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An Investigation of Cognitive- Electrophysiological Biomarkers and Symptom Profile in Attention- Deficit/Hyperactivity Disorder and Bipolar Disorder

Glenn L. Kitsune

MRC Social, Genetic and Developmental Psychiatry Centre
Institute of Psychiatry, Psychology & Neuroscience
King's College London

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Abstract

The first part of this thesis aimed to examine the stability and validity of potential cognitive-electrophysiological biomarkers in Attention-Deficit/Hyperactivity Disorder (ADHD) in a large sample of adolescents and young adults. In part two, this thesis proceeded to a cross-disorder comparison with Bipolar Disorder (BD) in a novel sample of adult women, beginning by investigating symptom overlap between the two disorders and testing the efficacy of standard clinical instruments to delineate ADHD from euthymic BD. The next two chapters then went on to investigate the ability of cognitive-electrophysiological markers to delineate ADHD from BD in this cross-disorder sample, both through re-examining event-related potential (ERP) components which were investigated in part one, and by exploring additional ERP components. Presented herein are data which demonstrate that ADHD-control differences are sensitive to differences in experimental context, such as recording duration, as well as sample characteristics and certain methodological factors such as electrode selection. This research identified possible candidate biomarkers for both ADHD and BD; including two disorder-specific cognitive-electrophysiological markers which dissociated ADHD from BD. A further comparison of symptoms of inattention, hyperactivity, mania, depression and emotional lability (EL) in ADHD and BD using typical diagnostic measures indicated that depression, mania and EL measures were not able to distinguish ADHD from euthymic BD. Conversely, ADHD measures had good discrimination potential, and may currently be the best available method of delineating ADHD from BD in clinical contexts. This thesis recommended further research to confirm if the potential cognitive-electrophysiological biomarkers highlighted here are reliable indicators for either ADHD or BD. Further work is also needed to clarify the effects of methodological and samples differences on reported findings in these disorders across lifespan.

Statement of work

The thesis is presented in two parts. The first part used data from the Sibling EEG Follow-up Study (SEFOS), which was a follow-up study which assessed a sample of 105 Attention-Deficit/Hyperactivity Disorder (ADHD) and 102 control sibling pairs (total n= 414 participants) on cognitive and electrophysiological measures. SEFOS was supported by generous grants from Action Medical Research and Peter Sowerby Charitable Foundation (grant reference GN1777). The second part of this thesis used data from a second study, the Female Experiences and Brain Activity (FEBA) Project, which was a novel cross-disorder investigation comparing adult women with ADHD, Bipolar Disorder (BD) and control participants (total n=60) on a range of clinical, cognitive and electrophysiological measures. This work was supported by Economics and Social Research Council (ESRC) studentship ES/100971X/1 awarded to Glenn Kitsune.

This thesis as presented here represents my own work. In chapters two and three, using data from the SEFOS study, I formulated research questions, processed and analysed the data from the two cognitive-electrophysiological investigations, and interpreted the findings under the supervision of Dr. Jonna Kuntsi and Dr. Gráinne McLoughlin. Also in conjunction with Dr. Jonna Kuntsi, Dr. Gráinne McLoughlin and Professor Philip Asherson, I was responsible for the development of the FEBA study, and undertook all regulatory and research governance steps required to conduct this research. I also managed the project throughout its active testing phase and was responsible for collecting all clinical and EEG data with assistance from research workers Sarah-Jane Gregori, Jessica Deadman and Hannah Collyer. For the three investigations reported in chapters four to six, I formulated the research questions, processed data, conducted analysis and interpreted the findings under the supervision of Dr. Jonna Kuntsi, Dr. Gráinne McLoughlin and Professor Philip Asherson.

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Thesis outline

This thesis is divided into two parts: part one consisting of two studies (SEFOS sample), and part two consisting of three further studies (FEBA sample). The content of each chapter is briefly described below:

Chapter one provides the introduction to the thesis with an overview and methodological critique of relevant literature conducted to date concerning diagnostic boundaries, clinical comparisons and cognitive-neuropsychological investigations of ADHD and BD.

Part 1

Chapter two examines the stability of ADHD spectral EEG profiles in a large adolescent and young adult sample across two resting state recordings separated by 1.5 testing session. This study evaluates a number of methodological approaches in examining spectral EEG and attempts to quantify the effect of IQ differences on reported case-controls differences.

Chapter three details an ERP study which aimed to confirm ADHD-associated deficits in a conflict monitoring task using ADHD, unaffected ADHD siblings and unaffected controls in a large sample of adolescents and young adults. This study also examines conflict monitoring deficits as a potential endophenotype for ADHD.

Part 2

Chapter four presents data from a cross-disorder comparison of symptoms in ADHD, BD and controls in an adult female sample, and examines the sensitivity and specificity of these measures to ADHD or BD. This chapter also describes the recruitment process for this sample and discusses how clinical assessments might be refined to better delineate ADHD and BD in clinical contexts.

Chapter five reports a study which utilised the same paradigm as that reported in chapter two, but extended into the cross-disorder sample in order to compare ADHD and BD ERP responses on a conflict monitoring task. This chapter goes on to suggest possible sources of sample heterogeneity within these disorders.

Chapter six presents data from a further ERP comparison between ADHD and BD in the cross-disorder sample, examining potential attentional deficits in the Novelty Oddball Task. This chapter also explores fronto-central theta power in relation to ERP components and highlights potential candidates for future research.

Chapter seven is the overall discussion, which summarises the findings presented in the preceding chapters, reviews the clinical implications of this research, discusses avenues for future studies and outlines the limitations of the studies undertaken in this thesis.

Distinct and original contributions

A list of publications arising from this thesis is provided in Appendix 1. Chapter two represents a research article published in a scientific journal. Chapters three to six are adaptations from manuscripts currently in preparation. Work from this thesis has also generated four poster presentations at international conferences.

This work represents an original contribution and advancement of knowledge in several areas of research, as summarised by the following:

Chapter two explored changes in spectral resting state EEG across a recording session using data recorded at **two separate time points** recorded 1.5 hours apart **in a large sample of over 160 participants**. This time-sensitive approach is rare in EEG ADHD research, and therefore represents valuable new data.

Chapter two also **evaluated the effect of using different methodological approaches**, such as electrode selection or controlling for IQ on ADHD-control spectral profile differences, which has not previously been undertaken in a consistent manner in other research.

Chapter three investigated the ERP correlates of performance monitoring deficits in ADHD, unaffected sibling and unrelated controls in a combined sample of over 370 participants representing the **single largest study of this kind in ADHD to date**.

Chapter three attempted to **replicate in a large sample** findings from two smaller studies which suggested that conflict monitoring deficits represent an endophenotype for ADHD.

Chapter four assessed ADHD and BD adults on a battery of common clinical ADHD and BD assessments, to identify symptom overlap and provide data on the potential for misdiagnosis between these two disorders. **No other study has to date cross-compared ADHD and BD on such a large range of clinical measures.**

Chapters four, five and six report clinical, behavioural and cognitive-electrophysiological research data on a sample of **adult women with ADHD, a group for which very limited data currently exists**, as most previous research on ADHD has focused on males only.

Chapters five and six report data from two **cross-disorder cognitive-electrophysiological comparisons between ADHD and BD** in a novel sample of adult participants; a currently understudied area of research.

Chapter 1 - An Introduction to the Search for Biomarkers in Attention-Deficit/Hyperactivity Disorder and Bipolar Disorder

1.1 Biomarkers for psychiatric illness

Psychiatric illness is currently diagnosed based on behavioural observations and description of symptoms, which have been clustered into diagnostic categories, based on symptom patterns and co-occurrence. These diagnostic systems, the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2013) and the Classification of Mental and Behavioural Disorders (World Health Organisation, 1992), are categorical in nature with illness definitions being added or refined over time as increasing knowledge around symptom patterns has emerged. These standard categorical frameworks have been important in providing mental health professionals with a consistent language to discuss psychiatric illness and have formed the cornerstone of diagnosis, treatment and psychiatric research since their introduction in the early 20th century. However, as they are based on categorical definitions, these frameworks have had to utilise standardised cut-offs between “normal” and “abnormal” classifications. This can mean that those with significant symptoms and/or impairments but not fully meeting criteria for a particular diagnosis are treated very differently from those who might only have marginally more severe symptoms but reach a clinical threshold (Morris and Cuthbert, 2012). Furthermore, many common symptoms overlap between diagnostic classifications, and as these criteria are reliant on changeable observations and self-report of

symptoms, there can sometimes be disagreement between clinicians as to diagnosis within the same individual (Freedman et al., 2013). There is also differing expressions of symptoms within diagnostic classifications, meaning phenotypes can be heterogeneous (Miller, 2010).

Indeed, the growing body of psychiatric quantitative genetic literature have clarified that illness risk is likely to be conferred by a large number of genes, each contributing a very small effect to underlying neurophysiological anomalies (Smoller et al., 2013), or by extremely rare mutations which contribute larger effects (Malhotra and Sebat, 2012, Williams et al., 2012). This implies that there can be both shared and unique pathways to the same symptoms or neurophysiological deficits, making the task of identifying the biological causes of psychiatric disorders a challenging prospect. It has therefore been suggested that in order to advance our understanding of complex heterogeneous psychiatric illnesses, a new more adaptable research framework is needed, which integrates the increasing amounts of biological evidence from the fields of neuroscience and genetics. One such approach is the NIHR's Research Domain Criteria (RDoC) (National Institute of Mental Health, 2014, Insel et al., 2010), which aims to link individual observable symptoms with abnormalities in underlying neurobiological systems. These approaches are data-driven, rather than being constrained by existing diagnostic boundaries, but argue that psychiatric illnesses may be considered as a cluster of greater or lesser deviations from normal functioning in multiple brain systems, such as those responsible for cognitive function, arousal or mood (Insel et al., 2010). The study of these biological markers, or "biomarkers", which are objectively measured indicators of a biological state or condition (Biomarkers Definitions Working Group, 2001), may therefore also provide clarity relating to the boundaries and overlap between current categorical definitions of mental illness, further help us understand the aetiology of these disorders and suggest new avenues for the treatment and management of symptoms (Morris and Cuthbert, 2012). In this thesis, I

present several studies which have attempted to identify biomarkers and have examined symptom overlap in two potentially related disorders: Attention Deficit/Hyperactivity Disorder (ADHD) and Bipolar Disorder (BD); specifically to explore potential similarities and differences in underlying neurocognitive systems, and ultimately contribute to potential future developments of a biologically grounded framework for understanding mental disorders.

1.2 Clinical expressions of ADHD and BD

1.2.1 Clinical symptoms and epidemiology of ADHD

DSM-IV (American Psychiatric Association, 2000) classification of ADHD, as used in this thesis, consists of nine inattention items, six hyperactivity items and three impulsivity items, grouped into inattention and hyperactivity-impulsivity subscales. A clinical diagnosis of ADHD requires the presence of six or more symptoms on at least one subscale, which are maladaptive and inconsistent with developmental level, for a period of at least six months. Symptoms must have caused some impairment before age seven, in at least two or more settings such as school and home, and must not occur exclusively as part of another disorder. Clear evidence of significant impairment in social, academic or occupational functioning must also be present. If scores of six symptoms are present on both subscales then a diagnosis of combined type ADHD is made, otherwise predominantly inattentive or predominantly hyperactive-impulsive diagnosis may be applied depending on symptom distribution. However, these subtypes have been shown to be unstable in longitudinal follow-up, with 50% changing between subtypes (Valo and Tannock, 2010), and those with the hyperactive-impulsive subtype being particularly likely to shift to a combined type diagnosis (Lahey et al., 2005). This subtype instability may

therefore either represent a tendency for symptom range to broaden with age or, more likely, an inaccurate representation of the underlying disorder by existing diagnostic criteria.

The recent update to the criteria with DSM-5 recognised subtypes as unstable by redefining them as 'current presentations' (American Psychiatric Association, 2013). However, the existing structure has been retained, with minor corrections including the requirement for symptoms to occur before age seven being increased to twelve. In addition, diagnosis of ADHD in adulthood has been acknowledged, adding adult specific examples to symptom items, and reducing symptom requirements to four symptoms on either subscale, as it has been recognised symptom severity declines with age (Biederman et al., 2000, Faraone et al., 2006). There are indications that these changes have increased prevalence rates across the whole age spectrum, and may also increase the heterogeneity of ADHD presentation (van de Glind et al., 2014, Vande Voort et al., 2014). However, these broader criteria may arguably better represent the underlying phenotype.

ADHD-type symptoms appear throughout the population at subclinical levels, so ADHD should be considered a continuous dimensional trait (Chen et al., 2008, Hudziak et al., 1998). Quantitative genetic investigations support the concept of ADHD diagnostic criteria as representing the extreme end of a continuum for inattention and hyperactive/impulsive symptoms, at which meaningful levels of impairment are likely to be present (Larsson et al., 2012, Levy et al., 1997). Thus, although the epidemiology of ADHD is better explained as continuous trait, use of a categorical definition is justified when interested in clinically

significant expressions of the syndrome, such as when making treatment decisions (Haslam et al., 2006).

Using DSM-IV criteria, the average childhood prevalence of an ADHD diagnosis is 5%, although reports of prevalence have ranged from 1%-20% (Polanczyk et al., 2007). In general, ADHD symptom severity, and therefore prevalence, declines with age in studies using DSM-IV criteria (Simon et al., 2009). ADHD has been reported to persist into adulthood in approximately 15% of childhood cases, with residual sub-clinical symptoms and impairments into adult life in an additional 50% of cases (Faraone et al., 2006). Estimates for adult prevalence range from 1% to 6% (Das et al., 2012, Kessler et al., 2006, Murphy and Barkley, 1996, Weiss et al., 1985, de Zwaan et al., 2012), averaging around 3-5% based on DSM-IV criteria (Faraone and Biederman, 2005, Willcutt, 2012), which may now be higher under DSM-5 classifications which has a reduced requirement for the number of symptoms present (Vande Voort et al., 2014). Prevalence is highly sensitive to the diagnostic criteria used in defining the diagnosis, with DSM-III or ICD-10 definitions producing lower prevalence rates against DSM-IV criteria, which are lower again than those estimates created using DSM-5 criteria (Lee et al., 2008, Skounti et al., 2007, Vande Voort et al., 2014). This variability in classification of ADHD underlies the importance of identifying robust reliable biomarkers for the disorder.

1.2.2 Gender difference in ADHD symptoms

In community sampling of child and adult ADHD the ratio of males to females meeting DSM-IV clinical thresholds is placed at 1.6-2.3 : 1 (Ramtekkar et al., 2010, Scahill and Schwab-Stone, 2000), although gender distributions of adults attending clinics are roughly equal, meaning that one possibility is that men may be less disposed to seek out psychiatric support (Retz-

Junginger et al., 2012). Another alternative is that developmental differences in men and women alter gender prevalence ratios over time (Onnink et al., 2014), although the persistence of ADHD symptoms into early adulthood is equal in girls and boys (Biederman et al., 2004). However, other literature on symptom severity between genders is inconsistent. Some studies have suggested that women have greater severity of symptoms, impairments and increased levels of associated symptoms such as emotional lability and sleep disturbances, compared to men (Fedele et al., 2012, Robison et al., 2008). Yet other studies have observed increased primary symptoms in males compared to females (Gershon, 2002), or have concluded that there is little to suggest differences in the severity symptoms between adults males and females with ADHD (Rasmussen and Levander, 2009, Retz-Junginger et al., 2012, Wilens et al., 2009). This conclusion has been supported by large population-based studies of ADHD trait scores in which no gender differences in the rate of clinical-range ADHD symptoms have been reported (Das et al., 2012, de Zwaan et al., 2012). These inconsistencies in published findings are likely to arise out of the limited amount of data available for adult female ADHD populations in relation to their male counterparts, both in terms of symptom patterns and potential neurocognitive investigations.

1.2.3 Clinical symptoms and epidemiology of BD

Bipolar Disorder (BD) is characterised by long-term extreme episodic fluctuations in mood from depression to elation or manic states (Miklowitz and Johnson, 2006, Treuer and Tohen, 2010). The 5 year relapse rate of mania or depression episodes has been placed at 73% (Gitlin et al., 1995), with episodes typically lasting between 2 and 7 months (Angst and Sellaro, 2000). Manic states are periods of elevated mood, which can include symptoms of euphoria, rapid speech, grandiosity, a decreased need for sleep, elevated hedonic pursuit with a lack of

inhibition, distractibility and racing thoughts. Symptoms of psychosis, such as delusion and hallucinations, can also be common in the more severe form of the disorder, but are not required for diagnosis (American Psychiatric Association, 2013). Between these episodes, sufferers do not usually display extreme symptoms of mania or depression but many mild to moderate sub-syndromal symptoms and residual impairments do persist during periods of euthymia (Fava, 1999, Judd and Akiskal, 2003, Post et al., 2003).

BD is another example of a highly heterogeneous diagnostic classification, showing varied expression among those with the disorder, and with symptom severity also viewed as falling along a continuum (Ghaemi, 2013, Judd and Akiskal, 2003, Merikangas et al., 2011). Varying severity of mania, hypomania and depression symptoms are common, with psychosis and/or rapid cycling also being associated with BD in a proportion of cases (Akiskal et al., 2005, Judd et al., 2002, Schneck et al., 2004). This therefore argues for the possibility that the phenotype may have several aetiologies deriving from differing deficits in underlying neuro-cognitive systems. The DSM-IV categorical definition of the disorder, used in this thesis, identifies three mutually exclusive categories: Bipolar Disorder I (BD-I), Bipolar Disorder II (BD-II) and Cyclothymia (American Psychiatric Association, 2000). BD-I is the most severe form requiring at least one lifetime episode of mania lasting a week or more, and often is accompanied by depressive episodes. The boundaries between BD-I and BD-II as categorically differing conditions is contested (Parker and Fletcher, 2014), but according to DSM-IV diagnosis of BD-II requires a hypo-manic episode, which has similar symptoms to mania but which is not severe enough to cause marked social or occupational impairment. The category of Cyclothymia captures those with chronic symptoms of mood instability over two years, but whom do not meet criteria for manic or major depressive episodes. DSM-5 has preserved these criteria and thresholds, and has not substantially altered reported prevalence of BD (Fassassi et al., 2014),

however one addition has been the inclusion of ‘persistently increased goal-directed activity or energy’, or hyperactivity, as a description of a manic or hypo-manic state.

This disorder typically has onset in late teens or early adulthood (Merikangas et al., 2011). Estimates of lifetime prevalence for combined BD-I and II range from 1% to 3.9%, with BD-I prevalence being estimated as ranging from between 0.6% to 2.2% (Judd and Akiskal, 2003, Kessler et al., 2005, Lee et al., 2009, Merikangas et al., 2007, Merikangas et al., 2011). There are indications that epidemiological data is influenced by the measures and exact criteria used, with small alterations leading to large increases in prevalence rates, highlighting the argument that these diagnostic boundaries are to some degree arbitrary, in that they do not fully capture the underlying phenotype, as moderate sub-threshold symptoms are relatively common (Judd and Akiskal, 2003, Lee et al., 2009, Mitchell et al., 2013).

1.2.4 Gender difference in BD symptoms

Equivalent prevalence rates for BD-I have been observed in both men and women, although BD-II is reported to occur more frequently in women, owing to an increase propensity to depression symptoms in this gender (Malhi et al., 2009, Schneck et al., 2004). However, a more recent epidemiological study found elevated lifetime rates of BD-I in men and confirmed higher rates of BD-II in women (Merikangas et al., 2011). Other studies have generally reported that mania symptom severity, prevalence of psychotic symptoms, total number of episodes, and age of onset are similar in men and women (Hendrick et al., 2000, Kawa et al., 2005, Kessing, 2004). However, rates of comorbid disorders are frequently reported to be greater in

men (Hendrick et al., 2000, Kawa et al., 2005, Kessing, 2004), as with ADHD (Kessler et al., 2006). Evidence also exists suggesting rapid cycling forms of BD-I and II may also be more common in women (Schneck et al., 2004).

1.2.5 Comorbidities and familial relationship in ADHD and BD

In both ADHD and BD, co-occurring psychiatric disorders are common, especially substance abuse disorders in BD; and depression and conduct disorders in ADHD (Gillberg et al., 2004, Jensen et al., 1997, Mitchell et al., 2004, Strakowski and DelBello, 2000, Treuer and Tohen, 2010). ADHD and BD also frequently co-occur (Faraone et al., 1997, Faraone et al., 2001). A systematic review suggested that the comorbidity between the two disorders in adults may be up to 10-21% in ADHD, and up to 5-20% in BD (Asherson et al., 2014b).

Twin and family studies have shown both ADHD and BD to be highly heritable psychiatric disorders (Levy et al., 1997, Lichtenstein et al., 2009, Smoller and Finn, 2003), with family studies also showing that ADHD and BD aggregate in families at higher than expected rates (Faraone et al., 2012). For example, the incidence of ADHD in the offspring of parents with BD-I is reported at 30% (Birmaher et al., 2009). This suggests the presence of some shared genetic or environmental factors between ADHD and BD. Cross-disorder Genome Wide Association studies (GWAS) have provided confirmation that a set of common genetic variants confer risk for several psychiatric disorders including ADHD and BD, possibly as a consequence of an atypical neurodevelopmental trajectory (Smoller et al., 2013). These large scale genomic investigations also indicate that the range of variance in risk explained by common genetic mutations is larger in ADHD and BD than autistic spectrum disorder, schizophrenia and major depression, highlighting that the risk factors for these two disorders are likely to be common in

the general population (Lee et al., 2013). A more detailed discussion of molecular genetics research for ADHD and BD falls beyond the scope of this summary; however for the purposes of this thesis, it should be noted that evidence indicates some common genetic factors between ADHD and BD which may contribute to atypical neurodevelopmental trajectories and therefore may underlie shared abnormalities in higher order neurocognitive systems.

1.2.6 Overlap of symptoms in ADHD and BD

Diagnostic formulations for both ADHD and the manic phase of BD include common symptoms such as distractibility, psychomotor restlessness, talkativeness, lack of social inhibition and impulsivity (Galanter and Leibenluft, 2008, Kent and Craddock, 2003); many of which persist as milder stable traits in euthymic BD (Najt et al., 2007, Peluso et al., 2007). Debate over delineation has also ensued regarding evidence of mood dysregulation, such as irritability and emotional lability in ADHD, which match the symptoms of mood fluctuation in BD (Chan et al., 2011, Geller et al., 2002, Skirrow et al., 2009, Skirrow et al., 2012, Skirrow and Asherson, 2013). The introduction of DSM-5 has further blurred these boundaries, recognising mood dysregulation as an associated feature of ADHD, and hyperactivity as a symptom of BD (American Psychiatric Association, 2013). Such similarities can lead to challenges in distinguishing the two disorders, or recognising comorbidity in clinical practice where many atypical cases of both ADHD and BD present, and where the primary diagnosis (ADHD, BD or both) is unclear (Asherson et al., 2014a, Atmaca et al., 2009, Carlson, 1998, Galanter et al., 2005). Further complications arise when considering the fluctuation of symptoms over time, particularly related to the episodicity in BD and the milder clinical expressions of each disorder along their respective spectrums, for instance adult inattentive ADHD which can show relatively few easily observable symptoms or BD-II where there may not be noticeable

impairment in general functioning (Hantouche et al., 1998, Hudziak et al., 1998, Judd and Akiskal, 2003, Levy et al., 1997).

Although conceptually issues of symptom overlap may only represent poor diagnostic delineation by clinical categorisation or be the result of common aetiological pathways; in the clinical diagnosis of ADHD or BD accurate delineation can be a critical issue as treatments differ (stimulants or atomoxetine for ADHD, and antipsychotics or mood stabilisers for BD) and misdiagnosis can result in individuals being administered inappropriate treatments with adverse effects or the potential to exacerbate symptoms (Asherson et al., 2014b, Atmaca et al., 2009). Clinical delineation is further complicated by unresolved debate around the relationship between mood dysregulation and ADHD, and therefore the boundaries of each condition (Skirrow and Asherson, 2013). Furthermore, in relation to BD, whereas the episodicity of symptoms was thought to be the key identifying feature of the disorder, there is now debate over which definitions of episodicity are required for diagnosis across lifespan, as some authors have proposed that BD presents with chronic mood symptoms of anger and irritability at younger age ranges, concurrent with those ages where ADHD is typically diagnosed (Geller and Luby, 1997, Pavuluri et al., 2005).

1.2.7 Delineation using clinical measures

To date very few studies have attempted to delineate these two disorders using direct comparison on standard clinical measures which might be employed in a clinical environment; those that have done so have been small and have used a limited range of self-report

measures. One such comparison using a depression scale showed both clinical groups to have elevated scores compared to controls (Torralva et al., 2011). Another study reported that ADHD measures were effective at distinguishing ADHD from BD, but that the ADHD group had higher depression and manic symptoms than euthymic BD participants (Ibanez et al., 2012). The comparative degree of these overlapping symptoms and their severity in each disorder therefore remains an important question to clarify, along with the effectiveness of clinical measures to delineate ADHD and BD in a cross-disorder comparison studies.

1.2.8 Section summary

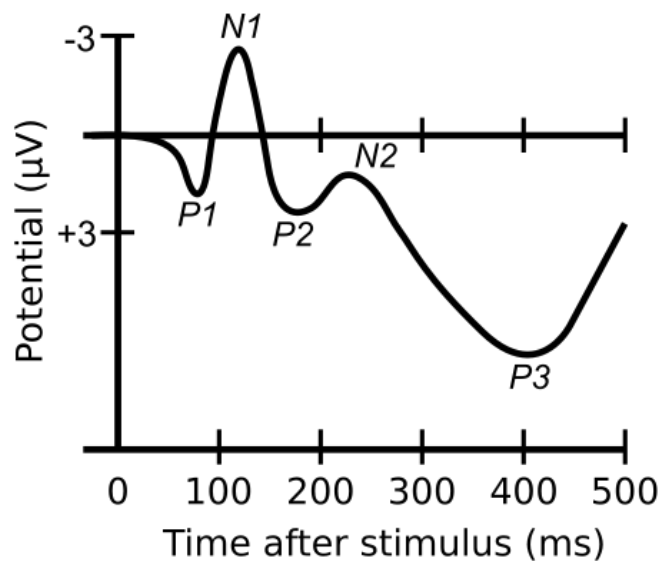
BD and ADHD share several symptoms with indications of a genetic relationship between the two disorders, suggesting some common aetiological pathways between them. However, as both diagnoses have other non-shared characteristic symptoms, and have different effective treatments, there are also clearly divergent aetiological pathways underling these separate clinical expressions. Purely based on the clinical observation of symptoms, it is clear that the boundaries between ADHD and BD are, however, blurred, with empirical evidence examining the precise nature of shared vs. specific deficits still lacking, of which one question is the role of mood instability within each disorder. Neurocognitive evidence may therefore be essential in formulating theories to understand this pattern of shared and non-shared symptoms, familial/genetic relationships and broad heterogeneity within ADHD and BD, as such approaches may be able to highlight individual common or specific deficits in neurocognitive processes related to cognitive, valance and motivational cognitive systems.

1.3 Cognitive and neurophysiological impairments

1.3.1 Neurophysiological methods

Beyond symptom observation, cognitive neuropsychological approaches can be used to further help elucidate the boundaries between these disorders. For instance, performance on neuropsychological tests can indicate impaired executive function or attentional processes, which can then be further investigated at the layer of cognition processes with the use of direct sub-second functional neuroimaging, such as electroencephalography (EEG) and event-related potentials (ERPs) to search for atypical patterns of brain activity. Electrophysiological techniques, including EEG and ERP, record small voltage fluctuations in brain activity which can either be evoked by particular stimuli or arise as part of background processes such as arousal or activation. Electrophysiological activity recorded at the scalp is proposed to represent the summed voltage from a number of different cortical sources (Woodman, 2010). In ERP analysis, the averaging of activity over multiple stimulus- or response-locked trials can remove the spontaneous background EEG fluctuations unrelated to the event and produce characteristic positive and negative deflections in voltage with functional significance. The nomenclature of these individual components is often dictated by their polarity (P = positive, N = negative) and order of occurrence within the waveform (P1, N1, P2, N2, etc.) (Figure 1.1).

Figure 1.1. Simulated ERP waveform showing several components and typical naming conventions



In this image negative voltages are plotted upwards, a common convention in older ERP studies. More recent studies now usually opt to plot positive voltages upwards, so positive components appear above the 0 μV baseline.

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Raw EEG recordings consist of multiple overlaid waveforms of different frequencies (Hz), with higher frequency waveforms having shorter wavelengths between each peak and trough. In quantitative-EEG analyses, a raw recording is split into its constituent frequencies and the power of each measured to provide indications of activity and variability. Traditionally, spectral EEG has been divided in several bands each with particular functional significance including arousal and attention: delta (0.5 – 3.5 Hz), theta (3.5 -7.5 Hz), alpha (7.5 – 12 Hz), beta (12 – 30 Hz), and gamma (30+ Hz). These approaches are becoming more sophisticated, in relation to the analysis techniques available to reduce noise and isolate individual sources of EEG activity,

such as the use of Independent Component Analysis (ICA) to extract individual components from raw EEG data, and source based localisation approaches which are able to approximate the spatial location of ERP source generators within the cortex (McLoughlin et al., 2014a). This has meant EEG and ERP measures are becoming increasingly useful in psychiatric contexts, as they provide reliable, highly heritable and sensitive methods for measuring brain functions across a wide age range, without ceiling effects, and with high levels of internal consistency and temporal stability (McLoughlin et al., 2014a, Olvet and Hajcak, 2009b, Olvet and Hajcak, 2009a). In this way, research can begin to map out deficits in specific components of neurocognitive systems in each disorder, including arousal states, attention, inhibition and perceptual processes, and their temporal sequence, enabling detailed delineation of underlying neurophysiological processes, thereby allowing us to understand the relationship between these cognitive impairments and observable behaviours or symptoms (Banaschewski and Brandeis, 2007). Furthermore, examination of these neurobiological correlates, although initially based upon the categorical diagnostic definitions, is potentially capable of moving beyond potentially arbitrary diagnostic distinctions to explore how individual system-level cognitive abnormalities collectively contribute to overall syndromes or impairment as observed in any given psychiatric illnesses (Insel et al., 2010). In this way, such methods may provide insight into the commonalities, characteristic differences, and within-disorder heterogeneity (through the exploration of functional subgroups), which could be of great value in furthering our understanding of the aetiologies of psychiatric illnesses, their relationships to one another, and provide new markers to support diagnosis and treatment in clinical settings.

The use of ERP and EEG measures as potential endophenotypes has been proposed (Banaschewski and Brandeis, 2007). Endophenotypes are defined as traits, such as a cognitive impairment, which share genetic factors with a disorder and may therefore represent an

intermediate phenotype or an associated pleiotropic phenotype. It has been proposed that individual traits (i.e. endophenotypes) associated with a disorder may be less genetically diverse than the disorder concept as a whole, and therefore enable the study of underlying pathways (Gottesman and Gould, 2003, Kendler and Neale, 2010). EEG and ERP measures, are well suited to this approach as they may represent an intermediate level measure between genetic susceptibility and behaviour (Tye et al., 2011). As endophenotypes are likely to also be present at a level proportional to one's genetic susceptibility for the trait, they would be expected to be observed in genetically related individuals. Family studies are therefore able to take advantage of this potential endophenotype indicator by examining if EEG or ERP deficits observed in those with psychiatric illness are also present in first-degree relatives at intermediate levels. While only twin studies can distinguish genetic factors from the influence of shared environment, suitable twin samples with adequate numbers of probands with psychiatric diagnoses are rarely available and therefore sibling designs are commonly employed when recruiting samples from clinics.

1.3.2 Cognitive-neurophysiological abnormalities in ADHD

A range of cognitive deficits are associated with ADHD in both children and adults, including deficits in working memory, planning and organisation, set shifting, processing speed, attention regulation, variability in reaction times and response inhibition (Doyle, 2006, Kofler et al., 2013, Tamm et al., 2012, Willcutt et al., 2005). Measures of reaction times (in particular reaction time variability, RTV), response inhibition and sustained attention (indexed, for example, by commission errors and omission errors on a go/no-go task, respectively), consistently show impaired performance in children and adolescents with ADHD (Klein et al., 2006, Kuntsi et al., 2009, Willcutt et al., 2005). Incentives can affect performance on RT tasks

in children with ADHD, as RTV has been reported to show ADHD-sensitive improvement under reward conditions (Andreou et al., 2007, Kuntsi et al., 2009, Uebel et al., 2010), although this has not been observed in some studies (Kofler et al., 2013), suggesting ADHD performance can be highly sensitive to exact task parameters. In contrast, the elevated omission or commission errors did not show modification by incentives in ADHD, suggesting different underlying processes (Kuntsi et al., 2009). The dissociation between RT and accuracy processes has been further supported by work using multivariate familial factor analysis, which indicated the familial covariance of RT measures vs. those of accuracy measures (omission errors and commission errors) separated into two separate factors, indicating two separate familial processes were related to the impaired performance in ADHD: one relating to bottom-up arousal regulation, indexed by the speed and consistency of reaction time performance, and the other relating to top-down sustained attention and inhibition processes as indexed by omission and commission errors (Kuntsi et al., 2010).

A general IQ deficit of 7-12 points is also associated with ADHD (Kuntsi et al., 2004). One view relates this to attentional-arousal problems, which have themselves been linked to lower levels of scholastic achievement (Biederman et al., 2006). However, other studies have shown the genetic covariance of IQ to be largely independent from the covariance between ADHD and reaction time or executive function measures (Rommelse et al., 2008, Wood et al., 2010, Wood et al., 2011). This suggests that the IQ deficits seen in ADHD may be the result of a yet unknown aspect or component in the underlying pattern of cognitive deficits in ADHD. Overall, in terms of neuropsychological understanding of ADHD, evidence points to several distinct deficits in ADHD which commonly co-occur within the phenotype, and may therefore be related via a common atypical neurodevelopment pathway. However questions remain about the relationship of these deficits to one another, their interaction, the relationship between

specific cognitive deficits and broader ADHD symptoms, and to the variability of impairments in these systems across individuals with ADHD. That being the case, there remains much work to do in order to demonstrate if these neuropsychological performance indicators are reliable indicators of the ADHD phenotypes and if they represent stable biomarkers which might be useful in diagnostic contexts.

In relation to neuroimaging research, a meta-analysis of 55 fMRI studies in ADHD reported evidence for fronto-parietal and ventral hypoactivation in children, which are networks associated with executive processes and attention; while in adults, only hypoactivation in fronto-parietal networks were identified, although visual and dorsal attention systems showed hyperactivation, suggesting a compensatory role (Cortese et al., 2012). The number of EEG and ERP investigations into the cognitive processes of ADHD are increasing but much work remains to be done to provide a full mapping of cognitive deficits in ADHD at a functional level. For example, DSM-5 highlights that individuals with ADHD typically show increased slow-wave EEG power (American Psychiatric Association, 2013), which is thought to be related to arousal dysregulation in ADHD; yet results to date, particularly in more recent studies have called into question the consistency of these indicators, suggesting that the picture of spectral EEG anomalies in ADHD may be more complex than initially envisaged (Arns et al., 2013, Liechti et al., 2013).

In both the child and adult ADHD ERP research, overall, the most commonly altered attentional and inhibitory ERP correlates include the go-P3 (impaired target processing to rare targets, 'oddballs'), no-go-P3 (inhibition), cue-P3 (attentional orienting) and CNV (response

preparation) on the cued continuous performance task (CPT). Research using this paradigm has proved valuable in beginning to understand the relationship of cognitive deficits in ADHD, showing that abnormal inhibitory processing in ADHD is typically preceded or accompanied by attentional processing deficits, which also show genetic/familial effects (Albrecht et al., 2013, Albrecht et al., 2014, Cheung et al., under review, Doehnert et al., 2013, McLoughlin et al., 2011). There is also growing evidence of performance monitoring deficits in ADHD, observed on tasks such as the Eriksen Arrow Flanker Task, which have highlighted N2 and error-related negativity (ERN) abnormalities in both children and adults (Albrecht et al., 2008, Geburek et al., 2013, Johnstone et al., 2009, McLoughlin et al., 2009, McLoughlin et al., 2014b, Wild-Wall et al., 2009). ERN deficits have also been reported in some studies using the Go/NoGo paradigm, which have also shown, more robustly, attenuation of the Pe component in children and adolescents with ADHD, which is a positive error-detection component elicited by an error response (Groom et al., 2010, Groom et al., 2013, O'Connell et al., 2009a, Wiersema et al., 2009). Abnormalities of P2, N2 and P3 components have also been reported in some studies using the oddball task, which may suggest altered attentional resource allocation processes in ADHD (Barry et al., 2003, Gumenyuk et al., 2004, Holcomb et al., 1986, Marzinzik et al., 2012, Ozdag et al., 2004).

ERP components are also good candidates as endophenotypes of ADHD and have been studied in this regard. In ERP studies of both children and adults using the flanker task, there are indications that first degree relatives show intermediate conflict monitoring deficits relative to ADHD and control groups, as indexed by N2 and ERN components (Albrecht et al., 2008, McLoughlin et al., 2009). Similarly, fathers of children with ADHD, show intermediate deficits in cue-P3 and no-go-P3 components in the CPT, which are related to attentional and inhibitory processes, in comparison to adults with ADHD (McLoughlin et al., 2011). These endophenotype

studies have highlighted initial candidates for subsequent molecular genetic investigations which are now yielding results, for example indicating that certain genetic polymorphisms have specific effects on cue-P3 amplitude and attentional performance (Albrecht et al., 2014). Furthermore, there is evidence of links between the ERN and the dopaminergic function which suggest that impairments in this component may be the consequence of altered neural signalling (Meyer et al., 2012). As ADHD status has also been repeatedly linked to altered dopaminergic genetic markers (DiMaio et al., 2003, Kirley et al., 2002, Swanson et al., 2000), the study of ERP measures, such as the ERN and N2 components may provide further evidence for dopaminergic signalling theories of ADHD.

Although evidence of cognitive deficits in ADHD is emerging across several related neurocognitive domains, sketching out the dimensions of impairment in this broad heterogeneous diagnostic concept will require much more research, as on the whole studies remain sparse and findings not widely replicated, meaning additional factors which might influence results (i.e. methodology, age, gender, sample characteristics etc.) have not been fully explored. However, evidence from neuropsychological and electrophysiological studies, taken together, does provide strong indications for an emerging pattern of cognitive impairments in ADHD. Yet, data that are acutely lacking relate to the specificity of these impairments to ADHD, either individually or as a 'profile', or whether these emerging electrophysiological indicators only represent common markers of cognitive impairment for general psychiatric illness. This question must first be answered to determine if such indicators are of use within the context of diagnostic delineation.

1.3.3 Cognitive-neurophysiological abnormalities in BD

In comparison to those with ADHD, who show impaired performance from childhood, people diagnosed with BD do not show evidence of impaired premorbid functioning (Reichenberg et al., 2002). However, neuropsychological studies reveal that cognitive performance can be severely impaired during manic or depressive phases showing that adults with BD consistently present with impairments in executive functions, and in particular, verbal working memory, attention and psychomotor speed (Fleck et al., 2003, Glahn et al., 2007, Martinez-Aran et al., 2004). Relatives of individuals with BD also show impairments in verbal working memory and other aspects of executive functions, suggesting some familial influence in these neurocognitive deficits (Glahn and Burdick, 2011). Impairments in BD persist during phases of remission, with significant residual deficits in verbal memory and executive functioning being consistently reported during euthymic phases of the disorder (Bora et al., 2009, Frangou et al., 2005, Robinson et al., 2006, Thompson et al., 2009). Premorbid IQ in BD does not show differences from the general population, with IQ showing a weak association with BD in general, even as the disorder progresses (Toulopoulou et al., 2006, Zammit et al., 2004), although impaired performance is observed on some specific areas of intellectual testing such as Block Design and Digit Symbol tasks (Frantom et al., 2008). Experimental cognitive designs, which seek to map performance deficits in specific underlying cognitive systems, is a relatively underdeveloped area in the field of BD research, compared to that of ADHD. A few studies have presented evidence suggesting that RTV may be increased in adolescents with BD (Bora et al., 2006, Brotman et al., 2009), although this metric remains uncommon in BD research generally, and the findings require further replication.

Familial studies have suggested potential neurocognitive endophenotypes for BD. Verbal memory and working memory are the most consistently found to be impaired in family members of people with BD (Balanza-Martinez et al., 2008). Recent research supports this indicating that executive function deficits are the primary candidates as endophenotypes of BD, showing impairment in both BD participants and their first-degree relatives (Civil Arslan et al., 2014, Schulze et al., 2011). Twin-studies have also highlighted response inhibition as showing impairment in both BD twins and their unaffected co-twins (Juselius et al., 2009).

In ERP studies, reports of early perceptual deficits as indicated by abnormalities in P50 and Mismatched Negativity (MMN) components are often reported in BD, indicating potential pre-attentive dysfunctions (Cabranes et al., 2013, Jahshan et al., 2012, Maekawa et al., 2013, Onitsuka et al., 2013, Swann et al., 2013). Little work has been conducted examining conflict monitoring components in BD, such as the ERN and N2, yet given that BD and depression have been linked to potential deficits in dopaminergic signalling (Dunlop and Nemeroff, 2007, Strakowski et al., 2005), which have in turn been linked to the ERN component (Meyer et al., 2012), research directly examining these components in BD would be beneficial. Attenuation of later P3 components in BD, related to attention and processing speed (Bestelmeyer, 2012, Bestelmeyer et al., 2009, Degabriele and Lagopoulos, 2009), is also a common finding, with evidence of similar impairments among their first-degree relatives, indicating a contribution of familial factors to this indicator (Pierson et al., 2000). Yet, overall, familial investigations using ERP outcome measures in BD remain limited.

Similar deficits in the P3a component, assumed to reflect covert orienting or shift in attention, have also been evidenced in BD, albeit much less frequently (Jahshan et al., 2012). Also observed less consistently are P2 abnormalities during the auditory oddball task, which may relate to psychotic features found in some expressions of the disorder (Ethridge et al., 2014). In EEG studies, elevated delta and theta power and decreases in alpha power have been associated with BD (Degabriele and Lagopoulos, 2009); a similar profile to that found in some studies of ADHD, creating questions as to whether there are commonalities in brain dysfunction and therefore the specificity of such measures.

Taken together, cognitive and electrophysiological studies indicate that impairments in BD can be severe and persist during periods of euthymia. However, the understanding of how these performance abnormalities relate to deficits in underlying cognitive systems in BD is less well developed than in the study of ADHD at present. Investigation of these potential biomarkers has to date been largely limited to a few cognitive components, such as the P3 component in the oddball paradigm, but investigations into the broader range of specific cognitive processes which could be altered in BD is notably lacking. One example is that of performance monitoring correlates, such as the N2 and ERN components, in tasks with considerable attentional load and perceptual conflict between target and distractor stimuli. If we are to understand the full profile of cognitive deficits in BD, along with the interrelationships between these areas of impairments, researchers must first map out the understudied avenues of cognitive performance in BD, and then compare recorded deficits to those of other disorders to illuminate the pattern of characteristic deficits in BD vs. those shared with other psychiatric disorders. It is in this way that research into neurobiological systems may improve our understanding to the aetiology of BD, helping to clarify diagnostic distinctions with those overlapping disorders such as ADHD.

1.3.4 Cross-disorder comparisons

Cross-disorder comparisons using ERP techniques between ADHD or BD and other psychiatric disorders are present in the literature; with BD being most commonly compared with schizophrenia (Chun et al., 2013, O'Donnell et al., 2004, Souza et al., 1995), while ADHD has been compared, for example, with schizophrenia (Groom et al., 2008) and with autism (Tye et al., 2014). Certain disorder-specific differences and commonalities have been highlighted, demonstrating the growing value of cross-disorder approaches to chart functional neurocognitive boundaries between diagnostic classifications. However, there is a strong need for more data and the application of advanced methodological and analytical approaches.

Data on direct comparisons between ADHD and BD samples for cognitive and ERP measures is very limited, particularly for adult populations, and are needed to elucidate whether symptom similarities in ADHD and BD reflect identical or unique underlying impairments (Skirrow et al., 2012). While data is currently sparse, there are suggestions that cognitive performance may show both shared and unique impairments between ADHD and BD. A review of neurocognitive studies in each disorder concludes that, although there were similarities in neuropsychological deficits, ADHD and BD may be associated with different executive function deficits (Walshaw et al., 2010). Direct comparisons of ADHD and BD adults have shown common deficits in both disorders, such as visual and spatial working memory deficits (Baez et al., 2014), as well as some specific differences, such as memory acquisition and storage in BD, unlike ADHD which did not show recognition deficits for previously learned stimuli (Torralva et al., 2011).

Literature directly comparing reaction time performance across ADHD and BD is also limited, particularly for adult samples, with results reported in current studies being variable and inconclusive. One study examining RT measures in children, found higher RTV and slower mean reaction time (MRT) in those with comorbid ADHD and BD compared to ADHD children without comorbidities (Mattis et al., 2011). In contrast, another study of early onset BD and ADHD in adolescents reported increased RTV in ADHD and ADHD with comorbid BD, but reduced RTV in BD compared to these other groups. This caused the study to conclude that undiagnosed comorbid ADHD may account for many of the neurocognitive deficits observed in BD (Udal et al., 2014). Another study reported RTV deficits in both ADHD and BD but in different tasks, leading the authors to conclude that these deficits are related to impairments in different underlying neurocognitive systems in ADHD compared to BD (Dickstein et al., 2005).

Direct comparisons of brain structure in ADHD and BD in child and adult samples also support views of a neurobiological dissociation between them, with disorder-specific structural MRI differences being identified particularly in subcortical regions and the prefrontal cortex for ADHD, and thalamic, orbital-prefrontal and nucleus accumbens for BD (Biederman et al., 2008, Lopez-Larson et al., 2009). Functional measures also provide supporting evidence for disorder specific differences. Using fMRI, one study showed that, although response inhibition was impaired in both children with ADHD and BD-I, the brain regions involved in their inhibitory processes differed suggesting two distinctive neurocognitive aetiologies for the impairment (Passarotti et al., 2010). Studies of face emotional processing using fMRI also showed differences between ADHD and BD, with the former showing increased activation of the

amygdala, and the latter showing reduced activation of working memory circuits in different studies (Brotman et al., 2010, Passarotti et al., 2010).

EEG and ERP comparison studies between ADHD and BD remain limited, although have been appearing more frequently over the last few years. In each case the investigations represent an example of a study comparing a particular cognitive deficit in ADHD and BD, with the samples mostly being small and therefore results preliminary and requiring replication. An investigation examining feedback-related negativity (FRN) and P3 in a gambling task, using a sample of adults with BD (n = 13), ADHD (n = 12) or controls (n = 25), reported that both the BD and ADHD groups showed impairments in cortical response based on feedback (FRN). The authors suggest that this indicates that impulsivity, rather than information provided by task feedback, was driving responses in both disorders (Ibanez et al., 2012). Furthermore, in this study, the BD group showed enhancement of the P3 component relative to reward magnitude, also observed in controls, although this effect was absent from the ADHD group, which instead showed an equivalent P3 response to both large and small rewards. Another study compared adults with ADHD (n = 16), BD (n = 14), schizophrenia (n = 15), the unaffected relatives of schizophrenia participants (n = 14) and controls (n = 41) using a face-emotional processing task (Ibanez et al., 2014). In this study ADHD, BD and schizophrenia groups all showed N170 deficits, linked to the processing of emotional stimuli, suggesting a shared impairment in this domain for all three disorders (Ibanez et al., 2014). A further study adopted a graph theory approach, examining the EEG functional connectivity of scalp regions using the temporal variability of delta activity (0.5 - 3.5 Hz) in a sample of adult ADHD (n = 9), BD (n = 11) and control participants (n = 15). Their data suggested that ADHD was linked to increased variability, related to connectivity abnormalities, while participants with BD showed less variability and had evidence of more long-range neural connectivity (Barttfeld et al., 2014).

Finally, another study using resting-state EEG data from adults with ADHD (n = 21) or BD (n = 22) examined mathematical approaches of classifying groups using EEG data, reporting the successful identification of ADHD and BD participants in a test sample around 80% of the time, based on EEG data alone. However, this study was largely focused on the application of mathematical models to complex data rather than clinical applications of this approach, making its validity, when applied to a general sample, unclear (Sadatnezhad et al., 2011). These studies overall indicate that there is growing suggestive evidence of neurocognitive distinctions between ADHD and BD, although a full neurobiological understanding of them is far from resolved, beyond a few basic dissociations in those cognitive domains which have been chosen for study to date. Nonetheless, despite their relative infrequency and small sample sizes, cross-disorder comparisons between ADHD and BD have shown potential contributions in increasing the neurocognitive understanding of these disorders. This area would now benefit greatly from further cross-disorder investigations in larger samples, targeting areas of investigation relevant to the common behavioural symptoms of ADHD and/or BD.

1.3.5 Gender differences in cognitive-electrophysiological research on ADHD and BD

No previous studies, to the best of our knowledge, have explored the effects of gender on EEG or ERP outcome measures in BD. In ADHD, the majority of data from EEG and ERP studies consist of a high proportion of data from male participants, with a few exceptions described here. EEG resting-state studies in girls with ADHD have suggested that while the overall pattern of ADHD-linked deficits is similar to that of boys, there is evidence for reduced variability in EEG power in girls (Clarke et al., 2003, Dupuy et al., 2011). Direct comparisons between boys and girls with ADHD have evidenced topographic differences in EEG power,

indicative of different cortical maturational patterns between the genders (Dupuy et al., 2013, Hermens et al., 2005a). Although data are limited to a single study, similar findings of topographic EEG differences between men and women have been reported in a gender comparison of adults with ADHD (Hermens et al., 2004). ERP studies which have explored gender differences in ADHD are also fairly uncommon, although a meta-analysis of six studies was performed and indicated that P3 target response in the Go/NoGO paradigm was more highly attenuated in females participants with ADHD compared to male participants with ADHD (Szuromi et al., 2011). However, as female participants have been shown to display a differing P3 response to stimulus novelty (Yuan et al., 2012), and differing N2 response to conflict monitoring demands (Clayson et al., 2011) compared to males in general population samples, it would seem important to collect data and compare case-control differences in female samples independently from male samples. This seems particularly important in ADHD, where data from adult female samples is currently very limited.

1.3.6 Section Summary

Individually, there is strong, well-replicating evidence for cognitive and neurophysiological impairments in ADHD and BD, which is starting to elucidate the underlying neurobiological underpinnings of each disorder, and which will be vital in developing biologically-informed classifications and diagnostic aids in each disorder. However, data on the specificity of proposed biomarkers is lacking from this growing field of research. The few neurophysiological comparison studies between ADHD and BD to date, and particularly those using EEG and ERP techniques which have the potential to directly measure cognitive processes with high temporal resolution, have been impressive in their ability to identify various shared and specific neurobiological deficits in each case. However, consistently the samples employed in

these studies have been small and results have yet to be replicated. There also remain many cognitive processes known to be impaired in one disorder but which have yet to be studied in the other; and many which have not been the subject of direct comparison between the disorders to determine specificity. Only with such work using cognitive-electrophysiological methods among others, in conjunction with consistent replication and an increased understanding of heterogeneity in neurocognitive processes within each disorder, will researchers eventually close in on reliable biomarkers for ADHD and BD.

***Chapter 2 - A Matter of Time: The Influence of
Recording Context on EEG Spectral Power in
Adolescents and Young Adults with ADHD***

A Matter of Time: The Influence of Recording Context on EEG Spectral Power in Adolescents and Young Adults with ADHD

Glenn L. Kitsune · Celeste H. M. Cheung · Daniel Brandeis · Tobias Banaschewski · Philip Asherson · Gráinne McLoughlin · Jonna Kuntsi

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Abstract Elevated theta or theta/beta ratio is often reported in attention deficit hyperactivity disorder (ADHD), but the consistency across studies and the relation to hypoarousal are increasingly questioned. Reports of elevated delta related to maturational lag and of attenuated beta activity are less well replicated. Some critical inconsistencies could relate to differences in recording context. We examined if resting-state EEG power or global field synchronization (GFS) differed between recordings made at the beginning and end of a 1.5 h testing session in 76

adolescents and young adults with ADHD, and 85 controls. In addition, we aimed to examine the effect of IQ on any potential group differences. Both regional and midline electrodes yielded group main effects for delta, trends in theta, but no differences in alpha or theta/beta ratio. An additional group difference in beta was detected when using regions. Group by time interactions in delta and theta became significant when controlling for IQ. The ADHD group had higher delta and theta power at time-1, but not at time-2, whereas beta power was elevated only at time-2. GFS did not differ between groups or condition. We show some ADHD-control differences on EEG spectral power varied with recording time within a single recording session, with both IQ and electrode selection having a small but significant influence on observed differences. Our findings demonstrate the effect of recording context on resting-state EEG, and highlight the importance of accounting for these variables to ensure consistency of results in future studies.

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G. L. Kitsune (✉) · C. H. M. Cheung · P. Asherson · G. McLoughlin · J. Kuntsi
MRC Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK
e-mail: glenn.kitsune@kcl.ac.uk

J. Kuntsi
e-mail: jonna.kuntsi@kcl.ac.uk

D. Brandeis · T. Banaschewski
Department of Child and Adolescent Psychiatry and Psychotherapy, Central Institute of Mental Health, Medical Faculty Mannheim/Heidelberg University, Mannheim, Germany

D. Brandeis
Department of Child and Adolescent Psychiatry, University of Zurich, Zurich, Switzerland

D. Brandeis
Center for Integrative Human Physiology, University of Zurich, Zurich, Switzerland

D. Brandeis
Neuroscience Center Zurich, University of Zurich, Zurich, Switzerland

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Introduction

Electrophysiological approaches provide a temporally precise method for recording electrical brain activity. They enable the direct investigation of subtle changes in cortical arousal, which are highly relevant for the study of attention-deficit/hyperactivity disorder (ADHD) where arousal dysregulation has been observed (Banaschewski and Brandeis 2007). Spectral electroencephalogram (EEG) is traditionally described as separate frequency bands: delta (0.5–3.5 Hz), theta (4–7.5 Hz), alpha (7.5–12.5 Hz), beta

(12.5–30 Hz) and gamma (30+ Hz) (Tye et al. 2011). In control populations, compared to at-rest, cognitive tasks elicit reduction in alpha, suggesting that attenuation in alpha is associated with cognitive or attentional demands (Klimesch 2012). Similarly, increased arousal and attentional engagement through eye opening in the resting state not only induces global power reduction, but also topographic changes with decreases in frontal delta and theta activity, and frontal increases in beta activity (Barry et al. 2007), suggesting that the relationship between theta and beta activity may be an important marker of activation, while arousal seems more closely linked to global power and alpha activity reductions (Barry et al. 2007). Studies differ in whether data has been collected under eyes-open (EO) or eyes-closed (EC) conditions. Direct comparisons of EO and EC conditions in children and adults with ADHD suggest that EEG power differences are limited to an enhancement of alpha, and more tentatively, an attenuation of beta activity in the EC condition (Loo et al. 2009; Nazari et al. 2011; Woltering et al. 2012). Alternative group-level Independent Component Analysis (gICA) approaches, which may be more sensitive to spectral power differences than conventional techniques, identified reduced delta, alpha and beta voltage power and current source density in adults with ADHD compared to controls during both EC and EO conditions (Ponomarev et al. 2014).

The DSM-5 highlights that individuals with ADHD typically show increased slow-wave EEG (American Psychiatric Association. 2013). However, reported EEG spectral profiles in ADHD are far from consistent, and the extent to which these EEG indicators are useful in clinical settings remains unclear (Banaschewski and Brandeis 2007; Cortese 2012; Liechti et al. 2013).

The most consistent findings in earlier resting-state investigations of ADHD using both EO and EC data were of elevated theta or theta/beta ratio (T:B) in children, adolescents, and adults (Barry et al. 2010, 2009; Bresnahan et al. 1999; Clarke et al. 2001b, 2003b; Koehler et al. 2009; Lansbergen et al. 2011; Shi et al. 2012; Snyder et al. 2008; Woltering et al. 2012). Yet, some recent studies have failed to replicate these findings (Buyck and Wiersma 2014; Liechti et al. 2013; Loo et al. 2009; Ogrim et al. 2012; Poil et al. 2014; Ponomarev et al. 2014; Skirrow et al. paper under review; Swartwood et al. 2003; van Dongen-Boomsma et al. 2010), or have reported contrasting findings of attenuated T:B in adults with ADHD (Loo et al. 2013). These differences are unlikely to be due to EO or EC condition differences, as both positive and negative T:B findings have been reported in comparison studies (Lansbergen et al. 2011; Liechti et al. 2013; Loo et al. 2013, 2009; Ogrim et al. 2012; van Dongen-Boomsma et al. 2010; Woltering et al. 2012). A recent meta-analysis,

conducted on studies using EO data, demonstrated that the reported T:B effect size showed a strong relationship with year of publication, declining over time (Arns et al. 2013). Arns et al. suggest this might be due to testing context differences between studies, the trend for reduced sleep duration in children across years, or sample differences.

The consistency of delta and beta differences in ADHD is more limited. Enhanced delta activity has been reported in children with ADHD (Barry et al. 2010; Bresnahan et al. 1999; Nazari et al. 2011; Swartwood et al. 2003), but may reflect a maturational lag and is also not consistently replicated in children (Clarke et al. 2002c, 2003b; Liechti et al. 2013), or adults (Koehler et al. 2009; Liechti et al. 2013).

Beta activity findings are conflicting in both EO and EC data, with a meta-analysis and other studies of children, adolescents and adults reporting attenuation (Barry et al. 2010; Bresnahan et al. 1999; Clarke et al. 2006; Shi et al. 2012; Snyder and Hall 2006); while other studies report enhancement in ADHD adults compared to children (Poil et al. 2014), enhancement in a subset of children who have high hyperactive/impulsive symptoms (Clarke et al. 2001b, 2007), or in specific narrow-band beta frequency ranges (Loo et al. 2009). However, many studies fail to observe case–control differences in beta activity, in either children or adults (Buyck and Wiersma 2014; Koehler et al. 2009; Lansbergen et al. 2011; Liechti et al. 2013; Loo et al. 2013; Nazari et al. 2011; Ogrim et al. 2012; van Dongen-Boomsma et al. 2010; Woltering et al. 2012).

The inconsistencies in reported case–control differences contrast with spectral EEG's robust sensitivity to age and maturational lag (Bresnahan et al. 1999; Liechti et al. 2013; Loo et al. 2013; Ogrim et al. 2012; Poil et al. 2014; Snyder and Hall 2006) and could reflect factors such as decreasing ADHD symptoms with age (Snyder and Hall 2006), ADHD subtype (Buyck and Wiersma 2014; Clarke et al. 2001a; Loo et al. 2013, 2010), medication (Clarke et al. 2003a, 2002a; Loo et al. 2004), and co-occurring symptoms of depression or disruptive behaviours (Clarke et al. 2002b; Loo et al. 2013). Few studies have directly explored the potential effects of IQ on EEG power in ADHD with most studies using samples with normal range or matched IQs, despite lower IQ commonly being associated with ADHD. One study on 40 children with ADHD reported EEG power to be similar in subgroups of children with both high and low IQ (Clarke et al. 2006), while (Chabot and Serfontein 1996) reported that, although there were ADHD-associated differences in spectral EEG for both low and high IQ groups, low IQ did contribute to generalised EEG differences in terms of greater asymmetry, and reduced alpha and/or theta power. This suggests that lower IQ, while not being the dominant cause of spectral profile differences seen in ADHD, may contribute to group differences in studies where the ADHD sample show typical lower mean

IQ scores and where IQ is not otherwise controlled. Studies should therefore attempt to examine the influence of IQ on results, by comparing results with and without controlling for the effects of IQ on their data.

Other possible explanations of the inconsistencies observed between the studies could be related to differences in recording context (i.e., when recordings are conducted in relation to the start or end of a recording session or other experimental demands), which might influence the level of arousal in participants. Arousal may be more variable in ADHD and can affect symptom severity and performance (Sergeant 2005; Van der Meere 2002), and may therefore vary throughout an experimental recording session. For example, rest-to-task comparisons show prominent EEG power differences (Loo et al. 2013; Nazari et al. 2011; Ogrim et al. 2012), while Koehler et al. (2009) report reduced beta and T:B differences between two resting state recordings completed at the beginning and end of the Eriksen Flanker Task.

We therefore hypothesised that differences in recording context, such as whether recordings are made at the start or end of an experimental session, may alter spectral EEG case-control differences, as the novelty of the testing environment declines with time, especially over longer recording durations. This study investigated if spectral power and global field synchronization (GFS) varies between ADHD and control groups in conventional spectral bands (delta, theta, alpha, beta) and in theta/beta ratio between recordings made at the beginning and end of a 1.5 h cognitive-EEG testing session. As a further post hoc analysis, we additionally examined whether IQ influences any ADHD-control differences that emerge.

Methods and Materials

Sample

ADHD and control participants who had taken part in our previous research (Chen et al. 2008; Kuntsi et al. 2010), were invited to take part in this follow-up study. In the initial study, ADHD participants aged between 6 and 17 were recruited from specialist clinics in the UK from among those who had a clinical diagnosis of DSM-IV combined subtype ADHD during childhood, as determined by a paediatrician or child psychiatrist. The control group were recruited from primary (ages 6–11 years) and secondary (ages 12–18 years) schools in the UK. At follow-up in this study, participants were aged between 13 and 25, and for this investigation ADHD participants were reassessed and only those who continued to meet DSM-IV criteria for any ADHD subtype in adolescence/early adulthood were included in current analyses. All participants were of European Caucasian descent.

For both groups, the exclusion criteria, as defined by those used in the initial investigation, were IQ < 70, autism, epilepsy, learning difficulties, brain disorders and any genetic or medical disorder associated with externalising behaviours that might mimic ADHD. Written informed consent was obtained and the study was approved by the London-Surrey Borders Research Ethics Committee (NRES 09/H0806/58).

Six ADHD participants were excluded from the analysis (because of unusable EEG data (4) and <20 acceptable EEG segments (2)). Two control participants were excluded, as they met ADHD criteria based on parent report; and one further control participant had <20 acceptable EEG segments. The final sample consisted of 76 ADHD participants and 85 controls. The ADHD and control groups did not differ in age (ADHD: mean = 18.70, SD = 2.91; Control: mean = 18.29, SD = 1.76; $t = -1.362$, $df = 181$, $p > 0.5$), but differed significantly in full-scale IQ (ADHD: mean = 98.44, SD = 14.27; Control: mean = 111.67, SD = 12.86; $t = -6.547$, $df = 181$, $p < 0.001$) and in gender distribution (ADHD: 89 % male; Control: 99 % male; $\chi^2(1, n = 183) = 4.75$, $p = 0.03$).

Procedure

Participants attended a single research session for clinical interviews and cognitive-EEG assessments, as part of a larger study. A 48-hour ADHD medication-free period was required before the research session. Two 3-minute eyes-open resting state conditions were administered at the beginning and end of an extended 1.5 h cognitive-EEG test battery. Participants were requested to remain still, and keep their eyes on a fixed point in front of them for the duration of the recording.

Measures

ADHD diagnosis

Childhood ADHD was initially assessed using the Parental Account of Childhood symptoms (PACS) (Chen et al. 2008; Taylor et al. 1986a, 1986b), a semi-structured, standardised, investigator interview with high inter-rater reliability (Taylor et al. 1986a). During follow-up, ADHD status was confirmed using parental ratings of the Diagnostic Interview for ADHD in Adults (DIVA) (Kooij and Francken 2007) and the Barkley's Functional Impairment Scale (BFIS) (Barkley and Murphy 2006). A research diagnosis of ADHD was made if participants scored ≥ 6 on the DIVA for either inattention or hyperactivity/impulsivity scales, and ≥ 2 positive scores on ≥ 2 areas of impairments on the BFIS, based on DSM-IV criteria. Six participants were excluded from the sample, as they had

missing parent ratings of clinical impairment and their current ADHD status could therefore not be determined.

IQ

The vocabulary and block design subtests of the Wechsler Abbreviated Scale of Intelligence Fourth Edition (WASI-IV) (Wechsler 1999) were administered to all participants to derive an estimate of IQ.

EEG recording and Analysis

Two 3-minute fixed-gaze eyes-open resting conditions were carried out, at the beginning and end of a 1.5 h recording session. Participants completed three event related potential (ERP) paradigms between resting state recordings, administered in a fixed order (Continuous Performance Task (Doehnert et al. 2008); Eriksen Flanker Task (Albrecht et al. 2009); and the Fast Task (Andreou et al. 2007; Kuntsi et al. 2006)). The EEG was recorded from a 62 channel DC-coupled recording system (extended 10–20 montage), using a 500 Hz sampling-rate, impedances under 10 k Ω , and FCz as the reference electrode. The electro-oculograms (EOGs) were recorded from electrodes above and below the left eye and at the outer canthi.

The EEG data were analysed using Brain Vision Analyzer (2.0) (Brain Products, Germany). Raw EEG recordings were down-sampled to 256 Hz, re-referenced to the average of all electrodes, and digitally filtered using Butterworth band-pass filters (0.1–30 Hz, 24 dB/oct). Ocular artefacts were identified using independent component analysis (ICA) (Jung et al. 2000). All trials were also visually inspected for other subtle artefacts, and sections containing these were manually removed. Data with other artefacts exceeding $\pm 100 \mu\text{V}$ in any channel or with a voltage step greater than 50 μV were rejected. Where an entire channel was removed due to technical problems or electrical noise, topographic spline interpolation was used to replace the channel.

The cleaned continuous EEG was then segmented into 2-second epochs and power spectra computed using the Fast Fourier Transform with a 10 % Hanning window. Epochs were averaged to create group means. Bands were defined as delta 0.5–3.5 Hz; theta 3.5–7.5 Hz; alpha 7.5–12 Hz; and beta 12–30 Hz. Topographic maps, t-maps and band-power graphs were generated from scalp recordings of power at all electrodes (see supplementary material S1–S3). In order to attempt to replicate findings from the majority of previous studies (Clarke et al. 2002c, 2003b; Koehler et al. 2009; Lansbergen et al. 2011; Loo et al. 2009, 2004; Loo and Smalley 2008; van Dongen-Boomsma et al. 2010), EEG power was averaged into three regions from individual scalp electrodes (frontal: Fz, F1,

F2, F3, F4, F5, F6, F7, F8; central: Cz, C1, C2, C3, C4, C5, C6; parietal: Pz, P3, P4, P7, P8). For an additional comparison with more recent investigations (Buyck and Wiersema 2014; Liechti et al. 2013; Loo et al. 2013; Ogrim et al. 2012; Woltering et al. 2012) and to discount the effect of electrode selection, we also re-ran all analyses using only mid-line electrodes (Fz, Cz, Pz).

The observed absolute power within any given band is based upon the phase and amplitude of multiple EEG sources. When sources are phase-locked, they are synchronised, indicating they are simultaneously active within the brain. GFS (Koenig et al. 2001, 2005) is an index of phase synchrony at a given frequency. It provides an additional dimension beyond absolute power for understanding the global functional connectivity within these frequency bands, with the advantage of being a relative measure, which is not influenced by the choice of reference electrode. GFS provides a single score between 0 and 1, with zero indicating no synchrony between EEG sources, and 1 indicating all sources are in phase. GFS was computed for each 2-second epoch, averaged for each participant and then examined by frequency band.

Statistical Analyses

An exploratory analysis on age effects was carried out by comparing power within each band between the younger (13–18 years old) and older (>18) subsets within each group. Based on this analysis (supplementary material S4), which indicated the older group to have reduced power in all bands, we included age, along with gender, as covariates in all analyses. In addition, all analyses were re-run with IQ as an additional covariate to examine empirically the effects of IQ on EEG power. Mean power was non-normally distributed and transformed using log for conventional frequency bands, and square root for theta/beta ratio. A repeated measures analysis of covariance (ANCOVA) was carried out in SPSS (version 21) within each band (delta, theta, alpha, beta), for both EEG power and GFS measurements, and within theta/beta ratio for EEG power only. Two within-subjects factors were included: time (start and the end of the testing session) and region (frontal, central, parietal or Fz, Cz, Pz electrodes); and one between-subject factor (group). Where necessary, to examine group differences at either time-1 or -2 individually, subsequent follow-up ANCOVAs were performed using only group and region factors. We focused both on p-values ($p < 0.05$ for significance, and $p < 0.08$ for a trend) and effect sizes (eta squared (η^2)). Based on (Cohen's 1988, p.283), estimates for η^2 , 0.0099 constitutes a small effect, 0.0588 a medium effect and 0.1379 a large effect.

Table 1 Significance values and effect sizes for ANCOVA factors and interactions, controlling for age and gender

	Delta	Theta	Alpha	Beta	T:B
Time					
F	0.618	2.402	1.907	0.286	0.013
<i>p</i>	0.433	0.123	0.169	0.594	0.910
η^2	0.0038	0.0141	0.0113	0.0018	0.000
Region					
F	5.477	3.922	4.561	0.916	1.916
<i>p</i>	0.005*	0.021*	0.011*	0.401	0.149
η^2	0.0317	0.0233	0.0275	0.0058	0.012
Group					
F	4.294	3.747	1.635	5.478	0.067
<i>p</i>	0.040*	0.055 ^a	0.203	0.021*	0.796
η^2	0.0245	0.0191	0.0095	0.0288	0.000
Group* region					
F	2.023	1.376	0.364	0.464	1.461
<i>p</i>	0.134	0.254	0.695	0.594	0.234
η^2	0.0117	0.0082	0.0022	0.0029	0.009
Group* time					
F	3.479	3.717	0.832	0.582	3.112
<i>p</i>	0.064 ^a	0.056 ^a	0.363	0.447	0.080 ^a
η^2	0.0214	0.0218	0.0049	0.0036	0.019

Activity bands defined as: delta 0.5–3.4 Hz, theta 3.5–7.5 Hz, alpha 7.5–12 Hz, beta 12–30 Hz

* Denotes significant at $p < 0.05$

^a Denotes trend level effect at $p < 0.08$. Effect size (η^2): 0.0099 constitutes a small effect, 0.0588 a medium effect and 0.1379 a large effect

Results

Group Differences

An ANCOVA indicated significantly higher delta power in the ADHD group, compared to controls (Table 1 and Fig. 1a). A post hoc analysis showed that the group means (Table 2) differed significantly for delta power at time-1 ($F(1, 157) = 7.81, p = 0.01, \eta^2 = 0.0437$), but not at time-2 ($F(1, 157) = 0.36, p = 0.55, \eta^2 = 0.0022$). For theta band (Table 1 and Fig. 1b), an effect of group at trend level was observed. Post-hoc analysis indicated that the ADHD group had significantly higher mean theta power than controls at time-1 ($F(1, 157) = 6.46, p = 0.01, \eta^2 = 0.0329$) but not at time-2 ($F(1, 157) = 0.94, p = 0.33, \eta^2 = 0.0052$). In the alpha band (Table 1 and Fig. 1b), no significant group differences emerged. For beta activity, we observed a main effect of group (Table 1 and Fig. 1c), with post hoc analysis indicating a significantly higher mean beta power in ADHD than control group at time-2 ($F(1, 157) = 5.68, p = 0.018, \eta^2 = 0.0318$), but not at time-1 ($F(1, 157) = 2.90, p = 0.09, \eta^2 = 0.0154$). All main effect group

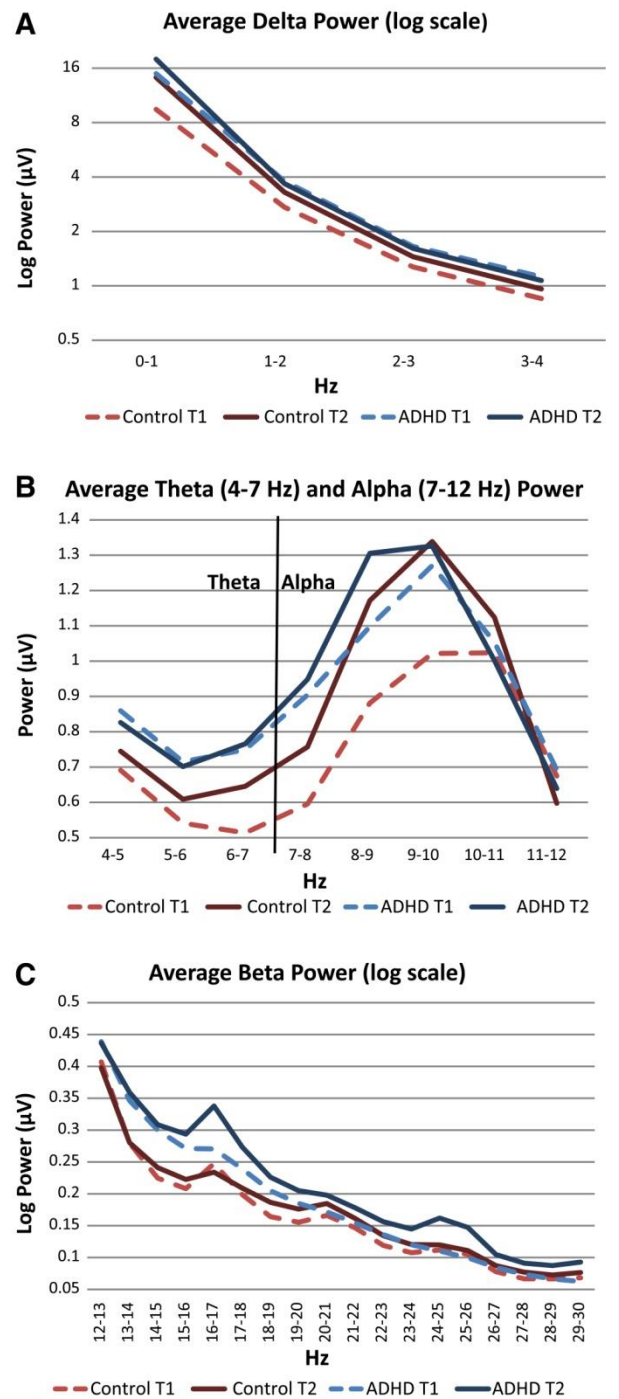


Fig. 1 Average spectral mean EEG power across bands. Average spectral power in ADHD and controls groups at time-1 and time-2, by frequency band. Plots represent mean power across from frontal, central and parietal regions in the ranges of **a** delta (0.5–3.5 Hz); **b** theta (3.5–7.5 Hz) and alpha (7.5–12 Hz) and **c** beta 12–30 Hz

comparisons in conventional bands had small effect sizes. The main effect of group for theta/beta ratio was not significant, and had a minimal effect size.

Table 2 Mean amplitude in μV and standard deviation (SD), prior to transformations, and with age and gender controlled for, in ADHD and control groups across frequency bands and theta/beta ratio at frontal, central and parietal regions

	Delta μV (SD)	Theta μV (SD)	Alpha μV (SD)	Beta μV (SD)	T:B μV (SD)
Frontal Region					
T1					
Control	3.585 (0.29)	0.557 (0.04)	0.567 (0.06)	0.146 (0.01)	2.127 (0.06)
ADHD	2.431 (0.19)	0.724 (0.04)	0.703 (0.06)	0.173 (0.01)	2.189 (0.07)
T2					
Control	4.436 (0.29)	0.654 (0.04)	0.652 (0.05)	0.157 (0.01)	2.190 (0.06)
ADHD	3.308 (0.2)	0.765 (0.04)	0.781 (0.06)	0.202 (0.01)	2.108 (0.06)
Central Region					
T1					
Control	3.361 (0.2)	0.563 (0.05)	0.698 (0.08)	0.153 (0.01)	2.120 (0.06)
ADHD	2.181 (0.19)	0.752 (0.05)	0.916 (0.08)	0.170 (0.01)	2.206 (0.06)
T2					
Control	3.793 (0.21)	0.606 (0.05)	0.822 (0.09)	0.155 (0.01)	2.192 (0.06)
ADHD	2.542 (0.19)	0.732 (0.05)	0.950 (0.1)	0.200 (0.01)	2.154 (0.07)
Parietal Region					
T1					
Control	3.029 (0.2)	0.696 (0.07)	1.193 (0.15)	0.186 (0.01)	2.060 (0.06)
ADHD	2.982 (0.27)	0.986 (0.07)	1.459 (0.16)	0.214 (0.01)	2.185 (0.06)
T2					
Control	2.935 (0.2)	0.788 (0.07)	1.438 (0.16)	0.195 (0.01)	2.139 (0.06)
ADHD	4.378 (0.3)	0.952 (0.07)	1.492 (0.17)	0.241 (0.01)	2.106 (0.07)

Activity bands defined as: delta 0.5–3.5 Hz, theta 3.5–7.5 Hz, alpha 7.5–12 Hz, beta 12–30 Hz. Regions are average power from individual electrodes: frontal: Fz, F1, F2, F3, F4, F5, F6, F7, F8; central: Cz, C1, C2, C3, C4, C5, C6; parietal: Pz, P3, P4, P7, P8

Group by Time Interactions

Group by time interactions emerged at trend level for delta and theta bands, and were not significant for alpha and beta bands. Effect sizes were small for delta and theta, and minimal in alpha and beta bands (Table 1). A trend-level group by time interaction was detected for theta/beta ratio, which had a small effect size. Post-hoc analysis did not show group differences in theta/beta ratio at either time-1 ($F(1, 157) = 1.08, p = 0.30, \eta^2 = 0.0066$) or 2 ($F(1, 157) = 0.350, p = 0.56, \eta^2 = 0.0021$).

Time

The main effects of time, independent of group, were not significant in any of the four spectral bands, or for theta/beta ratio (Table 1). Theta and alpha bands had a small effect size; in delta, beta and theta/beta ratio the effect size was minimal.

Controlling for IQ

To examine the effect of IQ on EEG spectral power, all analyses were re-run including IQ as an additional covariate.

This altered the significance of several comparisons (Table 3). Specifically, group differences in delta and beta bands weakened to trend level and or non-significance respectively, and the prior trend in theta became non-significant. However, in all three cases a small effect size was maintained. When controlling for IQ, group differences in alpha and theta/beta ratio remained non-significant, but the group by time interactions emerged as significant, although with small effect sizes, for delta and theta bands. Post-hoc analysis indicated that these significant group by time interactions in delta and theta bands were driven by significant group differences at time-1 (delta: $F(1, 157) = 7.32, p = 0.01, \eta^2 = 0.0412$; theta: $F(1, 157) = 5.07, p = 0.03, \eta^2 = 0.0255$), which were not present at time-2 (delta: $F(1, 157) = 0.09, p = 0.76, \eta^2 = 0.0006$; theta: $F(1, 157) = 0.26, p = 0.61, \eta^2 = 0.0015$). The trend level group by time interaction for theta/beta ratio became non-significant when controlling for IQ.

Analysis Using Mid-Line Electrodes

Re-running analysis based on mid-line electrodes, compared to frontal, central and parietal regions yielded similar results, with some exceptions. Without controlling for IQ, the reported group

Table 3 Significance values and effect sizes for ANCOVA factors and interactions, controlling for age, gender and IQ

	Delta	Theta	Alpha	Beta	T:B
Time					
F	0.006	0.393	0.616	0.188	0.029
<i>p</i>	0.94	0.531	0.434	0.665	0.865
η^2	0.0000	0.0023	0.0037	0.0012	0.0001
Region					
F	2.874	1.735	2.638	0.245	1.008
<i>p</i>	<u>0.058^a</u>	<u>0.178</u>	<u>0.073^a</u>	0.783	0.366
η^2	0.0170	0.0105	0.0162	0.0016	0.0118
Group					
F	3.373	2.321	1.68	2.483	0.179
<i>p</i>	<u>0.068^a</u>	<u>0.13</u>	0.197	<u>0.117</u>	0.673
η^2	0.0195	0.0122	0.0098	0.0135	0.0004
Group* region					
F	1.214	0.673	0.277	0.113	2.148
<i>p</i>	0.298	0.511	0.758	0.893	0.145
η^2	0.0072	0.0041	0.0017	0.0007	0.0090
Group* time					
F	4.178	4.553	1.039	0.001	0.939
<i>p</i>	<u>0.043*</u>	<u>0.034*</u>	0.31	0.997	0.392
η^2	0.0257	0.0268	0.0062	0.0000	0.0194

Activity bands defined as: delta 0.5–3.5 Hz, theta 3.5–7.5 Hz, alpha 7.5–12 Hz, beta 12–30 Hz

* Denotes significant at $p < 0.05$, unadjusted

^a denotes trend level effect at $p < 0.08$. Underlined values indicated those which changed between significant/non-significant when including IQ as a covariate. Effect size (η^2); 0.0099 constitutes a small effect, 0.0588 a medium effect and 0.1379 a large effect

Table 4 Global Field Synchronisation Scores

	Delta GFS (SD)	Theta GFS (SD)	Alpha GFS (SD)	Beta GFS (SD)
ADHD				
T1	0.46 (0.04)	0.44 (0.03)	0.47 (0.04)	0.45 (0.04)
T2	0.46 (0.04)	0.44 (0.03)	0.46 (0.03)	0.46 (0.04)
Control				
T1	0.45 (0.03)	0.43 (0.03)	0.47 (0.04)	0.44 (0.03)
T2	0.45 (0.04)	0.44 (0.04)	0.47 (0.04)	0.46 (0.05)

Activity bands defined as: delta 0.5–3.5 Hz, theta 3.5–7.5 Hz, alpha 7.5–12 Hz, beta 12–30 Hz

by time trend for theta became significant ($F(1,157) = 6.92$, $p = 0.01$, $\eta^2 = 0.0274$), and group differences for beta became non-significant, although the small effect size remained ($F(1,157) = 4.19$, $p = 0.11$, $\eta^2 = 0.0141$). The significant difference in region for delta also became non-significant ($F(1,157) = 2.08$, $p = 0.13$, $\eta^2 = 0.0009$). When IQ was controlled for, an additional time by group interaction in alpha was detected ($F(1,157) = 2.21$, $p = 0.01$, $\eta^2 = 0.0132$), and

the trend for the group by time interaction in delta became significant ($F(1,157) = 5.03$, $p = 0.03$, $\eta^2 = 0.026$). Full results are reported in supplementary material (S5, S6 & S7).

Global Field Synchronisation

Mean GFS scores (Table 4) did not differ between groups at either time point, or between time-1 and 2 in any band (supplementary material S8). The addition of IQ as an additional covariate did not alter results. Age, as a covariate, had a significant relationship to GFS scores in all bands (supplementary material S8). We ran additional correlations to investigate the age effect further (supplementary material S9), which showed that age was positively correlated with GFS scores in the majority of bands, except time-1 beta and time-2 theta (which were at trend level) and time-2 beta (which was non-significant).

Discussion

We report evidence for the influence of time-context effects on whether EEG spectral power differences emerge between participants with ADHD and controls. At the start of the recording session, delta as well as theta power was elevated in the ADHD group, while at the end of the recording session ADHD was linked only to elevated activity in the beta band. In addition, trend level group by time interactions in delta and theta bands, which became significant when controlling for IQ, in conjunction with graphed power (Fig. 1), indicate that activity in delta and theta bands was consistently high in the ADHD group, whereas the control group showed time-related changes. This finding supports theories of hypoarousal in ADHD (Weinberg and Brumback 1990), which would argue for persistent under-activation in ADHD at both time points. Yet, work based on combining EEG with skin conductance recordings has associated increased alpha, instead of increased theta or T:B ratios, with hypoarousal (Barry et al. 2009), rendering this interpretation somewhat tentative. We did not find evidence for atypical T:B ratio or alpha activity in the current sample of adolescents and young adults with ADHD. In this investigation, as expected, IQ was significantly lower in the ADHD group (Kuntsi et al. 2004; Wood et al. 2011). Controlling for IQ slightly altered the pattern of results, reducing group main effects, but strengthening group by time interactions for delta and theta bands. This is consistent with the small but generalised effect of IQ on EEG power as reported by (Chabot and Serfontein 1996), and illustrates that IQ can influence EEG results and should be empirically explored in studies on populations with lower IQ scores, such as individuals with ADHD.

Our findings provide no support for the initial hypothesis that under-arousal (as reflected by increased theta or alpha) among individuals with ADHD is more likely to be observed in a familiar setting and is reduced in a novel testing environment. Instead they show that under-activation, as indexed by delta and theta activity, may be present throughout testing. However, other explanations could include the influence of the preceding tasks at time-2 which may have influenced arousal. Changes over time could be examined directly in future studies by conducting short resting-state recordings throughout the EEG session to explore whether activation changes in a linear fashion over time, or alternatively, changes in relation to other tasks the participants are asked to complete during the recording session.

We did not detect any significant differences in alpha band activity in this study. As alpha has been negatively correlated with arousal, differences were expected (Barry et al. 2009). The spectra (Fig. 1b) are suggestive of group and time differences in the lower alpha band, particularly around 8-10 Hz, but less so at higher frequencies. It is possible that potential group differences were obscured here by averaging activity across full-band ranges, although other groups have found alpha power increases in adults with ADHD using the full alpha band (Koehler et al. 2009). Future analyses could examine time-frequency data at finer resolution to provide more power to detect group differences.

This study also did not replicate elevated T:B in the ADHD group at either time point, despite a sample size of 76 participants with persistent ADHD and 85 controls. This finding is at odds with older studies (Barry et al. 2010; Bresnahan et al. 1999; Clarke et al. 2001b, 2003b; Koehler et al. 2009; Lansbergen et al. 2011; Shi et al. 2012; Snyder and Hall 2006; Woltering et al. 2012), but consistent with several more recent investigations (Buyck and Wiersema 2014; Liechti et al. 2013; Loo et al. 2009; Ogrim et al. 2012; Poil et al. 2014; Ponomarev et al. 2014; Skirrow et al. paper under review; Swartwood et al. 2003; van Dongen-Boomsma et al. 2010), although Buyck and Wiersema showed subtype differences, with adult inattentive-type ADHD having lower T:B than the combined-type ADHD or controls. This questions the reliability of spectral analysis of resting state data to discriminate ADHD adolescents and young adults from controls, particularly as expected maturational effects are observed in this data (supplementary material S4), and that this sample also shows typical ADHD associated impairments in ERP and spectral EEG comparisons in data from a Continuous Performance Task recorded between the two resting state recordings as reported here (Cheung et al. under review).

Our additional analyses indicated some effects relating to the selection of electrodes. Focusing on mid-line

electrodes (Fz, Cz, Pz) improved power to detect differences in theta and alpha bands. However, the opposite was observed for the beta band. T-maps indicated that group differences in beta activity at time-2 were detected broadly across multiple electrodes, while differences between time-1 and -2 in both the ADHD and control groups were greatest at fronto-lateral regions, including F7 and F8, which were included in our analysis as part of the frontal electrode region (supplementary material S2 & S3). Therefore, regions of electrodes which were more widely distributed across the scalp may have been more sensitive to beta differences, although were seemingly less sensitive to theta or alpha differences. This suggests that different methods of electrode selection may alter results, and as methods appear to have alternate sensitivity to detection of theta or beta power, may contribute to the declining replication of T:B differences in ADHD (Arns et al. 2013); particularly as most recent studies have favoured analysis of mid-line electrodes (Buyck and Wiersema 2014; Liechti et al. 2013; Loo et al. 2013; Ogrim et al. 2012; Woltering et al. 2012). Nonetheless, this cannot be the only factor influencing results, as we were unable to replicate T:B differences for ADHD using either method, similar to Liechti et al. (2013).

Differences in our results depending on electrode selection suggest that the standardisation of methods is important to ensure studies are comparable. As the maximal power of each band varies in location, adoption of new data-driven methods, as opposed to methods based on convention, may yield more reliable case-control differences. This might be achieved through analysis of all possible channel comparisons with appropriate multiple testing corrections (Poil et al. 2014; Woltering et al. 2012), by only selecting the channel where power is maximal based on topographic maps, similar to methods employed in ERP studies, or through the use of Independent Component Analysis to extract estimates of band power from multiple sources simultaneously (Ponomarev et al. 2014).

No group or condition differences in GFS scores were observed. Mean GFS scores were lower than in other published papers in adult and older adult populations, which are reported to be around approximately 0.5-0.55 (Kikuchi et al. 2007; Koenig et al. 2005; Ma et al. 2014; Pugnetti et al. 2010). In our study, age had a significant effect on GFS scores in most bands, in contrast to group status or condition variables. Significant correlations with age indicated that GFS score increased with age, which could suggest lower phase synchronization in younger participants at earlier stages of cortical maturation, compared to adult samples. This GFS increase parallels the spectral power reduction with maturation which also extended across bands, and demonstrates that GFS is sensitive to additional aspects of maturation. The finding is

also in line with other studies that identified higher GFS scores in adults compared to children during a working memory paradigm (Michels et al. 2012), and with the maturational increases reported for alpha GFS (Koenig and Pascual-Marqui 2009).

In conclusion, we demonstrate that ADHD-control differences on EEG spectral power varied with recording time within a single recording session and with the frequency bands, although the modest effect sizes indicated that case-control discrimination was insufficient for diagnostic applications at both recording times. Our findings suggest that recording delta and theta activity during resting state at the start of recording sessions, where case-controls differences are likely to be highest as a product of persistent hypoarousal in ADHD, offers methodological advantages. In contrast, as beta activity increases over time in the ADHD group compared to controls, case-control differences in beta are likely to become more prominent in resting-state data recorded at the end of recording sessions. Our post hoc comparisons also indicate that data from electrode regions, compared to midline electrodes, may be more sensitive to differences in beta band activity, but not activity in delta and theta bands. Overall, this suggests that research design may be optimised for ADHD case-control differences at specific spectral frequency ranges. Such optimisation is likely to also apply to subtyping/clustering and treatment prediction based on resting EEG. However, we also highlight the need for studies to adopt consistent methodologies in the recording of data and to account for other factors such as electrode selection in their analyses. We also demonstrated that IQ has a small but significant influence on observed differences, and therefore should be taken into account in future investigations. Equally, we provide further evidence showing that age correlates with both EEG power and GFS scores, and should continue to be accounted for in future studies. While overall our findings of case-control differences in specific EEG power bands supports the view of arousal dysregulation in ADHD, our findings also demonstrate the challenges associated with the analysis and interpretation of resting state data in ADHD. Therefore we suggest that, until the factors that can influence the pattern of results are better understood, the use of resting-state band power as an associated feature supporting diagnosis for ADHD in adolescents and young adults is premature.

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***Chapter 3 - Neurophysiological Conflict Monitoring
Impairments in Adolescents and Young Adults with
ADHD: A Comparison with Their Unaffected
Siblings and Unrelated Controls***

3.1 Abstract

Individuals with ADHD show behavioural difficulties compared to typically developing controls during performance monitoring tasks. However, few studies have investigated the neurophysiological correlates of error detection and performance monitoring during these tasks, with results being inconsistent. Questions also remain about possible familial associations with performance monitoring deficits, and whether such deficits represent stable endophenotypes in ADHD. One hundred and five adolescents and young adults with ADHD, 95 of their unaffected siblings and 136 unrelated controls were assessed on the Eriksen Flanker Task, where ERP performance monitoring correlates (N2, ERN, Pe) and performance variables were measured. Additionally, analysis was rerun on older and younger subgroups within the full sample (11-17, 18+) to examine potential developmental differences. The ADHD group was impaired on all performance measures compared to controls (correct hits, commission errors, omission errors, mean reaction time and reaction time variability (RTV)). In the incongruent condition, the ADHD group showed trend-level attenuation of the Pe amplitude component at channel Cz and trend-level attenuation of N2 amplitude at FCz compared to controls. Compared to siblings, both N2 and Pe components were attenuated at trend-level in ADHD. The groups did not differ on ERN amplitude at either Fz or FCz. No familial effects were

identified, with unaffected siblings not differing from controls on N2, ERP and Pe mean amplitude. This study reports evidence of potentially impaired conscious error processing in ADHD as indexed by Pe attenuation, which alongside observations of more omission errors and greater RTV, supports arguments for increased attentional lapses in ADHD. Finally, contrary to a recent meta-analysis of adolescent and adult participants of equivalent sample size, we did not find evidence of ERN amplitude attenuation in ADHD; which suggests variation in ERN findings within the literature may be due to methodological heterogeneity in studies to date.

3.2 Introduction

Attention-deficit/hyperactivity disorder (ADHD) occurs in around 5% of children (Polanczyk et al., 2007), frequently persists into adolescence and adulthood (Faraone et al., 2006), and manifests as symptoms of inattention and/or hyperactivity/impulsivity. Lapses in attention and distractibility in particular are thought to underlie performance monitoring deficits commonly observed in ADHD (Larson and Clayson, 2011).

Examination of event-related potentials (ERP) allows direct measurement of brain activity which correlates with performance on cognitive tasks, and so is important for better understanding deficits in the cognitive processes in ADHD. One example is the study of performance monitoring, such as error detection and conflict monitoring which support the adaptation of behaviour for optimum performance, yet which are likely to be impaired by the lapses in attention and distractibility present in ADHD (Larson and Clayson, 2011). Despite this,

use of ERP methods to study performance monitoring in ADHD has not yet been widely employed, with studies in larger samples remaining uncommon.

Performance monitoring has been linked to particular fronto-central negative deflections in ERP waves, which vary with task-demands and the accuracy of responses. When a participant makes a correct response to a target stimulus, the N2 component is elicited peaking approximately 200–400 ms post stimulus. When an error is made to the same target, a stronger error-related negativity (ERN or Ne) component is elicited in place of the N2, at around 50 ms post response (Falkenstein et al., 1991, Falkenstein et al., 2000, Segalowitz and Dywan, 2009, Yeung and Cohen, 2006). These components are highly correlated and are thought to both relate to competing or corrective process of conflict monitoring systems (Falkenstein et al., 2000, McLoughlin et al., 2009, Yeung and Cohen, 2006). Studies also indicate that ERN is consistent across different modalities and types of error (Riesel et al., 2013). The ERN is also followed by a P3-like centro-parietal positive deflection in amplitude (Pe), thought to represent the conscious processing of the error response related to processes to improve performance (Endrass et al., 2007, Falkenstein et al., 2000, Hughes and Yeung, 2011, Nieuwenhuis et al., 2001). In contrast to the Pe, the ERN is not dependent on the conscious perception of an error, which represents unconscious performance monitoring processes (Falkenstein et al., 2000, Nieuwenhuis et al., 2001). Further supporting evidence for this link comes from studies which show that the amplitude of the N2 and the ERN is increased when discrimination of target is confounded by similar distractors which presuppose an alternative response, indicating that these components may represent competing activation between the immediate erroneous response evoked by distractors and a subsequent corrective response (Carter and van Veen, 2007, Danielmeier et al., 2009, Donkers and van Boxtel, 2004, Nieuwenhuis et al., 2003, Yeung et al., 2004).

In ADHD, several studies examining the ERN and Pe components using Go/NoGo and flanker tasks in adults and adolescents were recently combined into meta-analysis. Although in the majority of these individual studies ADHD-control differences did not reach significance, likely due to small sample size, when aggregated in meta-analysis ERN attenuation in ADHD in both Go/NoGo and flanker tasks was reported (Geburek et al., 2013). For Pe, attenuation in the ADHD group was significant only in the Go/NoGo paradigm, as studies using the flanker paradigm reported more heterogeneous results. However, the authors indicate that they expect overall Pe attenuation in ADHD to emerge in the flanker task with additional data. In a recent review of nine studies of the ERN and Pe in childhood ADHD, albeit mostly very small studies, Shiels and Hawk (2010) concluded, in contrast to studies of older participants, that evidence for ERN attenuation in participants with ADHD was more inconsistent than reported deficits in Pe, with the majority of studies showing Pe attenuation in ADHD compared to controls. However, more recent studies have reported both ERN and Pe attenuation in children with ADHD on both Go/NoGo (Groom et al., 2013) and flanker paradigms (Rosch and Hawk, 2013).

Geburek et al. (2013) suggested that stronger Pe deficits would be more likely to be observed in childhood ADHD if Pe represented conscious recognition of an error, as adolescents and adults would have more conscious task processing resources available, and therefore early error processing deficits indexed by the ERN could be partially compensated for by allocation of additional monitoring resources. Yet, while ERN amplitude shows developmental increases in amplitude thought to be related to prefrontal cortex maturation, including the anterior cingulate cortex (ACC) (Segalowitz and Dywan, 2009), Pe amplitude appears more developmentally stable with age in children and young adults (Davies et al., 2004, Wiersema et al., 2007). In addition, Geburek et al.'s own exploratory analysis indicated no effect of age in their meta-analytic findings of the ERN and Pe, demonstrating that age was not a significant

moderator in adolescent and young adult samples (Geburek et al., 2013). It has also been shown that ERN and Pe deficits can be improved by performance-based rewards in ADHD groups compared to controls, or by methylphenidate medication in comparisons of ADHD participants on and off treatment (Groom et al., 2013). This shows that the additional allocation of cognitive resources can improve Pe amplitude and task-performance and also highlights that this improvement is possible in childhood samples. Therefore the variable results to date and evidence of the alteration of reported deficits by rewards suggest that the picture of ERN and Pe deficits is more complex than simple child/adult divisions of cognitive resource availability and demonstrates the need for additional research using larger samples, which span larger developmental windows. This would help to clarify if Pe deficits show developmental differences and whether it can be reliably associated with ADHD.

N2 attenuation in flanker tasks has been reported in children (Albrecht et al., 2008, Johnstone et al., 2009, Wild-Wall et al., 2009), adolescents (McLoughlin et al., 2014) and adults with ADHD (McLoughlin et al., 2009), although some studies with small samples have failed to replicate N2 deficits in ADHD (Johnstone and Galletta, 2013, Jonkman et al., 1999, Jonkman et al., 2007). N2 deficits in children and adults with ADHD have also been reported in additional paradigms which also involve conflict monitoring, such as auditory odd-ball and Go/NoGo paradigms (Barry et al., 2009, Groom et al., 2008, Woltering et al., 2013). Overall, however, studies with large samples examining the N2 in adolescent and adult populations remain rare.

One potential explanation for some variability in the N2 literature is the potential effects of IQ on ERP amplitudes. ADHD is associated with lower IQs (Kuntsi et al., 2004), yet IQ is a factor which is inconsistently controlled for in those studies where differences in mean IQ between ADHD and controls are present (Johnstone et al., 2009, Johnstone and Galletta, 2013, Jonkman

et al., 1999). Evidence from EEG studies indicates that reduced IQ in ADHD may have a small but significant influence effect on case-control differences in spectral EEG power (Chabot and Serfontein, 1996, Kitsune et al., 2014, chapter two), but studies have not yet attempted to quantify the effect of IQ differences on ERP performance monitoring correlates in ADHD.

Furthermore, there is some evidence that the performance monitoring correlates might represent familial endophenotypes for ADHD, as first-degree relatives have been reported to show intermediate profiles of attenuation compared to ADHD and control groups (Albrecht et al., 2008, McLoughlin et al., 2009). Endophenotypes are defined as traits which are influenced by the same genetic and shared environmental factors as the disorder and so could represent meditational intermediaries (Gottesman and Gould, 2003, Kendler and Neale, 2010). As heritability estimates for ADHD are high (Faraone et al., 2005), and ADHD is considered to be the extreme end of a quantitative trait for behaviours of inattention and hyperactivity within the general population (Levy et al., 1997), it is feasible that multiple genetic variants could contribute to the function of performance monitoring cognitive systems, and therefore some degree of performance monitoring deficits would be expected in first-degree relatives of individuals with ADHD. This hypothesis has been supported by preliminary data from first degree relatives collected using the Flanker Task, although both studies present their conclusions as tentative and have called for additional replication (Albrecht et al., 2008, McLoughlin et al., 2009). Although sibling designs cannot distinguish between genetic and shared environmental effects, there is limited evidence for the contribution of shared environment in ADHD (Burt, 2009), suggesting that familiarity reflects largely genetic influences.

Overall, additional research into performance monitoring in ADHD is required using larger samples including adolescents and young adults in order to clarify which deficits are reliably associated with ADHD, and to confirm if performance monitoring and error recognition deficits appear consistently across older and younger groups. Questions also remain about possible familial associations with performance monitoring deficits, and whether such deficits represent an endophenotype for ADHD. This study therefore aimed to compare N2, ERN and Pe components during a flanker task in adolescents and young adults with ADHD, against their unaffected siblings and unrelated controls. Previous literature predicted that the ADHD group would show attenuated N2, ERN and Pe components compared to controls, while their unaffected siblings would show an intermediate profile between these two other groups.

3.3 Methods

3.3.1 Sample

One hundred sixteen young adults and adolescents with ADHD, 96 of their unaffected siblings and 170 controls from sibling pairs who had taken part in a previous familial association study (Chen et al., 2008, Kuntsi et al., 2010), were invited to participate in this follow-up study. During the initial study ADHD participants aged between 6 and 17 years were recruited from specialist clinics in the UK from among those who had a clinical diagnosis of DSM-IV combined subtype ADHD during childhood. Closest-age siblings were also then recruited and assessed for ADHD using the same procedures. The control group was recruited from primary (ages 6-11 years) and secondary (ages 12-18 years) schools in the UK. In the follow-up study, participants were aged between 11 and 27, and for this investigation ADHD participants and unaffected siblings were re-assessed, with only ADHD participants who continued to meet DSM-IV criteria for any ADHD subtype in adolescence/early adulthood being included in current analyses, with

those who remitted being excluded from this analysis. Unaffected ADHD siblings (sibs) were also re-assessed to ensure that they did not meet DSM-IV criteria for ADHD. For all groups, the exclusion criteria, as defined by those used in the initial investigation, were the presence of autism, epilepsy, learning difficulties, brain disorders and any genetic or medical disorder associated with externalising behaviours that might mimic ADHD. All participants were of European Caucasian descent. Written informed consent was obtained and the study was approved by the London-Surrey Borders Research Ethics Committee (NRES 09/H0806/58).

Seven eligible ADHD participants were initially excluded from the analysis due to equipment failure (n=2) or incomplete EEG (n=3) or clinical data (n=2). Additionally, a further five participants (ADHD: n=4; sibs: n=1) were excluded from the N2 ERP data analysis as they had <20 acceptable ERP segments available after processing, leaving 105 ADHD participants, 95 sibs and 170 controls available. Seventy-eight participants (ADHD: n=27; sibs: n=17; controls: n=34) from the ERN/Pe analysis did not produce enough errors during the Flanker task to provide <20 acceptable ERP segments after processing (approximately 20% of each sample, similar to other studies using an identical paradigm: Albrecht et al. (2008) 10-15%; McLoughlin et al. (2009) 0-23%; and reflecting a comparable exclusion ratio across groups, $\chi^2(2) = 1.67$, $p = 0.43$), resulting in a final sample of 82 ADHD, 79 sibs and 136 controls. The impact of genetic relatedness between control participants was assessed using a mixed regression model which clustered by family status, and was found to not alter results. In the full sample, for both N2 and ERN analyses, the groups did not differ in mean age, although in sub-samples employed in secondary analysis there was a significant age difference between groups which was subsequently statistically controlled (Table 3.1). In all the group compositions studied, there were significant IQ and gender distribution differences between groups, which were also

controlled for during analysis. To assess the effects of IQ differences on reported findings the primary analysis were re-run without controlling IQ.

Table 3.1. Mean and standard deviation of Age and IQ, and percentage of gender for each group composition studied.

	N2 Analysis					ERN/Pe Analysis				
	ADHD	Control	ADHD Siblings	F	p	ADHD	Control	ADHD Siblings	F	p
Full Sample	n = 105	n = 170	n = 95			n = 82	n = 136	n = 79		
Age	18.4 (3.0)	17.8 (2.2)	18.4 (3.3)	2.5	0.09	18.2 (2.8)	17.7 (2)	18.2 (3.3)	1.7	0.19
IQ	97.6 (15.5)	109.8 (12.5)	102.6 (14.2)	6.3	0.04	97.6 (15.3)	108.9 (12.5)	101.7 (13.2)	19.5	0.001
Male (%)	85%	76%	41%	*52.4	0.001	89%	76%	46%	*39.5	0.001
Younger subset (11-17)	n = 47	n = 86	n = 44			n = 38	n = 73	n = 41		
Age	15.6 (1.5)	16 (1.5)	15.7 (1.6)	2.9	†0.06	15.6 (1.3)	16.1 (1.4)	15.6 (1.6)	2.1	0.12
IQ	95.9 (15.2)	106.1 (12)	97.2 (12)	25.5	0.001	95.5 (14.5)	105.5 (12.4)	98.8 (11.9)	8.5	0.001
Male (%)	81%	71%	45%	*14.0	0.001	87%	70%	49%	*13.4	0.001
Older subset (18+)	n = 58	n = 84	n = 51			n = 44	n = 63	n = 38		
Age	20.7 (1.6)	19.5 (1)	20.9 (2.2)	15.5	0.001	20.5 (1.5)	19.4 (1)	20.9 (2.3)	12.4	0.001
IQ	99.6 (15.7)	113.7 (11.8)	107 (14.5)	18.1	0.001	99.4 (15.9)	113 (11.4)	104.8 (13.9)	13.5	0.001
Male (%)	88%	82%	37%	*42.1	0.001	91%	83%	42%	*29.4	0.001

*Gender ratio tested with Chi-square rather than ANOVA hence test score is χ^2 not F. Bold denotes $p < 0.05$

3.3.2 Procedure

Participants attended a single research session for cognitive-EEG assessments, IQ assessment and clinical interviews. Prior to completing the task, participants completed 2 x 3 minute resting state recordings and a Continuous Performance task (Cheung et al., under review, Doehnert et al., 2008). ADHD participants were asked to not take stimulant medication 48 hours before testing, and all participants were asked to refrain from caffeinated drinks and nicotine two hours prior to the testing session.

3.3.3 Tasks and measures

The task was an adaptation of the Eriksen Flanker paradigm designed to increase cognitive load (Albrecht et al., 2009, McLoughlin et al., 2009). In each trial a central black fixation mark was replaced by a target arrow (a black 18 mm equilateral triangle). Participants had to indicate whether this arrow pointed towards the left or right by pressing corresponding response buttons with their left or right index fingers. Two flanker arrows identical in shape and size to the target appeared 22 mm above and below the centre of the target arrow 100ms prior to each target arrow. Both flankers either pointed in the same (congruent) or opposite (incongruent) direction to the target. As such, conflict monitoring is maximal during the incongruent condition. When the target appeared, both target and flankers remained on the screen for a further 150 ms, with a new trial being presented every 1650 ms. Trials were arranged in ten blocks of 40 trials. The task took approximately 13 minutes.

Congruent versus incongruent and the direction of responses (left versus right) were counter-balanced and randomised. After each block, feedback was presented on screen to emphasise both speed and accuracy, in order to encourage participants to make enough errors to enable analysis of ERN/Pe components, and enough correct responses for analysis of N2 components. Where participants made >10% errors on congruent or >40% errors on incongruent trials, they were instructed to slow down. Where participants made <10% errors on congruent or <40% errors on incongruent trials, they were instructed to perform faster. If neither rule applied, feedback informed participants to continue the same way. Two practice blocks of 24 trials were administered before the real task. Where necessary, participants were told to minimise movement or blinking.

The two-subtest form of the Wechsler Abbreviated Scale of Intelligence Fourth Edition (WASI-IV; (Wechsler, 1999)) was administered to all participants to derive an estimate of IQ.

3.3.4 EEG recording and analysis

Recording and analysis parameters from McLoughlin et al. (2009) were adopted. The EEG was recorded from a 62 channel DC-coupled recording system (extended 10–20 montage), using a 500 Hz sampling-rate, impedances under 10k Ω , and FCz as the recording reference. The electro-oculograms (EOGs) were recorded from electrodes above and below the left eye and at the outer canthi.

EEG data were analysed using Brain Vision Analyzer 2.0 (Brain Products, Germany). Raw EEG recordings were down-sampled to 256 Hz, re-referenced to the average of all electrodes, and filtered using Butterworth band-pass filters (0.1 to 30 Hz, 24 dB/oct). Ocular artefacts were identified using the infomax Independent Component Analysis algorithm (ICA, (Jung et al., 2000)). Sections of data containing artefacts exceeding $\pm 100 \mu\text{V}$ in any channel or with a voltage step greater than $50 \mu\text{V}$ were rejected. All trials were also visually inspected for other obvious movement or electrical artefacts, and sections containing these were removed manually.

Data were segmented based on three different response conditions: (1) stimulus-locked congruent trials where a correct response was made, (2) stimulus-locked incongruent trials where a correct response was made and (3) response-locked incongruent trials where an incorrect response was made. Individual averages were created based on each condition, requiring at least 20 clean segments for each participant. Baseline correction was applied using the -300 to -100 ms pre-target interval (-200 to 0 ms pre-flanker). After averaging, mean amplitude was calculated within a designated window, as defined by reference to the grand average. For the N2 in both conditions, this was 250 – 425 ms after flanker onset (150 – 325 ms after the target). For the ERN and Pe this was 0 - 150ms and 150 – 450 ms respectively after an incorrect response.

3.3.5 Statistical analyses

Performance measures were total number of correct hits, total number of errors, total number of misses, target reaction time (MRT, i.e. mean latency of responding in ms after target onset), within-subject variability in reaction times (RTV, SD of RTs). For all measures except total misses, scores were calculated independently for congruent and incongruent conditions. All performance data were non-normally distributed, and with the exception of RTV, were not able to be transformed successfully using any available transformations (cubic, square, square root, log, 1/square root, inverse, 1/square, 1/cubic). Group differences were therefore compared using non-parametric Kruskal-Wallis tests with appropriate post-hoc pairwise comparisons to resolve group differences. RTV data were successfully transformed using the 1/square transformation and compared using univariate ANOVA and post-hoc comparisons.

Maps of the topographic scalp distribution of activity revealed that the N2 and ERN components were maximal at fronto-central electrodes (Figure 3.1 and Figure 3.2). We analysed stimulus-locked N2 mean amplitude at Fz and FCz, with ANOVA carried out in SPSS (factors: group (ADHD, control, sibs), condition (congruent, incongruent) and site (Fz, FCz)). Similarly, response-locked ERN mean amplitude in the incongruent condition was also compared at Fz and FCz using ANOVA (factors: group (ADHD, control, sibs), and site (Fz, FCz)), with Pe mean amplitude being compared at Cz using univariate ANOVA (factors: group (ADHD, control, sibs)). IQ and gender were included as covariates in primary analyses. To examine the potential effect of IQ differences on results, primary analyses were re-run without using IQ as a covariate. In addition, given the large age range in this study and to further explore developmental effects in this ERP data, additional analysis was conducted by dividing the sample by age into two groups (11-17, 18+), and re-running analysis independently on each subset.

Pairwise post-hoc comparisons were conducted for all tests in conjunction with the calculation of effect sizes to fully explore the data (eta squared (η^2) for main effect and interactions, Cohen's d for post-hoc pairwise comparisons). Based on Cohen's (1988) estimates for η^2 , 0.0099 constitutes a small effect, 0.0588 a medium effect and 0.1379 a large effect; and for Cohen's d 0.2 constituting a small effect size, 0.5 a medium and 0.8 a large effect.

3.4 Results

In comparisons of behavioural performance all measures showed group differences. Post-hoc comparisons showed that the ADHD group was significantly different from controls on all performance measures, showing fewer correct hits, more commission errors (incorrect responses), greater MRT, and greater RTV in both conditions, as well as increased omission errors (non-responses) overall (Table 3.2). The ADHD group also differed from the unaffected sibling group on some measures recording fewer correct hits in both conditions, more commission errors in congruent condition, and greater RTV in both conditions, as well as increased commission errors overall. There were no significant differences between the sibling and controls groups on any measure.

Table 3.2. Means (standard deviation), significance testing and pairwise comparison for behavioural performance measures on the flanker task.

	Mean (SD)			Group comparison		Post-hoc pairwise comparison		
	ADHD	Siblings	Control	H	p	A-C	A-S	S-C
Correct hits cong	175.82 (33.96)	188.62 (17.42)	191.33 (16.72)	43.87	<0.001	<0.001	<0.001	0.4
Correct hits incong	126.39 (33.91)	141.15 (25.31)	145.18 (23.21)	29.89	<0.001	<0.001	<0.001	0.19
Commission errors cong	9.55 (15.79)	5.12 (5.74)	4.55 (7.49)	22.09	<0.001	<0.001	0.01	0.89
Commission errors incong	57.19 (20.77)	51.94 (18.4)	50.1 (18.28)	11.12	0.004	0.002	0.14	0.57
Omission errors (non-responses)	31.05 (49.43)	13.18 (24.53)	8.84 (22.92)	59.33	<0.001	<0.001	<0.001	0.29
MRT cong (ms)	353.24 (57.75)	346.54 (37.06)	340.44 (35.65)	7.27	0.03	0.01	0.62	0.24
MRT incong (ms)	447.66 (53.69)	445.13 (41.93)	436.76 (41.95)	8.69	0.01	0.02	0.97	0.08
RTV cong (ms)	109.74 (62.42)	89.04 (34.69)	82.28 (32.92)	*17.02	<0.001	<0.001	0.002	0.17
RTV incong (ms)	113.36 (75.02)	90.26 (37.6)	82.8 (34.57)	*16.12	<0.001	<0.001	0.003	0.19

*indicates F statistic not H. Bold denotes $p < 0.05$.

A = ADHD, C = Control, S = unaffected ADHD siblings, MRT = mean reaction time to correct hits, RTV = reaction time variability to correct hits (mean standard deviation of reaction time), cong = congruent condition, incong = incongruent condition.

Table 3.3. ANOVA significance testing and effect sizes for N2, ERN and Pe components across ADHD, control and ADHD sibling groups

		Test statistic (F)	p-value	Effect size (η^2)
N2	RM ANOVA			
	Site (Fz, FCz), Condition (Cong, Incong), Group			
	covariates: IQ and gender			
	Group	0.40	0.67	0.0021
	Site	2.10	0.15	0.0057
	Condition	10.36	*0.001	0.0265
	Site*group	1.86	0.16	0.0101
Site*condition	29.04	*<0.001	0.0108	
Condition*group	6.79	*0.001	0.0348	
ERN	RM ANOVA			
	Site (Fz, FCz); Group			
	covariates: IQ and gender			
	Group	0.68	0.51	0.0046
Site	4.13	*0.04	0.0131	
Site*group	2.25	0.11	0.0143	
Pe	Univariate ANOVA			
	Site (Cz); covariates: IQ and gender			
Group	3.00	*0.05	0.0188	

RM ANOVA = repeated measures analysis of variance, Cong = congruent condition, Incong = incongruent condition. N2 from trials where participants correctly responded to stimuli. ERN and Pe from response-locked trials where participants incorrectly responded to target stimuli.
† trend level ($p < 0.07$), * $p < 0.05$. η^2 effects sizes: 0.0099 small, 0.0588 medium and 0.1379 large.

Table 3.4. Mean amplitude (standard deviation), and pairwise comparisons for N2, ERN and Pe components in ADHD, unrelated controls and unaffected ADHD siblings

Condition and site	Mean amplitude in μV (SD)			Pairwise comparisons		
	ADHD	Control	ADHD Siblings	ADHD-Control p	ADHD-Sibs p	Control – Sibs p
N2						
Congruent Fz	-3.62 (3.05)	-2.89 (2.38)	-3.36 (2.59)	0.20	0.95	0.24
Congruent FCz	-1.55 (3.33)	-1.69 (2.58)	-2.01 (2.59)	0.34	0.18	0.57
Incongruent Fz	-4.3 (3.37)	-3.74 (2.73)	-4.02 (2.98)	0.67	0.88	0.81
Incongruent FCz	-1.9 (3.61)	-2.55 (3.15)	-2.65 (3.26)	†0.06	†0.07	0.81
ERN						
Incongruent Fz	-4.34 (2.54)	-4.15 (2.75)	-4.63 (2.87)	0.93	0.42	0.42
Incongruent FCz	-3.28 (2.73)	-4.05 (3.14)	-4.28 (3.32)	0.18	0.19	0.89
Pe						
Incongruent Cz	5.52 (3.31)	6.33 (3.76)	5.7 (3.65)	*0.02	†0.06	0.87

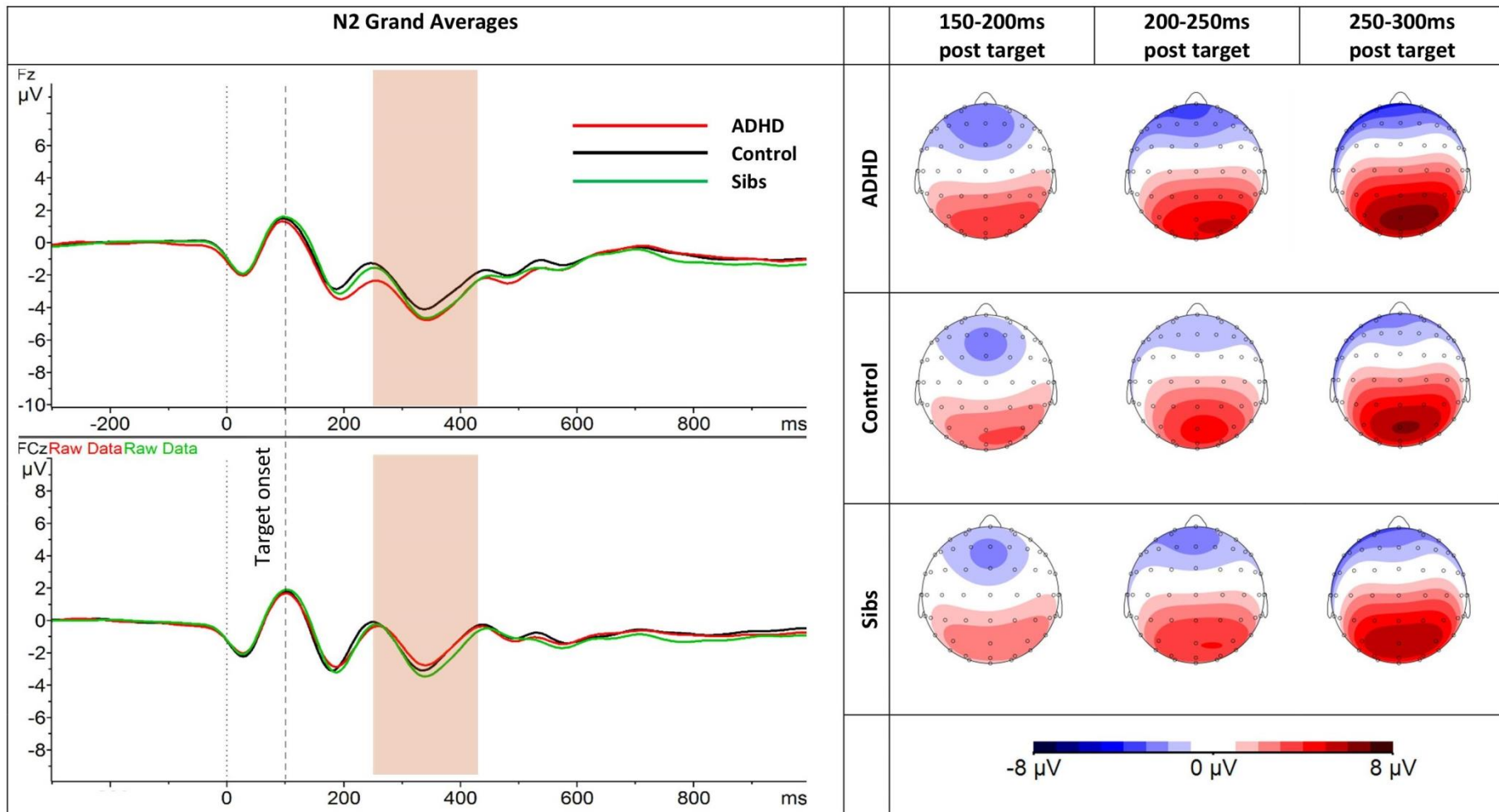
* $p < 0.05$, † trend level ($p < 0.07$)

Analysis of N2 amplitude indicated a main effect of condition with mean amplitude being enhanced in the incongruent condition (Table 3.3 & 3.4). Site also showed significant interaction with condition, with condition also showing a significant interaction with group. All significant results had a small effect size. There were no main effects of group or site independent of condition. Differences in N2 topographies and amplitude between the two conditions were apparent in grand averages and topographic maps (Figure 3.1). Post-hoc pairwise comparisons indicated that the ADHD group showed attenuation of N2 amplitude compared to both controls and unaffected siblings in the incongruent condition at trend-level at FCz, but not Fz. Unaffected siblings did not differ from controls at either FCz or Fz. N2 amplitude did not differ between any of the three groups in the congruent condition where conflict monitoring demands were lowest.

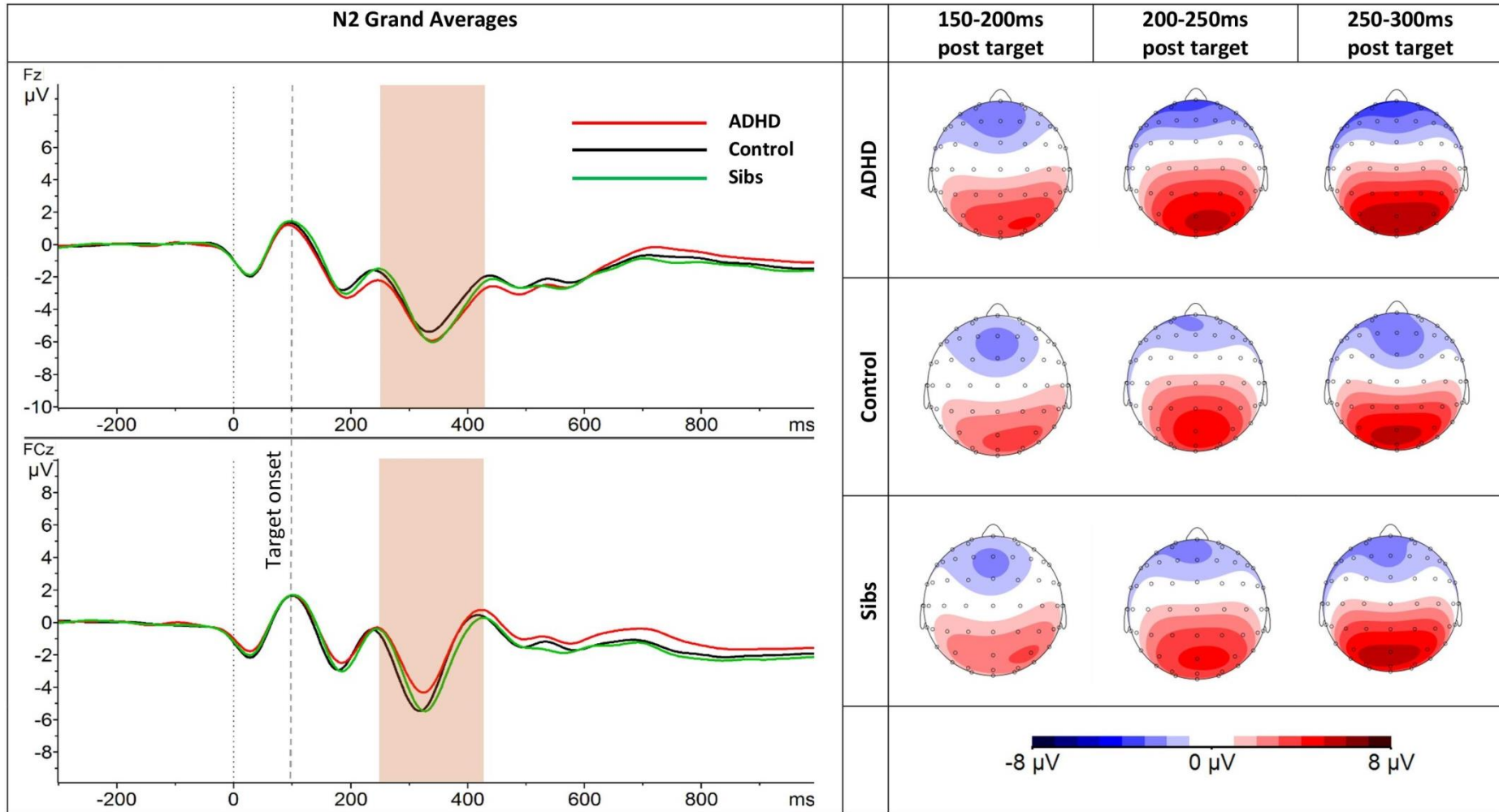
ERN mean amplitude showed a main effect of site, with the ERN being greater at Fz than FCz, but there was no significant main effect of group (Table 3.3), although grand averages seemed to suggest reductions in amplitude in the ADHD group at FCz (Figure 3.2a). The group*site interaction was not significant. Pe group comparison was significant, although showed a very small effect size. Grand averages (Figure 3.2b) were indicative of attenuated Pe in ADHD and siblings compared to controls, although statistical post-hoc comparisons indicated that the ADHD group had significantly attenuated Pe amplitude compared to the control group, and trend-level attenuation compared to the unaffected sibling group. Conversely, control and sibling groups did not actually statistically differ in Pe amplitude (Table 3.4).

Figure 3.1. Grand averages and topographic maps of mean amplitude for the N2 component in congruent and incongruent conditions for ADHD, control participants and unaffected siblings.

(a) Congruent Condition



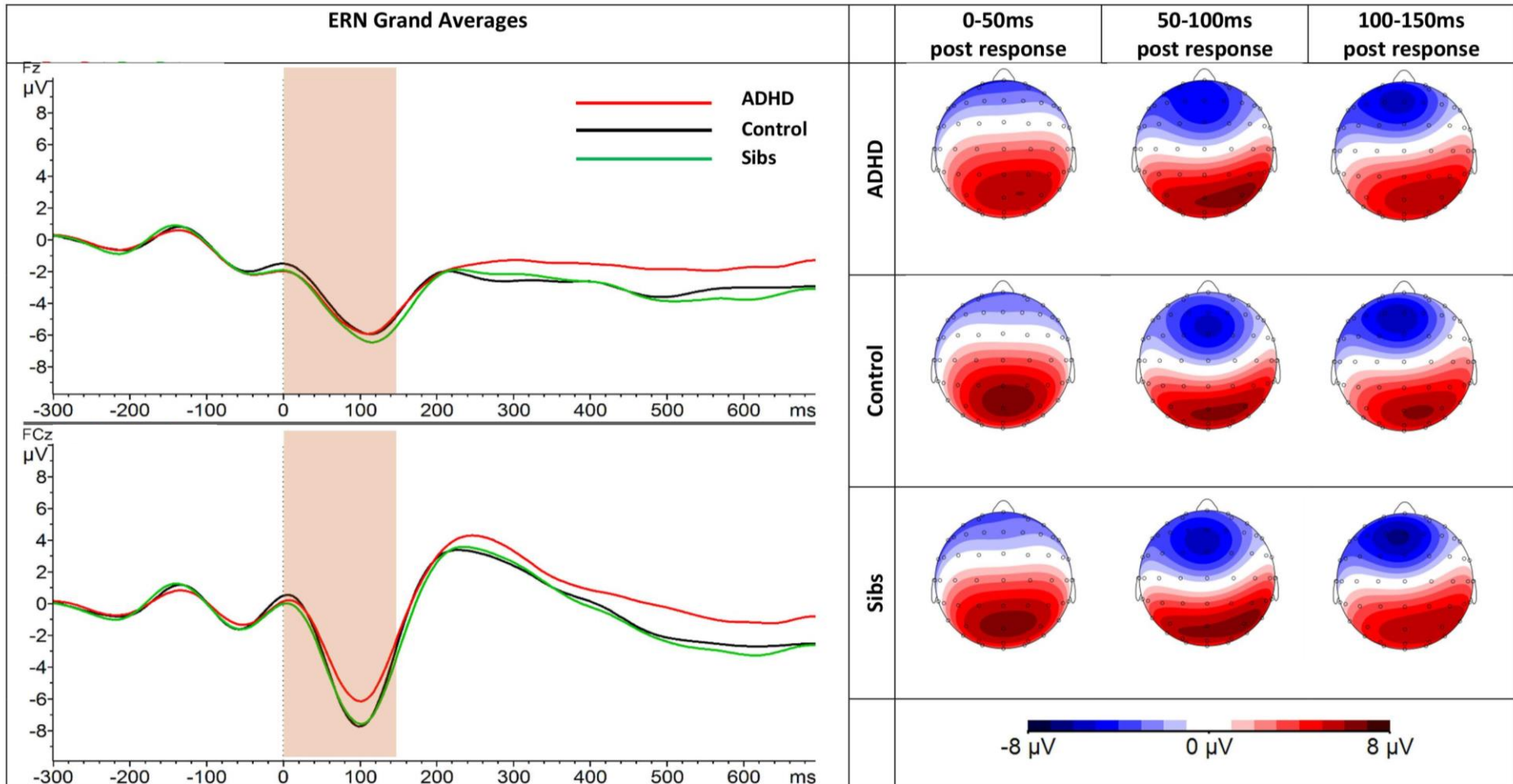
(b) Incongruent Condition



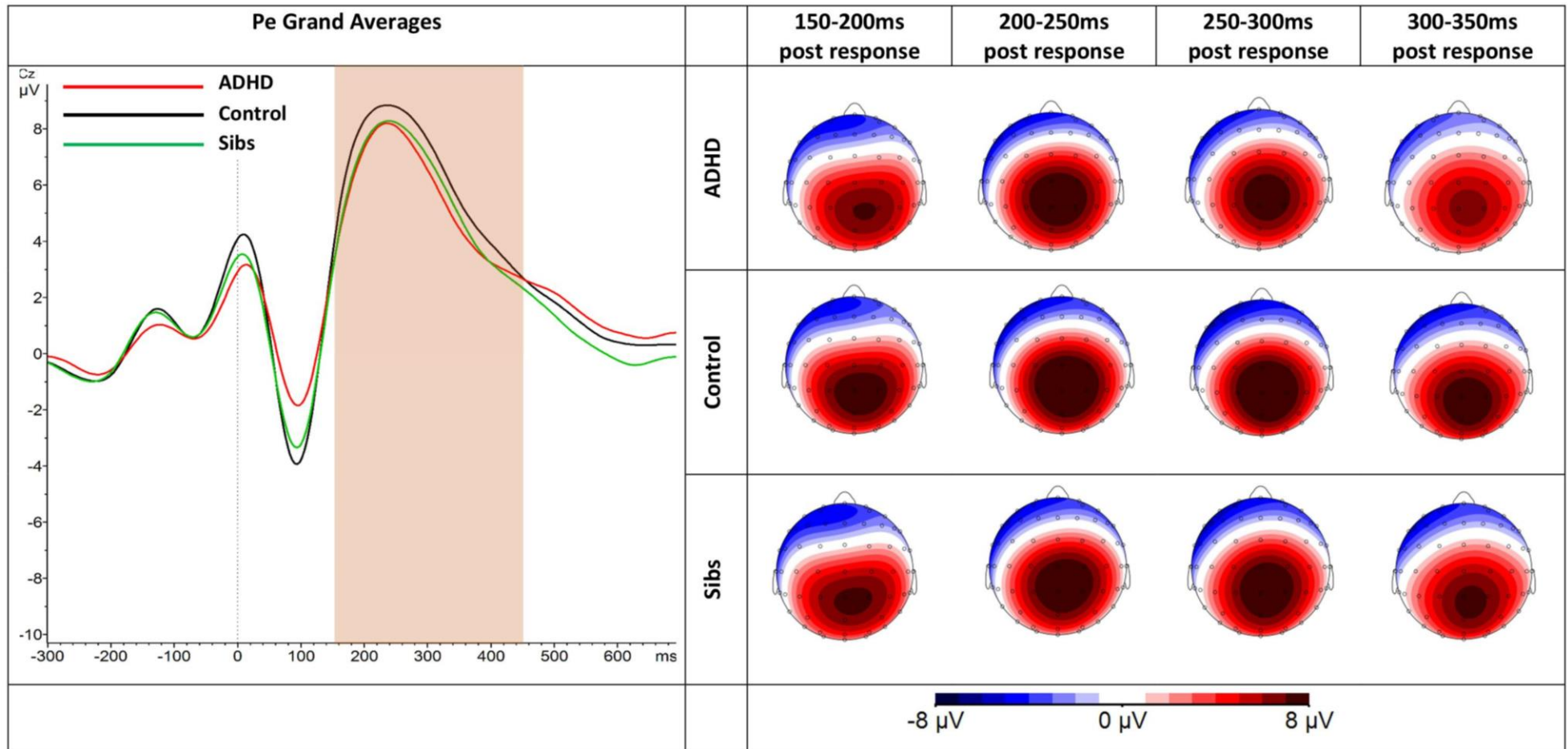
N2 is the mean event related potential (ERP) activity between 150-425 ms (window highlighted) on trials where participants correctly responded to the target stimuli

Figure 3.2. Grand averages and topographic maps of mean amplitude for response-locked ERN and Pe components in the incongruent condition for ADHD, control participants and unaffected siblings.

(a) ERN (Incongruent Condition)



(b) Pe (Incongruent Condition)



The ERN and Pe is the mean event related potential (ERP) activity between 0-150 ms and 150-450 ms after response respectively (window highlighted), on trials where participants made an error to target stimuli.

Rerunning of the primary analysis without IQ as a covariates did not alter overall N2 results; the condition main effect, and site*condition and conditions*group interactions remained significant (Table 3.5). However in the post-hoc analysis, the trends for ADHD-control and ADHD-sibling differences weakened (Table 3.6). In the ERN analysis, the main effect of site became non-significant and the interaction of site*group significant, although post-hoc comparisons continued to indicate no significant differences between any of the three groups. The Pe analysis weakened slightly to a trend-level overall, but continued to show significant attenuation in the ADHD group compared to controls, and trend-level differences between the ADHD group and sibling group in post-hoc analyses.

Independent analysis of older and younger subsets of the full sample revealed differences between the age groups. For the N2, the group aged 11-17 showed a main effect of condition, which was absent in the 18+ sample, with both groups also showing significant group*condition interactions (Table 3.7). Post-hoc analysis revealed further differences, with significant N2 enhancement in the ADHD group compared to controls being observed in the younger sample in the congruent condition at Fz electrode. In contrast, in the older subsample the ADHD group had attenuated N2 at trend-level compared to controls in the incongruent condition at FCz, the more centrally located electrode (Table 3.8). Group differences, either as a main effect or interaction with condition, were not observed for the ERN component within either age group. The Pe showed trend-level group differences in the younger sample group but not the older sample. Exploratory post-hoc analysis in the younger group of these components highlighted significant reductions in Pe amplitude in the ADHD group compared to controls, and trend-level reductions in amplitude compared to the sibling group, similar to the primary analysis in the full sample.

Table 3.5. ANOVA significance testing and effect sizes for N2, ERN and Pe components across ADHD, control and ADHD sibling groups, without IQ being controlled for in the analysis.

		Test statistic (F)	p-value	Effect size (η^2)
N2	RM ANOVA			
	Site (Fz, FCz), Condition (Cong, Incong), Group			
	covariates: IQ and gender			
	Group	0.49	0.61	0.0027
	Site	4.63	0.32	0.0124
	Condition	14.35	*<0.001	0.0372
	Site*group	1.78	0.17	0.0095
Site*condition	10.81	*0.001	0.0042	
Condition*group	9.74	*<0.001	0.0505	
ERN	RM ANOVA			
	Site (Fz, FCz); Group			
	covariates: IQ and gender			
	Group	0.57	0.57	0.0039
Site	1.51	<u>0.22</u>	0.0049	
Site*group	5.47	*0.01	0.0353	
Pe	Univariate ANOVA			
	Site (Cz); covariates: IQ and gender			
Group	2.70	†0.07	0.0171	

*RM ANOVA = repeated measures analysis of variance, Cong = congruent condition, Incong = incongruent condition. N2 from trials where participants correctly responded to stimuli. ERN and Pe from response-locked trials where participants incorrectly responded to target stimuli. † trend level ($p < 0.07$), * $p < 0.05$. η^2 effects sizes: 0.0099 small, 0.0588 medium and 0.1379 large. Cohen's d effect sizes: 0.2 small, 0.5 medium and 0.8 large.. Underlined values denote those where findings became significant or non-significant in comparison to results from the primary analysis which controlled for IQ differences between groups.*

Table 3.6. Mean amplitude (standard deviation) and pairwise comparisons for N2, ERN and Pe components in ADHD, unrelated controls and unaffected ADHD siblings, without IQ being controlled for in the analysis.

Condition and site	Pairwise comparisons		
	ADHD-Control p	ADHD-Sibs p	Control – Sibs p
N2			
Congruent Fz	0.33	0.73	0.12
Congruent FCz	0.70	0.26	0.36
Incongruent Fz	0.13	0.59	0.44
Incongruent FCz	<u>0.10</u>	<u>0.09</u>	0.67
ERN			
Incongruent Fz	0.61	0.56	0.25
Incongruent FCz	0.12	0.17	0.94
Pe			
Incongruent FCz	*0.03	†0.07	0.99

*† trend level ($p < 0.07$), * $p < 0.05$. Underlined values denote those where findings became significant or non-significant in comparison to results from the primary analysis which controlled for IQ differences between groups.*

Table 3.7. ANOVA significance testing and effect sizes for N2, ERN and Pe components across 11-17 and 18+ subgroups of full sample.

		Age 11 - 17			Age 18+		
		F	p	η^2	F	p	η^2
N2	RM ANOVA: Site (Fz, FCz), Condition (Cong, Incong), Group covariates: IQ and gender						
	Group	0.93	0.40	0.0106	0.40	0.67	0.0042
	Site	0.23	0.63	0.0013	3.24	†0.07	0.0165
	Condition	11.82	*0.001	0.0592	0.00	0.99	0.0000
	Site*group	0.84	0.43	0.0412	1.31	0.27	0.0648
	Site*condition	22.56	*<0.001	0.0172	3.54	†0.06	0.0023
	Condition*group	4.12	*0.02	0.0095	6.60	*0.002	0.0134
ERN	RM ANOVA: Site (Fz, FCz); Group; covariates: IQ and gender						
	Group	0.13	0.88	0.0017	1.62	0.20	0.0224
	Site	3.28	†0.07	0.0193	0.68	0.41	0.0048
	Site*group	2.12	0.123	0.0250	1.04	0.37	0.0146
Pe	Univariate ANOVA: Site (Cz); covariates: IQ and gender						
	Group	2.60	†0.07	0.0315	0.23	0.79	0.0031

*RM ANOVA = repeated measures analysis of variance, Cong = congruent condition, Incong = incongruent condition. N2 from trials where participants correctly responded to stimuli. ERN and Pe from response-locked trials where participants incorrectly responded to target stimuli. † trend level ($p < 0.07$), * $p < 0.05$, η^2 effects sizes: * 0.0099 small, ** 0.0588 medium and *** 0.1379 large.*

Table 3.8. Mean amplitude (standard deviation), and pairwise comparisons for N2, ERN and Pe components in ADHD, unrelated controls and unaffected ADHD siblings

a) Age 11 - 17

Condition and site	Mean amplitude in μV (SD)			Pairwise comparisons		
	ADHD	Control	ADHD Siblings	ADHD-Control p	ADHD-Sibs p	Control – Sibs p
N2	n = 47	n = 86	n = 44			
Congruent Fz	-4.69 (3.27)	-3.43 (2.53)	-4.27 (2.5)	*0.05	0.73	0.12
Congruent FCz	-2.33 (3.77)	-2.05 (2.63)	-2.87 (2.56)	0.59	0.37	0.13
Incongruent Fz	-5.76 (3.75)	-4.64 (2.78)	-4.99 (2.98)	0.12	0.64	0.35
Incongruent FCz	-2.52 (4.47)	-3.11 (3.28)	-3.5 (3.26)	0.69	0.17	0.29
ERN	n = 38	n = 73	n = 41			
Incongruent Fz	-5 (2.77)	-4.91 (3.03)	-5 (3.08)	-	-	-
Incongruent FCz	-3.52 (3)	-4.83 (3.57)	-4.46 (3.75)	-	-	-
Pe	n = 38	n = 73	n = 41			
Incongruent FCz	5.6 (3.45)	6.51 (4.04)	6.33 (3.85)	*0.04	†0.06	0.96

b) Age 18+

Condition and site	Mean amplitude in μV (SD)			Pairwise comparisons		
	ADHD	Control	ADHD Siblings	ADHD-Control p	ADHD-Sibs p	Control – Sibs p
N2	n = 58	n = 84	n = 51			
Congruent Fz	-2.76 (2.57)	-2.35 (2.1)	-2.55 (2.41)	0.39	0.83	0.56
Congruent FCz	-0.93 (2.82)	-1.31 (2.48)	-1.27 (2.41)	0.17	0.31	0.86
Incongruent Fz	-3.12 (2.49)	-2.81 (2.37)	-3.17 (2.73)	0.82	0.64	0.49
Incongruent FCz	-1.39 (2.65)	-1.99 (2.94)	-1.91 (3.09)	†0.06	0.11	0.99
ERN	n = 44	n = 63	n = 38			
Incongruent Fz	-3.76 (2.18)	-3.26 (2.09)	-4.22 (2.6)	-	-	-
Incongruent FCz	-3.08 (2.49)	-3.13 (2.27)	-4.09 (2.82)	-	-	-
Pe	n = 44	n = 63	n = 38			
Incongruent FCz	5.45 (3.23)	6.13 (3.42)	5.01 (3.34)	-	-	-

† trend level ($p < 0.07$), * $p < 0.05$

3.5 Discussion

In this study of N2, ERN and Pe components in the flanker task on a large sample of ADHD children and young adults we report a significant group*condition interaction in the N2, limited evidence for group differences on the ERN, and evidence for attenuation of the Pe component in ADHD. These results demonstrate impaired conflict monitoring and conscious error processing in ADHD. We also report highly significant differences between ADHD and control groups in all performance indices with fewer correct hits, increased commission errors, greater MRT and RTV, and increased omission errors being observed in the ADHD group, suggesting that these deficits may have contributed to impaired performance. Comparisons with siblings showed no differences from controls, with the ADHD group also having significantly reduced performance compared to siblings on many of the measures. We therefore find no evidence for performance monitoring deficits being an endophenotype for ADHD in the present study of adolescents and young adults.

Few of the performance indices were included in the meta-analytic results of behavioural data from adolescents and adult samples in Guburek et al. (2013); however, the present study does replicate their findings of increased commission errors in ADHD for flanker task performance data, in an equivalently sized ADHD sample. Two studies have tested RTV in the flanker, also reporting significantly greater variability in the ADHD group in adults (McLoughlin et al., 2009), and in adolescents (Albrecht et al., 2008), which we confirm in this sample. It is worth noting that these two studies and this investigation have all used an identical 3-arrow array version of the flanker task, with flanker arrows appearing 100 ms before the target arrow, which may be particularly effective at eliciting RTV differences, and may also underpin the consistency of these results. The value of measuring RTV is further highlighted by several other

neuropsychological studies which present evidence showing that RTV is a robust performance measure of ADHD (Adamo et al., 2012), potentially more so than for rates of errors (Kuntsi et al., 2010). Increasingly, studies are demonstrating that the examination of performance variability may be increasingly important in the understanding of cognitive impairments in ADHD, as performance may significantly improve by rewards or medication (Andreou et al., 2007, Castellanos et al., 2005, Epstein et al., 2006, Kuntsi et al., 2009, Leth-Steensen et al., 2000, McLoughlin et al., 2014b, Uebel et al., 2010). It would therefore be of benefit if future investigations could consistently report measures of variability such as RTV alongside MRT and other behavioural indices.

The flanker task, unlike the Go/NoGo paradigm, requires the participants to respond correctly or incorrectly to every trial. Although rates of omission errors (non-responses) were low compared to commission errors for all three groups, the ADHD group had a higher number of omission errors than control or sibling groups. This index may therefore be capturing performance interference arising from lapses in attention, which would prevent participants making correct or incorrect responses to targets during the task. It may therefore be valuable for future studies to also examine this measure independently of commission errors, to quantify if these markers represent different aspects of cognitive deficits in ADHD.

Trend-level N2 attenuation was observed in the ADHD group compared to both controls and unaffected siblings in the incongruent condition at FCz but not Fz, and not in the congruent condition. Firstly, this suggests that ADHD-sibling or ADHD-control differences may only emerge in high conflict conditions, and not when conflict demands are minimal. This is

consistent with the computational model of conflict monitoring, which suggests that the N2 represents dominant correct response programming before the correct response, which is then reinforced by continued stimulus processing (Yeung and Cohen, 2006). Critically, N2 amplitude is dependent on levels of conflicting incorrect stimuli processing (i.e. attending to the flanker stimuli) and thus the level of cognitive processing needed to overcome this. Applying this model to our findings of potential N2 attenuation in the ADHD group, our findings could suggest that this group did not perceive differences between flankers and targets and thus had reduced conflict processing. This theory is supported by performance data which showed that the ADHD group had an elevated number of omission errors, which may be indicative of increased lapses in attention, and highlights potential reduced attentional application to the task in the ADHD group.

We note that the pattern of results differed by electrode site, with all groups having comparable N2 mean amplitude at Fz where N2 amplitude was maximal. This, in addition to the absence of a group main effect, demonstrates that overall mean amplitude, and therefore the degree of conflicting incorrect response processing according to Yeung and Cohen (2006), did not differ between ADHD, sibling and control groups. However, the significant site*condition and condition*group interactions, supported by topographic maps of N2 mean amplitude, indicate that correct response programming may have been carried out differently in the ADHD group, having a more frontal scalp topography for the N2 component compared to controls and siblings.

Secondary analysis to examine the effect of IQ differences on results showed a small but significant effect on findings, slightly weakening several comparisons beyond significance thresholds when IQ was not controlled for. These results are consistent with similar exploratory analysis presented in chapter two (Kitsune et al., 2014), which further demonstrates the importance of considering the contribution from lower mean IQ when studying groups where this is common, such as within ADHD samples.

Within the age ranges of our sample, high levels of cortical maturation are underway, particularly in the prefrontal cortex and anterior cingulate cortex (Botvinick et al., 2001, Rubia et al., 2000, Shaw et al., 2007), thought to be source of the N2 and ERN components (Segalowitz and Dywan, 2009). In order to explore potential developmental differences across age, the sample was divided into 11-17 and 18+ groups and analysed separately. Group*condition interactions for N2 amplitude emerged at both time points, as with the primary analysis, yet post-hoc analysis revealed a different pattern of ADHD-linked differences compared to controls within each sub group, with the suggestion of frontal enhancement in the younger subset, and fronto-central attenuation in the older group. This contrast by age is suggestive of changing markers for atypical cortical maturation across adolescent and adulthood in ADHD, and may have implications for the identification of reliable biomarkers for ADHD.

There was limited evidence of ERN differences between the groups, which was unexpected given our large sample and high power to detect differences. For the Pe, there was evidence of attenuation in the ADHD group, indicating potentially reduced conscious error awareness in

children and adolescents with ADHD. Indications of potential Pe differences appeared stronger in the younger subgroup, but were absent in older subgroup, which is also consistent with other studies which have tended to find attenuated Pe amplitude in children opposed to adults (Herrmann et al., 2010, Jonkman et al., 2007, Rosch and Hawk, 2013). It has been argued that the Go/NoGo paradigm is more sensitive than the Flanker Task at detecting Pe attenuation in ADHD, as results have been more consistent to date (Groom et al., 2010, Groom et al., 2013, O'Connell et al., 2009a, Wiersema et al., 2009). However, our findings support the assertions of recent meta-analysis that more consistent Pe attenuation in the Flanker task was likely to emerge given additional data (Geburek et al., 2013).

ERN attenuation in ADHD was not apparent despite this finding being reasonably consistent among studies of children, adolescent and adults using the flanker paradigm (Albrecht et al., 2008, Chang et al., 2009, Herrmann et al., 2010, McLoughlin et al., 2009, Rosch and Hawk, 2013, van Meel et al., 2007). Those studies which have not reported differences have either consisted of small samples (Jonkman et al., 2007, Wild-Wall et al., 2009), or have reported ERN attenuation in younger adults with ADHD (mean age (sd) = 24.2 (3.1)) but not older adults (mean age (sd) = 40.9 (6.8) (Herrmann et al., 2010). ERN amplitude is known to increase during development, assumed to be the result of prefrontal cortex maturation (Segalowitz and Dywan, 2009) and then decreases with age in older adults (Falkenstein et al., 2001, Herrmann et al., 2010). These factors may therefore alter detectable ADHD-control differences across lifespan. However, there was no evidence for ERN differences in this sample either amongst older or younger subgroups during secondary analysis, which might suggest that other factors such as methodological differences or sample composition may explain the absence of ERN deficits in this study.

Generally studies investigating performance monitoring using the flanker task to date have been methodologically heterogeneous, which may partially explain inconsistencies in the literature (Shiels and Hawk, 2010). In this study, we adopted a mean amplitude measure as this method is more robust to the variability in peak amplitude (latency jitter), which can reduce the peak amplitude of ERP component, and may be particularly prevalent in ADHD (Lazzaro et al., 1997). The two other studies which used identical 3-arrow array versions of flanker task, and reported ERN attenuation in ADHD, both adopted a peak-to-peak measure of the ERN in reference to the preceding positive component, which may be susceptible to peak amplitude reductions on account of individual trial variability (Albrecht et al., 2008, McLoughlin et al., 2009). Our results may therefore be a more accurate reflection of unconscious error processing in ADHD, advancing that overall ERN amplitude is not reduced, only more variable on a trial by trial basis. Indeed, more recent studies suggest that measuring the variability in brain oscillations which underlie cognitive performance may be critical in understanding ADHD (McLoughlin et al., 2014b), and show that additional research using alternative methods is required to conclusively demonstrate whether ERN attenuation has a functional relationship with ADHD or whether the mixed findings to date have been a product of the variety of methods employed within the literature (Shiels and Hawk, 2010).

A further aim of this study was to examine if performance monitoring deficits showed the characteristics of a familial endophenotype, in that 'intermediate' deficits were apparent in first degree relatives, as suggested by other studies (Albrecht et al., 2008, McLoughlin et al., 2009). Although the large sample employed in this study should have meant it was well placed to detect familial factors hinted at in Albrecht et al. (2008), unaffected ADHD siblings did not differ from controls in any of the comparisons of performance or electrophysiological

measures which otherwise showed ADHD-control differences. Given that no differences were detected on performance measures between controls and ADHD siblings either, this suggests that methodological differences in ERP analysis are unlikely to be sole cause of differences in results between this study and others, and therefore questions whether performance monitoring deficits do represent familial endophenotypes for ADHD. However, although no statistically significant differences were present between siblings and controls for Pe, the grand average graphs and means did imply that ADHD and siblings showed similar attenuation in the Pe component, suggesting sample differences which were managed by the use of covariates may modify results. Further research will be required to clarify this matter, and the application of techniques such as sibling modelling is likely to give more information, such as whether ERP markers of performance monitoring deficits show familial covariation.

Overall, this study found evidence of altered performance monitoring processes in ADHD under high conflict conditions, with the ADHD showing a more frontally orientated topographic distribution of amplitude compared to controls, but with no overall differences where amplitude is maximal. Evidence of unstable deficits across older and younger subgroups argues for the differences being driven by atypical maturational processes in ADHD. No familial effects were detected, with unaffected ADHD siblings being indistinguishable from unrelated controls. Also despite a large sample, effect sizes were small, suggesting sample heterogeneity and/or methodological differences between studies may complicate the detection of stable performance monitoring biomarkers for ADHD. There was also evidence of impaired conscious error processing in ADHD, particularly among younger subgroups, alongside evidence of increased omission errors, which could be linked with lapses in attention, and greater RTV. This study did not find evidence of impaired unconscious error processing in this large sample of ADHD children and young adults, contrary to other studies including a meta-analysis with a

sample size equivalent in size to this investigation. Further replication will be required to fully evaluate these results in light of other studies, to determine if methodological factors are responsible for the differing pattern of results in the literature to date.

***Chapter 4 - Delineating ADHD and Bipolar
Disorder: A Comparison of Clinical Profiles in Adult
Women***

4.1 Abstract

Overlapping symptoms can make the diagnostic differentiation of attention-deficit/hyperactivity disorder (ADHD) and bipolar disorder (BD) challenging in adults using current clinical assessments. This study sought to determine if current clinical measures delineate ADHD from euthymic BD in adults, comparing relative levels of ADHD, BD and emotional lability (EL) symptoms. Sixty adult women with ADHD, BD or controls were compared on self-report and interview measures for ADHD symptoms, mania, depression, EL, and impairment. ADHD interview measures and self-ratings of ADHD symptoms best discriminated between ADHD and BD. Self-report measures of EL and depression showed non-specific enhancement in both clinical groups. BD-specific items may distinguish BD from ADHD if a retrospective time-frame is adopted. Using measures which capture specific symptoms of ADHD and chronicity/episodicity of symptoms facilitates the delineation of ADHD from BD.

4.2 Introduction

The diagnostic differentiation of attention-deficit/hyperactivity disorder (ADHD) from bipolar disorder (BD) is important for the correct treatment and management of both conditions (Asherson et al., 2014b, Atmaca et al., 2009, Galanter et al., 2005, Mosholder et al., 2009). Yet, similarities in symptoms such as restlessness, increased production of speech and distractibility in both conditions and evidence of persistent impulsive behaviours in euthymic BD (Najt et al., 2007, Peluso et al., 2007) can make differentiation of the two conditions challenging (Kent and Craddock, 2003, Galanter and Leibenluft, 2008). The emergence of evidence showing high levels of emotional lability (EL) in ADHD (Barkley and Fischer, 2010, Skirrow et al., 2012, Skirrow et al., 2014, Surman et al., 2013), independent of comorbidity (Skirrow et al., 2012), and the recognition of EL as an associated feature of ADHD (American Psychiatric Association, 2013), further complicate the diagnostic boundaries between ADHD and BD. Meta-analysis examining comorbidity of ADHD and BD in adults identified rates ranging from 5-47% (Wingo and Ghaemi, 2007), and studies of familial co-variation indicate that the disorders co-occur at a higher rate than in the general population, suggesting a potential familial relationship between them (Skirrow et al., 2012, Larsson et al., 2013).

Although delineation has been widely discussed in paediatric populations, there are few studies comparing the extent to which symptoms are similar or different between ADHD and BD in adult populations. The few direct comparisons used self-report measures of ADHD and depression symptoms, which were limited in their potential to delineate the two disorders (Ibanez et al., 2012, Torralva et al., 2011). The comparative degree and specificity of EL within each disorder is also an important question to clarify, as mood fluctuations are seen as a characteristic feature of BD, and could result in the misdiagnosis of adults with ADHD and high EL. The aim of this study was to determine the potential of current clinical measures to

delineate ADHD from BD in adults, comparing relative levels of ADHD, BD and EL symptoms across the two disorders.

4.3 Methods and Materials

4.3.1 Sample

Sixty adult women were recruited (20 with ADHD, 20 with BD and 20 control participants). Participants with ADHD were recruited from the National Adult ADHD Clinic at the Maudsley Hospital. Participants with BD were recruited from the Maudsley Psychosis Clinic and a sample that had previously participated in another research study (Hosang et al., 2012). Control participants were recruited from the Mindsearch volunteer database maintained by the Institute of Psychiatry, which comprises several thousand potential participants. Participants were randomly selected from all those meeting recruitment criteria for this study (described below).

4.3.2 Diagnosis and recruitment

Fifty-seven people with ADHD, 75 people with BD, and 120 controls matching requirements of age, gender and clinical diagnosis based upon DSM-IV criteria were approached to participate. The ADHD participants met current criteria for combined-type ADHD or inattentive-type ADHD with sufficient past reported symptoms of hyperactivity-impulsivity to have met combined-type criteria during childhood.

Participants in the BD group had a diagnosis of bipolar I disorder (BD-I) with evidence of a past manic episode lasting one week or more. BD-I patients were selected if they were currently euthymic. Eligibility to participate was ascertained by checking medical records for details of diagnosis and psychiatric history. Exclusions for all groups were drug or alcohol dependency in the last six months, autism, epilepsy, neurological disorders, brain injury, past ECT treatment, current involvement in another research trial likely to alter symptomatology, pregnancy or a limited proficiency in English language. Those with a reported diagnosed comorbidity of both ADHD and BD at screening or who were currently experiencing a manic episode were excluded. Other comorbidities in the clinical groups were permitted. This included one participant with comorbid Depression and one with Obsessive Compulsive Disorder (OCD) in the ADHD group, and one participant with comorbid anxiety disorder and one with borderline personality disorder (BPD) in the BD group. All primary analyses were later re-run after excluding these individuals, to check for the influence of these comorbidities on results. Control participants reporting a history of psychiatric disorders or currently taking medication at screening were excluded. Recruitment continued until 20 participants were recruited for each group (Table 4.1). Samples were age-matched at a group level during recruitment. ADHD participants were asked to stop stimulant medication 48-hours before research assessments. For ethical reasons, BD participants were not asked to stop taking mood-stabilisers or any anti-psychotic medication they had been prescribed. All participants were asked to refrain from caffeinated drinks and nicotine for two hours prior to the assessment session.

Table 4.1. Number of participants recruited and reasons for exclusion.

	ADHD	BD	Control
Number approached	57	75	120
Recruitment			
Un-contactable	17	26	45
Declined	4	15	25
Travel or childcare difficulties	5	4	5
Did not attend or cancelled	1	1	13
Exclusions			
Unsuitable diagnosis	3	7	
ADHD with comorbid BD	4		
Control with psychiatric disorder			8
Medical or neurological disorder	1		3
Autism	1		
Past ECT treatment		1	
Participating in another research trial	1		
Currently pregnant			1
Insufficient English language ability		1	
Final Sample	20	20	20

Abbreviations: attention-deficit/hyperactivity disorder (ADHD), bipolar disorder (BD), electroconvulsive therapy (ECT). An “unsuitable diagnosis” was a diagnosis of BD-II (i.e. without a manic episode) in the BD group, or an inattentive-subtype ADHD diagnosis with no evidence of symptoms of hyperactivity in childhood.

4.3.3 Procedure

Participants attended a single research session to complete self-report measures and clinical interviews alongside other research evaluations. All participants completed the same set of assessments. For informant ratings, participants were given a questionnaire to take home in a stamped address envelope, for a family member or close friend to complete. Interviews were

conducted by an experienced researcher (GK), trained by a consultant psychiatrist (PA) with experience of both ADHD and BD.

4.3.4 Measures

4.3.4.1 ADHD symptoms

Measures of ADHD symptoms were obtained using the 18-item Barkley Adult ADHD Rating Scale (BAARS-IV) (Barkley and Murphy, 2006), which consists of the DSM-IV items related to inattention and hyperactivity–impulsivity. Respondents indicated how frequently they experienced behaviours on a scale of 0 to 3 (never or rarely, sometimes, often, very often) during the past 6 months. Total scores were calculated for each symptom dimension. The Barkley’s functional impairment scale (Barkley and Murphy, 2006) used the same scoring system and was included with the (BAARS-IV) to create a third impairment subscale, indexing functional impairments across several domains including occupational, daily responsibilities and social relationships. Both self-rated and informant-rated versions of the BAARS-IV were used to obtain measures of ADHD symptoms.

The Diagnostic Interview for ADHD in Adults (DIVA) (Kooij and Francken, 2007) was used to assess ADHD symptoms in participants. The DIVA, like the BAARS-IV, consists of 18 items used to define the DSM-IV symptom criteria for ADHD, but is a semi-structured interview conducted by a trained clinical investigator. Each item is scored “yes”, if the behavioural symptom is

present *often* within the past 6 months. Outcomes were total current ADHD symptom score, and separate totals for inattentive and hyperactive-impulsive symptom domains.

4.3.4.2 Mania and depression symptoms

The Beck's Depression Inventory II (DI) (Beck et al., 1996) was included as a self-rated measure of depression symptoms. The scale has 21 questions, rated 0-3 based on the severity of symptoms, during the past two weeks. The test variable was total score.

The self-report Altman Self-Rating Mania Scale (ASRM) (Altman et al., 1997) was used to measure mania symptoms in the past week. This is a 5-item measure scored 0-4 based on the strength of the behaviour. The total score was used as the test variable.

A second measure of mania symptoms was collected using the Young Mania Rating Scale (YMRS) (Young et al., 1978), completed by the investigator following clinical interview. This 11-item measure uses subjective report of mental phenomena and clinical observations to rate behaviours associated with mania in the past 48 hours. Seven items are scored 0-4 based on severity and the remaining four items (irritability, rate or amount of speech, delusional/grandiose thought content, and severe aggressive or uncontrollable behaviour) are scored 0-8, as characteristic features of manic episodes. For this study, a change indicator asking "*Is this how you normally feel?*", scored yes/no, was added to each item to distinguish between episodic symptoms which are characteristic of BD, and the more stable trait-like

symptoms which are characteristic of ADHD. A further question asking “*Has there ever been a time other than the last 48 hours when you have felt...*”, was added to each of the 8 self-report items to count the number of symptoms experienced in the past, including worst ever episode, to determine the range of symptoms experienced by BD patients during episodes of mania. Outcomes for this measure were total score, number of present symptoms (excluding observer-rated items to make this comparable with the past symptoms scale) and number of past symptoms.

We also examined whether particular items on the YMRS, which related to specific symptom domains or loaded on previously identified factors, were able to delineate the two clinical groups. We compared two approaches. The first approach was based on diagnostic criteria for ADHD which grouped YMRS items on whether they overlapped with ADHD symptoms (increased motor activity/energy, increased rate of production of speech, and language/thought disorder including distractible thought processes and changing topics frequently); or did not overlap with ADHD (inappropriate elevated mood, increased/inappropriate sexual interest, delusions and grandiosity, and severe disruptive/aggressive or uncontrollable behaviour); or are associated features of ADHD that overlap with BD (difficulty sleeping and irritable mood). The second approach used three groupings previously identified by Hanwella and de Silva (2011) in a factor analysis of YMRS items, which were labelled: irritable mania (increased motor activity/energy, irritable moods, and severe disruptive/aggressive or uncontrollable behaviour); elevated mania (elevated mood, language/thought disorder, sexual interest and insight); and psychotic mania (increased motor activity/energy, motor activity, delusions and grandiosity, and appearance).

4.3.4.3 Emotional lability

The self-rated Affective Lability Scale Short Form (ALS-SF) (Oliver and Simons, 2004), comprising of 18 items scored 1-4 (very un-descriptive, rather un-descriptive, rather descriptive, very descriptive) was used as one of two measures of mood lability. The ALS-SF measures fluctuations from a normal mood to other emotional states from moment to moment during the past week, and has been shown to comprise of three domains of anxiety–depression, depression–elation and anger (Oliver and Simons, 2004). Total overall score and total score on each subscale were used as the test variables.

The second measure of emotional lability was the auxiliary subscale of the Centre for Neurologic Study-Lability Scale (CNS-LS) (Moore et al., 1997), adapted by removing two items related to impatience which have clear overlap with impulsive symptoms of ADHD. This created a self-rated 8-item measure focusing on negative emotions, such as getting easily frustrated, upset and angry occurring in the past month and past 5 years. Each item is scored on a scale of 0-4 (applies never, rarely, occasionally, frequently, most of the time), based on the frequency of each experience. Total scores for the past month and past 5 years were used as the test variables.

4.3.4.4 Intellectual Ability

The Wechsler Abbreviated Scale of Intelligence Fourth Edition (WASI-IV) (Wechsler, 1999) was administered to all participants to derive an estimate of IQ.

4.3.5 Statistical Analyses

Across the three samples, rating scale data were normally distributed for the BAARS-IV impairment scales (self-rated and informant), the ALS total score and the hyperactive-impulsive subscale of the DIVA. Otherwise, the most appropriate transformations were applied to the data (log or square-root). For the ALS and YMRS subscales, no available transformations normalised the data, so non-parametric Kruskal-Wallis tests were used. Group differences in normal and transformed-normal data were tested using univariate ANOVAs. Where appropriate, pairwise comparisons were conducted to discriminate which groups differed. On the YMRS, the number of symptoms past and present were compared using repeated-measures ANOVA to explore the interaction of group and symptom change over time. Additional post-hoc pairwise comparisons were used to investigate both group differences and differences between the number of past and presents symptoms within group. Analyses were carried out using STATA (Version 11) and SPSS (Version 21). Given the large number of subscales used in this study, and therefore high number statistical comparisons and associated risk of type-I error, all reported p-values were adjusted for multiple testing using family-wise Bonferroni corrections to maintain $\alpha = 0.05$ for all 20 independent tests employed in the primary analysis and all subsequent post-hoc comparisons.

4.4 Results

The groups did not differ in mean age (Mean (SD): ADHD = 37.4 (7.65); BD = 40.3 (7.68); Control = 36.7 (4.28); $F = 1.63$, $p = 0.21$) or IQ (Mean (SD): ADHD = 104.5 (17.85); BD: 108 (12.50); Control = 112.35 (14.21); $F = 1.37$, $p = 0.26$). Mean scores on outcome measures with

adjusted p-values are shown in Table 4.2 and the standardised differences between groups for all measures are shown in Figure 4.1.

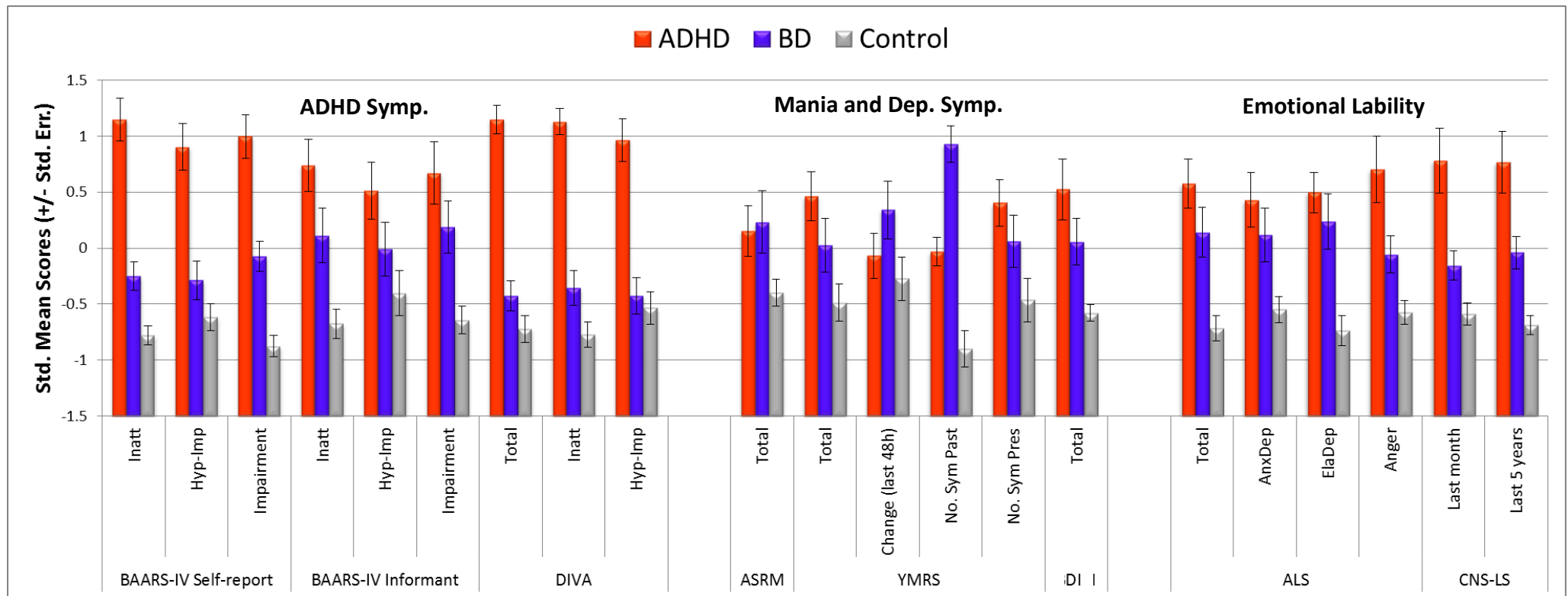
Table 4.2. Mean and standard deviations for ADHD and BD symptom measures and emotional lability measures.

	total n	ADHD Mean (SD)	BD Mean (SD)	Controls Mean (SD)	PAIRWISE COMPARISONS		
					ADHD-BD Adj. p	ADHD-Control Adj. p	BD-Control Adj. p
BAARS-IV self-rated							
Inatt score	58	19.17 (6.22)	8.40 (4.39)	4.35 (2.91)	<0.001***	<0.001***	0.01**
Hyp-Imp score	60	15.75 (6.23)	7.75 (5.26)	5.55 (3.62)	<0.001***	<0.001***	0.38
Impairment score	58	19.58 (7.58)	10.00 (5.26)	2.85 (3.84)	<0.001***	<0.001***	<0.001***
BAARS-IV informant							
Inatt score	51	12.38 (5.67)	8.60 (5.63)	3.85 (3.53)	0.18	0.001***	0.03*
Hyp-Imp score	51	9.94 (5.63)	7.07 (5.15)	4.90 (4.89)	0.34	0.02*	0.80
Impairment score	50	12.47 (7.51)	9.07 (6.35)	3.25 (3.92)	0.37	0.001***	0.02*
DIVA							
Total score	60	13.45 (3.02)	4.95 (3.27)	3.35 (2.96)	<0.001***	<0.001***	0.34
Inatt symptoms	60	7.55 (1.61)	2.95 (2.14)	1.65 (1.57)	<0.001***	<0.001***	0.10
Hyp-Imp symptoms	60	5.90 (2.36)	2.00 (2.03)	1.70 (1.78)	<0.001***	<0.001***	1.94
ASRM							
Total score	58	4.63 (3.98)	4.95 (5.03)	2.42 (2.09)	2.66	0.31	0.39
YMRS							
Total score	60	13.35 (7.35)	10.05 (8.06)	6.15 (5.68)	0.07	0.003**	0.74
No. current symptom	60	4.70 (2.03)	3.95 (2.28)	2.80 (1.91)	1.57	0.03**	0.82

		PAIRWISE COMPARISONS						
	total n	ADHD Mean (SD)	BD Mean (SD)	Controls Mean (SD)	ADHD-BD Adj. p	ADHD-Control Adj. p	BD-Control Adj. p	
DI	No. past symptoms	60	4.60 (1.47)	7.10 (1.86)	2.35 (1.87)	0.03**	<0.001***	<0.001***
	State change (past 48h)	60	2.05 (1.54)	2.75 (1.97)	1.70 (1.49)	1.08	1.49	0.11
	Total score	60	17.50 (14.54)	11.90 (11.11)	4.35 (4.03)	0.33	<0.001***	0.003***
ALS-SF								
	Total score	60	41.35 (12.73)	35.65 (12.87)	24.50 (6.61)	0.33	<0.001***	0.01**
	Anxiety-depression score	60	11.50 (4.71)	10.15 (4.64)	7.25 (2.27)	0.70	0.01**	0.20
	Elation-depression score	60	19.45 (5.17)	17.80 (7.05)	11.55 (3.79)	1.10	<0.001***	0.01**
	Anger score	58	10.61 (4.86)	7.70 (2.79)	5.70 (1.81)	0.11	<0.001***	0.34
CNS								
	Past month score	59	15.79 (11.21)	7.45 (5.24)	3.60 (4.03)	0.03*	<0.001***	0.10
	Past 5 year score	59	19.32 (11.34)	11.75 (6.09)	5.70 (3.67)	0.09	<0.001***	0.03*

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. "Adj p" family-wise Bonferroni corrected post-hoc p-values. "State change (past 48h)" indexes manic-like symptom change in the past 48 hours (appearing or disappearing). Other abbreviations: Inattention (Inatt), Hyperactive-Impulsive (Hyp-Imp), Barkley Adult ADHD Rating Scale-IV (BAARS-IV), Diagnostic Interview for ADHD in Adults (DIVA), Altman Self-Rating Mania Scale (ASRM), Young Mania Rating Scale (YMRS), Beck Depression Inventory (DI), Affective Lability Scale (ALS), Centre for Neurologic Study-Lability Scale (CNS-LS).

Figure 4.1. Group differences on ADHD, mania, depression and emotional lability measures, as standardised scores with standard error.



Standardised means total scores for each measure or subscale. ADHD symptoms are presented in the first part, mania and depression symptoms in the second and emotional lability in the third part of this graph. "Change (48h)" indexes manic-like symptom change in the past 48 hours (appearing or disappearing). "No. Sym Past" measures current manic-like symptoms, "No. Sym Past" measures symptoms experienced in the past. Other abbreviations: Inattention (Inatt), Hyperactive-Impulsive (Hyp-Imp), Anxiety-Depression (AnxDep), Elation-Depression (ElaDep), Barkley Adult ADHD Rating Scale-IV (BAARS-IV), Diagnostic Interview for ADHD in Adults (DIVA), Altman Self-Rating Mania Scale (ASRM), Young Mania Rating Scale (YMRS), Beck Depression Inventory (DI), Affective Lability Scale (ALS), Centre for Neurologic Study-Lability Scale (CNS-LS).

4.4.1 ADHD Symptoms

Group differences were present for: DIVA total symptom score ($F(2,57) = 37.65, p < 0.001$), inattention ($F(2,57) = 33.68, p < 0.001$) and hyperactive-impulsive subscales ($F(2,57) = 25.65, p < 0.001$); self-rated BAARS inattention ($F(2,55) = 40.51, p < 0.001$) and hyperactive-impulsive ($F(2,57) = 18.39, p < 0.001$) subscales; and informant-rated BAARS inattention subscale ($F(2,48) = 12.05, p = 0.01$). Post-hoc analysis indicated that both ADHD and BD groups had higher ADHD symptom scores than controls on self and informant reported ADHD rating scales. However, only the ADHD group had higher current ADHD symptom scores compared to controls when the DIVA interview was used as the measure of ADHD symptoms.

The ADHD group had significantly higher symptoms than the BD group for the DIVA and self-rated BAARS scores, but not for the informant-rated BAARS. To quantify the degree to which the DIVA and self-rated BAARS scores can distinguish between patients with ADHD and euthymic BD we calculated receiver operating characteristic (ROC) scores. To compare the BAARS with the DIVA we made binary variables from the BAARS scores for the absence (never, rarely or sometimes) or presence (often, very often) of each individual ADHD item. The results are summarised in Table 4.3 with optimal thresholds that balance sensitivity against specificity. There was very good sensitivity (90%) and specificity (95%) for the DIVA interview, particularly for the inattentive items when the symptoms threshold of 6 or more symptoms was applied. This compared to a much lower sensitivity of 65-70% using the BAARS, although specificity remained high (95-100%).

Table 4.3. Receiver Operating Characteristics (ROC) scores showing sensitivity and specificity of BAARS and DIVA measures to ADHD diagnosis compared to BD diagnosis.

	ROC scores			
	AUC	Threshold	Sensitivity	Specificity
BAARS inattention	0.87	6/9	0.70	0.95
BAARS hyper-imp	0.83	6/9	0.45	0.90
BAARS total score	0.89	11/18	0.65	1.00
DIVA inattention	0.95	7/9	0.90	0.95
DIVA hyper-imp	0.89	6/9	0.55	0.90
DIVA total score	0.97	11/18	0.90	0.95

Abbreviations: Barkley Adult ADHD Rating Scale (BAARS), Diagnostic Interview for ADHD in Adults (DIVA), Area under the curve (AUC).

4.4.2 Impairment

Ratings of impairment showed significant group differences on both self-rated ($F(2,55) = 41.55$, $p < 0.001$) and informant ($F(2,47) = 10.92$, $p = 0.003$) scales. Both clinical groups reported elevated impairment compared to controls on both scales. The ADHD group had elevated scores compared to the BD group on the self-report measure, but not the informant measure.

4.4.3 Mania and depression

Group differences in self-reported current manic symptoms on the ASRM were not significant ($F(2,55) = 1.71, p = 1.00$). Self-rated current depression symptoms on the DI showed group differences ($F(2,57) = 13.79, p < 0.001$), with both ADHD and BD groups reporting higher scores than controls, but not differing compared to each another (Table 4.2).

The YRMS interview showed a nominal group difference in total score for current symptoms (unadjusted $p = 0.005$), which did not survive α -correction ($F(2,59) = 5.78, p = 0.10$). On the extension questions added for this study, the groups did not differ in the proportion of mania symptoms which had changed within the past 48 hours ($F(2,57) = 1.31, p = 1.00$). A repeated-measures ANOVA, comparing the number of past symptoms with the number of present symptoms, showed a significant main effect of group ($F(2,57) = 6.88, p < 0.001$), time period ($F(1,57) = 15.56, p = 0.01$) and interaction of time period x group ($F(2,57) = 12.03, p < 0.001$). Overall, post hoc tests indicated that the BD group had a higher number of mania symptoms in the past, but that the two clinical groups did not differ in the number of current symptoms. The ADHD group also showed more current mania symptoms than controls, although BD-control differences were not significant (Table 4.2).

We further examined if subsets of items from the YMRS were better able to discriminate ADHD from BD than the full measure, based on symptom frequency (Table 4.4). The symptom-based division of items only discriminated ADHD from BD using the non-ADHD overlapping symptoms grouping (inappropriate elevated mood, increased/inappropriate sexual interest, delusions

and grandiosity, and severe disruptive/aggressive or uncontrollable behaviour) and then only for past 'worst episode' symptoms and not current symptoms. Both clinical groups had elevated scores compared to controls on the ADHD overlapping symptom grouping (increased motor activity/energy, increased rate of production of speech, and language/thought disorder including distractible thought processes and changing topics frequently) for both current and past symptoms, but did not differ between themselves. The shared associated symptom grouping (sleep disturbance and irritability) indicated elevated scores for past symptoms in the BD group compared to controls, but no differences for other comparisons. The factor-based item groupings did not show any group differences for current symptoms. For past symptoms, on both elevated mania (elevated mood, language/thought disorder, sexual interest and insight) and psychotic mania (increased motor activity/energy, motor activity, delusions and grandiosity and appearance) item groupings the BD group had elevated scores compared to ADHD and controls. Additionally, on the psychotic mania cluster the ADHD group had higher scores than controls. For irritable mania items (increased motor activity/energy, irritable moods, and severe disruptive/aggressive or uncontrollable behaviour) both clinical groups scored higher than controls, but did not differ compared to one another.

Table 4.4. Young Mania Rating Scale (YMRS), a comparison of different item groupings to delineate ADHD from bipolar disorder.

A) Current number of symptoms

	Kruskal-Wallis		Pairwise Comparisons		
	H	Adj. p	ADHD-BD Adj. p	ADHD-Control Adj. p	BD-Control Adj. p
Symptoms based					
ADHD overlapping	17.27	<0.001***	0.32	<0.001***	0.04*
ADHD non-overlapping	0.21	1	-	-	-
Shared ADHD associated	9.14	0.12	-	-	-
Factor based					
F1. Irritable mania	8.68	0.16	-	-	-
F2. Elevated mania	5.25	0.86	-	-	-
F3. Psychotic mania	4.94	1	-	-	-

B) Past number of symptoms

	Kruskal-Wallis		Pairwise Comparisons		
	H	Adj. p	ADHD-BD Adj. p	ADHD-Control Adj. p	BD-Control Adj. p
Symptoms based					
ADHD overlapping	27.33	<0.001***	0.98	<0.001***	<0.001***
ADHD non-overlapping	31.54	<0.001***	<0.001***	1	<0.001***
Shared ADHD associated	18.21	<0.001***	0.13	0.09	<0.001***
Factor based					
F1. Irritable mania	24.64	<0.001***	1	<0.001***	<0.001***
F2. Elevated mania	19.29	<0.001***	0.006***	0.67	<0.001***
F3. Psychotic mania	32.89	<0.001***	0.02*	0.02*	<0.001***

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. "Adj p" batchwise Bonferroni corrected post-hoc p-values. Symptom-based item groupings consisted of the following items: ADHD overlapping (increased motor activity/energy, increased rate of production of speech, and language/thought disorder including distractible thought processes and changing topics frequently), ADHD non-overlapping (inappropriate elevated mood, increased/inappropriate sexual interest, delusions and grandiosity, and severe disruptive/aggressive or uncontrollable behaviour), and shared ADHD associated symptoms (difficulty sleeping and irritable moods). Factor-analysis based item groupings consisted of the following items: irritable (increased motor activity/energy, irritable moods, and severe disruptive/aggressive or uncontrollable behaviour), elevated mania (elevated mood, language/thought disorder, sexual interest and insight), and psychotic mania (increased motor activity/energy, motor activity, delusions and grandiosity and appearance).

4.4.4 Emotional Lability (EL)

Group differences were detected for ALS total scores ($F(2,59) = 11.86, p = 0.001$), the elation-depression subscale ($H(2) = 17.60, p < 0.001$) and the anger subscale ($H(2) = 17.20, p < 0.001$). Group differences for the anxiety-depression subscale did not survive α -correction ($H(2) = 9.34, p = 0.18$). Post-hoc pairwise comparisons did not distinguish ADHD and BD groups on either total scores or subscales (Table 4.2). The ADHD group had higher scores compared to controls on all scales of the ALS, with the BD group showing higher scores than controls on total score and the elation-depression subscale.

The CNS-LS, indicated group differences on both time spans (last month: $F(2,56) = 11.35, p < 0.001$; last 5 years: $F(2,56) = 12.04, p = 0.001$). For CNS-LS ratings of EL in the last month, the ADHD group had elevated scores compared to both BD and controls, with the BD group not differing from controls (Table 4.2). For ratings based on *worst ever* in the last 5 years, both clinical groups had higher scores than controls, but were undifferentiated compared to each other.

4.4.5 Comorbidities

Primary analyses were rerun after excluding the four individuals which had a diagnosed comorbidity (ADHD: one depression, one OCD; BD: one BPD, one anxiety disorder). Overall, the results did not change with these participants excluded, except for two post-hoc pairwise comparisons, which then became non-significant after correcting for multiple testing. These

were the ADHD-BD comparison on the CNS-LS (last month), where the adjusted p-value became non-significant (adj. p = 0.11, unadjusted p = 0.04) and the ADHD–control comparison for the number of present symptoms on the YMRS which weakened to a trend level (adj. p = 0.07, unadjusted p = 0.008).

4.5 Discussion

In this study we investigated the similarities and differences between female patients with typical ADHD, Bipolar I Disorder (during euthymic periods) and healthy controls, using standard measures used in the diagnostic assessment of ADHD and BD. Using ratings for the current mental state, increased levels of ADHD and depression symptoms, emotional lability and functional impairment were seen in both the ADHD and euthymic BD groups compared to controls. The ADHD group generally showed higher levels of psychopathology than the euthymic BD group, particularly for current symptoms of emotional lability and mania. Using retrospective ratings for mania on the YMRS, which would measure past manic episodes, gave higher ratings in the BD than the ADHD group, although both groups had higher ratings than the controls. The DIVA interview was the best instrument for separating out the two clinical groups, with high sensitivity and specificity for ADHD. Overall, these findings show a significant level of residual symptoms and impairments in BD patients during euthymic periods, which was similar to the ADHD patients for depression and impairment, but did not reach the levels of ADHD, mania and emotional lability symptoms seen in the ADHD group.

4.5.1 Distinguishing euthymic BD from ADHD

Making this distinction is important because BD patients often present with continued mood symptoms and functional impairments in between major affective episodes, raising the question of whether any observed psychopathology is due to persistence of BD or could be due to comorbid ADHD. Indeed this study showed considerable overlap between euthymic BD and ADHD using both rating scale and interview measures. Yet it was possible to distinguish between the ADHD and BD groups. We found that the interview measure for current ADHD symptoms provided very good sensitivity (around 90%) and specificity (around 95%) to identify ADHD in comparison with BD. In contrast, the self-reported ADHD measures showed enhancement of scores in both clinical groups, although self-ratings of ADHD inattention were moderately good at separating ADHD from BD. For BD the best discrimination came from the use of the YMRS mania interview, which was sensitive to differences between ADHD and BD groups when using a retrospective 'worst ever' adaption included for this study. However, even using retrospective data, the ADHD group showed a significant level of symptoms on the YMRS, and for current symptoms the ADHD group had more mania symptoms than the euthymic BD group. These findings are similar to those reported in previous studies. For the ADHD measures, the inattentive symptoms gave the best discrimination of ADHD from BD for both the self-rated and interview measure. This is similar to the results of Ibanez et al. (2012), who report higher self-rated inattention scores in ADHD compared to BD or control groups using the same self-rated scale of ADHD used in this study, although they did not observe a significant BD-control difference.

The Altman Self-Rating Mania Scale (ASRM) and the Beck Depression Inventory (DI) were not able to distinguish the two clinical disorders. High depression scores for both clinical groups

highlight that symptoms of depression are commonly seen in ADHD. This replicates findings from Torralva et al. (2011) and Ibanez et al. (2012) of elevated depression scores on the DI in ADHD compared to BD.

Current symptom score and number of current symptoms on the YMRS mania interview showed that the ADHD group had higher levels of mania symptoms compared to both the controls and the euthymic BD group. These results, collected using the standard form of the measure, highlight the potential difficulties of delineating ADHD and BD using cross-sectional (present state) mania measures, and replicate findings for Ibanez et al. (2012), which reported higher mania symptom scores in the ADHD group compared to controls on this measure. In contrast, when the scale was applied to the number of past symptoms, the BD group had a greater number of mania symptoms than the ADHD or control groups, even though the ADHD continued to report higher past symptoms than controls.

Overall, these findings illustrate the considerable overlap of symptoms in ADHD and BD. We found greater specificity for the ADHD symptoms elicited at interview to correctly identify the ADHD group, than for the traditional BD symptoms to correctly separate BD from ADHD. Thus the two disorders can usually be distinguished through a combination of detailed symptom review, elicited using a clinical interview, with a consideration of the time course and episodicity of the symptoms that are present. These data also illustrate the importance of considering ADHD in patients presenting with chronic (non-episodic and trait-like) mood symptoms, including symptoms of mania, depression and emotional lability.

4.5.2 Use of the YMRS

We completed further exploratory analyses to investigate whether particular YMRS items might be specifically associated with either ADHD or BD. We compared a three-cluster DSM symptom model (ADHD overlap; no-overlap; mood and sleep problems) against an empirically-derived three-factor model (irritable mania; elevated mania; psychotic mania) identified by Hanwella and de Silva (2011). For current symptom scores, group differences were only found on the ADHD overlapping symptoms item grouping, consisting of increased motor activity/energy, increased rate of production of speech and language/thought disorder items, where both clinical groups scored significantly higher than controls. No other differences were found for the symptom-based or factor-based model. In line with our other analysis, this implies that the YMRS is poor at distinguishing ADHD and euthymic BD in its standard form.

For the number of past symptoms, based on worst ever episode, more differences emerged due to the higher number of symptoms reported by the BD group during past manic episodes. For the overlapping symptom grouping from the symptom-based model, and the irritable mania grouping from the factor-based model, both clinical groups had high scores compared to controls, indicating that these clusters both capture shared symptoms. However, only the elevated motor activity item was common between them (overlapping items: motor activity, speech rate, language/thought disorder; irritable mania: motor activity, irritability, disruptive/aggressive behaviour). Scores on item groupings for overlapping symptoms, mood, elevated mania and psychotic mania were all higher for the BD group, compared to both ADHD and control groups.

Overall, these preliminary findings suggest that ADHD and BD might load separately on specific items within the YMRS, and therefore development of a subscale designed to delineate ADHD from euthymic BD in adults may be possible. However, as indicated by our findings, any measure will require a retrospective component to fully delineate ADHD from BD.

4.5.3 Chronicity and validity of symptom measurement

The interview measures provided better discrimination between ADHD and BD. One reason for this is likely to be that an interviewer is able to explore both the nature and time course of symptoms during an interview, to ensure any reported symptoms meet the question criteria. The DIVA measure provides several examples of behaviours associated with each symptom, allowing the interviewer to qualitatively explore each symptom before rating as present or absent. In contrast, the self-report measures only provide a question, but no examples and rely on the interpretation of an untrained person. This means that it is unknown if the items are being scored based on equivalent symptoms, as well as severity of symptoms, within each clinical group. In terms of the time course, the wording in the rating scales is also more ambiguous. For example, the DIVA interview items are scored when symptoms are present for at least six months or more. Although to a lesser extent this is also true of the self-report ADHD measures, the wording of questions is more ambiguous, stating that symptoms should be present *during* the last six months. These ratings could therefore reflect symptoms of any duration during this period, rather than the sustained trait-like symptoms that characterise ADHD.

The YMRS, on the other hand, is designed specifically to evaluate manic symptoms in a short-time window (past 48 hours). Although our findings suggest that this measure would be effective at delineating ADHD from BD as a retrospective measure, or during a BD manic episode, it was not effective at delineating ADHD from euthymic BD based on current symptoms alone. The YMRS therefore has discriminatory potential, and could be adapted either through development of a specific subscale using items which load selectively onto one of the clinical disorders, or by adapting the measure to compare the episodicity of symptoms; thereby making the distinction between chronic trait symptoms of ADHD from the episodic symptoms of BD. Our findings support arguments that chronicity versus episodicity is a key delineating factor between ADHD and BD in adulthood (Skirrow et al., 2012).

4.5.4 Emotional Lability (EL)

EL is associated with both ADHD (Skirrow and Asherson, 2013) and euthymic BD (Judd et al., 2003). Our study supports the view of EL as a largely non-specific set of symptoms that are seen across different disorders, with high EL scores seen in both the ADHD and euthymic-BD groups compared to controls. Indeed, EL occurred at higher rate in the ADHD patients, consistent with the emerging view of EL as an associated feature of ADHD. EL cannot therefore be relied upon to discriminate ADHD from BD. For this reason the current absence of EL from the DSM-5 ADHD criteria, but its inclusion as a characteristic feature of ADHD that supports the diagnosis of ADHD, remains a sensible decision (American Psychiatric Association, 2013). Health care professionals need to be reminded that the classification systems are not designed to capture all aspects of a clinical condition, but to provide an optimal algorithm that helps to

separate one condition from another. In this regard, the DSM-5 ADHD items appear to be more specific to ADHD than the DSM-5 BD items are to BD (particularly if the definition of BD symptoms reflecting a change from the pre-morbid mental state is ignored).

4.5.5 Impairment Ratings

ADHD participants showed more functional impairments than BD and controls, yet the BD group also showed higher levels of impairment compared to controls. This suggests that while impairment is known to be present in both disorders (Brassett-Harknett and Butler, 2007, Samalin et al., 2014), ADHD seem to be more severely impaired than BD patients during periods of euthymia (Judd et al., 2005). Examining retrospective impairment may also be useful at delineating ADHD from BD as evidence suggests that people with BD show normal pre-morbid functioning (Reichenberg et al., 2002), while ADHD is associated with chronic functional impairment throughout lifespan (Brassett-Harknett and Butler, 2007).

4.5.6 Limitations

The samples are relatively small, consisting of selected patients with typical ADHD, typical BD-I and healthy controls, and focuses only on female participants. It is therefore not clear the extent to which these findings will generalise to more complex patients, of both genders, showing features of both ADHD and BD. ADHD is considered to reflect the extreme and impairing tail of a dimensional trait and symptoms commonly may also occur at sub-diagnostic levels (Hudziak et al., 1999, Simon et al., 2009). This means that BD patients are expected to display some ADHD traits as part of a normal population distribution. However, we were

unable to determine if the elevated ADHD symptoms in our BD sample represent a manifestation of BD or an independent subclinical expression of ADHD. Additional replication using prospective approaches would be useful to determine if the development of a subscale based on item grouping in the YMRS has clinical utility for delineating ADHD from BD.

4.5.7 Conclusion

Overall, we show that ADHD is a chronic, impairing disorder, with a high degree of EL and hyperactivity which could be confused with symptoms of mania. Measures such as the DIVA interview which combine both a detailed disorder specific description of ADHD symptoms with a temporal component that captures the distinction between sustained traits and episodic symptoms that reflect a change in the pre-morbid mental state are best at discriminating ADHD from BD. We therefore conclude that interview measures combined with a developmental account of symptoms and impairments provide good discrimination compared to rating scale data, and should always be used as the primary diagnostic tool.

Chapter 5 - Neurophysiological Stimulus Processing
Impairments Distinguish Women with Bipolar
Disorder from Women with ADHD

5.1 Abstract

To better delineate underlying cognitive-neuropsychological differences between attention deficit hyperactivity disorder (ADHD) and bipolar disorder (BD), this study aimed to compare adult women with ADHD or BD and control participants on event-related potential (ERP) components during a conflict monitoring task. Fifty-seven adult women were compared on the Eriksen Flanker task: 18 with ADHD, 20 with BD and 19 controls. We examined the amplitude of the N2 component at Fz and FCz electrodes, and the P2 component at FCz. A group main effect for N2 amplitude emerged at trend level, but with a medium effect size. A post-hoc analysis indicated that the BD group had attenuated N2 power, compared to the ADHD group. Differences in the P2 were significant, with the BD group having an enhanced P2 compared to the ADHD group, and trend-level differences compared to controls. Both N2 and P2 comparisons showed medium effect sizes. This study suggests that the N2 and, particularly, the P2 warrant further investigation as ERP markers for delineating ADHD from BD. Future larger-scale studies may be able to clarify further the underlying cause of N2 attenuation and P2 enhancement in BD, and elucidate the functional relationship of these components to cognitive impairments in ADHD and BD.

5.2 Introduction

In adults, attention-deficit/hyperactivity disorder (ADHD) occurs in around 3% of the population (Faraone and Biederman, 2005), and bipolar disorder (BD) in around 1% (Fajutrao et al., 2009). Although separate diagnoses, ADHD and BD can share symptoms such as distractibility, psychomotor restlessness and talkativeness (Kent and Craddock, 2003, Skirrow et al., 2012). Evidence of mood dysregulation in ADHD, such as irritability and emotional lability, highlights an additional area of overlap (Skirrow and Asherson, 2013). The symptomatic similarities emphasise the need to identify objective biomarkers that can help delineate the boundary between ADHD and BD.

The study of event-related potentials (ERP) permits direct real-time examination of covert brain processes which underlie performance on cognitive tasks. Integral aspects of cognitive behaviour include error detection and conflict monitoring, which support decision making and the modification of behaviour. Performance monitoring has been linked to the N2 component, a negative deflection around 200 - 400 ms post stimulus with a fronto-central scalp distribution; and following errors, the ERN, a fronto-central deflection, which peaks around 50ms post-response, and the Pe, which peaks around 150 - 450 ms post-response with a centro-parietal scalp distribution (Botvinick et al., 2001, Falkenstein et al., 1991, Falkenstein et al., 2000, Larson and Clayson, 2011, Yeung and Cohen, 2006). The ERN, unlike the Pe, is not dependent on the conscious perception of an error (Falkenstein et al., 2000, Nieuwenhuis et al., 2001) supporting links to unconscious stimuli perception, and may represent competing activation between the immediate erroneous response and a subsequent corrective response (Carter and van Veen, 2007, Yeung et al., 2004). The Pe is thought to represent the conscious processing of the erroneous response (Falkenstein et al., 2000, Nieuwenhuis et al., 2001). The N2 may index processes involved with the processing of competing responses as it shows

enhancement when target stimuli are masked with alternate stimuli, representing higher conflict between target and distractor stimuli (Donkers and van Boxtel, 2004, Danielmeier et al., 2009, Nieuwenhuis et al., 2003).

A recent meta-analysis of seven studies using Go/NoGo and flanker tasks to examine ERN and Pe components in adults and adolescents with ADHD concluded that there was support for ERN attenuation in both tasks, and Pe attenuation in the Go/NoGo task (Geburek et al., 2013). Several studies also observe an attenuation of the N2 component in participants with ADHD, compared to controls, in flanker paradigms. N2 attenuation has been reported in children (Albrecht et al., 2008, Johnstone et al., 2009, Wild-Wall et al., 2009), adolescents (McLoughlin et al., 2014b) and adults (McLoughlin et al., 2009) with ADHD, although not in all studies (Johnstone and Galletta, 2013, Jonkman et al., 1999, Jonkman et al., 2007). N2 attenuation in children and adults with ADHD has also been reported using other conflict monitoring tasks, such as the auditory oddball (Barry et al., 2009) and Go/No-Go paradigms (Groom et al., 2008, Woltering et al., 2013), but not in the Continuous Performance Task where level of conflict are lower (Banaschewski et al., 2004, Fallgatter et al., 2004, Overtoom et al., 1998). Overall, there is evidence for attenuated ERN and N2 ERP amplitudes, the neurocognitive correlates of conflict monitoring, in children and adults with ADHD, particularly in flanker tasks, which have higher conflict-monitoring demands. Although some studies have failed to detect differences, many have had small samples, and therefore null findings may be due to limited power or other study/task-specific contextual differences.

To date, few studies have examined the neurobiological correlates of performance monitoring in BD. No published ERP studies using flanker paradigms were identified. One study, however, using the auditory oddball paradigm with participants with psychotic BD reported reduced

amplitude in the target-linked N2 (Ethridge et al., 2012). Symptoms of distractibility and restlessness are associated with manic episodes in BD, yet individuals who are euthymic still demonstrate residual impairments in functional performance (Henry et al., 2013), meaning performance monitoring deficits could be present and detectable using brain-level ERP measures during the euthymic state. However, at present direct ERP comparisons between adults with ADHD or BD are sparse, being limited to one published study of reward processing, which examined an ERN based on negative feedback (FRN) and reward-sensitive P3 in a gambling task (Ibanez et al., 2012). This study found BD and ADHD both showed similar deficits on the FRN compared to controls, while P3 enhancement for a larger reward was attenuated in ADHD and enhanced in BD, compared to controls. Other studies of the cognitive neurophysiological correlates of BD report abnormalities in early unconscious sensory components, such as the mismatch negativity (MMN) and P50, indicating pre-attentive dysfunction (Cabranes et al., 2013, Onitsuka et al., 2013, Swann et al., 2013), as well as sensory gating deficits (Lijffijt et al., 2009, Swann et al., 2013) and enhancement of the later P2 (P200), associated with initial conscious awareness, in BD participants with psychosis, compared to healthy controls (Ethridge et al., 2014). It is therefore likely that BD participants might also show deficits in conscious and unconscious conflict processing and performance monitoring components.

The aim of this study was to directly compare N2, ERN and Pe components during a conflict monitoring task in adults with ADHD, BD and controls. Previous literature suggested that the ADHD group would show attenuated ERN and N2 components compared to controls. However, we were unable to make predictions for the BD group due to the absence of similar studies. Following initial results we also undertook an additional data-driven analysis of the P2 component in these three groups. This study examined differences between the clinical groups in order to better delineate underlying cognitive-neuropsychological differences between

ADHD and BD. In addition, we focus on an all-female sample, in order to match the groups on gender and to address the relatively neglected area of ADHD among adult women.

5.3 Methods

5.3.1 Sample

Sixty adult women aged between 20 and 52 years were recruited into the study. Two ADHD participants were later excluded from the analysis due to poor EEG data quality, and one control participant was excluded because testing notes and performance data indicated she did not perform the task correctly. The final sample was 18 with ADHD, 20 with BD and 19 control participants ($n = 57$). Mean age and IQ did not differ by group (age: mean age (SD): ADHD = 38.1 (7.68), BD = 40.3 (7.68), Control = 36.8 (4.38), $F = 1.35$, $p = 0.27$; IQ: mean (SD): ADHD = 106.2 (16.56), BD = 108.0 (12.50), Control = 112.4 (14.21), $F = 0.93$, $p = 0.40$). Participants with ADHD were recruited from the National Adult ADHD Clinic at the Maudsley Hospital. Participants with BD were recruited from the Maudsley Psychosis Clinic and from a previous research study (Hosang et al., 2012). Control participants were recruited using the Mindsearch volunteer database maintained by the Institute of Psychiatry, which comprises of several thousand potential participants. Participants were randomly selected from all those meeting recruitment criteria. This study was approved by the Camberwell St Giles Research Ethics Committee (approval number 11/LO/0438). All participants provided informed consent.

Diagnosis in the clinical groups was confirmed from medical records, following DSM-IV criteria. ADHD participants had a current combined-type diagnosis or a current inattentive-type diagnosis with sufficient symptoms of hyperactivity in childhood to meet a childhood

combined-type diagnosis. Participants in the BD group had a diagnosis of bipolar I disorder (BD-I), having experienced manic episodes, but were currently euthymic (see chapter 4 for sample recruitment details). Exclusions for all groups were drug or alcohol dependency, autism, epilepsy, neurological disorders, brain injury, past ECT treatment, current involvement in treatment trials, pregnancy, or a limited proficiency in English language, as determined by an initial screening prior to recruitment and with reference to the participant's medical records. Those with a diagnosed comorbidity of both ADHD and BD or those currently experiencing a manic episode were excluded. Control participants with a history of psychiatric disorders were also excluded. ADHD participants were asked to not take stimulant medication 48 hours before testing. BD participants were not asked to stop taking mood-stabilisers or any anti-psychotic medication they had been prescribed, as it would not be ethical to do so. Information on participants' current medication usage was collected in order for us to try to determine the effect of medication in ERP data. All participants were asked to refrain from caffeinated drinks and nicotine two hours prior to the testing session.

5.3.2 Procedure

Participants attended a single 4.5 hour research session (including breaks) for cognitive-EEG assessments, IQ assessment and clinical interviews. Prior to completing the Eriksen Flanker Task (Albrecht et al., 2008, McLoughlin et al., 2009), participants completed 2 x 3 minute resting state recordings and a Continuous Performance Task (Doehnert et al., 2008).

5.3.3 Tasks

The task was an adaption of the Eriksen Flanker paradigm designed to increase cognitive load (Albrecht et al., 2008, McLoughlin et al., 2009). In each trial a central black fixation mark was replaced by a target arrow (a black 18 mm equilateral triangle). Participants had to indicate whether this arrow pointed towards the left or right by pressing corresponding response buttons with their left or right index fingers. 100 ms prior to each target arrow, two flanker arrows identical in shape and size to the target appeared 22 mm above and below the centre of the target arrow. Both flankers either pointed in the same (congruent) or opposite (incongruent) direction to the target. As such, conflict monitoring is maximal during the incongruent condition. When the target appeared, both target and flankers remained on the screen for a further 150 ms, with a new trial being presented every 1650 ms. Trials were arranged in ten blocks of 40 trials. The duration of the task was approximately 13 minutes.

Congruent versus incongruent and the direction of responses (left versus right) were counter-balanced and randomised. After each block, feedback was presented on screen to emphasise both speed and accuracy, in order to encourage participants to make enough errors to enable analysis of ERN/Pe components, and enough correct responses for analysis of N2 components. Where participants made >10% errors on congruent or >40% errors on incongruent trials, they were instructed to slow down. Where participants made <10% errors on congruent or <40% errors on incongruent trials, they were instructed to perform faster. If neither rule applied, feedback informed participants to continue the same way. Two practice blocks of 24 trials were administered before the real task. Where necessary, participants were told to minimise movement or blinking.

The Wechsler Abbreviated Scale of Intelligence Fourth Edition (WASI-IV; (Wechsler, 1999)) was administered to all participants to derive an estimate of IQ.

5.3.4 EEG recording and statistical analysis

Recording and analysis parameters from McLoughlin et al. (2009) were adopted. The EEG was recorded from a 62 channel DC-coupled recording system (extended 10–20 montage), using a 500 Hz sampling-rate, impedances under 10 k Ω , and FCz as the recording reference. The electro-oculograms (EOGs) were recorded from electrodes above and below the left eye and at the outer canthi.

EEG data were analysed using Brain Vision Analyzer 2.0 (Brain Products, Germany). Researchers were blind to group status during processing prior to analysis. Raw EEG recording were down-sampled to 256 Hz, re-referenced to the average of all electrodes, and filtered using Butterworth band-pass filters (0.1 to 30 Hz, 24 dB/oct). Ocular artefacts were identified using the infomax Independent Component Analysis algorithm (ICA; (Jung et al., 2000)). Sections of data containing artefacts exceeding $\pm 100 \mu\text{V}$ in any channel or with a voltage step greater than $50 \mu\text{V}$ were rejected. All trials were also visually inspected for other obvious movement or electrical artefacts, and sections containing these removed manually.

Data were segmented based on two different response conditions: (1) stimulus-locked incongruent correct trials, and (2) response-locked incorrect trials. Individual averages were created based on each condition, requiring at least 20 clean segments for each participant.

Baseline correction was applied using the -300 to -100 ms pre-target interval (-200 to 0 ms pre-flanker). After averaging, mean amplitude was calculated within a designated window defined by reference to the grand average. For the N2, a 100 ms window was used at 250-350 ms from flanker onset, as this window captured all N2-like components from individual participants.

After processing error trials, only 31 participants had the necessary 20+ clean segments required for producing reliable grand averages (ADHD = 10, BD = 10, Control = 11). We reviewed grand averages created using lower thresholds of 15 and 10 clean segments (with samples of 40 and 51 participants respectively), but as the ERN and Pe components varied between averages generated using 10, 15, and 20 segment thresholds, we did not consider these suitable for further analysis (graphs S10, supplementary material). We therefore focus on N2 response to correct trials where a higher number of clean segments were available. We analysed data from the incongruent condition only, as our previous investigation showed an absence of ADHD-control differences in the congruent condition where conflict was minimal (chapter 3). The number of clean segments available did not differ significantly by group (mean (SD): ADHD = 133 (39), BD = 140 (42), control = 160 (27); $F(2,56) = 2.37$, $p = 0.10$). N2 amplitude data were normally distributed. Maps of the topographical scalp distribution of activity revealed that the N2 component was maximal at fronto-central electrodes (Figure 5.1). We analysed stimulus-locked N2 peaks at Fz and FCz, with ANOVA carried out in SPSS (factors: group and site (Fz, FCz)).

As there is evidence of abnormalities in early sensory components in BD, and based on results from the N2 analysis and grand averages, we conducted an additional data-driven analysis on the P2 component recorded at FCz. We analysed the mean amplitude 150 - 250 ms after stimuli presentation, using ANOVA (factors: group and site). P2 mean amplitude data was

normally distributed. For standard statistical tests, we present both p-values and effect sizes (eta squared; η^2). Based on Cohen's (1988, p.283) estimates for η^2 , 0.0099 constitutes a small effect, 0.0588 a medium effect and 0.1379 a large effect. As both windows were 100 ms in duration we were able to carry out P2-to-N2 average power comparisons; an area-based equivalent of a peak to peak comparison. N2 mean amplitude was subtracted from P2 mean amplitude to give an indication of amplitude change between these two components. Group differences were compared using univariate ANOVA. To assess if participants' current treatments may have influenced N2 or P2 mean amplitude, we also calculated the means and effect size for those taking and not taking certain classes of medication (mood stabiliser, anti-depressant, anti-psychotic, and stimulant) within each group.

Performance measures were total number of errors (error), target reaction time (MRT, i.e. mean latency of responding in ms after target onset), within-subject variability in reaction times (RTV, SD of RTs) and total number of omission errors (non-responses to target). All measures except total omission errors were compared at congruent and incongruent conditions separately. As performance variables were non-normally distributed, the most effective transformation was adopted for each; square root for commission errors, inverse for MRT and logarithm for RTV and omissions errors. Univariate ANOVAs were employed to test for group differences within each measure, with repeated-measures ANOVA being used to examine condition differences for commission errors, MRT and RTV.

5.4 Results

A greater number of errors ($F(1, 54) = 319.83, p < 0.001$), higher MRT ($F(1, 54) = 677.49, p < 0.001$) and RTV ($F(1, 54) = 677.49, p < 0.001$) were observed in the incongruent, compared to the congruent, condition. However, no significant group differences were observed in either condition for commission errors, MRT or RTV, or total number of omission errors (Table 5.1).

A trend-level group difference emerged for N2 amplitude which showed a medium effect size ($F(1,54) = 2.61, p = 0.08, \eta^2 = 0.0881$). Post-hoc analysis indicated that the BD group had a significantly attenuated N2 compared to the ADHD group ($p = 0.04$), with the attenuation compared to controls at trend level ($p = 0.08$). ADHD and control groups did not differ significantly ($p = 0.76$). A significant main effect of site (Fz, FCz) also emerged, with the N2 being greatest at FCz ($F(1,54) = 9.16, p = 0.004, \eta^2 = 0.1404$), with no group and site interaction observed ($F(2,54) = 1.05, p = 0.36, \eta^2 = 0.0066$).

Table 5.1. Mean scores, standard deviations (in brackets) for behavioural performance measures.

Condition	Mean (SD)			F (1,54)	p
	<i>ADHD</i>	<i>BD</i>	<i>Control</i>		
Omission errors (all)	5.88 (7.36)	8.55 (15.47)	4.47 (5.86)	0.31	0.74
Commission errors congruent	8.44 (20.1)	6.35 (12.98)	6.37 (10.98)	0.19	0.82
Commission errors incongruent	37.89 (19.88)	32.4 (22.56)	30.53 (15.36)	0.93	0.40
MRT hits congruent	374.03 (39.19)	375.52 (47.67)	360.41 (44.88)	0.85	0.43
MRT hits incongruent	463.73 (57.1)	467.46 (51.31)	451.15 (45.88)	0.46	0.63
RTV hits congruent	95.43 (31.3)	87.71 (29.08)	82.07 (32.13)	1.285	0.29
RTV hits incongruent	102.65 (26.61)	99.63 (26.88)	96.89 (31.69)	0.30	0.74

MRT (mean reaction time to correct hits in milliseconds); RTV (variability of reaction time for correct hits in milliseconds).

Figure 5.1. Grand average event related potentials to correct trials, showing attenuated N2 response (negative-peak within greyed section) in the bipolar group compared to ADHD and control groups. Scale shows ms from target, flankers stimuli precede target by 100ms.

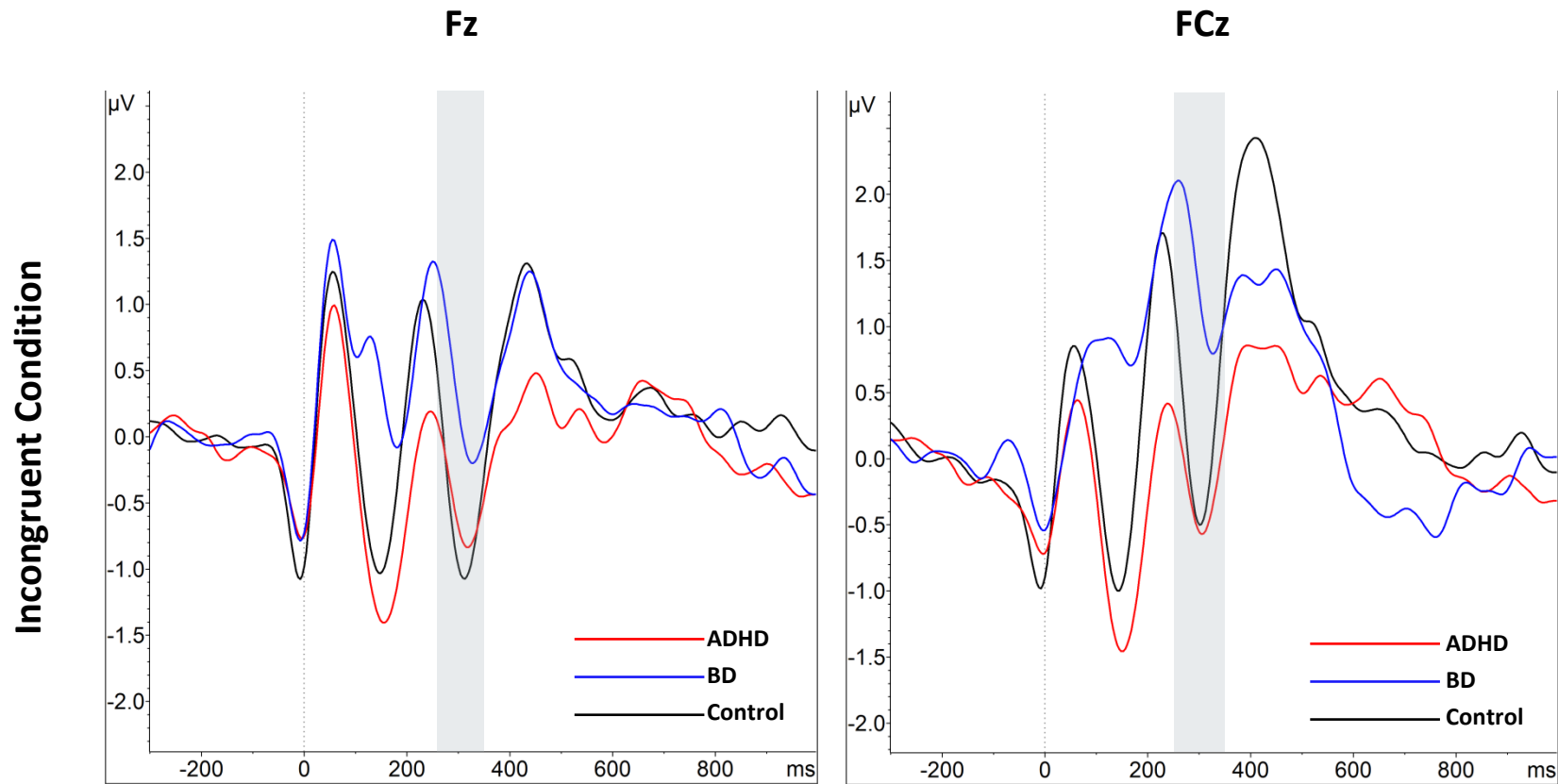
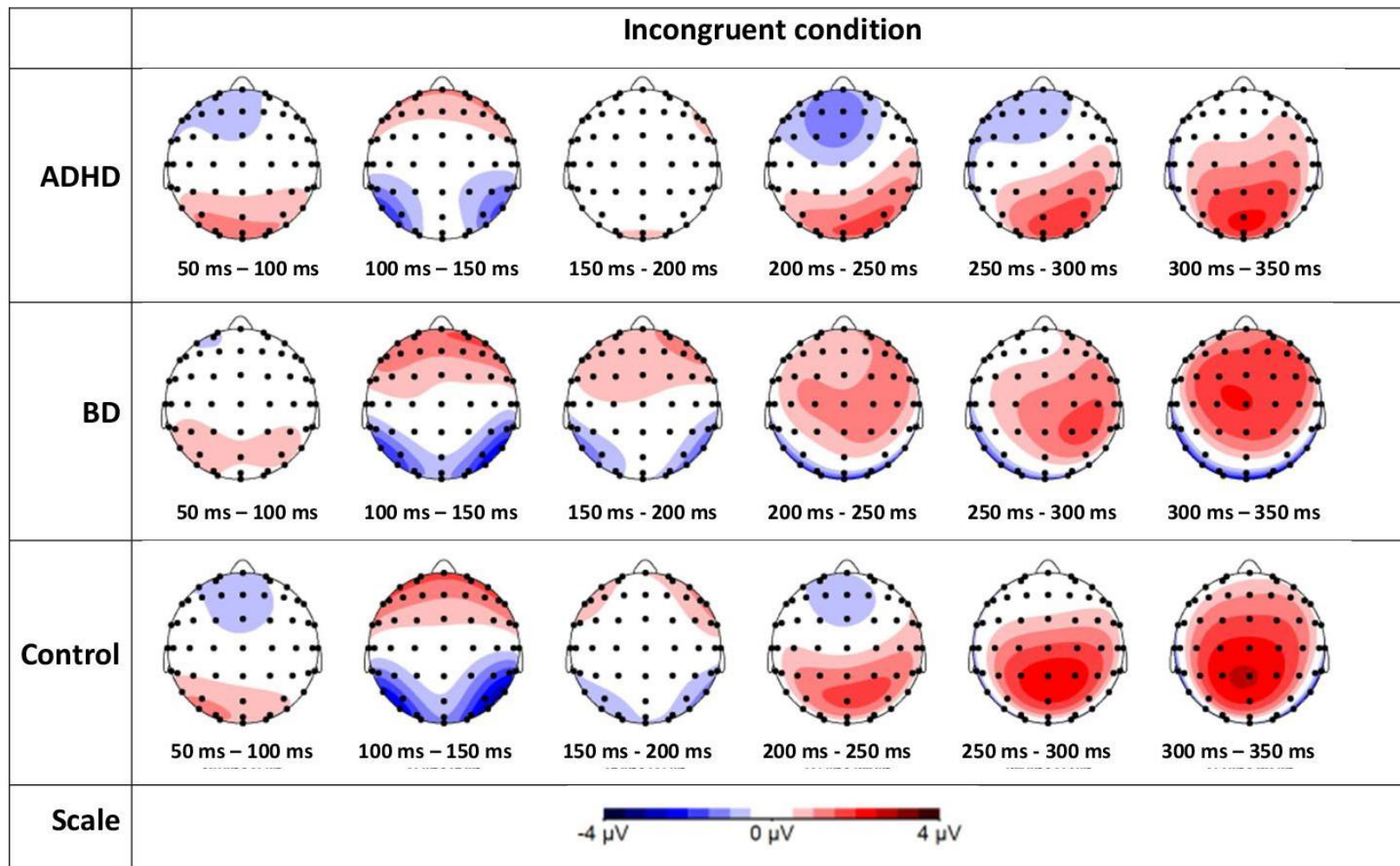


Figure 5.2. Topographic maps of amplitude change over time in the N2 window measured from flanker onset, showing a frontal-central negative component (N2) in the ADHD and controls groups but not the bipolar group, which instead showed a stronger preceding centralised



Topographic maps indicated a clear N2 frontal-central negative component in the ADHD and control groups, which was not apparent in the BD group (Figure 5.2, 200 - 250 ms). Instead, the BD group showed a persistent fronto-central P2 component (apparent in Figure 5.2 at 150 - 200ms), followed by centralised positivity during the N2 time window. To examine group differences in this preceding P2 component, we undertook an additional analysis to examine P2 mean amplitude between 150 - 250 ms after stimulus presentation. A group difference with a medium effect size was observed in P2 mean amplitude at FCz ($F(2,59) = 3.40, p = 0.04, \eta^2 = 0.1120$), with the BD group showing a higher amplitude than the ADHD group ($p = 0.012$) but not the control group ($p = 0.35$).

Comparison of amplitude change between P2 and N2 (P2-N2 complex) indicated a trend-level group difference with a medium effect size ($F(2,54) = 3.05, p = 0.06, \eta^2 = 0.1015$). Post-hoc comparisons showed the BD group to have reduced amplitude change compared to the ADHD group ($p = 0.02$), with the reduction compared to the control group being at trend-level ($p = 0.08$). The ADHD and control groups did not differ in mean amplitude difference between the P2 and N2 ($p = 0.57$)

Table 5.2. Group means and standard deviation (in brackets) of N2 and P2 mean amplitude, and P2-to-N2 change in mean amplitude, in the incongruent condition.

		ADHD	BD	Control
N2 (μV)	Fz	-44.64 (171.44)	42.02 (208.49)	-47.44 (171.93)
	FCz	-20.29 (178.95)	140.21 (236.87)	19.49 (206.28)
P2 (μV)	FCz	-0.48 (1.43)	1.22 (2.19)	0.60 (2.28)
P2-N2 (μV)	FCz	19.81 (177.96)	-139.00 (235.10)	-18.89 (204.43)

A proportion of both clinical groups were taking anti-depressant medication (ADHD: 17%; BD: 40%). Some participants in the BD group were also taking other treatments (mood stabiliser: 70%; anti-psychotic: 40%). Of the ADHD participants, 72% were being treated with stimulant medication, but ceased treatment 48-hours prior to testing. Within-group samples were too small for statistical comparisons; however, effect size calculations indicated that in the BD group mood stabilisers may have had a medium effect increasing positivity for N2 and P2 mean amplitude (i.e. reducing N2 negativity), anti-depressants may have had a small effect increasing the negativity of N2 mean amplitude, while anti-psychotics showed limited effect on either N2 or P3. In the ADHD group, comparison groups were very small and must be cautiously interpreted; however, anti-depressants may have had a large effect increasing negativity of N2 and P2 components, while previous treatment with stimulant medications may have had a medium effect in attenuating the N2 and small effect in attenuating the P2 (supplementary material table S11).

5.5 Discussion

We report suggestive evidence for an attenuation of the N2 in women with BD during the Flanker task, which was not observed in women with ADHD or control women. Although the group main effect was at a trend level, the effect size for N2 differences was medium and the post-hoc comparison between BD and ADHD groups emerged as significant. Additional analyses further suggested that the attenuated N2 may be linked to the preceding positive P2 component, which was elevated in the BD group, compared to the ADHD group. Together, these findings indicate potential neurophysiological impairments in women with BD that distinguish them from women with ADHD.

In relation to potential N2 differences between ADHD and BD groups, computational modelling by other groups suggests that the N2 represents dominant correct response programming before response, which is then reinforced by continued stimulus processing (Yeung and Cohen, 2006). In this computational model, N2 amplitude is dependent on levels of conflicting incorrect response processing (i.e. attending to the flanker stimuli) and thus the level of correct response processing needed to overcome this. In our study, if interpreted using this cognitive model, it would suggest that the BD group was experiencing reduced levels of conflict processing compared to ADHD and potentially the control group. Yet, our finding of an enhanced preceding P2 component in the BD group suggests that N2 attenuation in this group may not be due to differences in conflict monitoring, but rather potentially differences in initial conscious perception of the stimuli, compared to the ADHD group. As ERP components are additive, the preceding positive P2 component in the BD group would reduce the negativity of the N2 component at the scalp, which may otherwise be typical without the presence of this enhanced positivity.

Our grand averages suggest that the P2 had similar amplitude in both BD and control groups, while the topographic maps show that in the BD group there is an additional persistence to this component not seen in ADHD and control groups. Although we were unable to directly examine component latency in this study (due to adopting a mean amplitude measure which can be more robust than peak amplitude to the intra-individual variability across trials common in ADHD, which may reduce the amplitude of ERP components (McLoughlin et al., 2014a)), the grand averages were suggestive of latency differences in the P2 component in the BD group. One possibility is that this might be related to desynchronised frontal midline theta

oscillations (McLoughlin et al., 2014b) or early pre-attention and sensory gating deficits frequently reported in BD (Cabranes et al., 2013, Swann et al., 2013, Lijffijt et al., 2009).

As amplitude change between P2 and N2 appeared greatest in the control group, we carried out comparison of a combined P2-N2 statistic, which showed the ADHD group to differ from the BD group, with an additional trend level difference between BD to control groups. This P2-N2 component therefore seemed to have some validity in distinguishing BD from the other groups, and may be a useful measure of the range of amplitude change between P2 and N2 components in this paradigm.

We did not identify N2 differences between ADHD and control groups that had been reported in previous studies (Albrecht et al., 2008, Johnstone et al., 2009, McLoughlin et al., 2009, McLoughlin et al., 2014b, Wild-Wall et al., 2009). This could relate to sample differences, as the current study is the first one, to the best of our knowledge, with adult female participants. The only other previous study on adults with ADHD consisted of male participants (McLoughlin et al., 2009). The ERN, the equivalent component to the N2 elicited by errors, shows developmental changes in amplitude, increasing from childhood to adolescence and then decreasing in older adults (Falkenstein et al., 2001, Herrmann et al., 2010, Segalowitz and Dywan, 2009). It is therefore possible that the N2 shows similar developmental differences across lifespan which may reduce differences between ADHD and controls in older samples, perhaps contributing to that absence of differences in this sample which had a higher mean age than the other adult sample of McLoughlin et al. (2009). Future studies should therefore attempt to explore potential gender and age differences in N2 amplitude across lifespan in a

larger mixed sample, in order to understand if potential developmental effects on the N2 follow similar patterns of the ERN.

We cannot rule out the possibility that our results would have been influenced by the systemic medication differences between groups. Addressing treatment effects on ERP power is challenging in cross-disorder investigations, where ethical restrictions limit experimental manipulation of prescribed medication. Specifically, in our study, as in similar previous studies, it would have been unethical to request participants with BD to stop mood-stabilising or anti-psychotic medication prior to the assessments. Our BD group showed reduced N2 and enhanced P2 amplitude, using a novel paradigm for this sample, of whom 70% were taking mood-stabilising and 40% anti-psychotic medication, which could potentially have contributed to these ERP differences. The full effects of medications on ERPs are still poorly understood, with most studies in both clinical and control populations focusing on the effect of medications on the P3 component, suggesting anti-depressant, clozapine antipsychotic medication, and mood-stabilisers may normalise the P3 component in psychiatric disorders (Anderer et al., 2002b, Anderer et al., 2002a, Karaaslan et al., 2003, Barratt et al., 2003, Galletly et al., 2005, Umbricht et al., 1998, Urasaki et al., 1994, Tumay et al., 2013, Smith et al., 2006). For the P2, there is some evidence that both mood stabilisers and anti-depressants may normalise the P2 in BD compared to controls (Ethridge et al., 2014, Swann et al., 2013). In this study, although we were not able to perform tests of statistical significance due to small numbers in the sub-groups (supplementary material table S11), effect sizes were suggestive of the influence of mood-stabilisers being one of increasing ERP positivity (i.e. attenuation the N2 and enhancing the P2), while the influence of anti-depressant medication to be one of increasing negativity of the N2 component (i.e. enhancement). This suggests that the effect of medication use on N2 and P2 components in these disorders is likely to be complex, and we acknowledge this factor

as a potential confound of our study. Subsequent studies will require samples which are medication naive or non-adherent to their treatment, in order to fully determine if our findings represent a potential objective marker for BD, a medication effect, or a contribution of both.

Our sample, being a pilot investigation, consisted of relatively small samples, with modest differences being identified. Replication using a sample with additional power, or methods which provide an improved signal-to-noise ratio, such as single-trial source-based measures (McLoughlin et al., 2014a), are now necessary to confirm results. We were also unable to examine the ERN/Pe components due to insufficient number of clean error trials post-processing. Higher numbers of errors could be obtained by increasing the difficulty or duration of the task to allow analysis of these components. Further group comparisons using the novelty oddball task, which is known to elicit the P3 component and has been previously used in the study of BD (Fridberg et al., 2009), would be useful to provide a broader context to ADHD-BD ERP comparisons.

In conclusion, we show that in this adult female population there is suggestive evidence of N2 attenuation in the BD group, which may be linked to significantly elevated P2 amplitude in the BD group, compared to the ADHD group. Future studies can investigate whether this could reflect early sensory processing deficits previously observed in BD, or alternatively potential slow-wave synchronicity differences, warranting further investigation of these ERP markers for delineating ADHD from BD.

Chapter 6 - The Allocation of Attentional Resources and Theta Activity as Candidate Discriminators of ADHD and Bipolar Disorder

6.1 Abstract

This study aimed to investigate if attentional resource allocation processes in Attention Deficit Hyperactivity Disorder (ADHD) and Bipolar Disorder (BD) differ, despite symptomatic similarities in attentional deficits. Over-allocation of attention resources to task-irrelevant stimuli, such as novel distractors or non-target stimuli, may interfere with task-relevant processing in these disorders, underpinning common behavioural performance and cognitive electrophysiological deficits; yet direct comparisons between these disorders remain limited. Fronto-central theta power, an index of cortical activation, may also be associated with the efficiency of attentional resource allocation in psychiatric and control populations. This study compared P3a and P3b event related potential components, which are indices of attentional resource allocation, and fronto-central theta power in adults with ADHD and BD. Participants were tested on an auditory novelty oddball task, consisting of frequent non-target tones, infrequent target tones and novel distractor sounds. P3b at Pz was measured in the target condition, and the P3a at FCz was measured in the novel condition. Estimates of theta power (3.5 - 7.5 Hz) at FCz were calculated in both conditions. The sample consisted of 59 adult women, 19 of whom had ADHD, 20 had BD and 20 were control participants. Group differences in P3a or P3b amplitude were not significant, and small effect sizes were present

between the psychiatric groups and controls for the P3b, and between the BD group and other groups for the P3a. Theta activity showed a main effect of condition, being greater in the novel compared to targets condition, but no significant effect of group status was detected. Theta power correlated significantly with P3b amplitude in the ADHD group but not in the other groups. At the performance level, the BD group also had elevated mean reaction times to target stimuli (MRT) compared to the ADHD and controls groups, but groups did not differ on variability of reaction times. Overall, we were unable to identify statistically discernable group differences in ERP amplitude or theta power between ADHD, BD and control groups in this sample of adult women using the oddball task, although we identify candidates for further study, particularly P3a amplitude in the novel condition, which was correlated with theta power in the ADHD group, but not in the BD or control groups. Both theta power and the P3a component have been linked independently to attentional processes in ADHD, and the relationship between them may be an important avenue for future investigation. The older age of this sample, compared to many other studies of ADHD, or potentially gender effects, might account of the null findings in this study. We also report that MRT to targets was able to discriminate BD from ADHD in this sample of adult females.

6.2 Introduction

Attention-Deficit Hyperactivity Disorder (ADHD) is characterised by lapses in attention, poor focus, and hyperactivity. These characteristics overlap with some symptoms of Bipolar Disorder (BD), such as heightened distractibility and restlessness, which can appear as behaviourally similar to the symptoms of ADHD, even during euthymic periods (Henry et al., 2013, Kent and Craddock, 2003, Kitsune et al., submitted, chapter 4, Skirrow et al., 2012). The underlying neurophysiological patterns, which give rise to these symptoms, are yet to be

elucidated but may relate to attentional resource allocation deficits or inefficiencies (Kok, 2001, Kramer et al., 1985, Sawaki and Katayama, 2006). No direct comparison of attentional resource allocation between ADHD and BD has been carried out to our knowledge but is needed to clarify the functional processes in either disorder, and to address questions as to whether abnormalities are related to deficits in a common attentional neurocognitive system or whether common behavioural deficits arise from divergent neurocognitive processes, representing markers useful in the delineation of ADHD and BD.

The study of event-related components (ERP) and electroencephalography (EEG) power is ideally suited to indexing sub-second cognitive processes such as attentional orientation. The P3 (P3b) is a commonly studied ERP component thought to represent conscious stimulus evaluation and memory updating (Polich, 2007). As an attention-driven comparison process, the P3b indexes the allocation of attentional resources, as P3b amplitude decreases inversely with secondary task difficulty (Kok, 2001, Kramer et al., 1985). Most consistently studied in the oddball paradigm, the P3b shows higher amplitude following an uncommon target stimulus than task-irrelevant non-target stimuli, and manifests as a large positive deflection in summed potential between roughly 200-800ms, peaking at around 300ms, at the central parietal electrode (Pz) (Polich, 2007).

A second P3 component, the P3a, is thought to represent unconscious attentional orientation to unpredictable changes and is elicited by infrequent novel stimuli (Snyder and Hillyard, 1976, Squires et al., 1975). This component habituates rapidly, has a shorter peak latency around 250-400 ms, and is maximal at fronto-central electrodes (Courchesne et al., 1975, Polich,

2007). As with the P3b, P3a amplitude has been shown to vary with experimental conditions such as task difficulty (Katayama and Polich, 1998), and is larger following non-familiar distractors than familiar ones (Polich, 2007).

Abnormalities in the P3 components have been argued to be markers of psychiatric psychopathology (Carlson et al., 1999, Ford, 1999, Jahshan et al., 2012, Jeon and Polich, 2003, Porjesz et al., 2005). Widely studied in schizophrenia research, indications are that P3a and P3b amplitude attenuation relates to reduced processing resources or deficits in attentional resource allocation (Grillon et al., 1990). In BD, attenuated P3b amplitude has been observed in the auditory oddball paradigm for participants with Bipolar I Disorder (BD-I), the more severe form of the disorder (Bestelmeyer et al., 2009, Bestelmeyer, 2012), and their relatives (Pierson et al., 2000) but not in those with Bipolar II Disorder (BD-II), a less severe form of the disorder (Andersson et al., 2008). Comparisons between participants with BD and schizophrenia suggest that P3b deficits are unable to distinguish the two disorders, leading to suggestions that P3b attenuation may be a marker for psychosis-associated neurophysiology in both BD and schizophrenia (Bestelmeyer et al., 2009, Ethridge et al., 2012). This is compatible with cognitive models of the P3b as an index for attentional resource allocation, as psychosis would interfere with the normal attentional response, and therefore alter P3b amplitude. Fewer studies have examined the P3a in BD, but those that have indicate attenuation in both participants with BD-I and BD-II using the three-stimulus auditory oddball paradigm (Andersson et al., 2008, Jahshan et al., 2012), although no P3a amplitude differences are identified using visual equivalent of the same paradigm (Bestelmeyer, 2012).

P3 components have been more widely studied in ADHD owing to their relevance to attentional processing deficits. However, few studies have examined P3 amplitude in adults, with the available data being limited to Go/NoGo and Continuous Performance Tasks (CPT) which show evidence for P3b attenuation in ADHD (Szuromi et al., 2011); yet data from adult females with ADHD is particularly sparse. Attenuated P3b amplitude, compared to controls, has been reported in children and adolescents with ADHD in the auditory oddball task in some studies (Barry et al., 2003, Holcomb et al., 1986, Johnstone and Barry, 1996, Jonkman et al., 1997, Ozdag et al., 2004), but not others (Hermens et al., 2005c, Groom et al., 2008, Lazzaro et al., 1997, Lazzaro et al., 2001). Studies of the P3a are much more limited but there are reports of amplitude attenuation in children and adolescents with ADHD compared to controls on the oddball paradigm, and other tasks using novel auditory distractors (Gumenyuk et al., 2004, Gumenyuk et al., 2005, Kemner et al., 1996). Some evidence also exists for an elevated P3a response to novelty in adults with ADHD (Marzinzik et al., 2012). Age has been cited as the possible factor in the heterogeneity of results to date (Barry et al., 2003), although this has not been examined directly in developmental studies.

Potential P3 abnormalities in ADHD, BD and other disorders could be the result of an inefficient allocation of the limited attentional resources available (Sawaki and Katayama, 2006). For example, allocation of attentional resources to task-irrelevant stimuli such as novel distractors or non-target stimuli may interfere with task-relevant processing, particularly when target and non-target stimulus are similar, manifesting as a reduced P3b amplitude on target trials. Behavioural performance in ADHD supports this model, with ADHD participants often showing lower target hit rate, longer mean reaction times to targets, and increased commission errors to non-targets and novel stimuli, suggesting interference with task-relevant processing (Holcomb et al., 1986, Nigg, 2005, Sergeant et al., 2002). This model assumes that

efficient allocation of attentional resources is represented by a large P3b response to targets. It is currently unclear if this model extends to the P3a response to novel stimuli, as although this component is thought to be engaged in an independent orienting response from the memory updating response to repeated target and non-target stimuli (Polich, 2007), this process may be influenced by attentional resource allocation deficits if these behaviours involve multiple related processes. However, support for a distinction in these processes comes from a study which showed that the P3a was elicited even when novel stimuli are task-relevant, and therefore could not be contributing task-irrelevant interference (Debener et al., 2005).

Elevated frontal-central theta activity (3.5 - 7 Hz) has also been reported in ADHD during attentional tasks (Hermens et al., 2005b). Specifically, fronto-central theta has been implicated in response to novelty during trials eliciting the P3a (Demiralp et al., 1999, Fallahpour et al., 2010). In ADHD, fronto-central elevated theta power compared to controls is reported in response to target stimuli in the oddball paradigm (Fallahpour et al., 2010), while in contrast, attenuated theta in relation to targets has been reported in oddball paradigm in BD (Atagun et al., 2013). Elevated frontal-central theta may be associated with deficits in the orientation to task-relevant information (Basareroğlu et al., 1992, Yordanova and Kolev, 1998), and has also been implicated in arousal regulation in resting state conditions (Lazzaro et al., 1999). Recent work is supportive of a relationship between fronto-central theta activity, attention and behavioural performance, showing that increased variability of reaction times in ADHD, thought to be caused by lapses in attention, and theta activity are phenotypically and genetically linked (McLoughlin et al., 2014b). Further examination of fronto-central theta activity in relation to P3 indexes of attention, may therefore clarify if theta power is associated with attentional resource allocation in psychiatric and control populations.

This study aimed to investigate if attentional resource allocation processes in ADHD and BD were similar in light of symptomatic similarities in attentional deficits. We compare P3a amplitude to novel stimuli and P3b amplitude to target stimuli between groups. In addition, we also examine stimulus-linked fronto-central theta activity in novel and target conditions, to investigate the relationship between theta and attentional resource allocation in these disorders. We predict that greater theta activity will be observed in the novel condition compared to targets in ADHD, BD and control groups. Based on previous literature, in both novel and target conditions, we expected the ADHD group to show elevated theta power compared to controls, while we predicted the BD group to have reduced theta power, compared the control group.

6.3 Methods and Materials

6.3.1 Sample

One participant with ADHD was excluded from the analysis due to poor data quality. The final sample consisted of 19 with ADHD, 20 with BD and 20 control participants (n=59). Participants were aged between 20 and 52; mean age or IQ did not differ by group (age: mean (SD): ADHD = 38.1 (7.68), BD = 40.3 (7.68), Control = 36.8 (4.38), $F = 1.35$, $p = 0.27$; IQ: mean (SD): ADHD = 106.2 (16.56), BD = 108.0 (12.50), Control = 112.4 (14.21), $F = 0.93$, $p = 0.40$).

Participants with ADHD were recruited from the National Adult ADHD Clinic at the Maudsley Hospital. Participants with BD were recruited from the Maudsley Psychosis Clinic and from a previous research study (Hosang et al., 2012). Control participants were recruited using the Mindsearch volunteer database maintained by the Institute of Psychiatry, and were randomly selected from all those meeting recruitment criteria. This study was approved by the Camberwell St Giles Research Ethics Committee (approval number 11/LO/0438). All participants provided informed consent. Further details of the recruitment process are available in Kitsune et al. (submitted, chapter 2).

6.3.2 Procedure

Participants attended a 4.5 hour research session (including breaks) for cognitive-EEG assessments, IQ assessment and clinical interviews. Prior to completing the oddball task, participants completed 2 x 3-minute resting state recordings, a Continuous Performance Task (CPT)(Doehnert et al., 2008), and a variant of the Erikson Flanker task (Albrecht et al., 2009) in a fixed order.

6.3.3 Measures

Participants completed an auditory novelty oddball task, adapted from Laurens et al. (2005), consisting of 300 frequent non-target stimuli (1000 Hz tone), 50 infrequent target stimuli (1500 Hz tones) and 50 infrequent, unique non-repeating novel stimuli, consisting of digital noises such as whistles, buzzes and trills. The non-target, target and novel stimuli were presented

with a probability level of 0.75, 0.125, and 0.125, respectively. All stimuli had a duration of 200 ms, with 5 ms rise / 10 ms fall, and were separated with a random inter-trial interval of between 1000-1500 ms (average 1250 ms). The order of presentation was pseudorandom, while ensuring that no two low probability stimuli (target or novel) occurred consecutively. Stimuli were presented in eight blocks of 50 stimuli, with a short rest period between each block. Total task duration was approximately 12 minutes. Presentation of stimuli was via headphones at 90 dB sound pressure level. During recording participants were asked to still sit with their eyes-open and focused on a static fixation mark on a screen directly in front of them. Participants responded to targets by pressing a button with the thumb of their dominant hand. They were instructed to respond as quickly as possible to target stimuli, and not to respond to the infrequent novel and frequent non-target stimuli. Prior to recording, participants were familiarised with the paradigm using a 35 sec practice session to ensure comprehension.

Responses to target stimuli within 100-1000ms from onset were counted as correct response; failure to respond within this time window was registered as an omission error. Errors of commission were responses which occurred within 1000ms of the onset of a novel or non-target stimuli.

The Wechsler Abbreviated Scale of Intelligence Fourth Edition (WASI-IV)(Wechsler, 1999) was administered to all participants to derive an estimate of IQ.

6.3.4 EEG recording and analysis

The EEG was recorded from a 62 channels DC-coupled recording system (extended 10–20 montage), using a 500Hz sampling-rate, impedances under 10k Ω , and FCz as the reference electrode. The electro-oculograms (EOGs) were recorded from electrodes above and below the left eye and at the outer canthi.

The EEG data were analysed using Brain Vision Analyzer (2.0) (Brain Products, Germany). Raw EEG recordings were down-sampled to 256 Hz, re-referenced to the average of all electrodes, and digitally filtered using Butterworth band-pass filters (0.1 to 30 Hz, 24 dB/oct). Ocular artifacts were identified using an Infomax Independent Component Analysis algorithm (ICA, (Jung et al., 2000)). All trials were also visually inspected for other subtle artefacts, caused by muscle movements or jaw clenching etc., and sections containing these manually removed. Data with other artifacts exceeding $\pm 100 \mu\text{V}$ in any channel or with a voltage step greater than $50 \mu\text{V}$ were rejected. Any peripheral channels removed due to technical problems or electrical noise were replaced using topographic interpolation following the ICA step.

Raw EEG files were segmented based on: 1) target stimuli followed by a correct response and 2) novel stimuli without commission errors. Segments were stimulus-locked, of -200 ms to 1000 ms duration, and baseline corrected using the -200 to 0 ms pre-stimulus interval. Individual participant averages were created for each condition, but required at least 20 clean

trials for inclusion in the analysis. After averaging, mean amplitude was calculated within a designated window defined by reference to the grand average. Mean amplitude (μV) was calculated between 200 - 500 ms in novel condition at FCz in order to capture the P3a component and between 200 - 800 ms at Pz for the P3b component in target condition. Selection of electrodes were based on location of the maximal power on the scalp topographies within these time windows for the component of interest (Figure 6.1). Frontal mean theta power ($\mu\text{V} * \text{ms}$) between 3.5-7 Hz was calculated at FCz using Fast Fourier Transform (FFT), and then analysed in novel and target conditions separately.

The number of clean segments available did not differ significantly by group in the novel condition (mean (SD): *ADHD* = 46.8 (3.35), *BD* = 46 (3.53), *control* = 46.9 (2.29); $F(2,56) = 0.58$, $p = 0.56$). However, a group difference emerged for the number of clean segments available in the target condition (mean (SD): *ADHD* = 43.6 (4.97), *BD* = 40.4 (7.62), *control* = 45.1 (3.78); $F(2,56) = 3.63$, $p = 0.03$). There were no differences in number of segments between *ADHD* and *BD* groups ($p = 0.22$) or *ADHD* and *control* groups ($p = 0.81$), though the *BD* group had fewer clean segments available for analysis compared to *controls* ($p = 0.03$). However, all groups had sufficient number of segments for analysis.

6.3.5 Statistical analyses

ERP data were normally distributed. FFT data were non-normal and transformed using log which was the most effective transformation in this data, as determined by the 'ladder' command in STATA which compares the results of several different transformations on data

distribution. Group differences in P3a and P3b mean activity, in novel and target conditions respectively, were tested using univariate ANOVAs. Mean theta power was compared using repeated measures ANOVA (factors: group (ADHD, BD, control), condition (novel, target)). We report p-values (trends are reported at $p < 0.7$) and effect sizes for all analysis, using Cohen's d where 0.2 is considered a small effect size, 0.5 medium and 0.8 large (Cohen, 1988). Further correlations between FFT power and ERP amplitude were conducted to examine the relationship between these two measures.

Behavioural performance measures were the number of omission errors (non-responses) to target trials, mean reaction time (MRT) and reaction time variability (RTV) to targets, the number of incorrect responses to novel stimulus, and to non-targets stimulus (commission errors). MRT and RTV were normally distributed, and tested using univariate ANOVA. Number of target omission errors and novel commission errors were successfully transformed using square root, and tested with univariate ANOVAs. Number of non-target commission errors was not successfully transformed using any available transformation (cubic, square, square root, log, 1/square root, inverse, 1/square, 1/cubic), and was therefore tested using the non-parametric Kruskal-Wallis test.

6.4 Results

6.4.1 Behavioural indices

Group differences were observed in target MRT and the number of novel commission errors (Table 6.1). The BD group had significantly elevated MRT to targets compared to both ADHD

and control groups, with these two groups not differing. Commission errors to novel stimuli were elevated in the ADHD group compared to controls. The number of omission errors to target stimuli showed a trend level difference, with post-hoc comparisons suggesting that the BD may have recorded an elevated number of target omission errors compared to controls. There were no differences in target RTV or the number of non-target commission errors between the three groups.

6.4.2 ERPs

Grand averages and topographies (Figure 6.1) were suggestive of group differences in both novel and target conditions; showing reduced peak amplitude in the clinical groups, particularly the BD group, however neither of these comparisons reached statistical significance (Table 6.1). Effect sizes support the suggestion of potential modest group differences in the grand averages with a small effect size between the clinical groups and controls in the P3b in target condition and small effect sizes between the ADHD and BD, and control and BD groups in the novel condition (Table 6.1).

Table 6.1. Means (standard deviation), significance testing and effect sizes for performance indices, P3a and P3b ERP components, and FFT voltage in ADHD, bipolar disorder and control participants.

		ADHD	BD	Control	F†	P	Post-hoc pairwise (p)			Pairwise effect size (d)		
							ADHD- BD	ADHD- CTRL	BD- CTRL	ADHD- BD	ADHD- CTRL	BD- CTRL
Performance Variables												
Target hit MRT		450.88 (57.96)	508.97 (79.12)	451.75 (59.66)	4.98	0.01	0.03	1	0.03	0.84	0.01	0.82
Target hit RTV		107.19 (30.75)	115.88 (21.29)	101.14 (19.60)	1.87	0.16	-	-	-	0.32	0.23	0.72
Omission error		2.79 (2.9)	5.2 (5.52)	2 (2.58)	2.86	0.07	0.37	0.78	0.06	0.55	0.29	0.74
Novel c. error		1.21 (1.36)	0.6 (0.75)	0.45 (0.6)	3.55	0.04	0.13	0.04	0.95	0.56	0.72	0.22
Non-target c. error		0.79 (1.27)	1.15 (1.23)	0.65 (1.18)	2.8	0.25	-	-	-	0.29	0.11	0.41
ERP Mean Activity (µV*ms)												
Novel p3a	FCz	1.67 (1.58)	1.28 (2.07)	1.95 (1.47)	0.753	0.48	-	-	-	0.21	0.18	0.37
Target p3b	Pz	2.45 (1.22)	2.68 (1.73)	3.11 (1.88)	0.817	0.45	-	-	-	0.16	0.42	0.24
FFT Theta voltage (µV)												
Novel theta	FCz	0.86 (0.63)	0.67 (0.52)	0.82 (0.58)						0.32	0.06	0.27
Target theta	FCz	0.68 (0.59)	0.58 (0.5)	0.73 (0.68)						0.18	0.08	0.25
Condition					7.092	0.01				0.29	0.18	0.15
Group					0.641	0.53						
Group * condition					0.011	0.99						

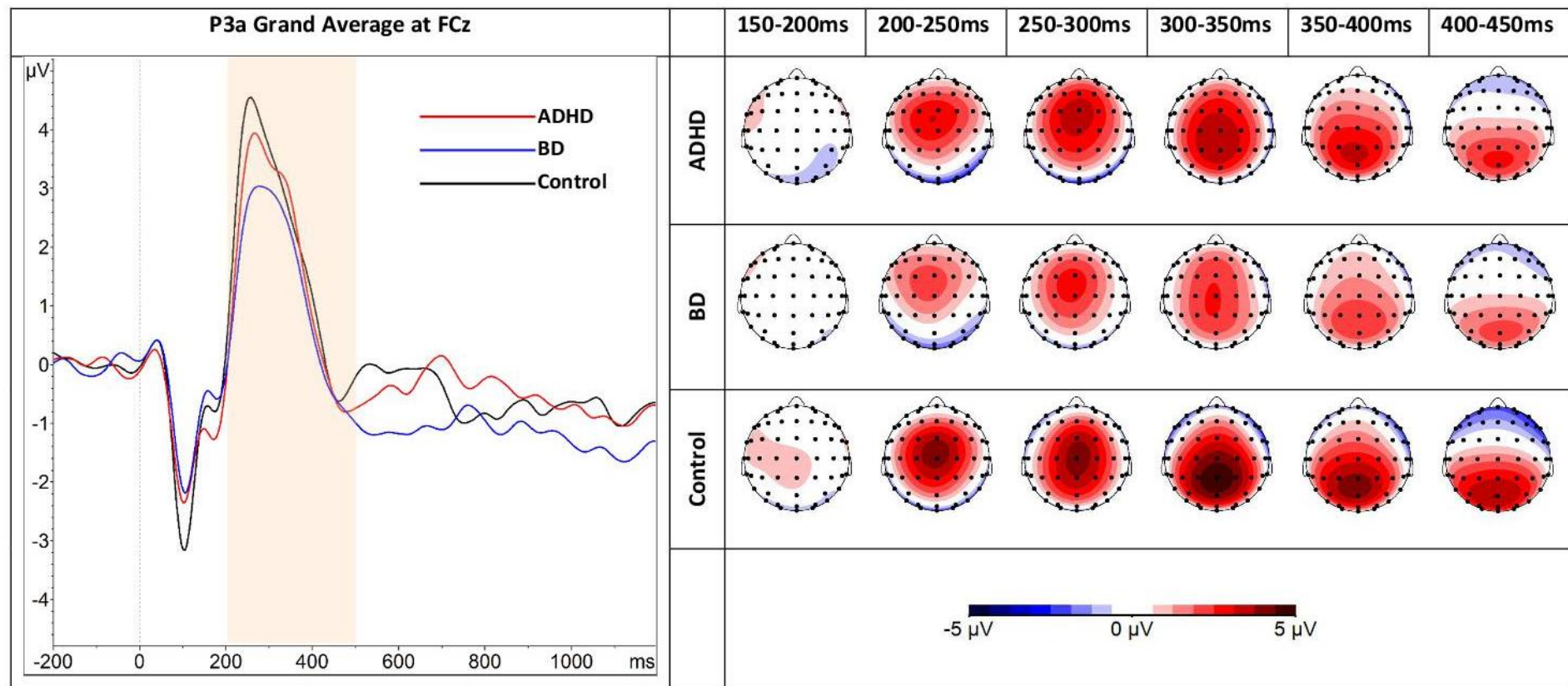
See over for legend

†H for non-target commission errors

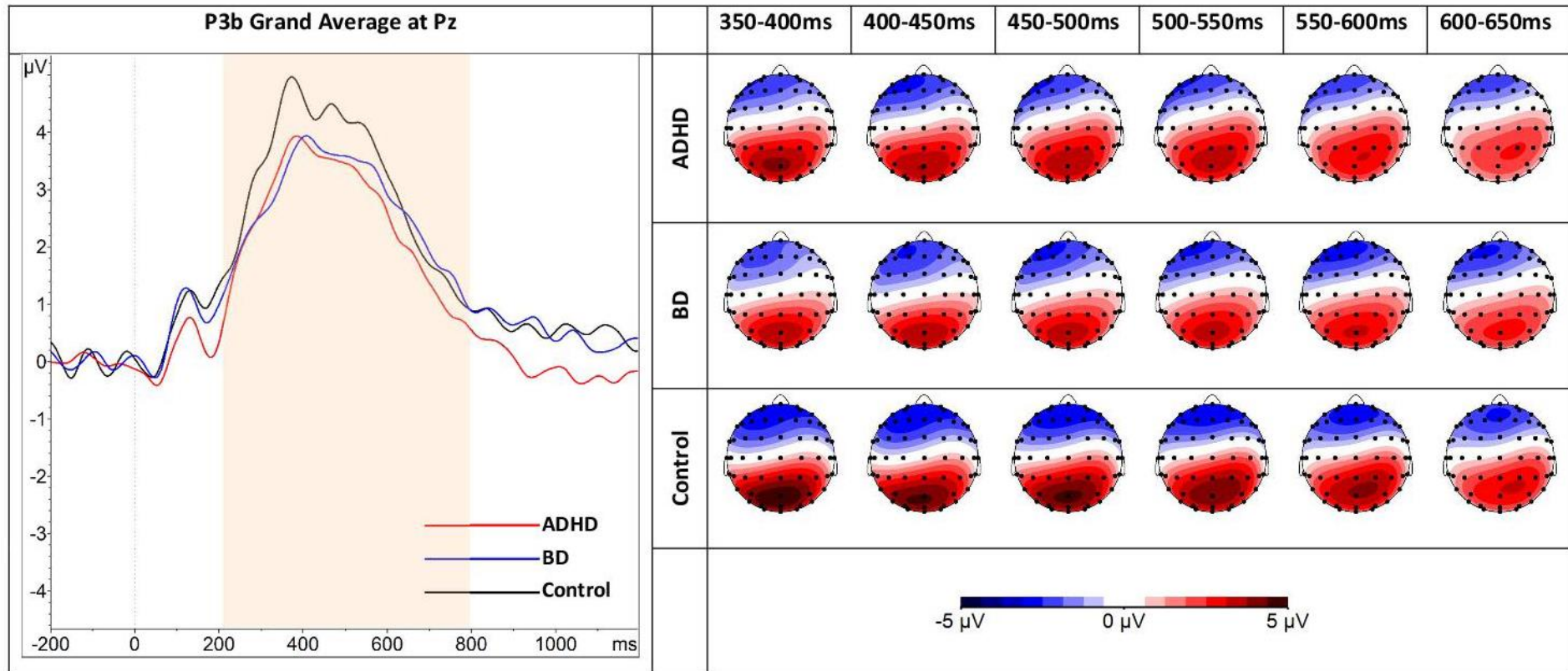
Target Hit MRT = reaction time of correct response to targets, Target Hit RTV = reaction time variability to targets (i.e SD of reaction time), Omission error = non-response to target stimuli, Novel c. error = number of commission errors to novel stimuli, Non-target c. error = number of commission errors to non-target stimuli. Target hit RT, Omission error and Novel c. error compared with univariate ANOVA (F), Non-target c. error compared with non-parametric Kruskal-Wallis test (H). Novel P3a is the mean event related potential (ERP) activity between 200-500 ms in response to novel stimuli on trials where participants did not make a commission error. Target P3b is the mean ERP activity between 200-800 ms where participants correctly responded to the target stimuli with a reaction time of between 100 – 1000 ms. FFT theta voltage is the mean theta (3.5 – 7 Hz) activity across 1000 ms stimulus locked epochs in novel or target conditions. Post-hoc and effect size comparisons: A-B = ADHD-BD, A-C = ADHD-Control, B-C = BD Control. Cohen's d effect sizes: 0.2 small, 0.5 medium and 0.8 large.

Figure 6.1. – Grand averages and topographic maps of mean activity for ADHD, bipolar disorder (BD) and control participants for a) P3a component in the novel condition b) P3b component in the target condition.

(a)



(b)



Novel P3a is the mean event related potential (ERP) activity between 200-500 ms (window highlighted) in response to novel stimuli on trials where participants did not make a commission error. Target P3b is the mean ERP activity between 200-800 ms (window highlighted) where participants correctly responded to the target stimuli with a reaction time of between 100 – 1000 ms.

6.4.3 Theta Activity

Fronto-central theta activity was compared in both conditions at FCz. In order to be able to address the research question of whether there are group differences in the change in power between target and novel condition, we tested all factors within a single repeated measures ANOVA. This indicated a significant main effect of condition, showing that theta power increased in the novel condition compared to the target condition (Figure 6.2). However, no main effect of group or a group by condition interaction was detected (Table 6.1). Effect sizes for ADHD and BD and BD and control comparisons in theta power in the novel condition were small, along with a further small effect size between BD and control groups for theta power in the target condition.

Correlations between ERP amplitude and FFT power in the ADHD group were significant in the target condition and were at trend level in the novel condition. P3 amplitude and FFT power were not significantly correlated in BD or control groups (Table 6.2).

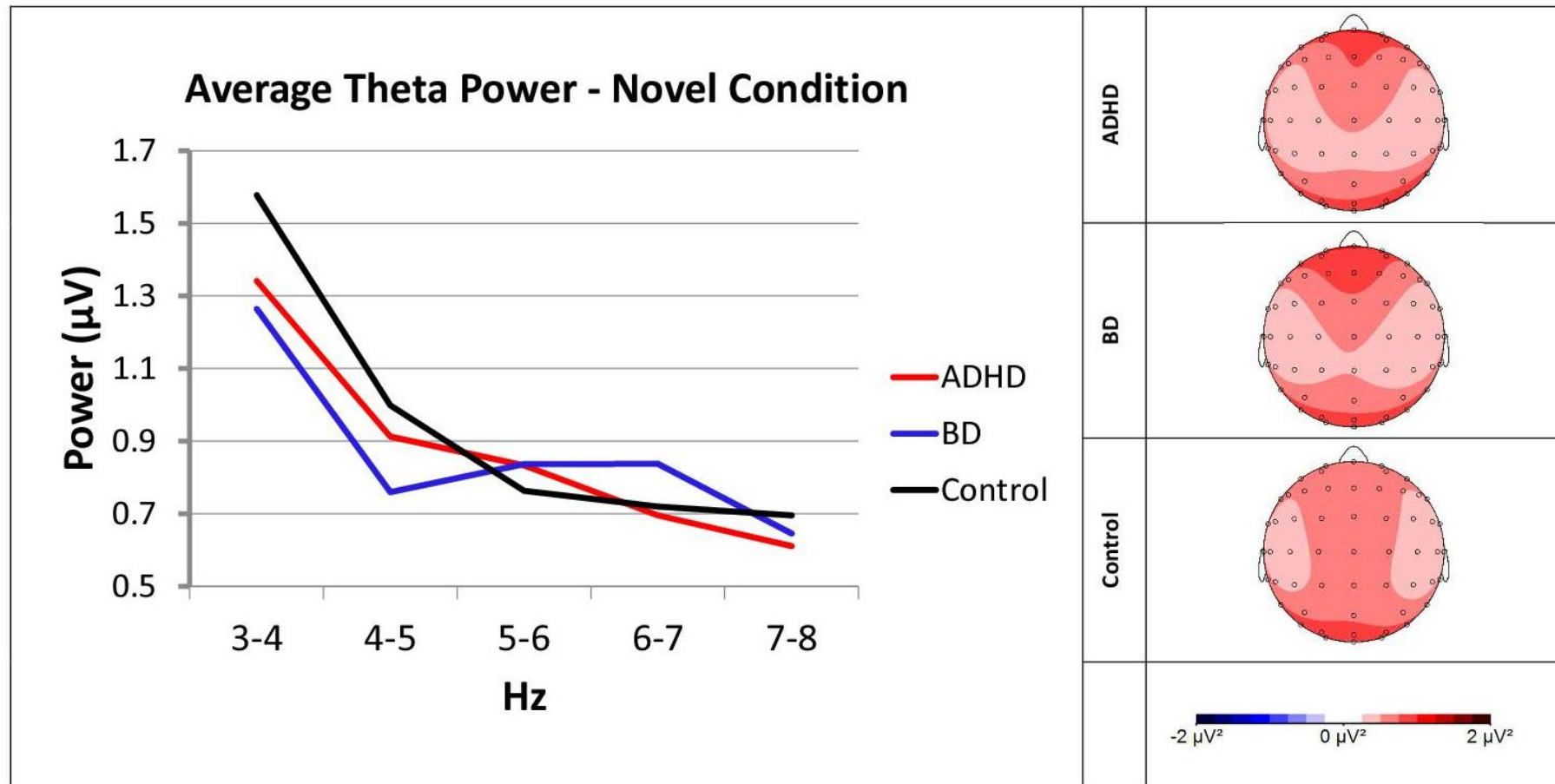
Table 6.2. Correlations between ERPs power and theta power in novel and target conditions.

		ADHD		BD		Control	
		Target	Novel	Target	Novel	Target	Novel
		Theta	Theta	Theta	Theta	Theta	Theta
Target P3b	r	0.50		0.08		0.14	
	P	0.03*		0.75		0.55	
Novel P3a	r		0.44		0.11		0.20
	p		0.06†		0.64		0.39

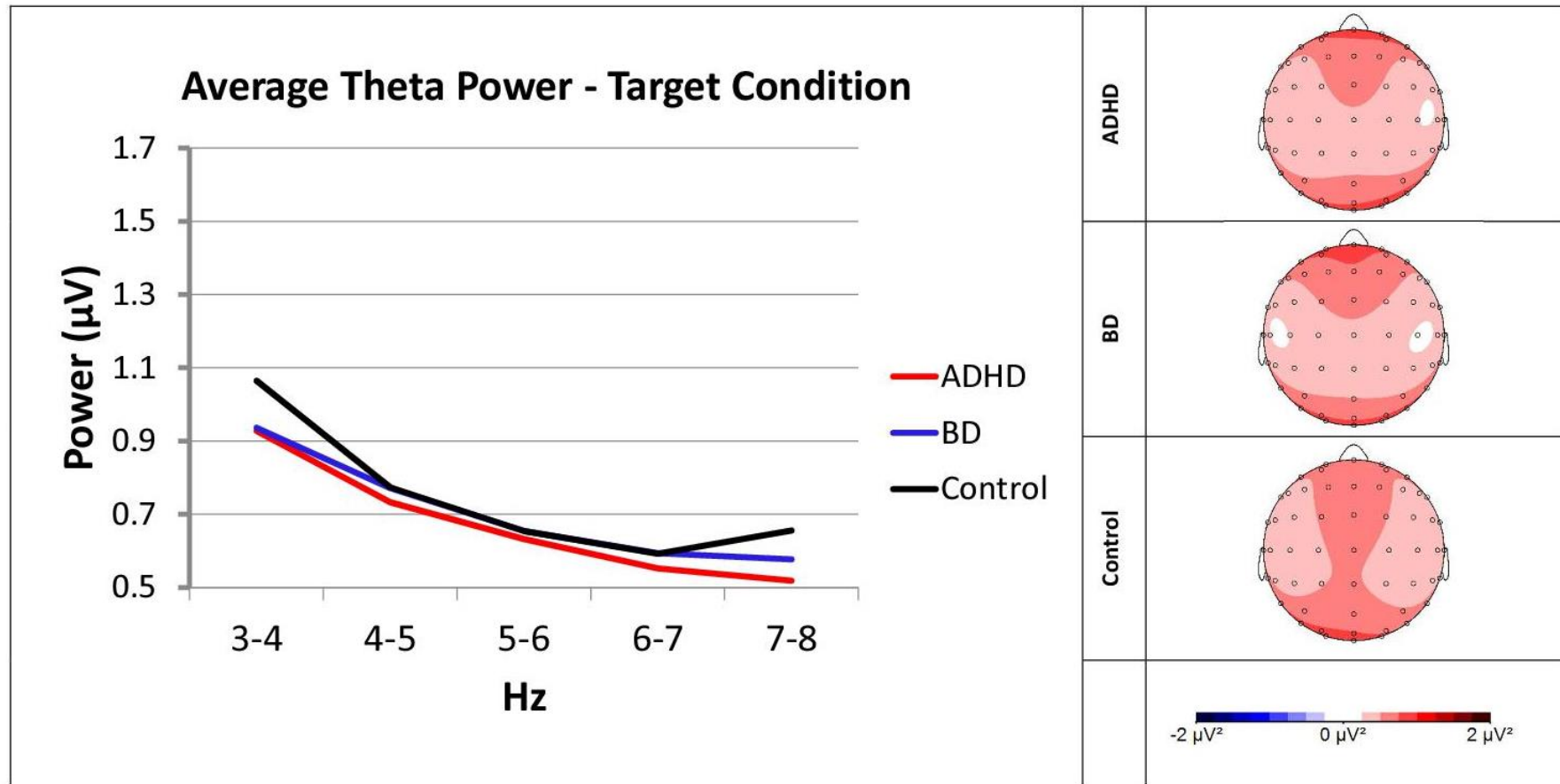
Novel P3a is the mean event related potential (ERP) activity between 200-500 ms in response to novel stimuli on trials where participants did not make a commission error. Target P3b is the mean ERP activity between 200-800 ms where participants correctly responded to the target stimuli with a reaction time of between 100 – 1000 ms. FFT theta voltage is the mean theta (3.5 – 7 Hz) activity across 1000 ms stimulus locked epochs in novel or target conditions. † = trend ($p < 0.07$), * $p < 0.05$.

Figure 6.2. Grand averages and topographic maps of mean theta power in novel and target conditions for ADHD, bipolar disorder (BD) and control participants.

(a)



(b)



Graphs show mean theta power across 1000 ms stimulus-linked epochs at FCz in both conditions. Theta power used in analysis: 3.5-7.5 Hz. Target condition includes only trials where participants correctly responded to the target stimuli with a reaction time of between 100 – 1000 ms. The novel condition only includes trials where participants did not make commission errors.

6.5 Discussion

Using a novelty oddball task, which measures attentional resource allocation, we identified increased target MRT in the BD group, which differentiated them from ADHD and control groups. We also found a significant increase for novel commission errors in the ADHD group compared to controls, replicating other findings suggestive of interference with task level processing (Holcomb et al., 1986, Nigg, 2005, Sergeant et al., 2002) and a trend level increase in target commission errors in the BD group compared to controls, suggesting further possible performance level-candidates for ADHD-BD differentiation, as effect sizes for ADHD-BD comparisons in both cases were medium. However, we did not observe differences in RTV to targets in this study, despite elevated RTV being frequently associated with ADHD (Kuntsi et al., 2014), which could be due to particular task demands in this paradigm (Kuntsi et al., 2013).

Comparisons of P3a, P3b and theta power did not show significant differences between ADHD, BD and control groups in this sample of adult women, which may argue against attentional resource allocation deficits underlying common symptoms in both disorders such as lapses in attention, poor focus and distractibility. Attenuation of the P3b component in BD has previously been reported in adults (Bestelmeyer et al., 2009, Bestelmeyer, 2012, Ethridge et al., 2012), and to a wider degree in children and adolescents with ADHD, although the area remains understudied in adults (Barry et al., 2003, Holcomb et al., 1986, Johnstone and Barry, 1996, Jonkman et al., 1997, Ozdag et al., 2004), However, in both disorders there are several example of studies which have failed to detect group differences (Andersson et al., 2008, Hermens et al., 2005c, Groom et al., 2008, Lazzaro et al., 1997, Lazzaro et al., 2001). This indicates that sample differences are likely to be responsible for the variability in reported findings, as both ADHD and BD are known to be heterogeneous diagnostic classifications

encompassing wide-ranging symptom profiles. In our study, the absence of group differences and the failure to replicate the P3b attenuation observed in some other studies is likely to be partly due to heterogeneity within the clinical samples. However, on some measures modest effect sizes were present for group comparisons, suggesting that with a larger sample group differences might emerge and factors of heterogeneity, which moderate group differences, might be identified by examining subgroups within the psychiatric samples. In particular the P3a in the novel condition might have future utility in differentiating ADHD from BD, as both ADHD-BD and BD-control comparisons showed small effect sizes supported by discernable peak differences on grand average graphs. We would therefore support the use of paradigms which explicitly evoke P3a response such as the novelty variant of the oddball paradigm, as this may warrant another investigation for the purpose of examine within-group heterogeneity in P3a response in larger samples. In contrast, P3b power to targets, the marker assessed in the much more commonly studied two-stimulus (target and non-target) version of the oddball, showed more limited potential for discriminating between the two psychiatric disorders in this sample of adult women, and may be a less preferred candidate for future study.

In comparisons of fronto-central theta power, a main effect emerged for condition, with the novel condition having higher power than the target condition, indicating that this measure was sensitive to experimental effects. However, no effect of group status was observed. As we were also unable to identify P3 attenuation in the clinical groups in this study, we were unable to confirm if fronto-central theta activity was linked to processes of attentional orientation. As with the ERP measures, some small effect sizes were present, showing that any potential differences in theta power between the groups is likely to be small and would require large samples, more sensitive theta recording or reduced sample heterogeneity in order to determine if this is a valuable avenue for further research. Estimates of effect size for ADHD-

control differences were minimal, suggesting that theta power was largely equivalent in these groups using the parameters adopted in this study. This is in contrast with the few studies which have examined fronto-central theta during the oddball paradigm in predominantly male children and adolescents with ADHD, which reported elevated frontal theta compared to controls in both target and novel conditions (Hermens et al., 2005b, Fallahpour et al., 2010). The absence of ADHD-control differences in theta power in our study may be due to the older age of our sample (mean = 38, SD = 6.78) compared to these studies. Theta power is known to decrease strongly with age in resting state investigations of healthy controls (Vlahou et al., 2014), which is replicated in ADHD samples (Kitsune et al., 2014, chapter 2, supplementary material, Liechti et al., 2013). However, we also cannot rule out the possibility that the differences between our findings and those of Harmen et al (2005b) and Fallahpour et al (2010) are due to gender differences, as this is the first study to examine this marker in a female sample, and no published studies to date have directly examined male-female theta power differences in ADHD.

All groups showed an increase in theta power between target and novel conditions, with a significant main effect present. However, the effect size of the theta increase between target and novel conditions in the ADHD group was nearly twice the size of those in the other groups. Although a condition x group difference was not observed in this study, the effect size between conditions in the ADHD group highlights a further potential avenue for future investigation. Related to this, in the ADHD group, correlations between theta power and P3b amplitude were significant, with a further trend ($p = 0.06$) observed in the novel condition. No significant associations between theta power and P3 ERP amplitude were observed in the other groups, supporting arguments that theta power may be specifically linked with deficits in attentional processes in ADHD (McLoughlin et al., 2014b). This therefore warrants additional

study in adult populations, as group differences in theta power may emerge with a larger sample.

One limitation of our study and a possible alternative explanation for our null findings is the effects of medication use in our data. Although the ADHD group abstained from stimulant medication use 48 hours prior to testing, participants BD group, and some in the ADHD group, continued to take other prescribed medications as it would not be ethical to ask these participants to cease taking these types of medications for testing. The full effects of medication usage on ERP amplitude are still poorly understood and evidence is inconsistent. While studies indicate that anti-depressant and clozapine antipsychotic medication may normalise P3 amplitude in psychiatric populations relative to controls (Anderer et al., 2002b, Anderer et al., 2002a, Barratt et al., 2003, Galletly et al., 2005, Karaaslan et al., 2003, Umbricht et al., 1998), many other studies report no medication effects on the P3 amplitude in a range of clinical disorders and ERP paradigms (Isintas et al., 2012, Korostenskaja et al., 2006, Semlitsch et al., 1993, Swann et al., 2013, van Laar et al., 2002, Vandoolaeghe et al., 1998). More consistently, mood-stabilisers have also been reported to reduce P3 amplitude (Smith et al., 2006, Tumay et al., 2013, Urasaki et al., 1994), although a recent study specifically examining the P3a in BD did not find differences related to mood stabiliser or antipsychotic medication use (Jahshan et al., 2012). To explore further, we calculated separate P3 mean amplitudes for ADHD and BD participants currently taken certain classes of medications (anti-psychotic, anti-depressant, mood stabiliser and stimulant) and those who were not, but within group samples proved too small for robust statistical comparison (Supplementary material S12). Furthermore, visual representation of ERP power by medication and group status was inconclusive (Supplementary material S13). In the novel condition, where distributions on these plots appeared more imbalanced, both ADHD and BD participants typically appeared at the lower ends of the distributions in both “yes” and “no” treatment groups for all medication classes including stimulants, which ADHD participants refrained from taking 48 hours before EEG testing. It was therefore not possible to resolve medication effects from those factors

associated with psychiatric group status in this study and we acknowledge the medication confound as a limitation, while suggesting that subsequent studies attempt to recruit samples which are medication naive or non-adherent to their treatment, in order determine the effects of medication on P3 amplitude.

In conclusion, at the performance level, we show reduced MRT to targets in the BD group, which discriminated them from both ADHD and control groups. We did not observe significant group differences in P3a or P3b amplitude or theta power using the novelty oddball task in this sample of adult women. However, we identify promising candidates for further study, particularly P3a amplitude in the novel condition, which was correlated with theta power in the ADHD group, but not in the BD or control groups. Although we find no support for our original hypothesis of attentional resource allocation deficits in the oddball task in these psychiatric populations, data in this area remain sparse, particularly in ADHD where the majority of existing studies have focused on predominantly male child and adolescent populations. Given theta power is known to decrease with age, the age of our sample may have contributed to this study being underpowered to detect attentional deficits. Potential gender differences in ERP or theta response in adult women with ADHD also remains to be ruled out in future investigations.

Chapter 7 - General Discussion and Conclusions

7.1 Summary of overall aims

The first part of this thesis aimed to examine the stability and validity of potential cognitive-electrophysiological biomarkers in Attention-Deficit/Hyperactivity Disorder (ADHD) in a large sample of adolescents and young adults. In part two, this thesis proceeded to a cross-disorder comparison with Bipolar Disorder (BD) in a novel sample of adult women, beginning by investigating symptom overlap between the two disorders and testing the efficacy of standard clinical instruments to delineate ADHD from euthymic BD. The next two chapters then went on to investigate the ability of cognitive-electrophysiological markers to delineate ADHD from BD in this cross-disorder sample, both through re-examining ERP components which were investigated in part one, and by exploring additional ERP components not previously studied in this body of work. This final chapter now takes an overview of the key findings in both parts of this thesis to draw together common themes and to highlight how these data illuminate the current understanding of diagnostic boundaries and cognitive deficits in ADHD and BD.

7.2 Principal findings

7.2.1 The consistency of EEG differences in ADHD

This thesis commenced with a study seeking to determine the consistency and reliability of proposed EEG resting state frequency-band biomarkers through comparing data recorded at two separate time points between ADHD participants and controls. In this study, the primary finding was of higher frequency power in ADHD at lower EEG frequency bands (delta and theta) at the beginning of a 1.5 hour testing session but not at the end, and of elevated power in higher frequency ranges (beta) at the end of the testing session but not at the beginning. This demonstrates that ADHD-control differences are sensitive to the effects of recording duration and under-arousal may vary with experimental context. Comparisons of different methodological approaches, such as electrode selection (midline vs grouped regions of electrodes) and controlling for IQ differences also altered some of the results, suggesting that reported findings are, to some extent, dependent on methods employed and that these factors require fuller consideration in future studies.

7.2.2 Indicators of performance monitoring deficits in ADHD

The second study, using a response-choice arrow flanker ERP paradigm, reported impaired conflict monitoring as indexed by attenuated N2 amplitude, and conscious error processing as indexed by attenuated Pe amplitude in adolescents and young adults with ADHD. We did not find evidence of impaired unconscious error processing as indexed by the ERN component, contrary to some other studies which have identified the ERN component as being impaired in ADHD. Comparisons between ADHD participants, unaffected siblings of those with ADHD, and controls did not show evidence that performance monitoring correlates had the characteristics

of an endophenotype for ADHD, as no familial effects were observed. For conflict monitoring, topographic maps indicated that the ADHD group did not have an overall reduced maximal N2 amplitude compared to controls, but did suggest a more frontal topographic distribution of the component. Combined with a comparison showing that older and young subgroups displayed different case-control conflict monitoring abnormalities, these data suggest atypical fronto-cortical maturation in ADHD participants, which may explain some inconsistencies across different samples to date.

7.2.3. Symptoms overlap between ADHD and BD

In the second part of this thesis the focus of investigation moved onto a cross-disorder comparison of BD and ADHD using clinical and ERP measures. This first study compared the two disorders across symptoms of inattention, hyperactivity, mania, depression and emotional lability (EL) as assessed using typical diagnostic measures commonly employed in clinical settings. This investigation showed that ADHD participants had a high degree of EL and hyperactivity symptoms which could be confused with the symptoms of manic episodes in BD, and which were not well delineated by standard mania and EL measures. However, this study also showed that ADHD interview measures had good discrimination potential, showing both sensitivity and specificity to ADHD on account of the inherent temporal component in assessment items, and therefore were recommended as the primary diagnostic tool for the delineation of ADHD and BD.

7.2.4 The specificity of conflict monitoring deficits in ADHD and BD

This investigation compared conflict monitoring processing in adult women with ADHD or BD in a flanker task, which were previously reported as potentially attenuated in children and adolescents with ADHD in chapter three. In this cross-disorder investigation, a suggestive reduction in N2 amplitude (trend-level $p = 0.07$) was observed in the BD group compared to the ADHD group. ADHD-control differences were not detected in this older adult sample, most likely due to age-related changes in N2 amplitude across lifespan. Differences in an early sensory processing component, specifically the P2 amplitude, were also observed in the BD group compared to the ADHD group, and with a trend-level difference being observed compared to the control group. This suggested that P2 amplitude enhancement could be a specific marker for BD in adult samples.

7.2.5 Attentional resource allocation in ADHD and BD

The fifth experiment presented in this thesis investigated indices of attentional resource allocation in ADHD and BD in a novelty oddball task, but found no evidence for differences in ERP components associated with attentional orientation to novelty or attentional resource allocation to targets. However, greater fronto-central theta power, which has been linked to deficits in attentional resource allocation, was correlated with the P3b component in the ADHD group but not in BD or control groups, suggesting this relationship may index an as yet unknown impairment related to attention in ADHD and would make a good candidate for further study. Increased reaction time to targets was also able to distinguish the BD group from ADHD group in this task.

7.3 Diagnostic complications in ADHD and BD

The symptom comparison study (chapter four) highlighted the complexities of symptom overlap between ADHD and BD, such as depression, hyperactivity and emotional lability, and showed how some standard clinical measures may not be well suited to delineating ADHD from euthymic BD. In order to reduce heterogeneity within the samples, this study focused on the relatively severe forms of each disorder (those with persistent ADHD with combined-type symptoms in childhood, and current euthymic Bipolar Disorder I), and excluded those who were likely to have a comorbidity of ADHD and BD. In a general psychiatric population, such as those likely to be encountered in clinical settings, a broader spectrum of both disorders will be present along with the presence of other comorbidities, meaning phenotypes will be less well defined and harder to identify. Moreover, although chapter four demonstrated that ADHD measures which capture episodicity were sensitive to diagnostic differences, many healthcare professionals may be unfamiliar with current best practice in relation to the key identifiers in each disorder. This suggests that although ADHD clinical measures were effective at delineating ADHD from BD, the high level of symptoms and impairment observed in ADHD, particularly those of depression and emotional lability, could still be confused with that of BD, and objective biological measures of either disorder would be diagnostically valuable. More generally, as discussed in chapter one, the shared or specific neurobiological aetiology of these disorders is still poorly understood, and studies such as those conducted for chapters two, three, five and six represent additional contributions to the growing body of work which ultimately aims to map out a new biologically grounded framework for understanding mental illness.

7.4 Contributions to a neurobiological understanding of ADHD and BD

The neurobiological understanding of ADHD and BD is currently quite limited, with literature being fairly sparse and studies often presenting a mixed pattern of results. Both parts one and two of this thesis sought to advance the understanding of cognitive and neurophysiological deficits in these disorders by using either 1) a large sample of ADHD adolescents and young adults or 2) a novel cross-disorder investigation of ADHD and BD in adult women. In combination, these approaches sought to examine the stability or specificity of potential biomarkers, in order to highlight shared and/or specific ERP impairments which may underlie behavioural, cognitive and symptomatic differences and similarities in these two disorders.

7.4.1 Biological markers

In the two cross-disorder electrophysiological studies undertaken there were two cognitive-electrophysiological markers which emerged as potentially being able to distinguish ADHD from BD. Firstly, in the study using an arrow flanker paradigm (chapter five), significant P2 enhancement was detected in the BD group compared to the ADHD group, with a further trend-level difference reported compared to controls. P2 enhancement in the BD group may have been responsible for the trend-level reduced negativity of the later N2 component in this group. There were further indications that a measure of amplitude change between P2 and N2 components (P2-N2 complex) may be useful in distinguishing ADHD from BD and could be a good candidate for further research, indeed the P2-N2 complex has also been linked to theta phase-locking (Freunberger et al., 2007, Kamarajan et al., 2008) which might also play a role in attention (McLoughlin et al., 2014b). The P2 component is thought to be associated with initial conscious awareness and stimulus classification (Crowley and Colrain, 2004), and so

abnormalities in the P2 in BD may be related to similar findings in other studies of early pre-attention and sensory gating deficits as cognitive impairments in BD. However, previous research specifically examining the P2 in BD is underdeveloped, with one other study finding the P2 was enhanced in BD participants compared to healthy controls, but which was attributed to the presence of psychosis in the clinical group (Ethridge et al., 2014). P2 abnormalities could represent a useful candidate marker for BD, one which appears to distinguish this group from ADHD participants in this sample. However, it is now important that further work is conducted to 1) determine if this measure is able to consistently distinguish BD from other groups, 2) assess other factors which might influence P2 amplitude (such as the presence of psychosis), and 3) to determine the general functional significance of the P2 components across modalities and different age groups. It would also be valuable to examine the functional relationship between P2 and N2 components in these disorders, to confirm if deficits represent a related series of cognitive processes or whether the interaction of their amplitudes is merely circumstantial (i.e two independent processes where activity is summed at a scalp level).

The second potential specific biomarker, this time for ADHD, was detected during an oddball paradigm (chapter six). This study examined P3a amplitude to novel stimuli (at Cz), P3b amplitude to target stimuli (at Pz) and fronto-central theta power (at FCz) in relation to both types of stimuli. Separately the ERP and EEG measures did not show group differences in ERP amplitude or EEG power but the correlation of theta power with P3b amplitude to targets was significant in the ADHD group but not BD or control groups. Furthermore, a similar pattern was observed in the novel condition, with the P3a component being correlated at trend-level in the ADHD group but not in the other groups. This suggests a particular functional relationship between the ERP measures of attention (P3a, P3b) and theta power in the ADHD group. This

idea is supported by research showing that theta has a role in arousal regulation, and so may therefore influence the efficiency of attentional processes in ADHD (Lazzaro et al., 1999). Other studies have also previously suggested a link between attentional processes and fronto-central theta activity in cognitive-electrophysiological studies (Demiralp et al., 1999, Fallahpour et al., 2010, Hermens et al., 2005b), including genetically-sensitive designs (McLoughlin et al., 2014b). Cognitive-energetic theories of ADHD suggest that due to persistent under-arousal, ADHD participants may require a higher level of overall arousal during tasks in order to maintain an equivalent performance level as controls (Sergeant, 2000, Sergeant, 2005). Theoretically then, it may be that in this study where attentional ERP components showed no group differences, the ADHD adults were adopting compensatory strategies to increase arousal and engagement with the tasks, which was apparent as a significant correlation between ERP and theta measures. Although this hypothesis remains to be tested directly, the fact that this correlation between ERP and theta activity was observed only in the ADHD group, and in both conditions, does recommend a further examination of this index as a potential marker for ADHD.

Enhanced P2 and correlated fronto-central theta-P3a/P3b activity represent the two strongest potential disorder-specific biomarkers to emerge from this body of work; one for BD and one for ADHD. Both have been identified in a small sample of adult women, and therefore require replication, as well as requiring further examination in other experimental contexts. This is needed to determine if these significant results are linked to particular characteristics of this sample, for instance the age or gender of these participants, and whether these results are mediated by other factors such as the presence of particular symptom expression, such as psychosis in BD. These results do, however, amount to two novel potential biomarkers, in a relatively understudied area of research, where this thesis has uniquely been able to show that

these indicators show potential to discriminate between ADHD and euthymic BD in an adult female sample.

7.4.2 Performance indices

Chapters three and five, using the Flanker Task, and chapter six using the Novelty Oddball Task reported results for several performance indices. In chapter six, mean reaction time (MRT) to targets distinguished the BD group from both ADHD and controls, and could be theoretically linked to evidence of early sensory processing deficits if the BD group required additional time in order to distinguish targets for non-target stimuli. Greater omission errors (missed targets) showed a trend-level difference in the BD group compared to controls and greater commission errors (erroneous responses to novel distractors) were present in the ADHD group compared to controls, replicating similar findings in other studies which are suggestive of interference with task-level processing in ADHD (Holcomb et al., 1986, Nigg, 2005, Sergeant et al., 2002). In the flanker task, the investigation presented in chapter three, using the large sample of adolescent and young adults with ADHD, reported that all performance indicators (commission errors (incorrect response to stimulus), omission errors (non-responses), mean reaction time (MRT) and reaction time variability (RTV)), showed significant ADHD-control differences. However, in chapter five using the same task to evaluate the cross-disorder sample of adult women, significant differences were not observed on any of these performance indices. However, between the two studies, mean scores on these indexes were similar. The exception to this observation was commission errors in the incongruent condition of the Flanker Task, where error rates appeared lower across all groups in the older adult sample than the adolescent and young adult sample, perhaps implying that ceiling effects could have contributed to some of the non-significant differences on performance measures in the older adult sample.

In summary, performance measures appear variable and are task dependent; although showed strong differences in some cases and therefore have value as indicators of cognitive deficits and can also support theoretical interpretations of cognitive-electrophysiological data. The observation of potentially specific deficits in each disorder might also be used to develop novel experimental designs to more easily explore the precise characteristics of neurobiological deficits in each condition using large samples; such as for instance how deficits in these conditions change over lifespan and whether energetic factors influence performance across the different types of measures and paradigms. In future, specifically examining correlations between cognitive-electrophysiological data and performance indices may help to illustrate, with greater clarity, the relationships between case-control differences in ERP or EEG measures and behavioural impairments. Examining such correlations will be increasingly important as research moves towards assessing the utility of alternative classification frameworks such as RDoC, which hinge upon identifying underlying impairments in neurocognitive systems across diagnostic boundaries through the use of converging evidence from multiple behavioural and neurophysiological indices.

7.4.3 Maturational factors

Chapter two provided evidence for variable cortical arousal in adolescents and young adults with ADHD, by demonstrating that resting-state EEG band power differences between ADHD and controls varied across time, between two recordings separated by a 1.5 hour testing session. Some previous literature had argued that EEG band power differences, such as the ratio of theta to beta activity (T:B), might represent a stable biomarker for ADHD, although more recent studies had contested these views (Arns et al., 2013, Liechti et al., 2013). The

resting-state investigation conducted here supported arguments that these EEG markers of ADHD are unstable, and are not reliable enough for diagnostic application when processed using standard analysis techniques. Furthermore, comparisons between older and younger subgroups within this sample indicated age-related changes in ADHD and control participants for EEG power, with reduced power in all bands being observed in the older groups. This was replicated in Global Field Synchronisation (GFS) scores, which were positively correlated with age, suggesting lower phase synchronization in younger participants at earlier stages of cortical maturation, compared to adult samples (Koenig and Pascual-Marqui, 2009). In chapter three, where evidence of deficits and altered topography of conflict monitoring processes in ADHD was presented, the exact nature of ADHD-control differences differed between older or younger subgroups of the full sample. The data from the first part of this thesis focused on adolescents and young adults with ADHD therefore suggests that ERP indicators for ADHD are somewhat fluid with age, supporting theories of delayed cortical maturation in ADHD (Rubia et al., 2000, Shaw et al., 2007). If correct, this would also explain why the pattern of results reported in EEG and ERP studies of ADHD have been inconsistent overall, as the ranges of age within a sample could alter results. Such finding may also suggest that differences could be easier to detect in adult samples, given a similar sample size, as there may be less neurophysiological heterogeneity caused by the extensive changes in neural connections which takes place as part of cortical maturation in adolescent samples.

7.4.4 Conflict monitoring

Chapters three and five both examined the N2 component, which is associated with conflict monitoring in the Flanker Task. Chapter three used an endophenotype approach in a large sample of adolescences and young adults, comparing N2 amplitude for participants with

ADHD, their unaffected siblings and unaffected controls, showing that there were suggestive (trend-level) differences in the ADHD group compared to controls. The unaffected ADHD siblings and control groups did not differ in this analysis. In contrast, chapter five compared N2 amplitude in adult women with ADHD, BD or controls. This analysis provided different results, showing suggestive (trend-level) N2 attenuation in the BD group, which was likely linked a significantly enhanced preceding P2 component, while the ADHD and control groups did not differ. The differences in results between chapters three and five show that the N2 does not represent a stable shared or specific biomarker for either of these disorders, without the consideration of other factors which may be influencing results, such as other preceding atypical components or sample age. These factors need to be carefully accounted for in future studies. The inconsistency of results between these two studies mimics that of the literature on N2 deficits in children with ADHD, where both positive and null findings are reported in the few published studies to date (Albrecht et al., 2008, Johnstone et al., 2009, Johnstone and Galletta, 2013, Jonkman et al., 1999, Jonkman et al., 2007, Wild-Wall et al., 2009), with a very limited number of adolescents or adults studies available for comparison (McLoughlin et al., 2009, McLoughlin et al., 2014b). The most likely factor to account for these mixed results in the two studies presented in this thesis, which had identical data collection and analysis procedures, is the age differences between the samples. As previously discussed, age is likely to play a significant role in the size of potential case-control differences and therefore in the power to detect them. There is evidence showing that the detection of performance monitoring deficit in ADHD may be increasingly difficult with advancing age, owing in a large part to the cognitive decline of control samples in older adults (Falkenstein et al., 2001, Herrmann et al., 2010). This may explain why ADHD-control differences were apparent in the adolescent and young adult ADHD sample, but were not observed in the sample of older adults tested in chapter five. Gender differences between the samples also remains a possible explanation, as the adolescent and young adult sample consisted of a mixed sample, which included a high number of male participants, while the older adult sample consisted

exclusively of women. As there is currently very little data available for women with ADHD, particularly amongst older adults, questions remain as to whether possible neurophysiological gender differences exist, which will only be conclusively determined once direct gender comparisons have been carried out in these paradigms.

7.4.5 Attentional resource allocation

In chapter six, this thesis investigated the specificity of P3a and P3b components and their relationship to theta power as markers of attentional resource allocation processes in ADHD and BD using a novelty oddball task. Overall, this study was not able to identify statistically discernible group differences in ERP amplitude or theta power between ADHD, BD and control groups in this sample of adult women. However, grand averages showed ERP amplitude which was indicative of potential differences in P3a and P3b components, suggesting that group delineation may have been possible with increased power. The P3b component has been argued to be a marker of psychiatric psychopathology (Carlson et al., 1999, Ford, 1999, Jahshan et al., 2012, Jeon and Polich, 2003, Polich, 2007, Porjesz et al., 2005). However, there are several examples of P3 deficits not being replicated in studies of ADHD and BD (Andersson et al., 2008, Groom et al., 2008, Hermens et al., 2005c, Lazzaro et al., 1997, Lazzaro et al., 2001). One view is that sample differences and ERP heterogeneity within these clinical samples could be masking potential effects and may pose challenges in searching for reliable biomarkers in ADHD and BD, which can both have a diverse manifestation of symptoms, even within the relatively well-defined more severe forms of each disorder. The pattern of null results for ERP amplitude measures reported in chapter six is not dissimilar to other studies which have been unable to detect previously reported differences in equivalent samples. This therefore highlights the need for research to move beyond current categorical models of

diagnostic classification for research samples, as this approach may be introducing heterogeneity via the inclusion of participants with different neurophysiological aetiology, which may be masking otherwise detectable neurophysiological differences (Insel et al., 2010, Morris and Cuthbert, 2012).

Furthermore, the absence of differences in attentional (P3a & P3b) components in chapter six in comparison with the suggestive differences in conflict monitoring (N2) components in chapter five in the same sample may indicate that unconscious cognitive processes could be more consistent and/or be less heterogeneous and offer better candidates for further study as biomarkers than attentionally dependent components. If lapses in attention were present this could affect indices of conscious cognitive processing, such as the P3 (Kam et al., 2012, O'Connell et al., 2009b), further increasing variability in trial-by-trial ERP response and reducing power to detect group differences in smaller samples. Although this variability itself, may be key to understanding the underlying cognitive impairments in BD and ADHD, the use of specific methods developed to investigate within-participant variability may more easily elucidate differences between clinical groups and controls than standard processing techniques, which rely on averaging of all trials during a recording session, including those trials where a reduced awareness may have been present.

7.5 Methodological factors

This thesis commenced with two studies seeking to examine the reliability of cognitive-electrophysiological markers for ADHD (chapters two and three): the first examining the consistency of EEG resting state band power differences at two separate time points, and the

other examining performance monitoring deficits in an ERP paradigm. In the resting state study, the primary findings indicated that case-control differences changed with recording context (i.e. whether a resting state recording was conducted at the beginning or end of an EEG recording session). This study also questioned the previous broad support for theta/beta ratio (T:B) as a potential EEG biomarker for ADHD, along with other recent studies (Arns et al., 2013, Liechti et al., 2013). This investigation went on to compare several different methodological approaches to determine if the adoption of alternative analysis approaches, such as the uses of midline electrodes vs regions consisting of grouped electrodes, could account for discrepancies between studies prior to 1998 and more recent investigations. Comparisons of analyses using data from electrode regions vs singular midline electrodes showed that the use of electrode regions was apparently more sensitive to beta activity while being less sensitive to theta and alpha band power, while the opposite was true for approaches using midline electrodes only. Although this study was unable to replicate T:B differences for ADHD using either method, similar to Liechti et al. (2013), this demonstrated that methodological differences could contribute to the variability of reported findings within the literature. In addition, as ADHD is commonly associated with lower IQ (Kuntsi et al., 2004), but is inconsistently controlled for in EEG analyses, this study went onto compare results with and without statically controlling for differences in IQ. The conclusions of this investigation were that IQ differences did have a small, but significant, effect on reported results, and may also contribute to some variability of published studies to date. However, the issue of co-varying IQ has also been regarded as problematic in psychiatric research where non-random group allocation is the norm, as in removing the covariate one also removes the proportion of the independent variable related to the covariate in question (Miller and Chapman, 2001). If the covariate and the independent variable are related, as may be the case with ADHD symptoms and IQ, subsequent statistical analysis only captures the aspect of ADHD symptoms score unrelated to IQ, and therefore may not fully capture the relationship between the independent and dependent variable fully (Dennis et al., 2009). In the study presented in

chapter two, this statistical effect may account for the reduction in significance of delta and theta group comparisons in secondary analysis which controlled for IQ. Ideally then, if controlling for IQ due to group differences, studies should also ensure that results are presented without such correction, so that the potential effect of removing the proportion of the independent variable which covaries with the covariate can be quantified.

The second study (chapter three), which reported impaired conflict monitoring and conscious error processing in ADHD, showed that although the ADHD group did not have reduced maximal N2 amplitude overall, a different topographic distribution of amplitude was present. Had this study elected to adopt an approach only comparing the groups at the electrode where N2 amplitude was greatest (Fz), it would not have reported significant site*group differences, providing another example to illustrate that methodological considerations can be critical in the accurate representation of neurophysiological differences between clinical groups and controls. Furthermore, despite this being the largest study of this kind to date, it did not find evidence of impaired unconscious error processing in ADHD. This was contrary to a number of other studies included in a meta-analysis which had identified this component (ERN) as being impaired in ADHD (Geburek et al., 2013). However, generally studies investigating performance monitoring using flanker tasks have been methodologically heterogeneous, which may partially explain inconsistencies in the literature thus far (Shiels and Hawk, 2010). Chapter three in particular adopted an area amplitude measure as this method is more robust to the variability in peak amplitude, suggesting that the results presented in this thesis may represent a more accurate reflection of unconscious error processing in ADHD. However, the inconsistency of approaches, and subsequently differences in results, illustrates how variability in methodological considerations may be contributing to difficulties in replicating potential finding and adding to the challenges in our understanding of the neurophysiological processes in ADHD.

Research into neurophysiological deficits in psychiatric disorders is a small but emerging field, with consensus around the best methodological approach to adopt in the collection and analysis of EEG and ERP data taking time to develop. However, it is clear that methodological factors can have a significant influence on results and many of the effects themselves remain poorly understood and require further study. It is therefore important that such variables are given fuller consideration in future studies, and multiple approaches tested, if this field is to produce evidence of robust, reliable biomarkers which have clinical utility.

7.6 Clinical implications

This thesis presents evidence for some potential markers of ADHD and BD; however, the overall picture is of potentially variable biomarkers, sensitive to sample characteristics and methodological factors. For example, the two studies focusing just on ADHD showed potential EEG biomarkers for ADHD which vary by methodology and context (Kitsune et al., 2014, chapter two), and age-dependent differences observed in ERP correlates of conflict monitoring in the Flanker task (chapter three). Both of these research areas can offer further contributions to the understanding of neurophysiological deficits in ADHD, although methodological and contextual variability will firstly need to be better understood. Given the currently poor conceptualisation of moderating factors and the potential for inconsistencies of findings, such indices would not currently seem suited to clinical use for diagnostic differentiation with other disorders without further study.

It may also be that EEG resting state paradigms inherently may not provide appropriately controlled conditions with which to reliably measure levels of cognitive activation, as there is little means of controlling or identify the cognitive processes occurring during resting state

conditions. If participants are engaged in a variety of uncontrolled mental activities, then there is likely to be a greater range of spectral power fluctuations and therefore reduced power for case-control differentiations. ERP measures or EEG collected under controlled conditions may therefore then be the preferred candidates for providing more consistent outcomes which would be essential in clinical environments, as task-based paradigms offer a higher degree of control over cognitive processes than resting state conditions. However, the ERP studies presented in this work show that there are many factors still to be understood, in particular developmental changes in ERP amplitude across lifespan, and how heterogeneity within the clinical samples studied contributes to the variability in reported findings to date. This suggests that the next steps in identifying ADHD and BD biomarkers will need to adopt consistent methodologies, more homogenous sample demographics and more subtle experimental manipulations in an attempt to control for the many factors which may be influencing findings and to confirm if there are particular biomarkers which can be consistently elicited under certain conditions. Indeed, on the basis of chapters two, three, five and six, it might be concluded that ERP measures currently appeared better suited to this, showing clearer case-control differences, presumably as task paradigms offer a higher degree of control over cognitive processes than resting state conditions.

Methodological factors such as electrode selection, and whether or not to account for other variables such as IQ, can also influence findings, but there is variability in the methodologies adopted in ERP analyses. It is therefore necessary to agree standard methodological approaches, such as how to deal with covariates, before these methods are recognised to have a viable clinical utility. Furthermore, currently analysis techniques require the use of averaging data from several participants in order to extract meaningful data from the background noise of EEG/ERP recording, which means that many research approaches are unsuited to providing

the individual-level data which would be required at a clinical level for diagnostic use. It will also be important to build up adequate data on the consistency and profile of ERP components in large control populations across lifespan to act as age-specific norms in order to provide reliable comparison samples for clinical research and assessments. Such clinical use may therefore not be possible until the use of more advanced methodological approaches, such as Independent Component Analysis (ICA) decomposition becomes widespread. This approach can in some cases provide improved signal-to-noise ratio to examine data from single participants compared to simple averaging approaches. Once data becomes available from several large-scale studies using these methods, it may be possible to demonstrate the reliability of candidate markers under a variety of conditions and across a range of clinical participants.

In chapter three, this thesis examined the ability of some standard clinical measures to delineate ADHD from euthymic BD. Although only an initial comparison in a small sample of adult women, it demonstrated that ADHD measures, which combine both a detailed disorder-specific description of ADHD symptoms with a temporal component, was able to discriminate between participants with ADHD or BD, unlike BD or emotional lability measures. Although these results require replication in larger, more representative clinical samples, they indicate that while a neurophysiological understanding of these disorders is still immature, ruling out ADHD with well-administered ADHD-specific clinical measures combined with good knowledge of the distinctions and commonalities between the disorders may currently be the best available method of delineating ADHD from BD in clinical contexts.

7.7 Future directions

7.7.1 Clinically relevant samples

From a clinical perspective chapter four evaluated symptom overlap between ADHD and euthymic BD. This study had defined inclusion criteria for the more severe forms of ADHD and BD, in an attempt to recruit a more homogeneous sample. However, comparisons which include additional samples closer to clinical realities would further enhance the usefulness of this research, as determining the potential for misdiagnosis between ADHD and BD under a broader range of conditions could be informative from a clinical perspective. For instance, it might be expected that delineation may be easier during manic episodes where BD symptoms are greatly pronounced, while in contrast differentiation may be more challenging in comparisons with Bipolar Disorder II and cyclothymia where reduced symptom severity is likely to make clinical identification more difficult; yet this remains to be confirmed empirically. In addition, due to ethical constraints, some of the BD group assessed in this body of work, as with most previous similar studies, were being treated with mood stabilisers and/or antipsychotic medications during testing. As the effects of medications on the outcome indices used here is poorly understood, particularly in relation to cognitive-electrophysiological measures, research on medication naive or non-adherent groups of BD participants would be valuable to qualifying possible effects on reported findings.

7.7.2 Understanding variability in results

The thesis put forward some cognitive-electrophysiological candidate biomarkers for ADHD and BD for future study, where replications should now be sought in additional independent samples. Evidence indicated that conflict monitoring correlates showed age-specific differences, which could relate to atypical cortical development in ADHD, and that EEG indices were susceptible to contextual differences, which may be due to short term fluctuations in

arousal or motivation during long experimental sessions. In light of this evidence of factors which can contribute to short and long-term variability in case-control differences, it is important to try to understand if these factors are contributing to inconsistencies in reported results within the literature. Firstly, studies should attempt to account for the effect of contextual factors on results, such as the influence of preceding paradigms or experimental procedures, which may alter arousal over time. This could be tested in greater detail by conducting studies where EEG resting state recordings are carried out at several points throughout a recording session, to explore how cortical activation, and potentially case-control differences, change throughout experimental durations. Rest-to-task or task-to-task transition experiments may also prove informative. Secondly, data on the change of cognitive deficits and electrophysiological response across lifespan is needed particularly for developmental disorders such as ADHD, to support interpretations of cortical maturational abnormalities and age-related decline in these samples, which may be contributing to variability in reported case-control differences. Two different approaches would be required for this. Firstly, existing studies, which have conducted age comparisons, have typically adopted the use of broad age groups (e.g. 7-18, 18+), which may not fully capture the rapidly changing processes of cortical maturation during adolescence. With larger samples there is the possibility of dividing groups into several smaller age bands or using continuum approaches, which may be better placed to investigate altered cortical maturation in ADHD samples and map out temporal changes with finer resolution. Alternatively, a superior but more challenging approach would involve longitudinal studies which repeatedly test the same participants throughout childhood and adolescence to examine changes within individuals. Secondly, there is also limited data available in cognitive-electrophysiological changes with age in older populations, particularly among those with ADHD or BD diagnoses. There is evidence showing that cognitive-electrophysiological response to stimuli may decrease with age in controls (Falkenstein et al., 2001, Herrmann et al., 2010), but it is not known if those with psychiatric disorders show similar patterns of decline throughout lifespan, and whether these factors alter observable

case-control differences, which may make the identification of deficits related to psychiatric disorders harder to distinguish in older age groups. Such studies would also require broad cross-sectional samples of different ages, or preferably take the form of longitudinal investigations, which may more conclusively quantify changes in cognitive-electrophysiological response across lifespan.

7.7.3 Advanced analysis approaches

Previous research, including studies presented here, contribute to suggestions that ADHD may be a disorder characterised by high variability in performance measures and cognitive-electrophysiological responses (Castellanos et al., 2005, Castellanos and Tannock, 2002, Lazzaro et al., 1997, Sonuga-Barke and Castellanos, 2007, Vaurio et al., 2009). The majority of common analysis approaches adopted in EEG and ERP studies, including those in this thesis, rely on several stages of averaging to remove noise and to extract meaningful waveforms from the data. However, these techniques also sacrifice trial-by-trial variations within each individual's data, meaning that the underlying variability in cognitive-electrophysiological response in ADHD may not be fully represented. In the absence of highly reliable biomarkers for ADHD, new standardised approaches are now required which have the power to directly examine the degree of variability in EEG or ERP response on a trial-by-trial basis in individual participants, while retaining the power to overcome the low signal to noise ratio in cognitive-electrophysiological data. Approaches such as time-frequency analysis or individual-level Independent Component Analysis (ICA) have potential in this regard as they can avoid group-level averaging, but are yet to reach the wide-spread usage required to produce the quantity of data necessary to conclude whether these methods produce a greater consistency of results than traditional approaches. However, the use of these newer techniques may be particularly important in order to study temporary lapses in attention thought to underlie the increased

RTV generally observed in ADHD, and theta power fluctuations which may also be linked to attentional deficits, as these indicators are difficult to examine in detail using conventional averaging approaches (McLoughlin et al., 2014a, McLoughlin et al., 2014b).

7.7.4 Reducing heterogeneity

In all studies reported in this thesis, including those with large samples (chapters two and three), the effect sizes for cognitive-electrophysiological group comparisons were generally small, suggesting that overall there was much within-group heterogeneity which could be limiting the studies' power to detect differences. Conceptually, the adoption of stringent inclusion criteria is undertaken to reduce sample heterogeneity by including only those participants meeting certain diagnostic criteria. However, even within these diagnoses, substantial heterogeneity may still be present due to different expressions of symptoms within the disorder between individuals, different aetiologies or other factors such as undiagnosed comorbidities, or the subclinical expressions of population traits which interact with the symptoms of the primary diagnosis. This issue is not limited to the investigations of this thesis, but is demonstrated by the lack of consistency in ADHD and BD neurophysiological research generally, and more broadly that of neurobiological research into psychiatric disorders as a whole, as evidenced the difficulties encountered in identifying generic variants associated with psychiatric illness in large scale Genome-Wide Association studies (GWAs). Such matters have led to proposals by NIHR of the Research Domain Criteria (RDoC) (National Institute of Mental Health, 2014), which advance that researchers now need to move beyond categorical definitions of psychiatric disorders in order to directly study common underlying impairments in neurocognitive systems across diagnostic boundaries. This approach aims to find new ways of grouping or separating clusters of symptoms based on dimensional deviations from typical functioning, and conceptualises existing diagnostic categories as the combined profile of

several specific cognitive or emotional impairments. It has been suggested that this data-driven neurobiological framework is necessary to tackle the heterogeneity and comorbidity observed in current clinical diagnostic categories, which are thought to be limiting the ability of neurophysiological and genetic studies to identify robust biomarkers associated with current disorder concepts (Insel et al., 2010). As the studies conducted as parts of this thesis show, larger samples which are restricted to only severe forms of these disorders, do not reduced heterogeneity enough to move our neurobiological understand of these disorders to the next level. This highlights the challenges associated with identifying disorder-specific markers on account of variability in case-control differences. Future research may be able to expedite progress by adopting a flexible dimensional model, which is likely to better represent the complex interplay of cognitive and neurological systems which underlie symptom patterns in psychiatric illness. The design of such studies might include samples of individuals with common symptoms such as attentional deficits, without having stringently defined diagnostic inclusion categories, and in doing so may then clarify the aetiologies of specific deficits at a level below that of clinical diagnosis. This approach may also better conceptualise comorbidities and co-occurring symptoms from the perspective of a collection of related deficits which may or may not have common shared aetiologies. Such approaches would also include a greater range of participants, such as those with less severe forms of disorders such as BD-II, and those with comorbidities which are often excluded from current research despite evidence that these are extremely common in psychiatric populations. Such samples would also be more representative of populations likely to present to mental health services, and therefore findings could offer further advantages of being more generalizable to typical clinical populations. Yet, it is also likely that these samples will need to be larger than those currently employed in neurophysiological studies, in order to have the power to identify subgroups within samples, and to make use of genetically sensitive designs. However, the low per-participant data collection costs and increasing sophisticated automatic analysis techniques mean that cognitive-electrophysiological approaches are well suited to this role, and hence the

next stage of research into biological markers for mental illness may take the form of very large-scale neurophysiological investigations able to resolve the aetiologies of symptoms in relation to specific cognitive deficits, unrestricted by arbitrary definitions of psychiatric disorders.

7.8 Limitations

7.8.1 Multiple testing corrections

The exploratory nature of the cognitive-electrophysiological investigations in this study meant that standard multiple testing corrections were not applied to avoid an increased type-II error rate, which may have prevented studies from identifying candidate biomarkers for future investigation. In light of the limited current knowledge of ADHD and BD neurocognitive processes, this was an undesirable outcome, so emphasis was placed on instead interpreting both effect sizes as well as significance levels. However, in light of the exploratory nature of this research, it is imperative that future replications are conducted before firm conclusions are to be drawn. In the investigation of symptom overlap (chapter four), the outcome measures were well tested clinical scales with norming data available. In this case, given the reliability of the clinical measures and the high number of individual tests employed, a more conservative approach was favourable and appropriate multiple testing corrections were adopted in this study.

7.8.2 Medication effects

A common challenge associated with psychiatric research and particularly cross-disorder investigations is accounting for potential medication effects within research data. In the samples employed here the ADHD group abstained from taking stimulant medication 48 hours prior to testing. However, it was not possible to control for the effects of previous long-term medication use in these studies. In the adult FEBA sample both the BD group and a few of the ADHD participants were taking non-stimulant medications, continued to take their prescribed treatments during testing, as the potential risk of adverse effects from stopping treatment would have been unethical. The effect of non-stimulant medications on EEG and ERP measures in these disorders is still poorly understood, with an inconsistent literature with positive and negative findings, suggesting paradigm specific and disorder-specific effects (Anderer et al., 2002a, Galletly et al., 2005, Jahshan et al., 2012, Karaaslan et al., 2003, Smith et al., 2006, Swann et al., 2013, Tumay et al., 2013, Umbricht et al., 1998). This means it is unclear to what degree medications may have affected results in the investigations using the adult sample in this thesis. Both chapters five and six undertook additional within-group comparisons of those taking medications against those who were not, in an attempt to quantify these differences; however, due to the small sample size in these pilot investigations, it was not possible to accurately resolve the effects on the data. Further work is therefore needed to directly examine the effect of medications in the ERP measures adopted here.

7.8.3 Sample size, age and gender effects

For the adult studies (chapters four, five and six) this sample represented a novel pilot sample, and was therefore of limited size, which may have reduced the samples ability to resolve those

differences with a small effect size. These studies therefore require replication in larger samples.

Chapters three and five both investigated N2 case-control differences in ADHD in two separate samples. Potential differences emerged in the large sample of adolescents which were predominantly male, but not in the smaller, older-adult female sample. It is likely that changes in N2 amplitude with age underlie these differences between studies, as chapter three also demonstrated different patterns of atypical N2 amplitude between older and younger subgroups within the larger adolescent sample. However, these studies did not directly test age-related differences between these two experimental samples, so this factor remains to be tested directly. In addition, possible gender differences were not tested directly and remain to be ruled out; as these could also have been contributing to different results between the studies.

7.8.4 Comorbidities and subclinical symptoms

In this thesis experimental samples were selected based on existing ADHD or BD diagnosis, with any with a diagnosed comorbidity between ADHD and BD being excluded during recruitment. However, given the shared symptoms between ADHD and BD, and the demonstrated complexities in diagnostic differentiation, it is possible that the adult FEBA sample may have contained some participants with undiagnosed ADHD in the BD sample and vice versa. Moreover, as both disorders are considered the extreme end of normally distributed behavioural traits in the general population, both groups would be expected to show some subclinical expressions of the other disorder. What remains unclear is whether

associated symptoms of these disorders, such as mood instability and depression in ADHD or hyperactivity in BD relate to the primary diagnosis or can be accounted for by co-occurring symptoms which do not have a shared aetiology. This research adopted the use of current diagnostic frameworks in sample selection to ensure research was relevant to current clinical conceptualisations; however, this meant that it was not able to generalise to broader clinical or non-clinical samples or fully explore the relationship between these disorders and their various comorbidities. Such work will be required to understand the nature of the relationship between the overlapping continuums of ADHD and BD symptoms fully.

7.9 Overall conclusions

In summary, this thesis aimed to understand and compare ADHD and BD based on cognitive-neurophysiological abnormalities and clinical symptoms. Presented herein was a comparison of the symptoms of inattention, hyperactivity, mania, depression and emotional lability (EL) in ADHD and BD using typical clinical diagnostic measures. Symptoms of depression, mania and EL were not found to reliably distinguish ADHD from euthymic BD, although conversely ADHD measures had good discrimination potential, on account of the inherent temporal component in assessment items, and may currently be the best available method of delineating ADHD from BD in clinical contexts. Cognitive-electrophysiological data also identified some possible candidate biomarkers for both ADHD and BD disorders, including two disorder-specific cognitive-electrophysiological markers which dissociated ADHD from BD. These studies also demonstrate that ADHD-control differences are sensitive to changes in activation over longer recording durations and also vary by age. However, the relatively small effect sizes observed in many cognitive-electrophysiological comparisons suggests that the broad disorder classifications and heterogeneity within these classifications will make resolving

the fine details of shared or specific cognitive impairments in ADHD and BD challenging. Moreover, these data also show that methodological and sample differences may be contributing to variability within the literature to date, and need to be further understood. Further comparison studies are needed, including ones which are able to explore differences within groups as much as between groups to understand shared vs characteristic deficits in different expressions of each disorder, and untangle confusion arising from symptom overlap and comorbidities. It is in this way that we will gradually move towards understanding the potentially varied neurobiological underpinnings of ADHD and BD, and perhaps in future, towards diagnostic models able to fully utilise biomarkers for effective clinical diagnosis and treatment.

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Appendix

Appendix 1. Publications and conference poster presentations arising from this thesis

Appendix 2. Supplementary materials for chapter 2

S1. Topographic maps showing scalp recorded power density in delta, theta, alpha, and beta bands

S2. T-maps showing time-1 activity relative to time-2 activity, across frequency bands and group status

S3. T-maps showing ADHD activity relative to control activity, across frequency bands and recording time

S4. Comparison of adolescents aged 12-18 and adults 18+ within ADHD and control samples.

S5. Mean amplitude in μV and standard deviation (SD), prior to transformations, and with age and gender controlled for, in ADHD and control groups across frequency bands and theta/beta ratio at Fz, Cz and Pz

S6. Significance values and effect sizes for ANCOVA factors and interactions, controlling for age, gender, using data from mid-line electrode (Fz, Cz, Pz).

S7. Significance values and effect sizes for ANCOVA factors and interactions, controlling for age, gender, and IQ, using data from mid-line electrode (Fz, Cz, Pz).

S8. Significance values for ANCOVA factors and interactions, controlling for age and gender, using global field synchronisation scores and showing covariate interaction with the dependent variable.

S9. Correlations of age with global field synchronisation.

Appendix 3. Supplementary materials for chapter 5

S10. Grand average for error trials, using different inclusions thresholds for number of good segments

S11. Mean N2 and P2 mean amplitude at FCz compared across those undergoing treatment with different classes of medications

Appendix 4. Supplementary materials for chapter 6

S12. Mean (standard deviation) P3a and P3b amplitude and mean (standard deviation) fronto-central theta power (μV) in novel and target conditions for those currently taking different classes of medications

S13. ERP power in target (P3b) or novel (P3a) conditions by medication status and group for mood stabiliser, antidepressant, antipsychotic and stimulant medication classes.

Appendix 1. Publications and conference poster presentations arising from this thesis

Published scientific journal papers

Kitsune GL., Cheung CHM., Brandeis D., Banaschewski T., Asherson P., McLoughlin G., Kuntsi J. (2014). A matter of time: the influence of recording context on EEG spectral power in adolescents and young adults with ADHD. *Brain Topography*

International conference poster presentations

(Published under name Mould, G. L. prior to Feb 2013)

Michelini, G., Kitsune, GL., Frangou, S., Hosang, GM., Asherson P., McLoughlin, G., Kuntsi. J. (2014)

Neurophysiological stimulus processing impairments distinguish women with ADHD from women with bipolar disorder

Poster presented at UK Adult ADHD Network (UKAAN) 4th Congress, 10th - 12th September, London, UK.

Michelini, G., Kitsune, GL., Frangou, S., Hosang, GM., Asherson P., McLoughlin, G., Kuntsi. J. (2014) Neurophysiological conflict monitoring impairments distinguish women with bipolar disorder from women with ADHD

Poster presented at Eunethydis 3rd International Conference, 21st - 24th May, Instabul, Turkey.

Kitsune, GL., Cheung, C., Banaschewski, T., Brandeis, D., Asherson, P., McLoughlin, G., Kuntsi, J. (2013) The consistency of ADHD-control differences in resting-state EEG power across time

Poster presented at Eunethydis 23rd Network Meeting, 3rd - 6th October 2013, Prague, Czech Republic.

Mould, GL., Cheung, C., Banaschewski, T., Brandeis, D., Asherson, P., McLoughlin, G., Kuntsi, J. (2012) An investigation of resting-state EEG power in adolescents with combined-type ADHD

Poster presented at Eunethydis 2nd International Conference, 23rd-25th May 2012, Barcelona, Spain.

Publications in preparation based upon thesis chapters

Based on chapter four

**Kitsune, GL., Kuntsi, J., Costello, H., Hosang, GM., McLoughlin, G., Asherson, P.,
(in preparation)**

Delineating ADHD and bipolar disorder: A comparison of clinical profiles in adult women

Based on chapters three and five

**Kitsune GL., Cheung CHM., Brandeis D., Banaschewski T., Hosang, GM., Michelini, G.,
Asherson P., McLoughlin G., Kuntsi J. (in preparation)**

Neurophysiological stimulus performance monitoring impairments in adolescents with ADHD,
and cross-disorder comparison in adult women with bipolar disorder or ADHD.

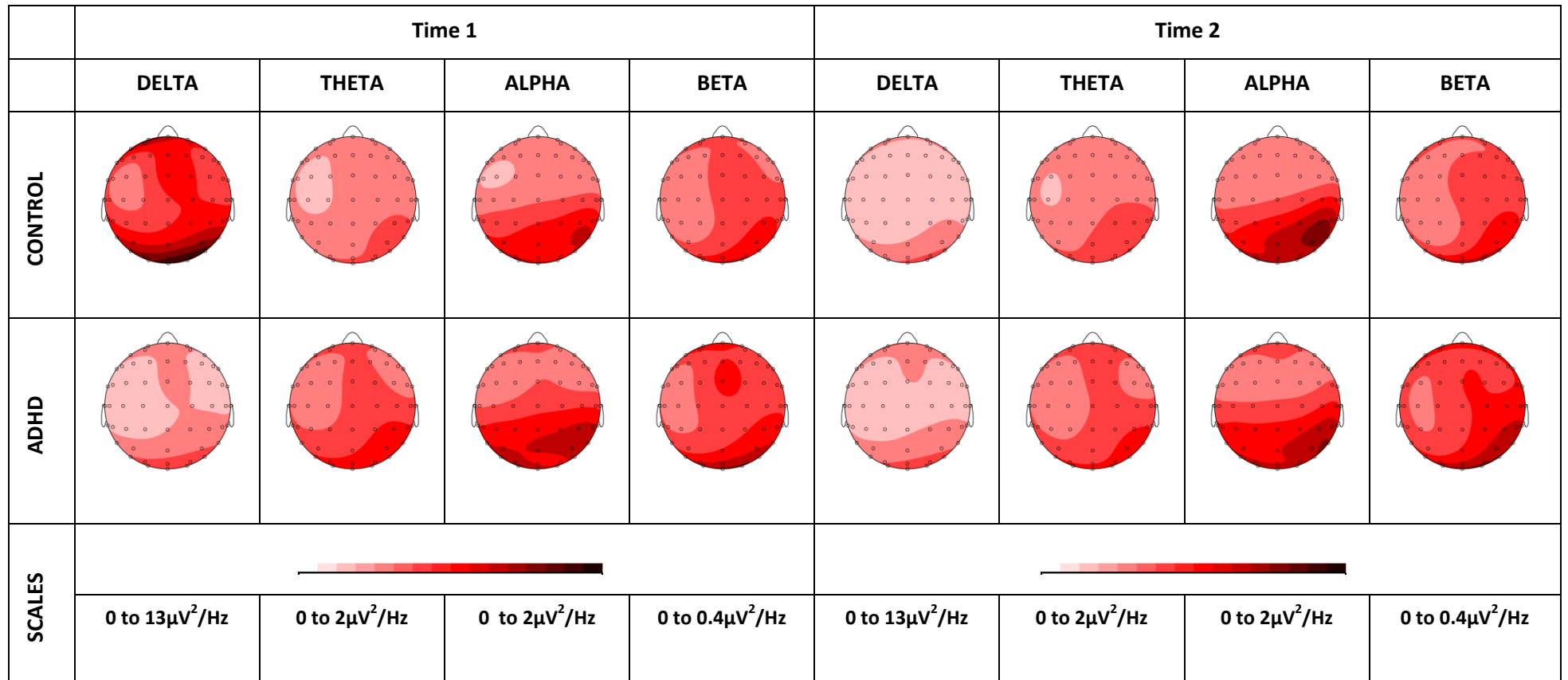
Based on chapter six

**Kitsune, GL., McLoughlin, G., Hosang, GM., Laurens, KR., Asherson, P., Kuntsi, J.(in
preparation)**

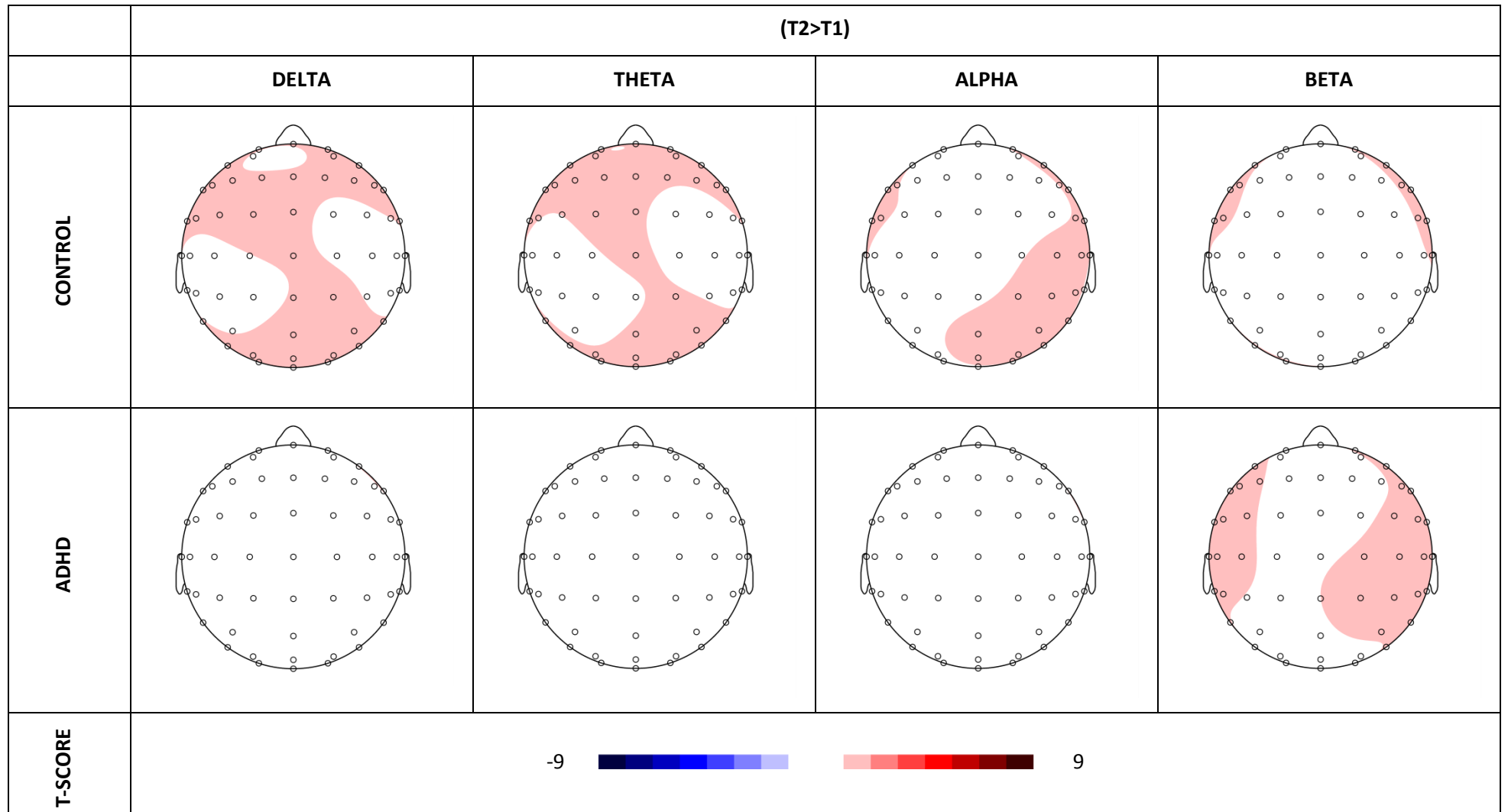
The allocation of attentional resources and theta activity as candidate discriminators of ADHD
and bipolar disorder

Appendix 2. Supplementary materials for chapter 2

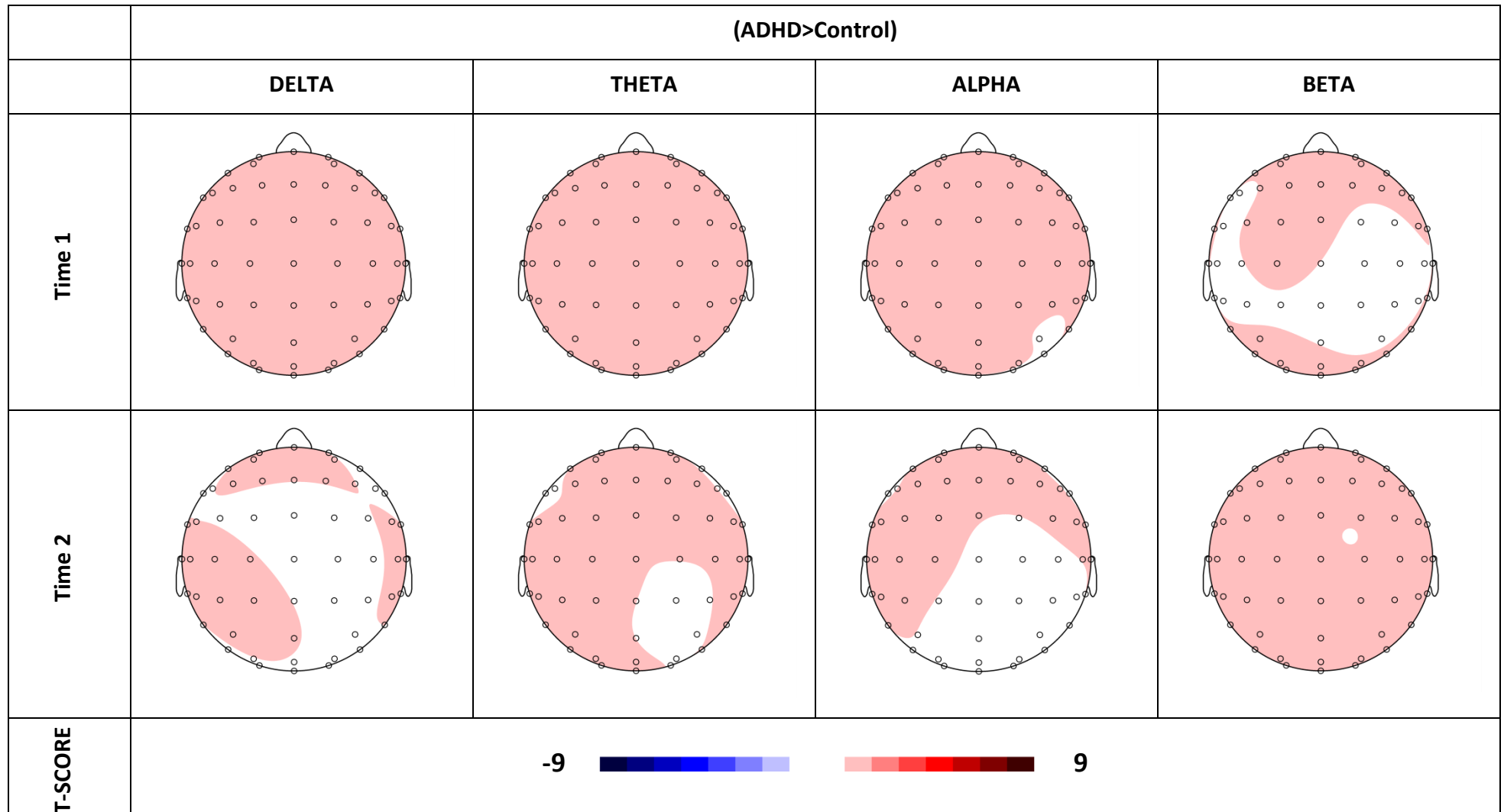
S1. Topographic maps showing scalp recorded power density in delta, theta, alpha, and beta bands



S2. T-maps showing time-1 activity relative to time-2 activity, across frequency bands and group status



S3. T-maps showing ADHD activity relative to control activity, across frequency bands and recording time



S4. Comparison of adolescents aged 12-18 and adults 18+ within ADHD and control samples.

		ADHD		test statistic		Control		test statistic		
		12-18	18+	age-comparison		12-18	18+	age-comparison		
Age	n			F	p			F	p	
		Region	μV (SD)	μV (SD)			μV (SD)	μV (SD)		
Delta	Time 1	Frontal	4.5 (2.6)	2.15 (0.92)	7.939	0.006*	2.8 (1.41)	1.91 (1.06)	10.129	0.002*
		Central	4.12 (2.69)	1.87 (1.02)			2.57 (1.42)	1.62 (0.75)		
		Parietal	5.96 (4.06)	2.79 (1.55)			3.52 (1.93)	2.24 (1.26)		
	Time 2	Frontal	4.44 (2.55)	3.04 (1.46)			3.69 (1.78)	2.79 (1.23)		
		Central	3.67 (2.76)	2.06 (1.05)			3.05 (1.81)	1.88 (0.88)		
		Parietal	5.46 (4.38)	3.03 (1.27)			4.34 (2.6)	2.64 (1.06)		
Theta	Time 1	Frontal	0.91 (0.56)	0.53 (0.3)	8.715	0.004*	0.65 (0.3)	0.41 (0.2)	17.515	0.001*
		Central	0.96 (0.71)	0.52 (0.35)			0.67 (0.34)	0.4 (0.18)		
		Parietal	1.25 (1.02)	0.7 (0.45)			0.81 (0.42)	0.53 (0.33)		
	Time 2	Frontal	0.87 (0.55)	0.64 (0.38)			0.74 (0.29)	0.54 (0.26)		
		Central	0.88 (0.75)	0.54 (0.37)			0.72 (0.39)	0.46 (0.24)		
		Parietal	1.1 (0.97)	0.75 (0.49)			0.93 (0.52)	0.61 (0.38)		

Alpha	Time 1	Frontal	0.81 (0.57)	0.57 (0.5)	3.738	0.057[†]	0.63 (0.4)	0.5 (0.62)	4.589	0.035*
		Central	1.07 (0.9)	0.73 (0.8)			0.82 (0.61)	0.54 (0.42)		
		Parietal	1.59 (1.24)	1.25 (1.49)			1.36 (1.34)	1 (1.39)		
	Time 2	Frontal	0.8 (0.45)	0.73 (0.67)	6.514	0.012*	0.72 (0.46)	0.58 (0.42)	6.389	0.013*
		Central	0.99 (0.83)	0.86 (0.96)			0.97 (0.87)	0.64 (0.59)		
		Parietal	1.41 (1.15)	1.48 (1.65)			1.64 (1.56)	1.22 (1.48)		
Beta	Time 1	Frontal	0.2 (0.13)	0.14 (0.06)	2.456	0.121	5.34 (2.69)	4.2 (2.07)	4.770	0.032*
		Central	0.21 (0.13)	0.13 (0.06)			5.26 (2.65)	4.24 (1.86)		
		Parietal	0.25 (0.14)	0.17 (0.07)			4.95 (2.38)	4.02 (1.88)		
	Time 2	Frontal	0.23 (0.15)	0.17 (0.07)	5.75 (2.88)	4.45 (1.95)	0.18 (0.1)	0.13 (0.05)	5.7 (2.83)	4.43 (1.99)
		Central	0.22 (0.15)	0.17 (0.11)			0.18 (0.12)	0.13 (0.06)		
		Parietal	0.26 (0.15)	0.21 (0.14)			0.22 (0.13)	0.17 (0.08)		
T:B	Time 1	Frontal	5.64 (2.83)	4.43 (1.99)	2.456	0.121	5.34 (2.69)	4.2 (2.07)	4.770	0.032*
		Central	5.75 (2.88)	4.45 (1.95)			5.26 (2.65)	4.24 (1.86)		
		Parietal	5.7 (3.03)	4.36 (1.98)			4.95 (2.38)	4.02 (1.88)		
	Time 2	Frontal	4.97 (2.62)	4.42 (1.57)	5.54 (3.39)	4.37 (1.76)	5.37 (2.51)	4.66 (1.69)	5.54 (3.39)	4.37 (1.76)
		Central	5.54 (3.39)	4.37 (1.76)			5.48 (2.53)	4.59 (1.76)		
		Parietal	5.23 (3.23)	4.26 (1.68)			5.34 (2.64)	4.2 (1.82)		

* $p < 0.05$; [†] $p < 0.08$; T:B theta/beta ratio; μV mean power; SD standard deviation

S5. Mean amplitude in μV and standard deviation (SD), prior to transformations, and with age and gender controlled for, in ADHD and control groups across frequency bands and theta/beta ratio at Fz, Cz and Pz

Electrode			Delta μV (SD)	Theta μV (SD)	Alpha μV (SD)	Beta μV (SD)	T:B μV (SD)
Fz	T1	Control	3.23 (2.22)	0.64 (0.36)	0.64 (0.53)	0.18 (0.17)	0.18 (0.17)
	T1	ADHD	4.29 (3.38)	0.85 (0.62)	0.8 (0.66)	0.22 (0.18)	0.22 (0.18)
	T2	Control	4.11 (3.28)	0.74 (0.4)	0.71 (0.51)	0.16 (0.12)	0.16 (0.12)
	T2	ADHD	4.52 (3.62)	0.85 (0.61)	0.85 (0.72)	0.21 (0.18)	0.21 (0.18)
Cz	T1	Control	2.07 (1.41)	0.56 (0.38)	0.62 (0.47)	0.19 (0.13)	0.19 (0.13)
	T1	ADHD	3 (3.59)	0.74 (0.64)	0.77 (0.75)	0.19 (0.17)	0.19 (0.17)
	T2	Control	2.59 (1.44)	0.66 (0.37)	0.71 (0.68)	0.19 (0.17)	0.19 (0.17)
	T2	ADHD	2.72 (1.92)	0.7 (0.55)	0.78 (0.87)	0.23 (0.21)	0.23 (0.21)
Pz	T1	Control	2.84 (1.85)	0.7 (0.5)	1.26 (1.49)	0.18 (0.13)	0.18 (0.13)
	T1	ADHD	4.3 (3.72)	0.96 (0.91)	1.43 (1.49)	0.2 (0.14)	0.2 (0.14)
	T2	Control	3.58 (3.42)	0.81 (0.76)	1.7 (2.39)	0.18 (0.14)	0.18 (0.14)
	T2	ADHD	4.03 (3.37)	0.87 (0.85)	1.38 (1.47)	0.21 (0.17)	0.21 (0.17)

T:B theta/beta ratio; μV mean power; SD standard deviation; T1 time 1; T2 time 2

S6. Significance values and effect sizes for ANCOVA factors and interactions, controlling for age, gender, using data from mid-line electrode (Fz, Cz, Pz).

		Delta	Theta	Alpha	Beta	T:B
Time	F	0.00	1.60	0.90	0.01	0.14
	p	0.984	0.207	0.345	0.905	0.905
	η²	0.0001	0.0094	0.0054	0.0001	0.0001
Region	F	2.08	4.16	4.46	0.15	0.15
	p	0.127	0.016*	0.012*	0.860	0.860
	η²	0.0009	0.0248	0.0271	0.0009	0.0009
Group	F	6.92	2.97	1.14	4.19	2.62
	p	0.009*	0.870	0.288	0.107	0.107
	η²	0.0341	0.0150	0.0066	0.0141	0.0141
Group*Region	F	1.63	0.82	0.97	2.14	2.14
	p	0.198	0.440	0.380	0.120	0.120
	η²	0.0133	0.0049	0.0059	0.0133	0.0133
Group*Time	F	3.37	4.70	1.54	0.32	0.32
	p	0.068†	0.032*	0.217	0.570	0.570
	η²	0.0020	0.0274	0.0092	0.0020	0.0021

Activity bands defined as: delta 0.5-3.4Hz, theta 3.5-7.5Hz, alpha 7.5-12Hz, beta 12-30Hz. * denotes significant at $p < 0.05$. † denotes trend level effect at $p < 0.08$.

Effect size (η^2); 0.0099 constitutes a small effect, 0.0588 a medium effect and 0.1379 a large effect.

S7. Significance values and effect sizes for ANCOVA factors and interactions, controlling for age, gender, and IQ, using data from mid-line electrode (Fz, Cz, Pz).

		Delta	Theta	Alpha	Beta	T:B
Time	F	0.64	0.26	0.48	0.06	0.63
	p	0.425	0.610	0.827	0.802	0.802
	η²	0.0039	0.0015	0.0003	0.0004	0.0004
Region	F	3.52	2.09	2.53	0.68	0.68
	p	0.031*	0.125	0.091	0.505	0.508
	η²	0.0215	0.0126	0.0156	0.0043	0.0043
Group	F	3.74	1.57	0.98	0.70	0.70
	p	0.055†	0.212	0.324	0.403	0.403
	η²	0.0191	0.0081	0.0057	0.0039	0.0039
Group*Region	F	0.37	0.10	0.55	0.53	0.53
	p	0.658	0.893	0.577	0.591	0.591
	η²	0.0023	0.0006	0.0034	0.0033	0.0033
Group*Time	F	5.03	5.09	2.21	0.05	0.05
	p	0.026*	0.025*	0.014*	0.824	0.824
	η²	0.0305	0.0299	0.0132	0.0003	0.0003

Activity bands defined as: delta 0.5-3.4Hz, theta 3.5-7.5Hz, alpha 7.5-12Hz, beta 12-30Hz. * denotes significant at $p < 0.05$. † denotes trend level effect at $p < 0.08$.

Effect size (η^2); 0.0099 constitutes a small effect, 0.0588 a medium effect and 0.1379 a large effect.

S8. Significance values for ANCOVA factors and interactions, controlling for age and gender, using global field synchronisation scores and showing covariate interaction with the dependent variable.

		Delta	Theta	Alpha	Beta
Group	F	1.26	0.43	0.32	0.11
	p	0.263	0.512	0.575	0.738
Age	F	7.93	13.80	6.83	4.63
	p	0.005*	0.000*	0.010*	0.033*
Gender	F	6.63	6.28	0.01	0.37
	p	0.110	0.013*	0.936	0.543
Condition	F	0.01	3.21	0.27	0.04
	p	0.929	0.075†	0.607	0.849
Condition*Age	F	0.00	3.44	0.41	0.27
	p	0.964	0.066†	0.523	0.870
Condition*Gender	F	0.20	2.37	1.05	0.27
	p	0.653	0.126	0.308	0.606
Condition*Group	F	1.90	2.21	1.11	1.11
	p	0.170	0.139	0.295	0.294

Activity bands defined as: delta 0.5-3.4Hz, theta 3.5-7.5Hz, alpha 7.5-12Hz, beta 12-30Hz. * denotes significant at $p < 0.05$. † denotes trend level effect at $p < 0.08$.

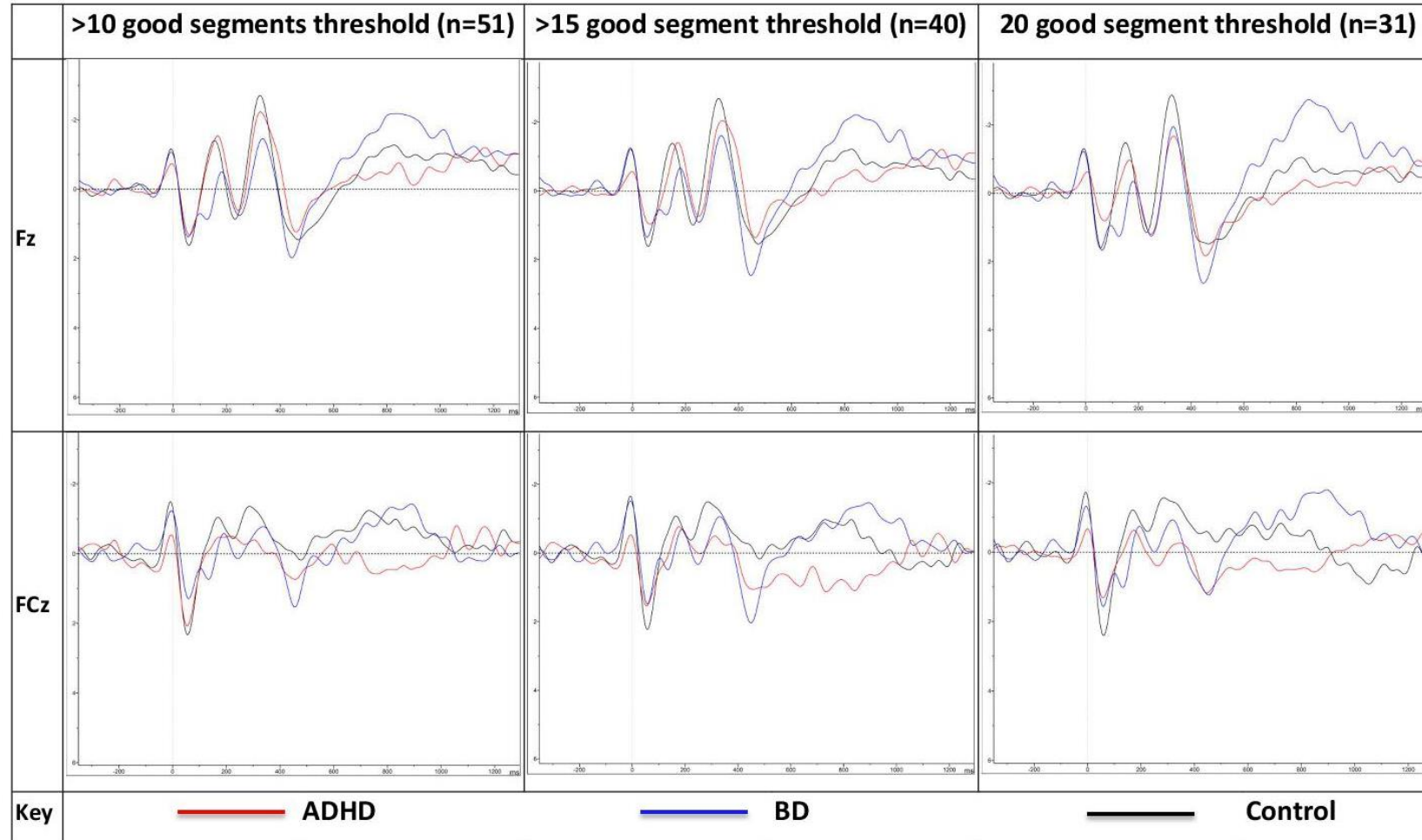
S9. Correlations of age with global field synchronisation.

	Delta T1	Theta T1	Alpha T1	Beta T1	Delta T2	Theta T2	Alpha T2	Beta T2
Pearson r	0.21	0.34	0.2	0.14	0.17	0.15	0.15	0.12
p	0.006*	<0.0001*	0.009*	0.068†	0.029*	0.062†	0.052*	0.132

*Activity bands defined as: delta 0.5-3.4Hz, theta 3.5-7.5Hz, alpha 7.5-12Hz, beta 12-30Hz. * denotes significant at $p < 0.05$. † denotes trend level effect at $p < 0.08$.*

Appendix 3. Supplementary materials for chapter 5

S10. Grand averages from error trials, using different inclusion thresholds for number of good segments



Due to the low number of participants with more than 20 clean segments available for each average, different inclusion thresholds for averages were compared in an attempt to include additional numbers of participants. However, grand average waves fluctuated based on thresholds, and therefore did not provide reliable data for analysis. We instead focused on the N2 analysis.

S11. Mean N2 and P2 mean amplitude at FCz compared across those undergoing treatment with different classes of medications

Taking medication		ADHD				BD			
		n	%	N2 (μ V)	P2 (μ V)	n	%	N2 (μ V)	P2 (μ V)
Mood stabiliser	Yes	0	0	-	-	14	70%	172.46 (259.23)	1.44 (2.19)
	No	18	100%	-	-	6	30%	64.96 (169.63)	0.7 (2.31)
	d			-	-			0.49	0.33
Anti-depressant	Yes	3	17%	-139.95 (119.71)	-2.19 (2.05)	8	40%	91.79 (194.12)	1.05 (2.14)
	No	15	83%	3.65 (182.09)	-0.14 (1.07)	12	60%	172.5 (264.75)	1.33 (2.32)
	d			0.93	1.42			0.34	0.12
Anti-psychotic	Yes	0	0	-	-	8	40%	148.44 (271.03)	1.2 (2.73)
	No	18	100%	-	-	12	60%	134.73 (223.8)	1.23 (1.89)
	d			-	-			0.06	0.01
Stimulant	Yes	13	72%	5.62 (190.92)	-0.28 (1.18)	0	0%	-	-
	No	5	28%	-87.65 (137.45)	-0.99 (2.03)	20	100%	-	-
	d			0.56	0.43			-	-

Cohen's *d* effect sizes: 0.2 small, 0.5 medium and 0.8 large.

Appendix 4. Supplementary materials for chapter 6

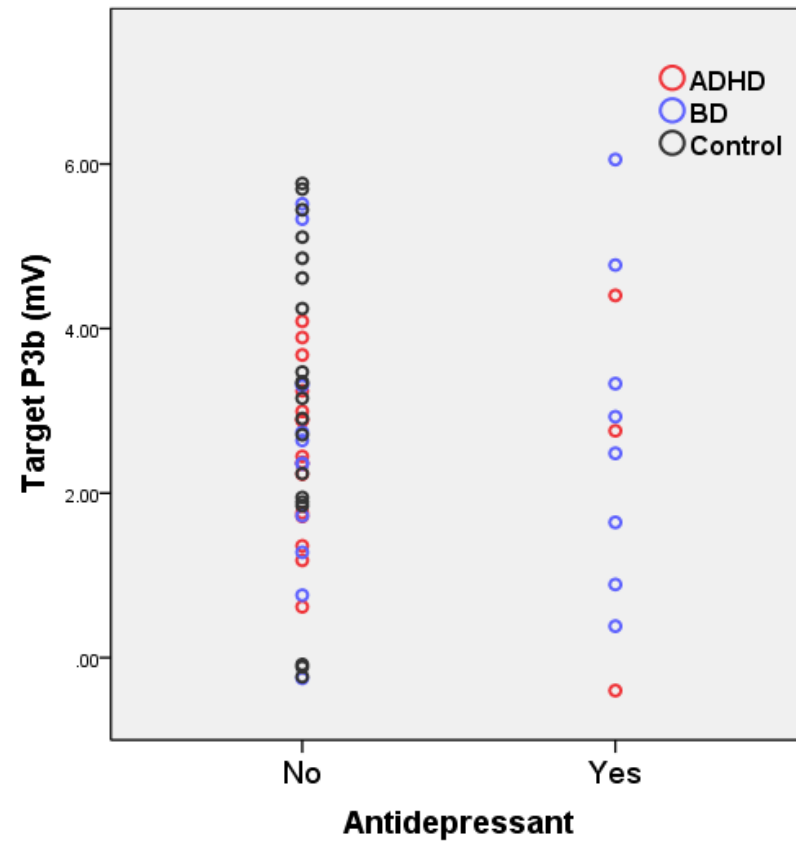
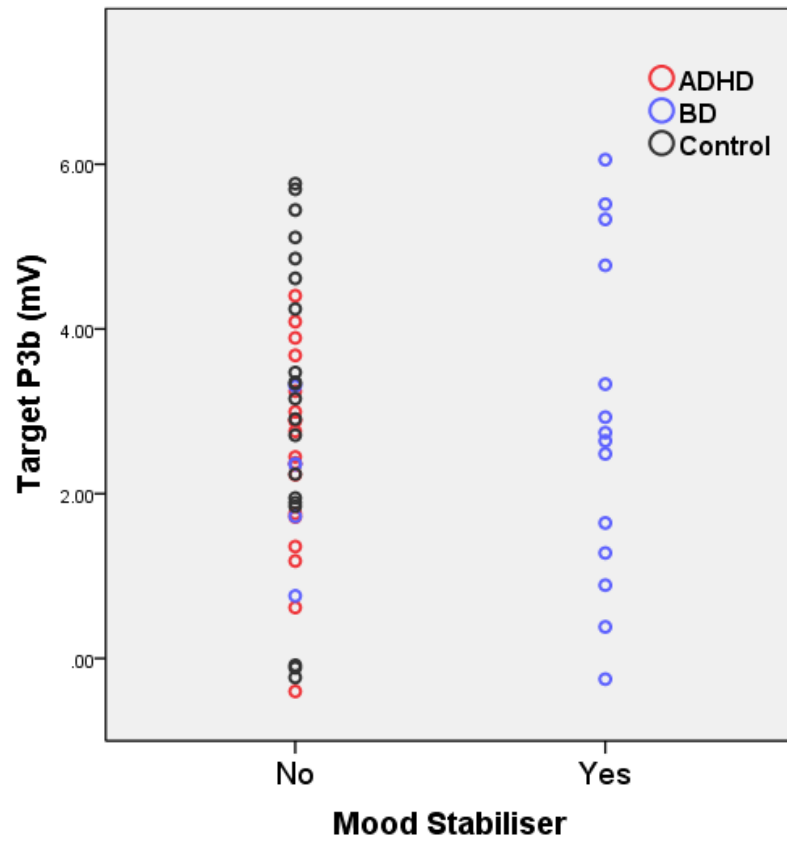
S12. Mean (standard deviation) P3a and P3b amplitude and mean (standard deviation) fronto-central theta power (μV) in novel and target conditions for those currently taking different classes of medications

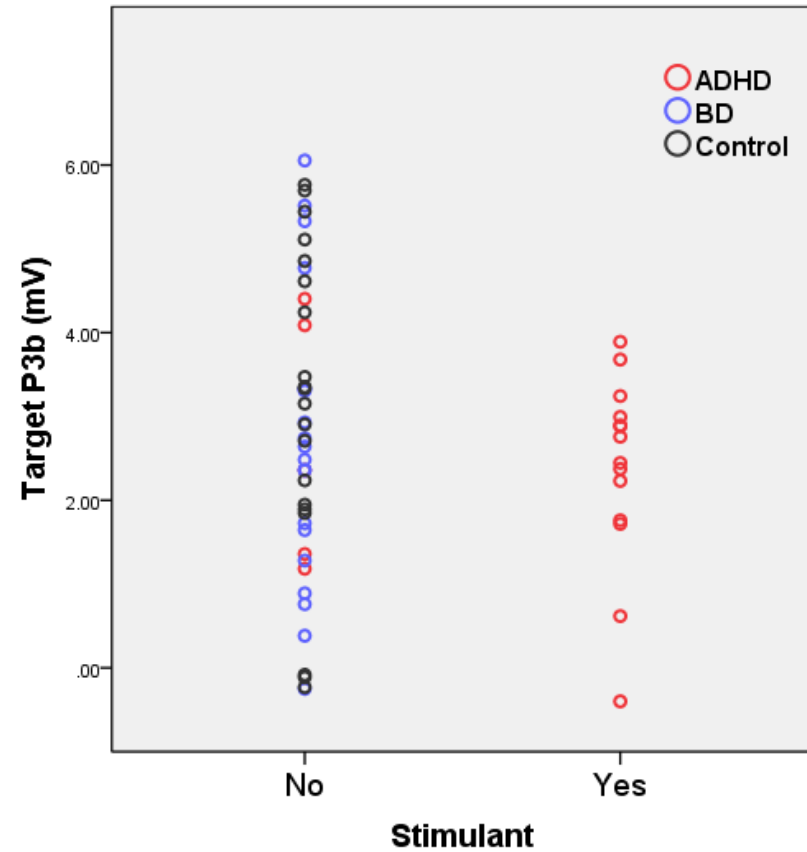
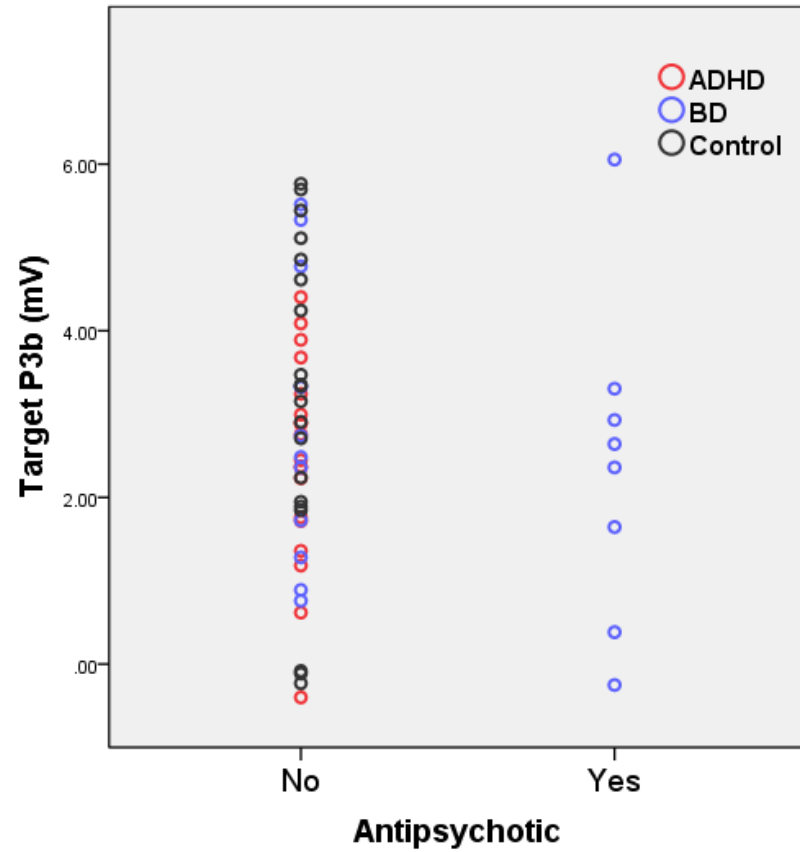
		ADHD					BD				
		n	Target P3b	Novel P3a	Target theta	Novel theta	n	Target P3b	Novel P3a	Target theta	Novel theta
Mood stab	YES	19	-	-	-	-	14	2.84 (1.98)	1.19 (2.16)	0.66 (0.46)	0.63 (0.29)
	NO	0	-	-	-	-	6	2.31 (0.98)	1.48 (2.04)	0.39 (0.57)	0.78 (0.9)
Antidep	YES	3	2.25 (2.44)	2.39 (3.3)	0.66 (0.56)	1.26 (1.08)	8	2.81 (1.92)	0.52 (2.15)	0.63 (0.59)	0.74 (0.3)
	NO	16	2.48 (0.99)	1.53 (1.19)	0.68 (0.62)	0.78 (0.53)	12	2.59 (1.68)	1.79 (1.95)	0.55 (0.45)	0.63 (0.64)
Antipsy	YES	0	-	-	-	-	8	2.38 (1.93)	0.91 (1.07)	0.52 (0.3)	0.56 (0.31)
	NO	18	-	-	-	-	12	2.88 (1.64)	1.52 (2.56)	0.62 (0.6)	0.75 (0.63)
Stim	YES	14	2.36 (1.16)	1.23 (1.29)	0.71 (0.64)	0.82 (0.54)	0	-	-	-	-
	NO	5	2.68 (1.5)	2.87 (1.84)	0.59 (0.49)	0.97 (0.9)	20	-	-	-	-

Abbreviations: Mood Stab: Mood stabiliser; Antidep: Anti-depressant medication; Antipsy: Anti-psychotic medication; Stim: Stimulant medication. ADHD participants were not taking stimulant medications at the time of testing. Novel P3a is the mean event related potential (ERP) activity between 200-500 ms at FCz in response to novel stimuli on trials where participants did not make a commission error. Target P3b is the mean ERP activity between 200-800 ms at Pz where participants correctly responded to the target stimuli with a reaction time of between 100 – 1000 ms. Target Theta and Novel Theta is the mean theta band power (3.5 – 7.5 Hz) across 1000 ms stimuli-linked epochs in those respective conditions.

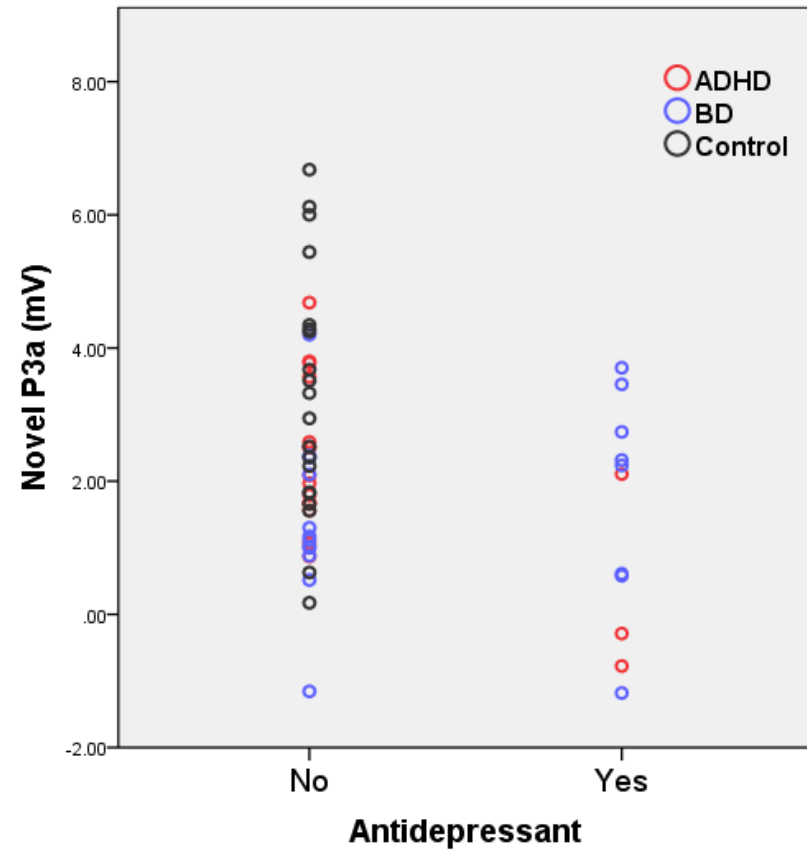
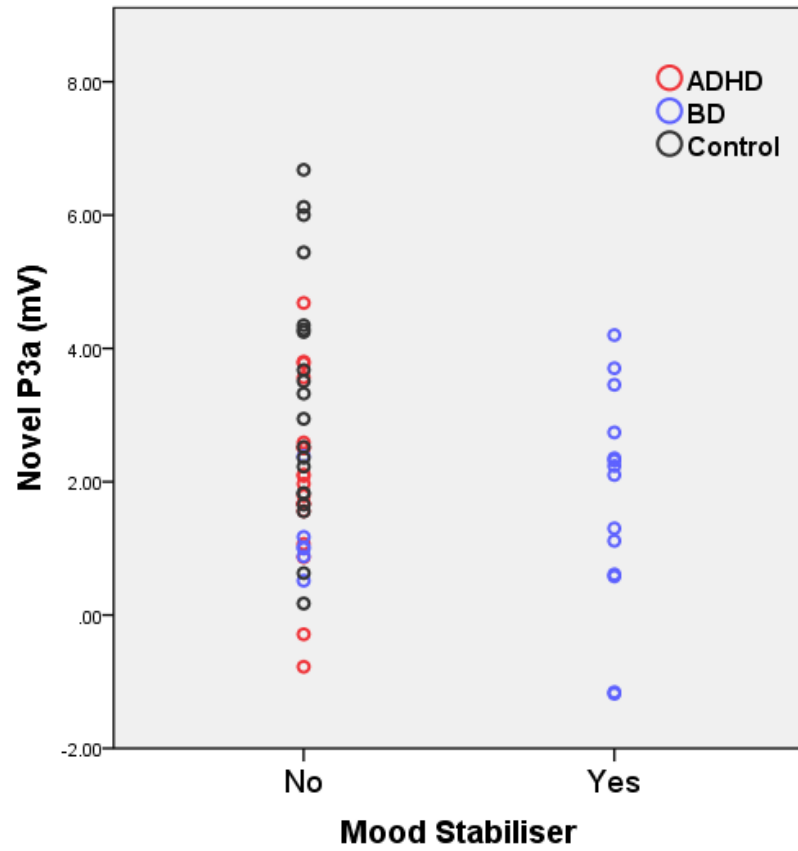
S13. ERP power in target (P3b) or novel (P3a) conditions by medication status and group for mood stabiliser, antidepressant, antipsychotic and stimulant medication classes.

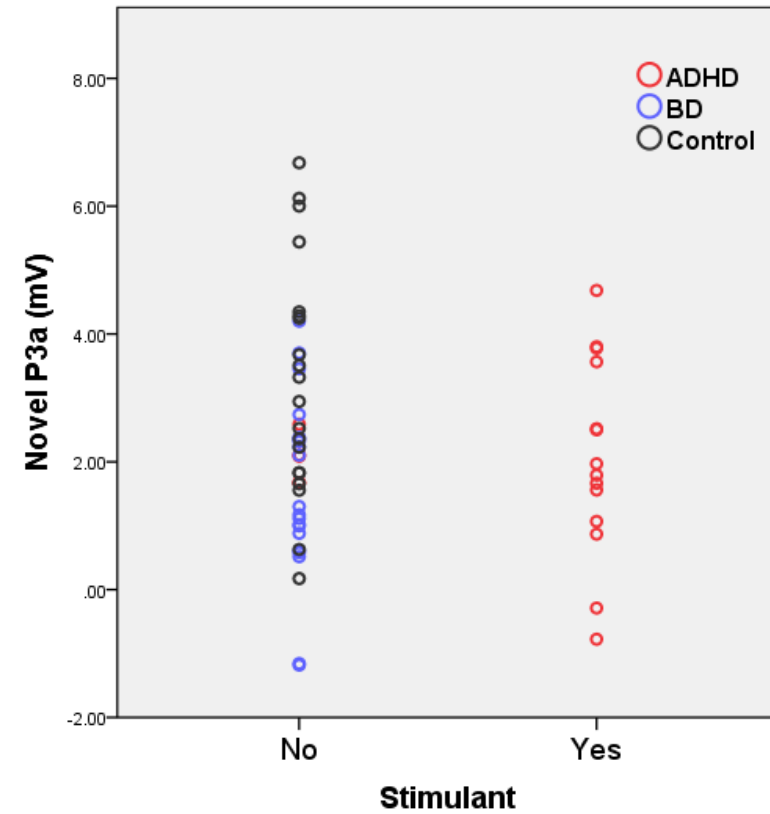
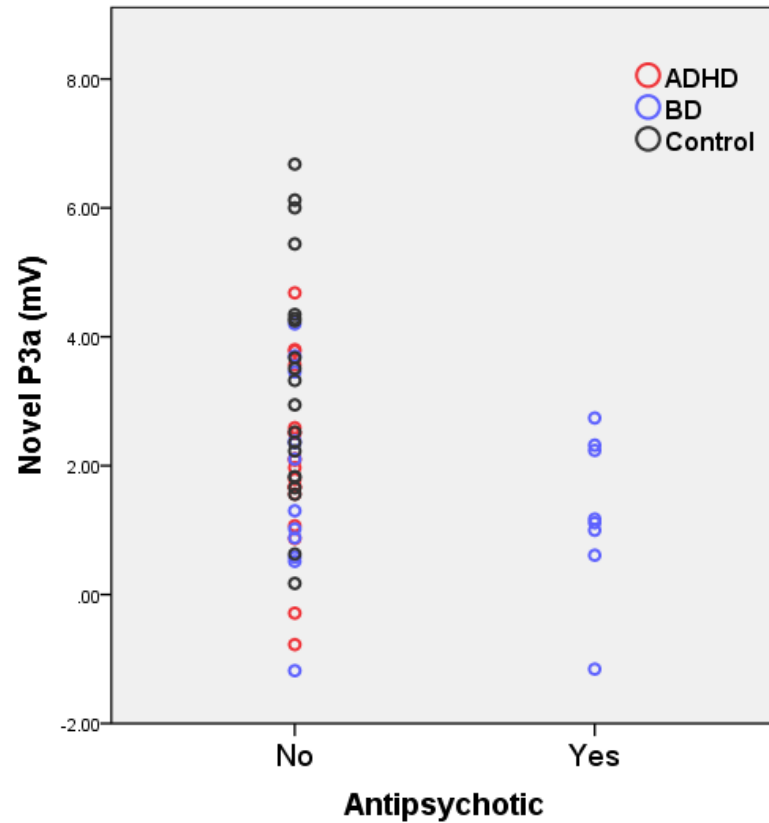
(a) Target Condition





(b) Novel Condition





Participants currently being treated with stimulants refrained from taking their medications 48 hours before testing, all other participants continued their normal treatment routine during testing. P3b as recorded at Pz, P3a as recorded at FCz. Theta activity in both target and novel conditions recorded at FCz. Theta power used in analysis: 3.5-7.5 Hz. Target condition includes only trials where participants correctly responded to the target stimuli with a reaction time of between 100 – 1000 ms. The novel condition only includes trials where participants did not make commission errors.