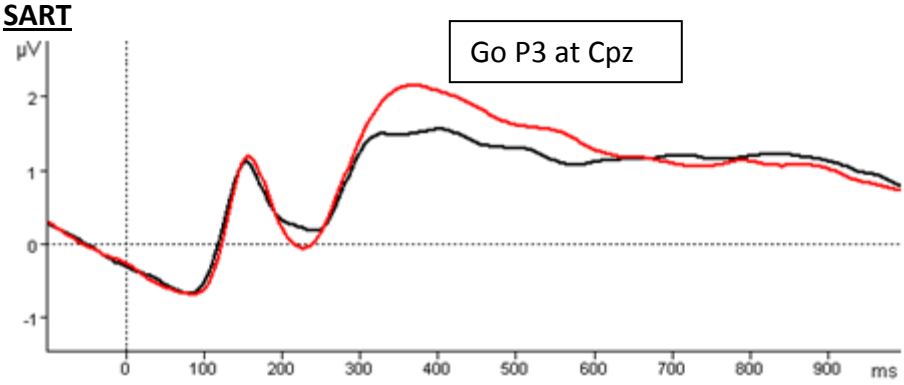
SART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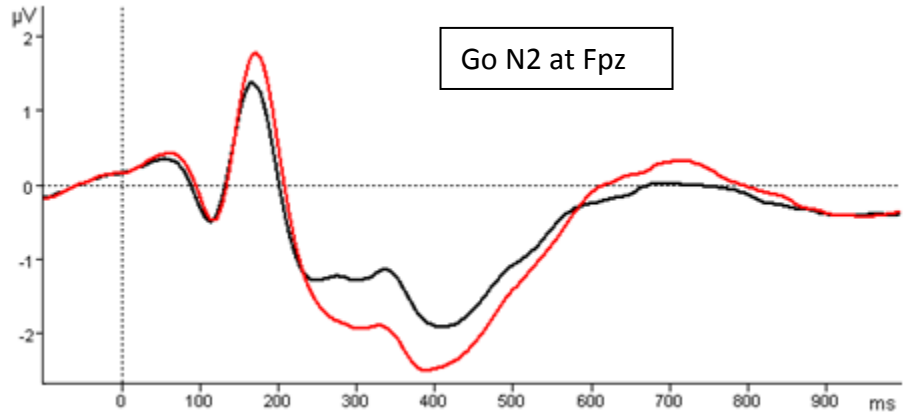
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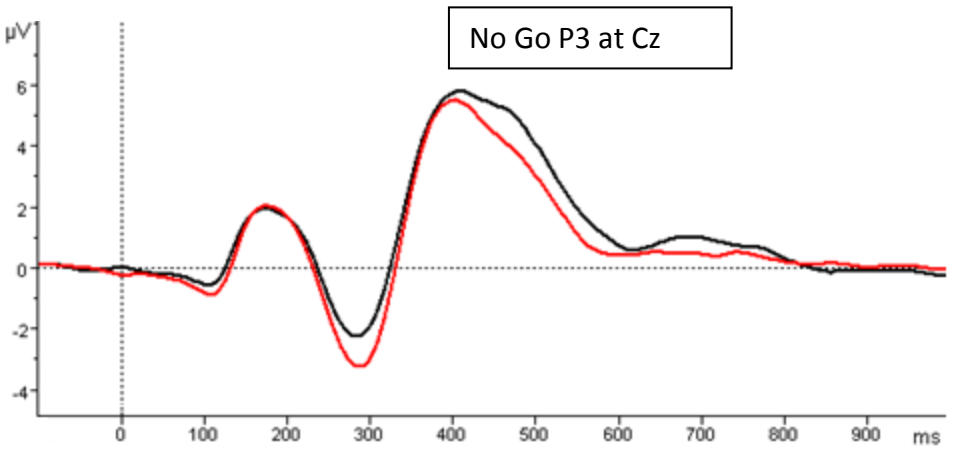
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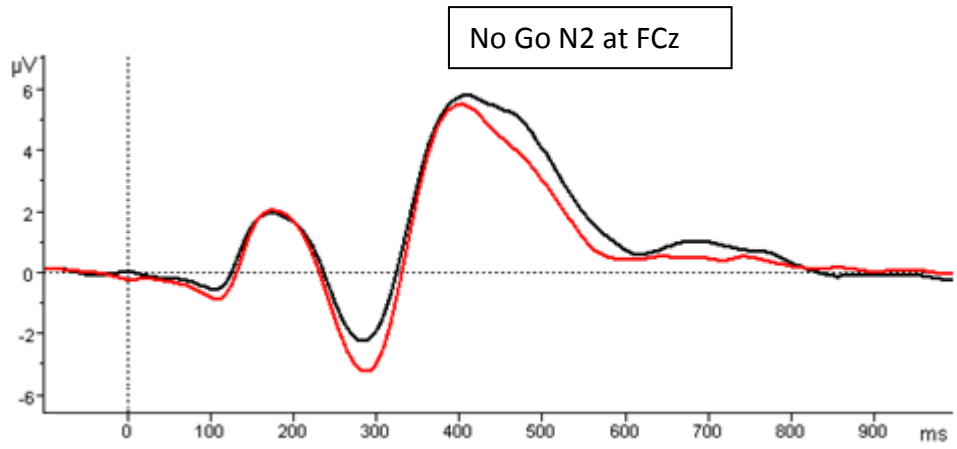
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Appendix 6: Correlational table of change (Δ) after treatment in task performance and electrophysiological measures

		Δ Comm-ission errors	Δ MRT	Δ CV	Δ Theta at Rest	Δ Theta in SART	Δ Theta Rest to task transition
Δ MRT	Corr. Sig.	-.54 0.02					
Δ CV	Corr. Sig.	0.78 <0.001†	0.54 0.02				
Δ Theta at Rest	Corr. Sig.	0.33 (**ρ**) 0.16	-0.12 (**ρ**) 0.62	0.05 (**ρ**) 0.82			
Δ Theta in SART	Corr. Sig.	0.45 0.05	-0.15 0.53	0.40 0.09	-0.02 (**ρ**) 0.93		
Δ Theta Rest to task transition	Corr. Sig.	0.16 (**ρ**) 0.49	0.04 (**ρ**) 0.86	0.05 (**ρ**) 0.82	-0.70 (**ρ**) 0.001†	-0.11 (**ρ**) 0.66	
Δ No-go-N2$_{SART}$	Corr. Sig.	0.04 0.88	0.01 0.97	0.18 0.46	0.22 (**ρ**) 0.36	-0.13 0.59	-0.15 (**ρ**) 0.54

Note: MRT, mean reaction time in milliseconds; SD-RT, within-subject variability in RTs in milliseconds; CV, Coefficient of variation (SD-RT/MRT). † differences robust to Bonferroni correction (adjusted p=.0024), (**ρ**) partial correlation with adjustment for age at assessment.