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The EEG activity of girls with attention-deficit/ hyperactivity disorder

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The EEG Activity of Girls with Attention-Deficit/Hyperactivity Disorder

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THESIS CERTIFICATION

I, Franca E Dupuy, declare that this thesis, submitted in partial fulfilment of the requirements for the award of Doctor of Philosophy, in the School of Psychology, University of Wollongong, is wholly my own work unless otherwise referenced or acknowledged. This document has not been submitted for qualifications at any other academic institution.

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ABSTRACT

This thesis examined the electroencephalography (EEG) activity of girls and women with Attention-Deficit/Hyperactivity Disorder (AD/HD). An eyes-closed resting condition was used in all five experimental studies. Absolute and relative power estimates were calculated in the delta, theta, alpha, and beta bands in all studies. Gamma power and the theta/beta ratio were included in some studies. The thesis began with a published review of EEG-AD/HD literature that highlighted the substantial lack of information on females and sex differences. The first three experimental chapters explored EEG differences between the Combined and Inattentive types of AD/HD within girls, aged 7-12 years. Chapter 3 focussed particularly on EEG sex differences within these AD/HD types, and Chapters 4 and 5 explored EEG differences within exclusive female subject groups. Results from these studies indicate that the EEG activity is large homogenous within girls with AD/HD, regardless of diagnosed type. Chapter 6 found that girls with AD/HD are hypoaroused, characterised by significantly reduced skin conductance levels (SCL), relative to controls. Absolute and relative gamma was also significantly reduced among girls with AD/HD. The final experimental chapter examined sex differences in the EEG activity of adults with AD/HD who had a previous childhood diagnosis of the disorder. This is the first study to recruit adult AD/HD subjects based on DSM-5 adult AD/HD criteria and the first to incorporate single-sex adult subject groups. Results indicate that there are significant sex differences in relative theta and the theta/beta ratio between men and women with and without AD/HD. This thesis concluded that there are female-specific EEG

anomalies and that the existing male-dominated EEG-AD/HD literature does not apply to females.

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1 OVERVIEW

1.1 Overview

Attention-Deficit/Hyperactivity Disorder (AD/HD) is one of the most well-known and well-researched psychiatric disorders of childhood. This neurodevelopmental condition is characterised by age-inappropriate behaviours of inattention, hyperactivity and impulsivity. This disorder typically emerges before age seven, is pervasive, and often chronic, with an estimated prevalence rate of 3-7% in school aged children (Pastor & Reuben, 2008; Polanczyk, de Lima, Horta, Biederman & Rohde, 2007; Skounti, Philalithis & Galanakis, 2007; Willcutt, 2012) and 2.5-5% in adults (Faraone & Biederman, 2005; Kessler et al., 2005, 2006; NICE, 2008; Nutt et al., 2007; Polanczyk & Jensen, 2008). It is widely acknowledged that AD/HD is found more often in males than females, with childhood male-to-female ratios ranging from 3:1 to 9:1 (Arcia & Conners, 1998; Gaub & Carlson, 1997; Hartung & Widiger, 1998; Rutter, Capsi & Moffitt, 2003) and adult male-to-female ratios estimated around 2:1 (Willcutt, 2012).

Over time the disorder has received many different names and abbreviations, partially reflecting the changing views of its aetiology and defining clinical features (Biederman & Faraone, 2005). The majority of this thesis has relied on the term and diagnostic criteria set out by the fourth edition text revision of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR; APA, 2000), while the last experimental chapter incorporated updated AD/HD criteria from the DSM-5 (APA, 2013).

1.2 Brief History of AD/HD

Arguably, the first example of a disorder similar to AD/HD was described by Dr. Crichton in 1798, who noted attentional problems ('mental restlessness') in some school-aged children (Barkley, 2008; Crichton, 1798; Palmer & Finger, 2001). Although Crichton's observations were strikingly similar to the Inattentive type of AD/HD, there was no mention of hyperactivity or impulsivity (Lange, Reichl, Lange, Tucha & Tucha, 2010; Palmer & Finger, 2001). Other early descriptions of AD/HD can be found in H. Hoffmann's witty poems, 'Fidgety Phil' and 'Johnny Look-in-the-Air' (Hoffmann, 1845; Thome & Jacobs, 2004). However, the scientific roots of AD/HD are traditionally attributed to Sir G. F. Still (Barkley, 2006; Doyle, 2004; Sandberg & Barton, 2002; Still, 1902). Still observed 43 children who had problems with sustaining attention, were overactive, aggressive, excessively emotional, and resistant to discipline. Similar to AD/HD; this observed behavioural pattern was more prevalent in boys than girls, and was evident by early school age (Still, 1902). However, some of the behaviour descriptions are now more closely linked to Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD). Still argued that these behaviours were caused by a 'defect in moral character' and were linked to brain damage (Still, 1902).

The correlation between early brain damage (i.e. birth defect or mild perinatal anoxia) and subsequent behaviour problems or learning difficulties was extended with Tredgold's work relating moral defect to a form of inherited brain damage (Tredgold, 1908). These links laid the foundations for subsequent relationships between hyperactivity and brain damage, further supported by the encephalitis epidemic of 1917-1918 (Conners, 2000; Ross & Ross, 1976). Many children who overcame the

often fatal encephalitis infection showed lasting symptoms of impulsivity, inattention and cognitive disturbances, and were socially disruptive (Ebaugh, 1923; Hohman, 1922; Strecker, 1929; Stryker, 1925). The term 'postencephalitic behavior disorder' encompassed these residual behaviours and was generally accepted to be the result of brain damage (Bender, 1942; Gibbs, Gibbs, Spies & Carpenter, 1964).

In the decades that followed, brain damage was central to hyperactivity and several labels, such as 'organic driveness' (Kahn & Cohen, 1934), 'restlessness syndrome' (Levin, 1938) and 'hyperkinetic disease' (Kramer & Pollnow, 1932) were used to describe this generally-consistent cluster of symptoms (hyperactivity, inattention and impulsivity). Children who displayed these behaviours were believed to have suffered some sort of brain damage, even if there was no evidence to suggest such damage occurred. The assumed causal connection between brain damage and symptoms of hyperactivity, impulsivity, and distractibility shaped the history of AD/HD (Cormier, 2008; Doyle, 2004; Rafalovich, 2001; Ross & Ross, 1976).

The accidental discovery of the benefits of Benzedrine (an amphetamine derivative) introduced pharmacotherapy for treating hyperactivity. Bradley (1937) observed behavioural and academic improvements in children who were given the drug to help alleviate the side effects of pneumoencephalograms (cerebrospinal fluid is drained away from the brain and replaced with air, oxygen, or helium to clearly see brain structures on an X-ray image). He also noted that the stimulant drug had an apparent paradoxical effect by subduing children who were hyperactive and impulsive, and benefitted those with poor memory, short attention span and learning difficulties (Bradley, 1937).

The 1950s focussed on the neurological mechanisms in the aetiology of hyperactivity. Laufer, Denhoff and Solomons (1957) argued that an abnormal function of the diencephalon, which is influenced by a dysfunctional central nervous system (CNS), may cause hyperactivity. Several studies argued that there were different cortical regions involved in a complex interaction of defective functions, irritation and inhibitory releases, and that these were responsible for childhood behaviour problems (Brock, 1948; Dusser de Bareene & McCulloch, 1941; Fulton, 1951; Penfield & Rasmussen, 1950). These findings helped develop the 'Hyperkinetic Impulse Disorder', naming hyperactivity as the central feature (Laufer & Denhoff, 1957, Laufer et al., 1957). Strauss and Kephart (1955) argued that if children with confirmed brain damage (either by known history or neurological examination) showed symptoms of hyperactivity, distractibility, impulsivity and cognitive deficits, then children who showed these same behaviours without any evidence of brain damage must have suffered from some sort of brain damage.

The concept of 'Minimal Brain Damage' (MBD) was developed to help identify children who displayed mild deviations from normal behaviours (Strauss & Lehtinen, 1947). The disorder was characterised by attentional, behavioural and cognitive deficits that were usually accompanied by dyslexia and language disorder (Birch, 1964; Burks, 1960; Herbert, 1964; Ounsted, 1955; Rutter, Graham & Birch, 1966). 'Soft' neurological signs aided in the diagnosis and offered evidence for MBD (Fadely & Hosler, 1992). However 'soft signs' were eventually phased out due to lack of consensus and inconsistent measurement criteria (Adams, Kocsis & Estes, 1974; Kessler, 1980).

Clements and Peters (1962) were one of the first to propose a shift away from minimal brain *damage* and towards minimal brain *dysfunction* by criticising the assumption of a causal link between brain function and childhood behaviour problems. Clements (1966) incorporated symptoms of inattention, hyperactivity and impulsivity into minimal brain dysfunction (also acknowledging a normal range of intelligence), and broadened the possible aetiology to include genetic variations, biochemical irregularities, perinatal brain insults, or resulting from illness or injury during critical CNS development and maturation. The expansion of possible causes helped to remove links between hyperactivity and brain *damage* per se and focussed on brain functioning (Barkley, 2006).

However, it was not long before this new MBD term was greatly criticised as an 'umbrella term' (Ross & Ross, 1976) and Rie (1980) argued that it was speculative with no solid empirical evidence. This MBD category was eventually divided into more specific behavioural and developmental disorders such as dyslexia, learning disabilities, hyperactivity, and language disorders (Barkley, 2006; Sandberg & Barton, 2002). These terms were based on observed disabilities rather than hypothesised underlying mechanisms.

A new concept of a 'Hyperactive Child Syndrome' was developed and published in the second edition of the DSM (DSM-II; APA, 1968). This syndrome was characterised as a single disorder, based on symptoms of overactivity, restlessness, distractibility, and a short attention span. Chess (1960) reported that children from her private practice presented with hyperactivity (as well as aggression and impulsivity), prior to age six with a 4:1 male-to-female ratio. Hyperactivity was the defining feature of this syndrome, and was believed to be benign and outgrown by puberty (Chess, 1960).

As research in North America focussed on this behavioural syndrome, Europe retained the earlier, more exclusive view of a brain damage syndrome. From here a divide formed; Europe, in particular Great Britain, viewed children with hyperkinesis, or hyperactivity, as in an extreme state of excessive activity. Although rare, this disorder was thought to occur in combination with other signs of brain damage, such as mental retardation (Taylor, 1988). North America, on the other hand, viewed hyperactivity as a more common behavioural disorder not necessarily associated with brain damage (Barkley, 2006). This split is still evident by two different diagnostic systems used; North America relies on the DSM and Great Britain utilizes the International Classification of Diseases (ICD). This thesis based AD/HD diagnosis on the DSM, and for this reason, the ICD will not be considered further. However, it is important to note that some research cited in this thesis may have referred to ICD criteria.

There was a shift in the 1970s away from hyperactivity and towards attentional aspects as the defining feature of the disorder. Douglas (1972) argued that deficits in sustained attention and impulse control were just as, if not more, important than hyperactivity (Douglas, 1972). Douglas (1972) suggested that inattention contributes to hyperactivity, as hyperkinetic children jump from one activity to another based on a short attention span, not as a result of their excessive motor activity. Douglas' argument was influential in the renaming and reshuffling of the disorder in the third edition of the DSM to 'Attention Deficit Disorder with or without hyperactivity' (ADD; APA, 1980). Inattention and impulsivity were the core features and two subtypes were listed based on the absence (ADD) or presence (ADD/H) of hyperactive symptoms. Although praised, Douglas' influential work marked the beginning of a continuing

argument over the disorder's true defining symptoms and features, which is yet to be fully resolved.

Although the third edition of the DSM introduced a more specific symptom list than previous editions, it was criticised for the reliance on a task force committee rather than valid empirical data (Cantwell, 1987). It was not clear if ADD with and without hyperactivity were qualitatively similar or not (Barkley, 2006). Carlson (1986) found that children with ADD were more likely to daydream, be sluggish, drowsy, hypoactive, and learning-disabled, but were less aggressive and less likely to be rejected by peers than children with ADD/H. Carlson (1986) suggested that the two subtypes should be regarded as separate and distinct disorders. In contrast, Maurer and Stewart (1980) and Rubinstein and Brown (1984) failed to find differences between the two subtypes. Once concerns that the ADD label downgraded hyperactive and impulsive symptoms, which were argued to be just as important as inattention, could no longer be ignored, the APA renamed ADD as 'Attention Deficit Hyperactivity Disorder (ADHD)' in the DSM-III-R and noted that inattention, hyperactivity and impulsivity were all equally important (APA, 1987; Stefanatos & Baron, 2007). Symptoms in this edition of the DSM were empirically derived from field trials and rating scales (Barkley, 2006; Conners, 2000).

The fourth edition of the DSM (DSM-IV) retained the ADHD label but introduced a slash to form 'AD/HD'. This was done to represent the recognition that AD/HD was characterised as a two axes disorder (inattention and hyperactivity-impulsivity), and was a complex, persistent, neurodevelopment condition (APA, 1994). Children were to be diagnosed before age seven, and problem behaviours had to be evident in two separate settings, a unique criterion. Three subtypes were named: Predominantly

inattentive type, Predominantly hyperactive-impulsive type, and the Combined type (APA, 1994). These AD/HD types are consistent with studies that showed two broad distinguishable behaviour dimensions that best described the disorder; inattention and hyperactivity-impulsivity (Bauermeister, Alegria, Bird, Rubio-Stipec & Canino, 1992; DuPaul et al., 1997; Lahey et al., 1988). These types brought back the possibility of diagnosing a purely inattention form of the disorder.

It is in this edition that AD/HD is recognised as a chronic, persistent condition that often remains in adolescence and adulthood (APA, 1994). The definition of AD/HD did not change between the fourth edition and the next text revision (DSM-IV-TR; APA, 2000).

1.3 Current Definition and Symptoms

The no longer current definition of AD/HD set out by the DSM-IV-TR (APA, 2000) characterises the disorder by two axes (inattention and hyperactivity-impulsivity) with three recognised subtypes: Predominantly inattentive, Predominantly hyperactive-impulsive and the Combined type. The Inattentive type is diagnosed when six or more of nine inattentive symptoms and less than six hyperactive-impulsive symptoms are present. The Hyperactive-Impulsive type is diagnosed when six or more of nine hyperactive-impulsive symptoms and less than six inattentive symptoms are present. The Combined type requires symptoms of both inattention and hyperactivity-impulsivity (six or more of nine symptoms in each set), and is the most common type (APA, 2000).

Inattention is defined by problems in focussing and maintaining attention, selecting where to focus attention, distractibility and forgetfulness (APA, 2000). Hyperactivity

refers to excesses in gross motor activity and appearing 'on the go', while impulsive individuals have difficulties in controlling or regulating urges, and find it challenging to await outcomes (APA, 2000).

The DSM-5 has only recently been released (APA, 2013). Updates to the current AD/HD diagnostic criteria in this edition include a symptom age-of-onset of 12 years (versus seven years in the DSM-IV) and this edition includes specific diagnostic criteria for older adolescents and adults (17 years +) with AD/HD. For an AD/HD diagnosis in adulthood, adults must present with a minimum of five inattentive and/or five hyperactive-impulsive symptoms (APA, 2013). The three subtypes have been renamed as presentations; Combined, Predominately inattentive and Predominately hyperactive-impulsive presentation, although the subtype definitions from the DSM-IV-TR have remained (APA, 2013). It is hoped that these updates to diagnostic criteria will include adults and females that would otherwise have been missed by the previous diagnostic criteria in the DSM-IV (Hechtman, French, Mongia & Cherkasova, 2011; Ramtekkar, Reiersen, Todorov & Todd, 2010). The diagnostic criteria based on the DSM-IV-TR have been used throughout this thesis as the release of the DSM-5 came after the completion of Chapters 2, 3, 4, 5 and 6. However, Chapter 7 implemented DSM-5 criteria.

1.4 AD/HD in Females

As mentioned, even at the beginning of the history of AD/HD, Still (1902) acknowledged that more boys than girls displayed the core symptoms of hyperactivity, impulsivity and inattention. History followed this notion, and girls were continually diagnosed less often than boys, and were believed to have a lower prevalence rate.

For this reason, research has largely focussed on males, and as a result, the current understanding of AD/HD is derived primarily from male cohorts (Arnold, 1996). This male dominated literature has long been applied to females with the disorder, despite consensus that AD/HD in females is a neglected area of research (Arnold, 1996; Kato, Nichols, Kerivan & Huffman, 2001; Heptinstall & Taylor, 2002). While females are included in AD/HD research, all too often they are grouped with males in mixed-sex subject groups, with too few females for separate analyses of females and/or sex differences (Berry et al., 1985; Hinshaw, 2002; Kato et al., 2001; Willcutt et al., 2012).

Although boys out-represent girls with AD/HD, there is emerging research that directly focuses on females and sex differences. Girls with AD/HD tend to present with lower levels of disruptive behaviours and higher levels of inattention and internalising symptoms (depression, anxiety) and social impairment (Biederman, et al., 2002; Carlson, Tamm & Gaub, 1997; Elkins, Malone, Keyes, Iacono & McGue, 2011; Gaub & Carlson, 1997; Gershon, 2002). As this behavioural pattern is less likely to disrupt, girls with AD/HD may be more easily overlooked than boys with AD/HD, missing out on a referral for diagnosis and treatment (Arnold, 1996; Biederman et al., 2002; Gershon, 2002; Quinn & Wigal, 2004). It has also been suggested that the symptoms girls with AD/HD most often display are not recognisable as characteristic of AD/HD (Quinn, 2005; Quinn & Wigal, 2004). Girls with AD/HD tend to show more symptoms of inattentiveness, poor school performance and depressive affect, which are less noticeable, and less troublesome, for adults (Berry et al., 1985; Elkins et al., 2011; Quinn & Wigal, 2004; Quinn, 2005). These behaviours are more likely to be overlooked by teachers and parents than disruptive, hyperactive, impulsive symptoms, which are more often seen in boys with AD/HD (Gaub & Carlson, 1997; Quinn, 2005).

This lack of recognition of girls with AD/HD could attribute to the absent female-specific diagnostic criteria (Hinshaw, 2002).

Electrophysiology is an area lacking in female-specific AD/HD research. Electroencephalography (EEG) is a non-invasive technique of recording electrical cortical activity via the scalp. There is a long and reliable history of EEG in AD/HD, with abnormal EEG recordings first reported in 'Childhood Behavior Disorder' and children with MBD (Solomon, Bradley & Jasper, 1938; Solomon, Jasper & Bradley, 1937). Subsequent decades of research have helped characterise AD/HD by a deviant baseline cortical pattern, specifically elevated slow wave activity (primarily theta) and reduced fast wave activity (primarily beta) (for reviews see Barry & Clarke, 2009; Barry, Clarke & Johnstone, 2003; Lansbergen, Arns, van Dongen-Boomsma, Spronk & Buitelaar, 2011; Loo & Barkley, 2005). However, these EEG-AD/HD studies have relied heavily on male or mixed-sex subject groups, with little attention afforded to females. Surprisingly, there has been no direct investigation into the appropriateness of assuming this male-dominant literature is valid and relevant for females with AD/HD.

1.5 Thesis Outline and Chapter Aims

The primary aims of this thesis were to: i) investigate and define the nature of resting EEG activity of females with AD/HD, including differences between AD/HD subtypes, ii) examine the hypoarousal model of AD/HD within females and iii) explore the existence of sex differences in the EEGs of adults with AD/HD. This thesis is comprised of individual studies that inter-link and connect; Chapters 2, 3, 4, 5 and 6 have been accepted for publication as separate studies in peer-reviewed scientific journals, while Chapter 7 has been submitted for publication. As such, chapter order

may not necessarily be in chronological order. There is unavoidably some repetition, especially in the introduction sections of each chapter. To help manage this repetition, only this brief overarching overview is included here.

The second chapter begins the thesis with a published review of the current literature on the EEG activity of females with AD/HD. The aim of this chapter is to explore and summarize the current understanding of EEG activity within females diagnosed with the disorder. The review highlights that the widespread and vast amount of data available on males with AD/HD dwarfs the limited information on and understanding of AD/HD-related EEG anomalies in females.

The third chapter begins the experimental studies by directly exploring sex differences between boys and girls diagnosed with the Combined and Inattentive types of AD/HD. The aim of this study is to comprehensively examine the EEG profiles of AD/HD types with a particular focus on sex differences.

The fourth chapter continues the investigation of EEG differences between AD/HD types, by focussing exclusively on female subject groups (aged 7-12 years). The aim of this study is to address a gap in the literature and report solely on EEG differences in girls with AD/HD.

The fifth chapter follows on directly to investigate why there is a disparity in EEG profiles of AD/HD types between boys and girls. The aim of this study is to re-examine the EEG activity between girls with the Combined and Inattentive types of AD/HD with an exaggerated behavioural gap.

Chapter 6 explores the hypoarousal model of AD/HD in girls. While this model has been examined in boys with AD/HD, it has never been directly investigated in girls with AD/HD.

The last experimental chapter, Chapter 7, aims to investigate sex differences in the EEG activity of adults with AD/HD. Research on adults with AD/HD is emerging, yet there remains little understanding of the disorder in adult females. This chapter directly examines sex differences within the EEG activity of adults with AD/HD, with a particular focus on women. This chapter implemented the new DSM-5 adult AD/HD diagnostic criteria, and is one of the first studies to do so. The DSM-5 is the first edition to include specific criteria for adults with AD/HD.

The final eighth chapter is the conclusion. The aim of this chapter is to consolidate all the original and important findings into a complete and comprehensive conclusion. Specific research directions are also described to further the scientific knowledge of female-specific EEG activity within the AD/HD population.

2 EEG ACTIVITY IN FEMALES WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

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2.1 Introduction

Attention-Deficit/Hyperactivity Disorder (AD/HD) is one of the most pervasive problems within mental health, and results in negative impacts on an individual's developmental, educational and vocational accomplishments, overall health and welfare (Baron, 2007). Although AD/HD is one of the most widely researched disorders, until recently, few researchers have considered the possibility of a separate female profile of AD/HD distinct from that of males. This has resulted in limited information being available about gender differences in this disorder. A comprehensive understanding of gender differences within AD/HD has public health and scientific importance for the advancement of women's health (Biederman & Faraone, 2004). This article reviews the current literature on EEG activity within AD/HD populations, with a specific focus on females and the lack of sex-specific investigations.

2.2 Attention-Deficit/Hyperactivity Disorder

The DSM-IV-TR conceptualises AD/HD as a developmentally-inappropriate and persistent pattern of inattention and/or hyperactivity-impulsivity (APA, 2000). Symptoms of inattention include difficulty sustaining attention, organizing, and completing tasks. Children with inattention appear not to listen or do not hear what is said. Symptoms of hyperactivity include fidgetiness and excessive motor activity above appropriate developmental stages. Hyperactive children cannot sit still, talk excessively and appear restless. Children with impulsivity have great difficulty with patience and delaying responses; they frequently interrupt and intrude on others. To be diagnosed with AD/HD, children must display significant impairments in at least two

environments and symptoms must be present prior to the age of seven (APA, 2000). There are three types of AD/HD: predominantly Inattentive, predominantly Hyperactive-Impulsive and the Combined type (APA, 2000). Although most AD/HD children will have some symptoms of both inattention and hyperactivity-impulsivity (leading to diagnosis of the Combined type if above thresholds in each dimension), some will have only one or the other symptom pattern. The Inattentive type is characterised by a predominant symptom pattern of inattention and the Hyperactive-Impulsive type demonstrate predominant symptoms of hyperactivity and impulsivity (APA, 2000).

Prevalence studies estimate that AD/HD affects 3-7% of school children (APA, 2000; Pastor & Reuben, 2008). Approximately 70% of AD/HD children will continue to have AD/HD in adolescence (Barkley, Fischer, Edelbrock & Smallish, 1990) and 30-50% will have the disorder into adulthood (Faraone et al., 2000; Weiss & Hechtman, 1993). Within general population samples, the Inattentive type is most prevalent, with an average estimate of 4.5%, while the Combined type was estimated at 1.9%, and the Hyperactive-Impulsive type at 1.7% (Gaub & Carlson, 1997). However, within clinic populations, the Combined type is two to four times more prevalent than the other two types of AD/HD (Wolraich, Hannah, Pinnock, Baumgaertel & Brown, 1996).

There is a general consensus that more boys than girls have AD/HD. Epidemiological studies show boy to girl ratios of 3:1, while clinic samples have ratios as high as 9:1 (APA, 2000; Arcia & Conners, 1998; Gaub & Carlson, 1997; Hartung & Widiger, 1998; Rutter, Capsi & Moffitt, 2003). In DSM-IV field trials, Lahey et al. (1994) found differences in male: female ratios between AD/HD types; 7.3:1 for the AD/HD Combined type, 4:1 for the Hyperactive-Impulsive type and 2.7:1 for the Inattentive

type. Several issues are evident in these ratio discrepancies: 1. there is a large difference between AD/HD females in clinic and community samples; 2. the ratio differences between males and females; and 3. the variability between AD/HD types.

Berry, Shaywitz and Shaywitz (1985) suggested that male to female ratio discrepancies could be partially explained by selective referrals as hyperactive boys are more likely than girls to be referred because they exhibit more disruptive behaviours that are deemed troublesome by adults. Girls tend to have lower levels of disruptive behaviours and higher levels of inattentiveness, social impairment and internalizing symptoms (Biederman et al., 2002; Carlson, Tamm & Gaub, 1997; Gaub & Carlson, 1997; Gershon, 2002). Two well-cited reviews (Gaub & Carlson, 1997; Gershon, 2002) found that girls with AD/HD tend to show less physical hyperactive symptoms than AD/HD boys, and have fewer externalizing behaviours. In place of excess motor activity, females will more often display other symptoms, such as hyper-talkativeness and high emotional reactivity (Quinn, 2005). Females with these behaviours are less likely to disrupt classrooms, and/or disturb teachers, so they are more likely to be overlooked for diagnosis and subsequent treatment (Berry et al., 1985; Biederman et al., 2002; DuPaul, et al., 2006; Gaub & Carlson, 1997; Gershon, 2002; Quinn, 2005; Sciutto & Eisenberg, 2007). If males are more likely than females to receive attention for their AD/HD behaviours, this could help explain why males are diagnosed with AD/HD more than females.

The DSM's diagnostic criteria for AD/HD are based primarily on research with school-aged boys (McBurnett et al., 1999) and as such, is highly likely to skew the inclusion/exclusion of AD/HD females, especially those who do not stand out with severe, overt behavioural symptoms (Staller & Faraone, 2006). Ohan and Johnston

(2005) found that mothers perceived DSM-IV AD/HD symptom criteria as descriptive of boys. An AD/HD diagnosis relies heavily on a parent's view of their child's behaviour, and if symptom criteria do not correlate with parent's behaviour descriptions, it can result in misdiagnosis. Waschbusch and King (2006) found that, using sex-specific norms for AD/HD evaluations, a group of impaired girls were identified that otherwise would have been missed. The importance of separate standards for rating AD/HD behaviours has been acknowledged (e.g., Conners' rating scales have gender-specific norms across age groups), yet the DSM-IV-TR does not include this factor in their diagnostic criteria (Rucklidge, 2010). As clinicians rely on DSM criteria for a clinical diagnosis, a lack of sex-specific norms may also help explain the large discrepancy in prevalence ratios between clinic and community samples.

Girls are twice as likely as boys to have the Inattentive type of AD/HD, and are more likely to have symptoms of inattention, rather than hyperactivity-impulsivity (Biederman & Faraone, 2004). Berry et al. (1985) found that girls with Attention Deficit Disorder (ADD) without hyperactivity were, on average, older at referral than boys, although they exhibited similar impairments. Berry et al. (1985) suggested that the clinical course of ADD is influenced by maturational factors that differ between boys and girls. Although the age-of-onset criterion for AD/HD is seven years, females appear to have a later age-of-onset, particularly in those with the Inattentive type (Lahey et al., 1994; McBurnett et al., 1999; Quinn, 2005; Wolraich et al., 1996). As symptoms of inattention are less disruptive and overt than those of hyperactivity-impulsivity, the higher instance of inattention in girls, relative to boys, could help explain the gender ratio discrepancy between the AD/HD types (Berry et al., 1985; Biederman & Faraone, 2004). Some females with AD/HD may go undiagnosed due to

less disruptive hyperactive and impulsive symptoms than boys, a greater likelihood of inattentive symptoms, or a later age-of-onset of symptoms.

Females with AD/HD are at greater risk of anxiety, depression, self-blame, shame and low self-esteem than AD/HD males (Kato, Nichols, Kerivan & Huffman, 2001; Quinn, 2005; Quinn & Nadeau, 2002). Adolescent females with AD/HD are also at greater risk of smoking, substance abuse, sexual promiscuity, unplanned pregnancy, peer rejection and social isolation (Berry et al., 1985; Biederman & Faraone, 2004; Quinn, 2005; Quinn & Nadeau, 2002). Oestrogen, a female hormone, has been found to influence the severity of AD/HD symptoms with females reporting becoming emotionally hyper-reactive during certain stages of their menstrual cycle, intensifying their AD/HD symptoms (Quinn & Nadeau, 2002; Ratey, Miller & Nadeau, 1995).

Differences in the presentation, identification and diagnosis of AD/HD between genders highlight important issues. Arnold (1996) expressed the importance of distinguishing normal sex differences from those that are attributable to AD/HD pathology. Females normally differ from males, and so normative sex differences need to be clearly distinguished from AD/HD-related sex differences (Arnold, 1996). As the Inattentive type is more common in females, and is suggested to be associated with a later onset of symptoms, the need to clarify if the life course of the disorder is different between genders is emphasized (Arnold, 1996). Yet, despite AD/HD being one of the most researched psychiatric conditions, females continue to remain under-represented in the literature. Most AD/HD studies have either excluded females, or used disproportionate male/female ratios, to reflect the comparatively small number of clinically-identified females, or to satisfy the desire for homogeneous groups (Berry et al., 1985).

2.3 EEG Activity in Children

Electroencephalography (EEG) measures brain function through the analysis of electrical activity at the scalp, generated by underlying brain structures (Becker & Holtamnn, 2006). Resting EEG activity provides useful information on the background cortical state, indexing substrates of behaviour and cognition (Barry, Clarke & Johnstone, 2003). Spectral analyses of EEG activity provide amplitude and power measures in the classical frequency bands: delta (<4 Hz), theta (4-7 Hz), alpha (8-12 Hz), beta (13-25 Hz) and gamma (30-80 Hz), and reflect information about the excitability of neural networks and their maturation (Cragg et al., 2011; Nunez & Srinivasan, 2006; Taylor & Baldeweg, 2002). Alpha wave activity is associated with a relaxed conscious state and will be disrupted with increased mental load, beta wave activity is evident during cognitive processing, while the slower wave forms, delta and theta, are more commonly associated with immaturity and abnormalities (Andresassi, 2000). The gamma frequency band is considered to range from 30 to 80 Hz, and has been linked with cognitive functioning (Engel, Fries & Singer, 2001; Fell, Fernandez, Klaver, Elger & Fries, 2003; Herrmann, Frund & Lenz, 2010).

Cortical development is reflected in changes to childhood EEG activity. Generally, there is a predominance of slow-wave delta and theta in infancy, thought to reflect brain immaturity, and this increases in frequency with age (Benninger, Matthis & Scheffner, 1984; Hudspeth & Pribram, 1992; Tye, McLoughlin, Kuntis & Asherson, 2011). Maturational EEG studies generally report that with increasing age, low frequency band (delta and theta) activity decreases, and higher frequency band (alpha and beta) activity increases (Cragg et al., 2011; Gasser, Jennen-Steinmetz, Sroka,

Verleger & Mocks, 1988; Gasser, Verleger, Bacher & Sroka, 1988; Gmehlin et al., 2011; John et al., 1980; Matousek & Petersen, 1973; Matsuura et al., 1985). These changes are believed to begin over posterior brain regions (Clarke, Barry, McCarthy & Selikowitz, 2001a; Gasser, Jennen-Steinmetz, et al., 1988), followed by the central and frontal regions (Gasser, Jennen-Steinmetz, et al., 1988; Katada, Ozaki, Suzuki & Suhara, 1981; Matousek & Petersen, 1973). Like alpha and beta, gamma power increases with age, particularly over the frontal regions (Takano & Ogawa, 1998).

Clarke et al. (2001a) used easily interpretable estimates of absolute and relative powers to examine developmental EEG changes in 80 healthy children (40 boys, 40 girls, aged 8-12 years). Children showed decreasing absolute delta, relative delta and theta, and increasing relative alpha and beta with increasing age, consistent with the general consensus mentioned above. Clarke et al. (2001a) found that the decreases in delta and theta activity, and increases in alpha activity, occurred faster in the posterior regions than the frontal regions, consistent with Katada et al. (1981), Matousek and Petersen (1973) and Somsen, van't Klooster, van der Molen, van Leeuwen and Licht (1997). Clarke et al. (2001a) also noted differences in the rates of maturation between the midline sites (Fz, Cz and Pz) and the two hemispheres. Absolute delta activity and the theta/beta ratio were greater at the midline in younger children, before becoming more equipotential with increasing age; suggesting that EEG maturation occurs faster at the midline than in the hemispheres.

John et al. (1980) presented linear functions to predict the EEG composition for log-transformed relative power as a function of age; these equations were supported by Ahn, Baird and Kaye (1980), Alvarez, Valdes and Pascual (1987) and Clarke et al. (2001a). Others have suggested that developmental changes are due to periodic

growth spurts around six, ten and 14 years of age (Epstein, 1980; Thatcher, 1991). While maturational changes are believed to reflect underlying changes in cortico-cortical and cortico-thalamic networks (Lopes da Silva, 1991; Steriade, Gloor, Llinas, Lopes da Silva & Mesulam, 1990), the exact processes remain unclear. It has been speculated that they may reflect developmental changes in gray and white matter (Whitford et al., 2007) or increases in myelination or axon size (Segalowitz, Santesso & Jetha, 2010). However, these are not yet fully understood.

Studies of sex differences in the EEG maturation of healthy children have had mixed results. Some report no significant differences (Cohn, Kircher, Emmerson & Dustman, 1985; Gasser, Jennen-Steinmetz, et al., 1988; Matousek & Petersen, 1973); others suggest that EEG power matures earlier in females (Petersen & Eeg-Olofosson, 1971), and that females display an EEG maturational lag (Harmony, Marosi, Diaz de Leon, Becker & Fernández, 1990). The best supported finding is that maturation during childhood, reflected by increased relative alpha and a lower delta/theta ratio, occurs earlier in males than females (Clarke et al., 2001a; Harmony et al., 1990; Matthis, Scheffner & Benninger, 1980), but females have a greater rate of maturation (Benninger et al., 1984; Clarke et al., 2001a; Harmony et al., 1990).

Clarke et al. (2001a) found that healthy boys had more absolute theta, relative theta and relative alpha power activity than healthy girls. With increasing age, absolute delta, theta and alpha power decreased in girls, but remained relatively constant in boys. Barry and Clarke (2009) provided a summary of their EEG research to date, and stated that girls (8-12 years) had a more immature EEG profile than boys, evidenced by greater absolute and relative posterior delta, globally elevated absolute and relative theta, and reduced absolute and relative posterior alpha activity. The

girls' relative immaturity in the absolute delta and theta bands decreased with increasing age, but posterior absolute alpha continued to show immaturities compared with aged-matched boys. Cragg et al. (2011) mapped EEG maturation in ten-year-olds, tested three times over a three-year period. Although not as robust as previous studies, their results supported the earlier maturation in males and a greater rate of development in females. These studies indicate that girls have maturationally-delayed EEG activity compared with boys, but this lag disappears by adolescence, suggesting that although male EEG activity matures earlier, females catch-up in adolescence.

2.4 EEG Activity in AD/HD

The electroencephalogram has an established history within AD/HD – Solomon, Jasper and Bradley (1937) and Solomon, Bradley and Jasper (1938) suggested an underlying cerebral component could explain the high incidence of EEG abnormalities within 'Childhood Behaviour Disorder'. Favourable EEG and behavioural responses to commonly prescribed medications of the time (e.g. Dilantin & Phenobarbital) reinforced this idea (Cutts & Jasper, 1939; Lindsley & Cutts, 1940; Lindsley & Henry, 1942; Walker & Kirkpatrick, 1947). A clear understanding of EEG maturation and activity in males and females can help divide sex differences that are normally occurring from those that are related to AD/HD, and help determine if the life course of AD/HD is different between genders.

Although this is a female-focussed review, it is important to describe the current EEG profiles of AD/HD children. Note that these profiles are based on combined groups of males and females (or males alone) and while they should be interpreted with caution, they provide a framework for describing EEG activity within AD/HD.

Children (7-13 years) with AD/HD typically show globally elevated slow wave activity (absolute delta and theta) and globally reduced absolute alpha and beta activity compared to children without AD/HD (for overall reviews see Barry et al., 2003; Barry & Clarke, 2009). These children also have increased posterior absolute delta activity (Clarke, Barry, McCarthy & Selikowitz, 2001b, 2001c; Clarke, Barry, Dupuy, et al., 2011), and elevated absolute frontal theta activity (Chabot & Serfontein, 1996; Clarke, Barry, McCarthy & Selikowitz, 2002; Clarke, Barry, Dupuy, et al., 2011; Lansbergen, Arns, van Dongen-Boomsma, Spronk & Buitleaar, 2011; Mann, Lubar, Zimmerman, Miller & Muenchen, 1992). Within relative power; AD/HD children commonly show globally elevated relative theta and globally reduced relative alpha and beta activity (Barry & Clarke, 2009; Barry et al., 2009; Chabot & Serfontein, 1996; Clarke et al., 2001c, 2001d; Clarke, Barry, Dupuy, et al., 2011; Clarke, Barry, McCarthy & Selikowitz, 2011). A larger theta/beta ratio has consistently been found in AD/HD children, compared with healthy controls (Barry et al., 2009; Clarke et al., 2001c, 2001d; Clarke, Barry, Dupuy, et al., 2011; Clarke, Barry, McCarthy et al., 2011; Lansbergen et al., 2011; Janzen, Graap, Stephanson, Marshall & Fitzsimmons, 1995; Lubar, 1991; Monastra et al., 1999; Monastra, Lubar & Linden, 2001).

Adolescents with AD/HD continue to have significant impairments in attention, impulsivity and overactivity (Barkley, 1991). While only a small number of studies have examined EEG activity in AD/HD adolescents (14-17 years), relatively consistent findings have emerged. Generally, adolescents with AD/HD have elevated absolute theta and absolute alpha activity with a larger theta/beta ratio compared with aged-matched controls (Bresnahan, Anderson & Barry, 1999; Hermens, Kohn, Clarke, Gordon & Williams, 2005; Hobbs, Clarke, Barry, McCarthy & Selikowitz, 2007; Lazzaro

et al., 1998, 1999). AD/HD adolescents have also been found to have elevated absolute and relative delta compared with aged-matched controls (Bresnahan et al. 1999; Hobbs et al., 2007). Lazzaro et al. (1999) found that AD/HD adolescents had globally elevated absolute and relative alpha1 (8-9 Hz) activity, compared with controls. While there is variability amongst reports of beta power, most have found reduced relative beta activity in AD/HD adolescents compared with adolescents without AD/HD (Bresnahan et al., 1999; Hobbs et al., 2007; Lazzaro et al., 1998, 1999). A robust continuation of abnormally elevated theta activity in AD/HD adolescents strengthens the notion of AD/HD persisting beyond childhood.

Adults with AD/HD (18 years +) show a similar profile to adolescents. However, caution is urged during interpretation as conditions vary between studies, most notably eyes-open versus eyes-closed baseline EEG conditions; it is well accepted that differences between these two conditions lead to differences in power levels and topography (Barry, Clarke, Johnstone, Magee & Rushby, 2007). Generally, adults with AD/HD have greater absolute and relative delta, absolute and relative theta activity, and a larger theta/beta ratio compared with controls (Bresnahan et al., 1999; Bresnahan & Barry, 2002; Bresnahan, Barry, Clarke & Johnstone, 2006; Clarke et al., 2008; Hermens et al., 2004). Additionally, Koehler et al. (2009) found that adults with AD/HD had greater absolute alpha activity and increased absolute posterior theta power than controls. As with AD/HD adolescents, the beta band varies across studies; some have found that AD/HD adults have increased absolute beta activity (Bresnahan & Barry, 2002) and others report reductions in absolute beta activity (Clarke et al., 2008; Hermens et al., 2004), while Bresnahan et al. (1999) found absolute beta (in fronto-central regions) to be normal in AD/HD adults during an eyes-open condition.

In relation to AD/HD types, it has generally been reported that the Combined type of AD/HD is associated with greater EEG abnormalities than the Inattentive type of AD/HD, particularly in absolute theta and alpha bands (Barry & Clarke, 2009; Chabot & Serfontein, 1996; Clarke, Barry, McCarthy & Selikowitz, 1998, 2001c, 2001d). Chabot and Serfontein (1996) investigated EEG differences between ADD children with and without hyperactivity and concluded that the differences between the two clinical groups were in the degree, rather than type, of abnormality. Mann et al. (1992) found that boys with ADD without hyperactivity had increased frontal absolute and relative theta power and a greater decrease in posterior and temporal absolute beta power during sustained attention tasks compared with controls.

Clarke et al. (1998) investigated EEG differences between the Combined and Inattentive types of AD/HD and controls, in a mixed group of 60 children (48 boys and 12 girls). The Combined type group had greater relative posterior delta and global theta activity and less global relative alpha activity than the Inattentive type group. Clarke et al. (2001c) replicated these results with 120 children (96 boys and 24 girls), and also found that the Combined group had a greater theta/beta ratio and a reduced theta/alpha ratio than the Inattentive group. Clarke et al. (2001d) used equal numbers (40 boys and 40 girls) to compare AD/HD type differences in resting EEG activity. The Combined group had greater absolute and relative theta, higher theta/beta and theta/alpha ratios, and less relative alpha than the Inattentive group. The widespread significant differences between AD/HD types led Clarke et al. (2001c) to suggest that the two AD/HD types have separate neuroanatomical anomalies.

While EEG abnormalities have been consistently reported in AD/HD populations, the underlying nature and explanation of these abnormalities remain unclear.

However, the use of EEGs has helped shape two models that attempt to explain AD/HD abnormalities; the first suggests that AD/HD is the result of a maturational lag in Central Nervous System (CNS) functioning, and the second proposes that a developmental deviation results in AD/HD. Both models have received research attention, yet fail to fully explain the underlying nature of AD/HD. It is highly unlikely that one single model can capture and explain the disorder in its totality; nonetheless these models provide relevant information about the nature of EEG abnormalities in AD/HD.

The Maturational Lag model suggests that the AD/HD EEG abnormalities are due to a lag, or delay, in cortical development (Kinsbourne, 1973; Shaw et al., 2007). According to Kinsbourne (1973), AD/HD children are underdeveloped for their age and this is reflected in their cortical activity, which is similar to that of a healthy younger child. Support for this model is found in AD/HD symptom criteria, which refer to AD/HD behaviours that are inappropriate for the developmental stage, meaning that they may be found in younger normal children. Also, AD/HD symptoms improve with age – up to 50% of children grow out of AD/HD in adolescence and adulthood (APA, 2000; Biederman et al., 1994; Faraone et al., 2000). This suggests that children with AD/HD have a developmental delay compared to normally-developing children, and this delay remits by adulthood (Hill & Schoener, 1996).

However, the increasing recognition of AD/HD in adolescents and adults suggests that children do not always grow out of AD/HD. It has been estimated that about 30-50% will continue to have AD/HD into adulthood (Faraone et al., 2000; Weiss & Hechtman, 1993). A criticism of the Maturational Lag model is that it cannot account for adults who continue to have AD/HD. Bresnahan et al. (1999) examined age-related

quantitative EEG changes in AD/HD participants aged 6-42 years. The results showed that the AD/HD adults had increased absolute delta and theta activity compared to normal controls. Bresnahan and Barry (2002) found that 50 adults with AD/HD had elevated absolute delta, theta, alpha, beta, and total power, and relative theta activity compared to healthy controls. Clarke et al. (2008) also found adult AD/HD EEG profiles similar to AD/HD children: increased relative theta, and reduced relative beta at midline sites compared to aged-matched controls. These studies have found EEG abnormalities in adults with AD/HD, most notably in absolute delta and theta, and relative theta activity, arguing against the Maturational Lag model.

Lubar (1991) linked low skin conductance level (SCL; an indication of CNS arousal) in hyperactive children (Satterfield & Dawson, 1971) with an EEG study by Jasper, Solomon and Bradley (1938), who suggested that a shift from a resting to active state resulted in an EEG power shift from dominant theta and alpha activity to dominant beta activity. Lubar (1991) hypothesised that AD/HD children would have increased theta power with a reciprocal reduction in beta activity, and that this theta/beta ratio represented CNS hypoarousal. Mann et al. (1992) supported this notion and the theta/beta ratio became a popular marker for AD/HD. Satterfield, Cantwell and Satterfield (1974) found that hyperactive children had low CNS arousal levels (measured by SCL) and noted a negative correlation between CNS arousal levels and the severity of the hyperactive child's behavioural disturbances: the lower SCL, the greater behavioural disturbances. Satterfield et al. (1974) went on to discover that stimulant medications improved behaviour and CNS arousal levels. Increased theta with reciprocal reduced beta power, believed to reflect cortical hypoarousal, has been found consistently across AD/HD groups (Barry & Clarke, 2009; Barry et al., 2009;

Clarke et al., 2001c; Clarke, Barry, McCarthy et al., 2011; Lansbergen et al., 2011; Lazzaro et al., 1998, 1999).

However, Barry et al. (2004) examined the link between the theta/beta ratio and SCL activity in 24 healthy boys. There were no significant differences in either the theta or beta band as a function of arousal level, and there was no difference in the theta/beta ratio between high- and low-aroused children (measured via SCL). Instead, elevated SCL was significantly associated with decreased alpha activity, particularly in posterior and hemispheric regions (Barry et al., 2004). Barry et al. (2004) proposed that the theta/beta ratio may reflect differences in functionality of the basis of attentional processing. Barry et al. (2009) re-investigated the link between arousal and the theta/beta ratio in 30 AD/HD boys. The AD/HD boys had lower SCL, elevated absolute theta and a larger theta/beta ratio with reduced absolute alpha and beta activity compared with controls. While these results are consistent with previous AD/HD reports, they did not support the notion that theta/beta ratio reflects CNS arousal as there was no significant correlation between SCL and the theta/beta ratio. Instead, decreased relative alpha was correlated with elevated SCL, in both the healthy and AD/HD groups. Barry et al. (2004, 2009) proposed that the theta/beta ratio represents a substrate of activation, particularly in cognitive/attention tasks. Within AD/HD, this ratio signifies an impaired capacity for attentional tasks, a processing deficit, not an arousal deficit (Barry et al., 2009). Labelling EEG patterns in arousal terms need to be reconsidered as although the theta/beta ratio is a consistent marker for AD/HD, it does not indicate CNS hypoarousal (Barry et al., 2009).

Clarke, Barry, McCarthy, et al. (2011) correlated EEG abnormalities with core symptoms of AD/HD. In the 60 boys with AD/HD that participated, Clarke, Barry,

McCarthy, et al. (2011) correlated three AD/HD subscales of Conners' rating scales with anomalous EEG activity. Increased frontal absolute theta activity significantly correlated with the Inattentive and Total subscales. As elevated frontal theta activity is the most commonly reported EEG abnormality within AD/HD, the fact that it correlated with inattention helps explain why it is found in both the Inattentive and Combined AD/HD types (Clarke, Barry, McCarthy, et al., 2011). The theta/beta ratio correlated with the Hyperactive-Impulsive and Total subscales. This is interesting because Clarke et al. (2001b) had previously found that the theta/beta ratio matured at a faster rate in children with the Combined type of AD/HD and became similar to levels found in children with the Inattentive type of AD/HD by age 12. This was interpreted as indicating that hyperactivity was associated with the theta/beta ratio and the reduction in the degree of abnormality was related to a reduction in hyperactivity (Clarke et al., 2001b).

The use of EEG studies has also helped improve the understanding and use of AD/HD medications. Stimulant medications (namely dexamphetamine and methylphenidate) are widely used in the treatment of AD/HD, with clinically-significant benefits found in approximately 80% of treated patients (but leaving 20% with non-favourable responses; Swanson, McBurnett, Wigal & Pfiffner, 1993; Wilens & Biederman, 1992). Psychostimulants are thought to increase the arousal level of the CNS by stimulating the release, and inhibiting the reuptake, of the dopamine and noreadrenaline neurotransmitters (Biederman & Spencer, 1999; Durston, 2003; Lawrence et al., 2005). Early EEG studies on AD/HD medications had problems clearly defining global EEG changes due to medication (Chabot, Orgill, Crawford, Harris & Serfontein, 1999; Swartwood et al., 1998) and it was speculated that only those who

responded positively to medications would show EEG normalization (Loo, Teale & Reite, 1999).

Generally, in AD/HD children who respond well to psychostimulants, the medications appear to normalize EEG characteristics by decreasing abnormal absolute theta and increasing absolute beta activity levels (Clarke, Barry, Bond, et al., 2002; Clarke, Barry, McCarthy & Selikowitz, 2002; Clarke, Barry, McCarthy, Selikowitz, Brown, et al., 2003; Loo et al., 1999; Lubar, White, Swartwood & Swartwood, 1999). Rowe, Robinson and Gordon (2005) found a reduction of relative theta and alpha power with medication use in a small group of AD/HD adolescent males (12-17 years), trending towards normalization. In a group of 50 AD/HD adults (equal males and females); medication had similar effects to that found in children and adolescents (Bresnahan et al., 2006). Reductions were noted in absolute delta, absolute and relative theta, and total power, with the EEG profiles of AD/HD adults trending towards normalization.

Attention has turned to examining EEG differences between AD/HD patients who respond positively and negatively to medications. Work by Satterfield, Cantwell, Lesser and Podsin (1972), Satterfield, Cantwell, Saul, Lesser and Podsin (1973), and Satterfield, Lesser, Saul and Cantwell (1973) found that those who responded well to stimulant medications had greater EEG abnormalities, particularly in increased absolute delta and theta, compared to poor responders. Satterfield and Cantwell (1974) believed that these results indicated that good medication responders were cortically hypoaroused. Clarke, Barry, McCarthy & Selikowitz (2002) supported the notion that good medication responders have greater EEG abnormalities than poor responders; good responders to MPH had higher total power and a larger theta/beta ratio than poor responders. Clarke, Barry, McCarthy, et al. (2002) also investigated

EEG differences between good and poor responders to dexamphetamine, as there is variability among responses to stimulant medications (Chabot et al., 1999). Good responders to dexamphetamine also showed greater EEG abnormalities compared to poor responders, namely reduced relative alpha and beta activity, and greater posterior total power. Clarke, Barry, McCarthy, et al. (2002) concluded that good responders to popular psychostimulants appear to have more abnormal EEG profiles than poor responders.

It is important to note that all the EEG literature reviewed above was based on either disproportionate samples of males and females, or excluded females altogether. While it is commonly accepted that males and females are different, conclusions about AD/HD in females continue to be drawn from this male-dominated research. While there is increasing support for gender specific AD/HD profiles, small female numbers, referral bias and inappropriate diagnostic criteria hamper efforts to make genuine predictions on how males and females differ, emphasising that sex effects and differences should be part of the standard comparison in studies (Rucklidge, 2010).

2.5 EEG Activity in Females with AD/HD

The literature is scant and mixed on the EEG activity of females with AD/HD. The majority of research in this area included either males alone (e.g., Barry et al., 2009; Clarke, Barry, Bond, et al., 2002; Lansbergen et al., 2011; Lazzaro et al., 1998); or combined groups of males and females (i.e., Chabot & Serfontein, 1996; Clarke et al., 1998, 2001c, 2008; Hale et al., 2010). Significant behavioural differences between AD/HD males and females suggest that research which relies heavily on males cannot provide an adequate understanding of AD/HD in females.

Baving, Laucht and Schmidt (1999) investigated frontal activation patterns in 117 children with AD/HD (aged 4.5 and 8 years). Baving et al. (1999) found that 15 AD/HD girls (combined age groups) had significantly greater *left* frontal alpha power activation than aged-matched control girls, while AD/HD boys had significantly greater *right* frontal alpha power activation than control boys. Baving et al. (1999) suggested that the AD/HD girls' enhanced left frontal alpha power corresponds to a left frontal deficit. While the opposite direction of asymmetry in alpha power activation between AD/HD boys and girls was noted, Baving et al. (1999) could not link cognitive or behavioural effects to this observed EEG gender difference. It was suggested that gender-specific lines of development result in differing frontal alpha activation patterns between males and females, but this was not further investigated. Ultimately Baving et al. (1999) stressed the importance of gender-specific analyses in AD/HD.

Mentioned earlier, Clarke et al. (2001d) investigated age- and sex-related effects on the EEGs in equal-sized groups of 40 boys and 40 girls with AD/HD. The AD/HD girls (pooled AD/HD types) had greater absolute alpha, relative delta and theta activity, and more total power, and reduced absolute beta activity, than control girls. Between the AD/HD types, the girl Combined group had larger theta/alpha and theta/beta ratios than the girl Inattentive group, and those of both clinical groups were significantly greater than girl controls. However, the statistical design used did not include a separate, explicit analysis of the EEG activity within AD/HD girls.

Clarke, Barry, McCarthy, Selikowitz, Clarke, et al. (2003) addressed the above issue and recorded eyes-closed resting EEGs from 100 girls (aged 8-12 years) with AD/HD. The AD/HD girls had greater total power, more relative theta and less relative delta, alpha and beta than age-matched controls. Clarke, Barry, McCarthy, Selikowitz, Clarke,

et al. (2003) noted the novelty of a *global* deficiency of relative delta activity in AD/HD girls, whereas *excess posterior* relative delta activity had been more commonly found in male and mixed AD/HD groups (Matousek, Rasmussen & Gilberg, 1984; Clarke et al., 1998, 2001c, 2001d). Clarke, Barry, McCarthy, Selikowitz, Clarke, et al. (2003) followed on from two male cluster analysis studies (Clarke et al., 2001b, 2001c) that investigated the homogeneity of EEG activity in boys with the Combined and Inattentive types of AD/HD. Two distinct EEG profiles emerged, the first characterised by elevated total power, relative theta activity, a larger theta/beta ratio and a reduction in relative delta and beta activity (thought to represent cortical hypoarousal at the time of publication), and the second characterised by increased relative delta and relative theta, with reductions in relative alpha and relative beta activity (thought to represent a maturational lag). A third cluster, characterised by excess relative beta activity, believed to represent cortical hyperarousal, was found in boys with Combined type AD/HD (Clarke et al., 2001b). The same cluster analysis was done on this group of AD/HD girls (Clarke, Barry, McCarthy, Selikowitz, Clarke, et al., 2003). A two-cluster model emerged, with the majority of AD/HD girls (96%) showing greater relative theta and less relative delta and beta activity. The second cluster, only 4% of the total group, had elevated fronto-central total power, increased relative frontal theta activity and reduced relative delta, alpha and beta. Clarke, Barry, McCarthy, Selikowitz, Clarke, et al. (2003) suggested that the two clusters represented differing levels of cortical hypoarousal and were not necessarily qualitatively different. The cluster profiles of the female groups were highly homogenous, with the majority fitting into one cluster type, whereas the AD/HD boys were more evenly spread.

A study by Dupuy, Clarke, Barry, McCarthy and Selikowitz (2011) followed directly from Clarke et al. (2001b), and explicitly analysed EEG activity between the Combined and Inattentive types of AD/HD within three groups of 30 girls (8-12 years). The AD/HD girls (pooled types) had elevated total power, absolute delta and theta, and reduced relative beta activity, compared with controls. Between the clinical groups; the Combined type group had elevated absolute right theta power, greater midline-posterior absolute beta and relative alpha activity, reduced right relative delta activity, reduced left relative theta activity, and reduced relative beta activity within central regions of the hemispheres compared with the Inattentive type group. Although there were topographic differences, there were no significant global differences between the two AD/HD types. Global differences have been found previously in AD/HD males (Clarke et al., 1998, 2001c, 2001d), and these were so significant that the authors even suggested that the two AD/HD types could be neuroanatomically different. Dupuy et al. (2011) referred to the homogenous nature of EEG activity found in girls with AD/HD (Clarke, Barry, McCarthy, Selikowitz, Clarke, et al., 2003) and suggested that this could explain the discrepancy apparent between the EEG profiles of boys and girls with AD/HD. Dupuy et al. (2011) suggested that sex-biases in identification, referral and diagnosis of AD/HD could explain why global differences between clinically selected AD/HD types are so prominent in boys yet elusive in girls.

Girls with AD/HD have shown reduced relative beta activity with a reciprocal increase in relative theta activity compared with healthy girl controls (Clarke et al., 2001d; Clarke, Barry, McCarthy, Selikowitz, Clarke, et al., 2003; Dupuy et al., 2011). This elevated theta/beta ratio, originally thought to be 'cortical hypoarousal' and now believed to represent underlying deficits in attentional processing (Barry et al., 2009),

is a consistent profile among AD/HD populations, both in males and females. However, unlike boys, AD/HD girls have commonly shown abnormalities in absolute and relative delta and total power. However, further replication across populations would be beneficial to support these results.

While it was once assumed that children outgrew AD/HD by puberty, it is now overwhelmingly apparent that many continue to experience AD/HD in adolescence and adulthood. The estimated adult prevalence of AD/HD ranges from 1.2% to 3.2%, even up to 4.4% (Faraone, Biederman & Mick, 2006; Kessler et al., 2006), depending on selection criteria. An important limitation of the previous adolescent and adult EEG studies is lack of female inclusion; most excluded females (Hobbs et al., 2007; Lazzaro et al., 1998, 1999), while others had mixed groups (Bresnahan et al., 1999; Hermens et al., 2005). Only one study to date, Hermens et al. (2005), included a statistical analysis of EEG activity in female adolescents; 22 adolescent AD/HD females (aged 11-17 years) were part of a larger group of 70 AD/HD adolescents that had an eyes-closed resting EEG recorded with simultaneous electrodermal activity (EDA). Adolescent AD/HD females had elevated midline absolute theta power, decreased posterior absolute beta power with a slight increase of frontal absolute beta, and a larger theta/beta ratio compared with female controls. Hermens et al. (2005) also investigated sex differences, and found that while AD/HD male adolescents had greater global absolute theta activity, AD/HD female adolescents had a more specific frontal elevation of absolute theta activity. As reported in adults (Hermens et al., 2004), Hermens et al. (2005) replicated results that AD/HD adolescent males (but not females) had elevated global EEG theta activity, whereas AD/HD adolescent females (but not males) had decreased SCL. Hermens et al. (2005) suggested that differing and distinct core

neurobiological deficits underlie the developmental course of AD/HD between males and females. Importantly, to date, there have been no published AD/HD studies on EEG activity of adolescent or adult females alone.

Clark, Barry, McCarthy, Selikowitz and Johnstone (2007) investigated medication effects on the EEGs of 20 girls with AD/HD (aged 7-12 years). Eyes-closed EEG activity was recorded in girls with AD/HD both on and off medication (either 10 mg of Methylphenidate or 5 mg of Dexamphetamine). Girls with AD/HD (nil medication) had greater total power, absolute delta and theta, more relative theta and reduced relative delta and beta activity, compared with controls, similar to previous female EEG results. The EEGs from the medicated AD/HD girls showed a significant reduction in relative theta activity, with no difference from controls remaining in this frequency band, thought to reflect a complete normalisation of relative theta activity (due to medication). While previously published medication studies found theta activity trended towards normal levels (often not significant) (Clarke, Barry, Bond, et al., 2002, Clarke, Barry, McCarthy, Selikowitz, Brown, et al., 2003), this was the first to find a *complete* normalisation of relative theta. Clarke et al. (2007) considered that the EEGs of AD/HD girls may not be as abnormal as those of AD/HD boys, so EEG changes due to medication show greater normalisation because they were less aberrant to start with. A second possibility was that the dominant homogenous EEG profile found in AD/HD girls responds better to medication than other EEG profiles (Clarke et al., 2007).

Electrophysiological parameters are ideal for studying higher-level cognitive processes, such as attention, response selection and decision making, which are paramount in the study of AD/HD (McLoughlin, Kuntsi, Brandesi & Banaschewski 2005). Other aspects of EEG that are often utilized in AD/HD research are event-

related potentials (ERPs) and EEG coherence. Event-related potentials result from ongoing EEG that is averaged and time locked to stimulus or response events (Becker & Holtmann, 2006) and are believed to reflect discharges from large groups of neurons, linked to specific aspects of sensory and cognitive processing (Taylor & Baldeweg, 2002). Although not discussed here, ERPs provide detailed analyses of timing and location of specific aspects cortical information processing (Barry & Clarke, 2009) and has been widely used in AD/HD studies (for a review see Barry, Johnstone & Clarke, 2003). Coherence reflects time-locked joint EEG activity in different cortical regions within a particular frequency band (Shaw, 1981). Coherence offers valuable information on connectivity and AD/HD populations have shown marked deviations in collaborative brain activity between different cortical regions (for a review see Barry & Clarke, 2009). Although ERP and EEG coherence are beyond the scope of this review, they offer highly valuable information on the cortical processing and connectivity within AD/HD for both males and females.

2.6 Conclusions and Future Directions

The majority of AD/HD literature has relied heavily upon school-aged boys (Arnold, 1996) and is frequently applied to girls and women. Mounting evidence of gender disparities in the prevalence, presentation, and detection of AD/HD argues that this male-based literature is not necessarily appropriate for females. It is generally accepted that males and females normally differ, so it is a small step to agree that males and females are also likely differ importantly on aspects of AD/HD.

Electroencephalography is a reliable measure of electro-cortical activity and has reputable history in the study of AD/HD. While it is accepted that EEG maturation is

influenced by gender differences, many AD/HD investigations continue to pool males and females together. The small number of EEG studies of females with AD/HD presented in this review stresses the lack of knowledge on how electro-cortical activity is influenced by AD/HD in girls and women. In addition, to-date, there are no studies that have investigated EEG activity in adult women with AD/HD. As AD/HD often persists into adulthood, it is important to know if the life course of AD/HD differs between males and females. Although the literature is sparse on adult AD/HD, a few male-based EEG studies have been published in this area, but further research is needed.

The three types of AD/HD, predominantly Inattentive, Hyperactive-Impulsive, and Combined type, represent different manifestations of the disorder, based on prevailing symptoms. Significant EEG differences between the prevalent Inattentive and Combined types have been reported; in boys global differences were noted in absolute theta, alpha bands, theta/beta and theta/alpha ratios. However, girls did not produce these apparent global differences. Clinical populations of AD/HD girls have been found to have rather homogenous EEG profiles (Clarke, Barry, McCarthy, Selikowitz, Clarke, et al., 2003; Dupuy et al., 2011) (while AD/HD boys appear to be more heterogeneous). The majority of the reviewed studies relied on clinical samples; it would be worthwhile to invest in EEG research within community populations of AD/HD females to determine if reported EEG abnormalities are not merely limited to clinical populations. An insightful comment that evolved from a conference on AD/HD sex differences is that the awareness of female manifestations of AD/HD and sex differences will not only be useful to females but also contribute to a deeper understanding of the

disorder in general (Arnold, 1996). We need to build our research around that concept.

2.7 References

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3 SEX DIFFERENCES BETWEEN THE COMBINED AND INATTENTIVE TYPES OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: AN EEG PERSPECTIVE

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3.1 Introduction

Attention-Deficit/Hyperactivity Disorder (AD/HD), a debilitating childhood developmental condition, is characterised by behaviourally-inappropriate symptoms of inattention and/or hyperactivity-impulsivity (APA, 2000). There are three types of AD/HD: predominantly Inattentive, predominantly Hyperactive-Impulsive and the Combined type (APA, 2000). Although most children with AD/HD will have some symptoms of both inattention and hyperactivity-impulsivity (leading to diagnosis of the Combined type if above threshold in each dimension), some will have only one or the other symptom pattern. The Inattentive type is characterised by a predominant symptom pattern of inattention, and the Hyperactive-Impulsive type demonstrates predominant symptoms of hyperactivity and impulsivity (APA, 2000). Prevalence estimates are that AD/HD affects 3-7% of school children (APA, 2000; Pastor & Reuben, 2008; Willcutt, 2012). Within AD/HD, the Inattentive type is most prevalent, estimated to affect 3.6% of children, followed by the Combined type, which is estimated at 2.2%, and the Hyperactive-Impulsive type at 1.3% (Willcutt, 2012). Generally, more boys than girls have AD/HD; boy-to-girl ratios range from 3:1 to 9:1 (APA, 2000; Arcia & Conners, 1998; Gaub & Carlson, 1997; Hartung & Widiger, 1998; Rutter, Capsi & Moffitt, 2003). Slightly varying boy-to-girl ratios have been reported between the AD/HD types; the largest ratio difference was found in the Combined type, which was estimated at 2.6:1, followed by the Inattentive type at 2.2:1 and the Hyperactive-Impulsive type at 2.0:1 (Willcutt, 2012).

Although AD/HD is one of the most widely researched disorders of childhood, few have considered the possibility of a separate female profile, distinct from males, and

this has resulted in limited information on sex differences. Two well-cited reviews (Gaub & Carlson, 1997; Gershon, 2002) found that girls with AD/HD tend to show less physical hyperactive symptoms than boys with AD/HD, and have fewer externalizing behaviours. Both Gaub and Carlson (1997) and Gershon (2002) suggested that, compared with boys with AD/HD, girls with AD/HD have more intellectual impairments and higher rates of depression and anxiety. However, despite these findings, many AD/HD studies continue to neglect females, or use disproportionate male/female groups to reflect common ratios or to satisfy the desire for homogeneous groups (Berry, Shaywitz & Shaywitz, 1985; Rucklidge, 2010). Without a clear understanding of sex differences in AD/HD, some girls may go unrecognized. These are unable to benefit from appropriate diagnosis and treatment, and are at risk of negative impacts on their mental health and wellbeing (Rucklidge, 2010).

Resting electroencephalography (EEG) offers useful information on background cortical states, indexing substrates of behaviour and cognition (Barry, Clarke & Johnstone, 2003), valuable in understanding the nature of AD/HD. Resting state EEG power is valuable as an AD/HD diagnostic test when used as part of a comprehensive clinical assessment (Magee, Clarke, Barry, McCarthy & Selikowitz, 2005). There are relatively consistent EEG abnormalities noted among children with AD/HD (for overall reviews see Barry & Clarke, 2009; Barry et al., 2003). Briefly, these children typically have increased posterior absolute delta activity (Clarke, Barry, McCarthy & Selikowitz, 2001b, 2001c), and elevated absolute frontal theta activity (Chabot & Serfontein, 1996; Clarke, Barry, McCarthy & Selikowitz, 2002; Mann, Lubar, Zimmerman, Miller & Muenchen, 1992). Within relative power, children with AD/HD tend to have globally elevated relative theta, and globally reduced relative alpha and beta activity (Barry &

Clarke, 2009; Barry, Clarke, Johnstone, McCarthy & Selikowitz, 2009; Chabot & Serfontein, 1996; Clarke et al., 2001c, 2001d; Clarke, Barry, Dupuy, et al., 2011; Clarke, Barry, McCarthy & Selikowitz, 2011). A greater theta/beta ratio has consistently been found in AD/HD children, compared with healthy controls (Barry et al., 2009; Clarke et al., 2001c, 2001d; Clarke, Barry, Dupuy, et al., 2011; Clarke, Barry, McCarthy & Selikowitz, 2011; Janzen, Graap, Stephanson, Marshall & Fitzsimmons, 1995; Lansbergen, Arns, van Dongen-Boomsma, Spronk & Buitlearr, 2011; Lubar, 1991; Monastra et al., 1999; Monastra, Lubar & Linden, 2001). Note that these profiles are based heavily on research using boys or mixed-sex groups and, while they help to provide a framework for understanding EEG activity within AD/HD, results should be interpreted with caution.

The modest amount of published studies which have investigated EEG differences between AD/HD types suggest that the Combined type is associated with greater abnormalities, particularly in the theta and alpha bands, than the Inattentive type (Barry & Clarke, 2009; Chabot & Serfontein, 1996; Clarke, Barry, McCarthy & Selikowitz, 1998, 2001c, 2001d). Lubar (1991) found that boys with attention problems without hyperactivity had a larger frontal theta/beta ratio than boys without attention problems. Mann et al. (1992) found that boys with ADD (without hyperactivity) had increased frontal absolute theta power, and a greater decrease in posterior and temporal absolute beta activity, during sustained attention tasks. Chabot and Serfontein (1996) concluded that the EEG differences between children with ADD with and without hyperactivity were of degree of abnormality, and not type. Clarke et al. (1998) found, in a mixed group of 60 children (48 boys and 12 girls), that the Combined type had greater absolute delta and theta activity, and less absolute

alpha activity, than the Inattentive type. Clarke et al. (2001c) replicated these results with a larger group of 120 children (96 boys and 24 girls), and also found that the Combined type AD/HD group had a larger theta/beta ratio and a smaller theta/alpha ratio than the Inattentive type AD/HD group. Clarke et al. (2001d) used equal numbers of 40 boys and 40 girls to compare AD/HD type differences in resting EEG activity. The Combined type group had greater absolute and relative theta, larger theta/beta and theta/alpha ratios, and less relative alpha, than the Inattentive type group. Dupuy, Clarke, Barry, McCarthy & Selikowitz (2011) were the first to analyse EEG activity between the Combined and Inattentive types exclusively in girls with AD/HD (aged 8-12 years). Unlike males, there was a lack of significant global differences between the two types. This discrepancy between boys and girls with different AD/HD types suggests that sex may substantially influence the EEG profiles of this disorder.

To date, there has been no comprehensive EEG examination of sex differences between the Combined and Inattentive types. While Clarke et al. (2001d) included sex as a variable within a wider statistical analysis, their focus was on development. This paper is a re-analysis of data from Clarke et al. (2001d) that specifically examines sex differences between the Combined and Inattentive types of AD/HD.

3.2 Method

3.2.1 Participants

Three groups of 80 children (aged 8-12 years) participated. Of these, there were 40 boys and 40 girls diagnosed with the Combined type of AD/HD (AD/HDcom-b and AD/HDcom-g), 40 boys and 40 girls with the Inattentive type of AD/HD (AD/HDin-b and AD/HDin-g) and 40 healthy boy (CON-b) and 40 healthy girl (CON-g) controls. Clinical

participants were selected from a Sydney-based paediatric practice, and controls were recruited via local schools and community groups. All participants had a WISC-III IQ score of 85 or above. Participants had no history of medication use for any psychiatric disorder, and AD/HD participants were tested before any medication was prescribed.

Inclusion in the clinical groups was based on assessments made by both a paediatrician and a psychologist, and both were in agreement over the diagnosis. DSM-IV criteria were used to classify AD/HD children into either the AD/HDcom or AD/HDin groups. The clinicians based their diagnoses on behavioural observations, school reports, comprehensive histories given by parent/guardian, and any other relevant reports. Participants were excluded if they had a history of problematic prenatal, perinatal or neonatal periods, a history of CNS diseases, convulsions, or convulsive disorders. They were also excluded if there was evidence of a consciousness disorder, head injury with cerebral symptoms, paroxysmal headaches or tics, or if they met criteria for Conduct Disorder, Oppositional Defiant Disorder, an anxiety or depressive disorder, Asperger's or Tourette's Syndrome.

Inclusion in control groups was based on assessments involving parents/guardians, using the same procedure as the AD/HD participants described above. Controls had no problems during their prenatal, perinatal or neonatal periods, no disorders of consciousness, no head injuries resulting in cerebral symptoms, and no history of CNS diseases or obvious somatic diseases, no history of convulsive disorders or convulsions, tics, stuttering, paroxysmal headaches, enuresis or encopresis after the fourth year, and no psychiatric conditions. Controls displayed no deviation from normal development. No participants were included in any group if spike waves were evident in their EEG.

3.2.2 Procedure

Ethics approval for this study was obtained from the combined Illawarra Area Health/University of Wollongong Human Research Ethics Committee. Prior to the release of any clinical records or testing, the parent(s)/guardian(s) of each participant gave written informed consent, and all participants assented.

All participants were tested in a single session lasting about 2.5 hours. A psychometric assessment was performed first by a psychologist, which included the WISC-III, Neale Analysis of Reading, and the WRAT test of spelling ability. Then a five minute eyes-closed resting EEG was recorded while participants were seated in a reclining chair. An electrode cap ensured International 10-20 electrode placement. A single electro-oculogram (EOG) referenced to Fpz was placed near the right eye and a ground lead was placed on the left cheek. A linked ear reference was used, and reference and ground leads were 9 mm tin disk electrodes. The EEG activity in 21 derivations was divided into nine cortical regions by averaging in each region. These were the left frontal (Fp1, F3, F7), midline frontal (Fpz, Fz), right frontal (Fp2, F4, F8), left central (T3, C3), midline central (Cz), right central (T4, C4), left posterior (T5, P3, O1), midline posterior (Pz, Oz), and right posterior (T6, P4, O2) regions.

The EEG was Fourier transformed by a Cadwell Spectrum 32, version 4.22, using test type EEG, montage Q-EEG. The sensitivity was set at 150 µV/cm, low frequency filter 0.53 Hz, high frequency filter 70 Hz, with a 50 Hz notch filter. The reject level for the EOG was set at 50 µV. The sampling rate of the EEG was 200 Hz and the Fourier transformation used 2.56 s epochs.

Thirty 2.56 s epochs were selected from the live trace using both visual and computer rejects. These were further reviewed by a skilled technician and a minimum of 24 epochs were selected to obtain one min of data for analysis, a common EEG standard. The EEG was analysed in four frequency bands: delta (1.5-3.5 Hz), theta (3.5-7.5 Hz), alpha (7.5-12.5 Hz) and beta (12.5-25 Hz), and the total power (1.5-25 Hz). Relative power was calculated by dividing absolute power in each frequency band by the total power. The theta/beta ratio was also calculated by dividing theta activity by beta activity at each electrode site before averaging into regions.

3.2.3 Statistical Analysis

Analyses of variance were performed to examine the effects of region and group for each frequency band in absolute and relative power, total power and the theta/beta ratio. The effects of region were examined in two orthogonal three-level repeated-measures factors. The first of these was a sagittal factor, within which planned contrasts compared the frontal (F) region with the posterior (P) region and their mean (F/P) with the central (C) region. The second factor was laterality, within which planned contrasts compared the left (L) and right (R) hemispheres and their mean (L/R) with the midline (M) region. Within the group factor, planned contrasts compared clinical groups with the control group and the AD/HDcom group with the AD/HDin group. These analyses were carried out separately in boys and girls and *F* tests have (1, 117) degrees of freedom. These contrasts are planned and there are no more of them than the degrees of freedom for effect, no Bonferroni-type adjustment to α is required (Tabachnick & Fidell, 2007). An α level of .05 was used for statistical significance. There were no outliers.

3.3 Results

Table 3.1 shows mean age and IQ scores for the boy and girl AD/HD and control groups. No significant IQ differences were found between the Combined and Inattentive AD/HD groups for boy or girls. The boy AD/HD type groups had significantly lower IQ scores compared with the boy controls ($F = 18.62$, $p < .001$). The girl AD/HD type groups also had lower IQ scores compared with the girl controls ($F = 8.54$, $p < .001$).

Table 3.1 Mean age and IQ score for all subject groups

Group	Age(years) *(SD)*	IQ Score *(SD)*
CON-b	10.46 *(1.50)*	111.25 *(8.46)*
AD/HDcom-b	10.45 *(1.53)*	98.76 *(11.11)*
AD/HDin-b	10.47 *(1.51)*	98.00 *(8.46)*
CON-g	10.43 *(1.46)*	103.83 *(10.68)*
AD/HDcom-g	10.22 *(2.04)*	96.65 *(10.60)*
AD/HDin-g	10.38 *(1.46)*	94.78 *(9.70)*

3.3.1 Boys – AD/HD vs. Controls

3.3.1.1 Absolute Power

Figure 3.1 shows that the AD/HD boy groups, compared with boy controls, had more absolute delta activity in the posterior than frontal region (AD/HD-b > CON-b x F < P: $F = 4.86$, $p = .029$, $\eta_p^2 = .04$) and this was more evident at the midline than the hemispheres (AD/HD-b > CON-b x F < P x L/R < M: $F = 30.40$, $p < .001$, $\eta_p^2 = .21$). In absolute theta, compared with controls, the AD/HD boy groups had greater global theta power (AD/HD-b > CON-b: $F = 11.03$, $p = .001$, $\eta_p^2 = .09$) and this was more evident at the midline than the hemispheres (AD/HD-b > CON-b x L/R < M: $F = 9.98$, $p = .002$, $\eta_p^2 = .08$). Compared with controls, the AD/HD boy groups had reduced absolute

alpha activity across the scalp (AD/HD-b < CON-b: $F = 4.67$, $p = .033$, $\eta_p^2 = .04$). This reduction was more apparent in the posterior region (AD/HD-b < CON-b x F < P: $F = 8.43$, $p = .004$, $\eta_p^2 = .07$) and less in the central midline (AD/HD-b < CON-b x F/P > C x L/R < M: $F = 11.07$, $p = .001$, $\eta_p^2 = .09$). Figure 3.1 shows that AD/HD boy groups c.f. controls had reduced absolute beta activity across the scalp (AD/HD-b < CON-b: $F = 7.79$, $p = .006$, $\eta_p^2 = .06$). Like absolute alpha activity, this beta reduction was more evident in the posterior region (AD/HD-b < CON-b x F < P: $F = 4.09$, $p = .045$, $\eta_p^2 = .03$). This effect was greater in the right than left hemisphere (AD/HD-b < CON-b x F < P x L < R: $F = 6.02$, $p = .016$, $\eta_p^2 = .05$) and at the midline c.f. hemispheres (AD/HD-b < CON-b x F < P x L/R < M: $F = 9.29$, $p = .003$, $\eta_p^2 = .07$). This beta reduction was also less evident in the central region of the right hemisphere (AD/HD-b < CON-b x F/P > C x L < R: $F = 5.44$, $p = .021$, $\eta_p^2 = .04$). A total power increase was found to be greater at the midline in the AD/HD boy group c.f. controls (AD/HD-b > CON-b x L/R < M: $F = 4.06$, $p = .046$, $\eta_p^2 = .03$). These results are summarised in Table 3.2.

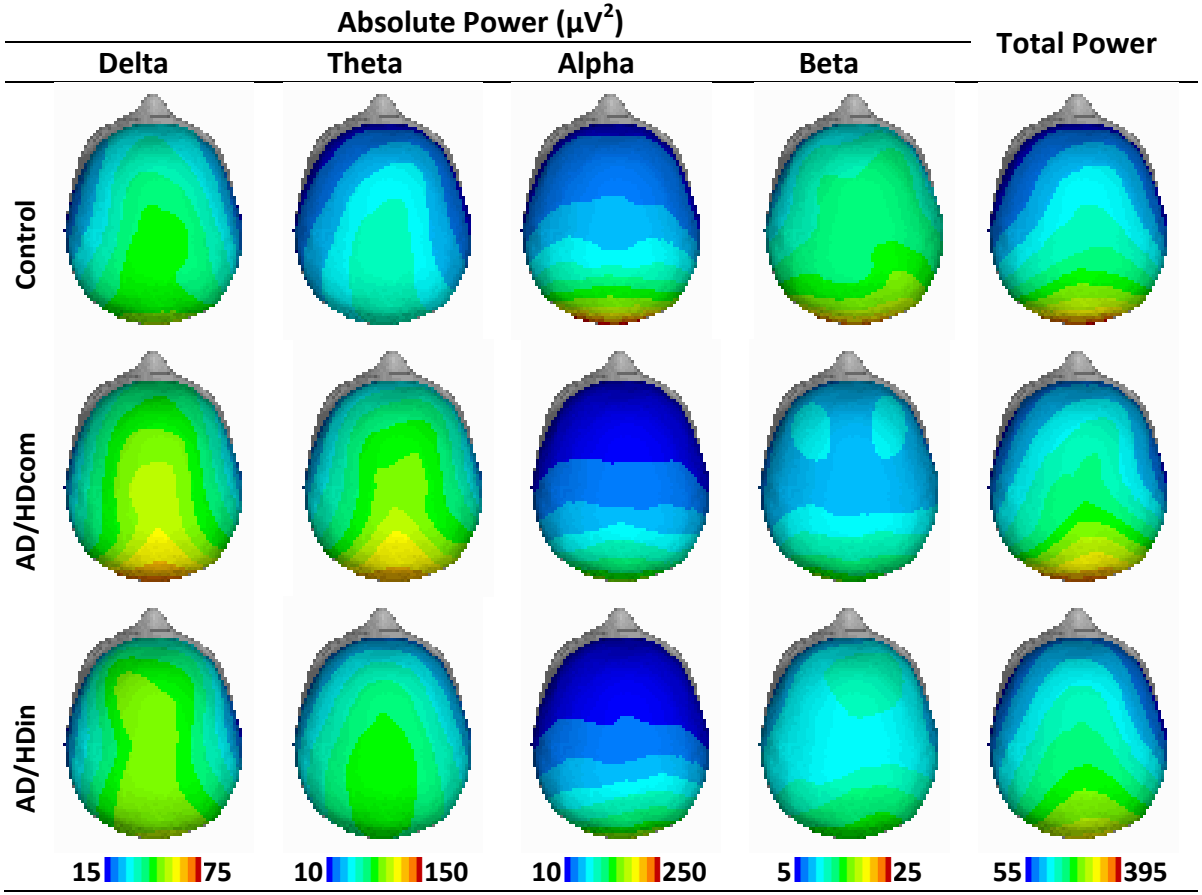

Figure 3.1 Topographic maps for absolute power for the boy AD/HD and control groups.

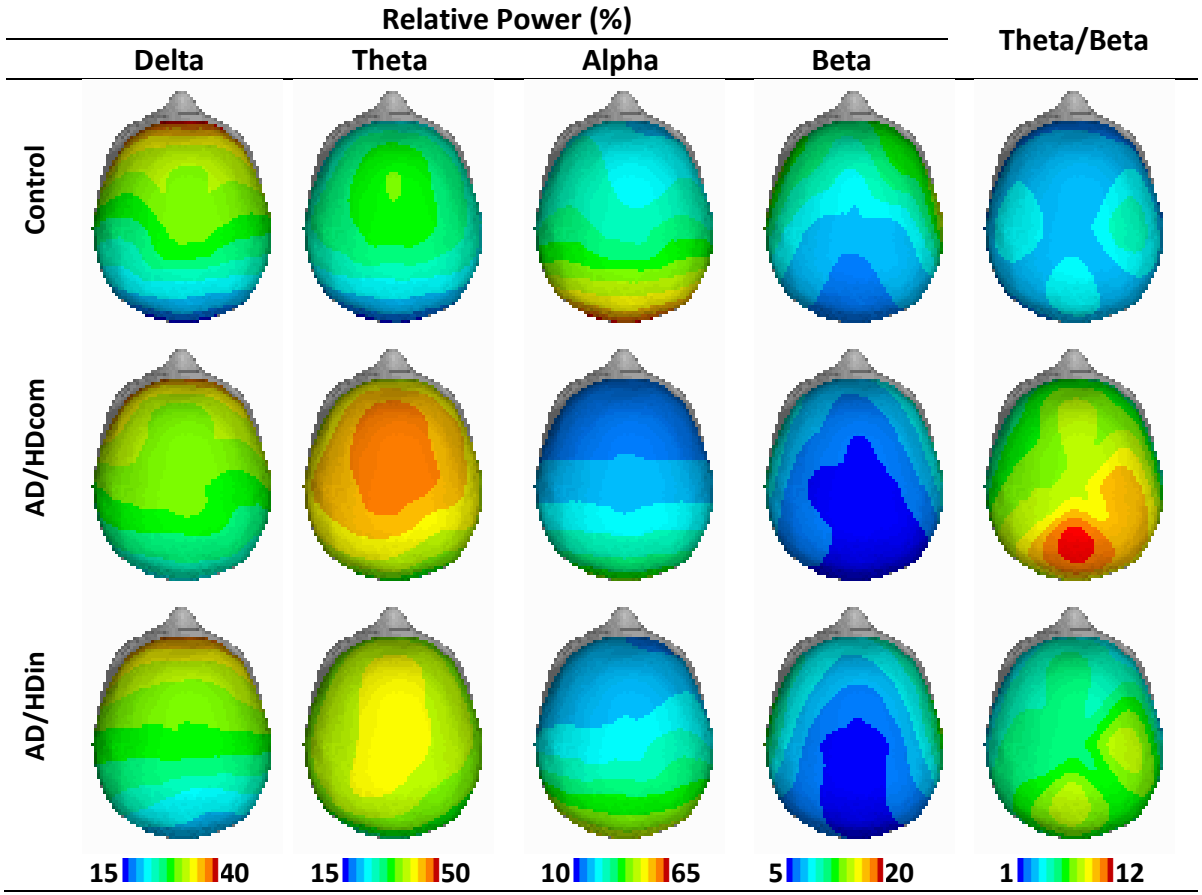

Figure 3.2 Topographic maps for relative power and theta/beta ratio for the boy AD/HD and control groups.

3.3.1.2 Relative Power

Figure 3.2 shows that relative delta was more reduced in frontal than posterior regions in the AD/HD boy groups compared with controls (AD/HD-b < CON-b x F > P: F = 10.49, p = .002, η_p^2 = .08). The AD/HD boy groups had globally elevated relative theta activity (AD/HD-b > CON-b: F = 61.59, p < .001, η_p^2 = .34) and globally reduced relative alpha activity (AD/HD-b < CON-b: F = 34.66, p = .001, η_p^2 = .23) across the scalp. This alpha reduction was more evident in the posterior region (AD/HD-b < CON-b x F < P: F = 8.11, p = .005, η_p^2 = .06). The AD/HD boy groups also had globally reduced relative beta activity (AD/HD-b < CON-b: F = 18.77, p < .001, η_p^2 = .14), that was more evident in the frontal region (AD/HD-b < CON-b x F > P: F = 16.74, p < .001, η_p^2 = .13) and in the right hemisphere (AD/HD-b < CON-b x L < R: F = 5.96, p = .016, η_p^2 = .05). The final column of Figure 3.2 shows that the theta/beta ratio across the scalp was larger in the boy AD/HD groups than in controls (AD/HD-b > CON-b: F = 21.98, p < .001, η_p^2 = .16), particularly in the posterior region (AD/HD-b > CON-b x F < P: F = 3.98, p = .048, η_p^2 = .03) and in the midline (AD/HD-b > CON-b x L/R < M: F = 18.94, p < .001, η_p^2 = .14). A summary of these results can be found in Table 3.2.

Table 3.2 Results for boy AD/HD and control groups.

	Delta	Theta	Alpha	Beta	Total Power
Main Effect		**AD/HD-b↑*** **	AD/HD-b↓*	AD/HD-b↓**	
F < P	AD/HD-b↑*		AD/HD-b↓**	AD/HD-b↓*	
F/P > C					
L < R					
L/R < M		**AD/HD-b↑****			**AD/HD-b↑***
F < P x L < R				AD/HD-b↓**	
F < P x L/R < M	AD/HD-b↑***			AD/HD-b↓**	
F/P > C x L < R				AD/HD-b↓*	
F/P > C x L/R < M			AD/HD-b↓***		

*p < .05, **p < .01, ***p < .001 (**bold** – comparable effect between sexes)

Note. The direction arrow is reversed where group x topography results are opposite to that stated in the Results section.

Table 3.2 cont. Results for boy AD/HD and control groups.

	Rel Delta	Rel Theta	Rel Alpha	Rel Beta	Theta/Beta
Main Effect		**AD/HD-b↑*** **	AD/HD-b↓***	**AD/HD-b↓*** **	**AD/HD-b↑*** **
F < P	**AD/HD-b↑****		AD/HD-b↓**	**AD/HD-b↑*** **	AD/HD-b↑*
F/P > C					
L < R				AD/HD-b↓*	
L/R < M					**AD/HD-b↑*** **
F < P x L < R					
F < P x L/R < M					
F/P > C x L < R					
F/P > C x L/R < M					

*p < .05, **p < .01, ***p < .001 (**bold** – comparable effect between sexes)

Note. The direction arrow is reversed where group x topography results are opposite to that stated in the Results section.

3.3.2 Girls – AD/HD vs. Controls

3.3.2.1 Absolute Power

Figure 3.3 shows that the AD/HD girl groups, compared with girl controls, had globally elevated absolute delta activity (AD/HD-g > CON-g: $F = 6.99$, $p = .009$, $\eta_p^2 = .06$), more apparent in the midline than the hemispheres (AD/HD-g > CON-g x L/R < M: $F = 6.91$, $p = .010$, $\eta_p^2 = .06$). Absolute theta activity was also globally elevated in the AD/HD girl group compared with girl controls (AD/HD-g > CON-g: $F = 19.00$, $p < .001$, $\eta_p^2 = .14$), more so in the midline (AD/HD-g > CON-g x L/R < M: $F = 14.36$, $p < .001$, $\eta_p^2 = .11$), but less so in the central region (AD/HD-g > CON-g x F/P > C: $F = 4.24$, $p = .042$, $\eta_p^2 = .03$). Compared with controls, the AD/HD girl groups had greater absolute beta activity at the midline (AD/HD-g > CON-g x L/R < M: $F = 4.13$, $p = .044$, $\eta_p^2 = .03$), more evident in the posterior region (AD/HD-g > CON-g x F < P x L/R < M: $F = 4.32$, $p = .040$, $\eta_p^2 = .04$). Figure 3.3 shows that total power was elevated globally in the AD/HD girl groups c.f. controls (AD/HD-g > CON-g: $F = 10.44$, $p = .002$, $\eta_p^2 = .08$), more so at the midline (AD/HD-g > CON-g x L/R < M: $F = 11.01$, $p = .001$, $\eta_p^2 = .09$). This last effect was more evident in the posterior region (AD/HD-g > CON-g x F < P x L/R < M: $F = 3.96$, $p = .049$, $\eta_p^2 = .03$). See Table 3.3 for a summary of these results.

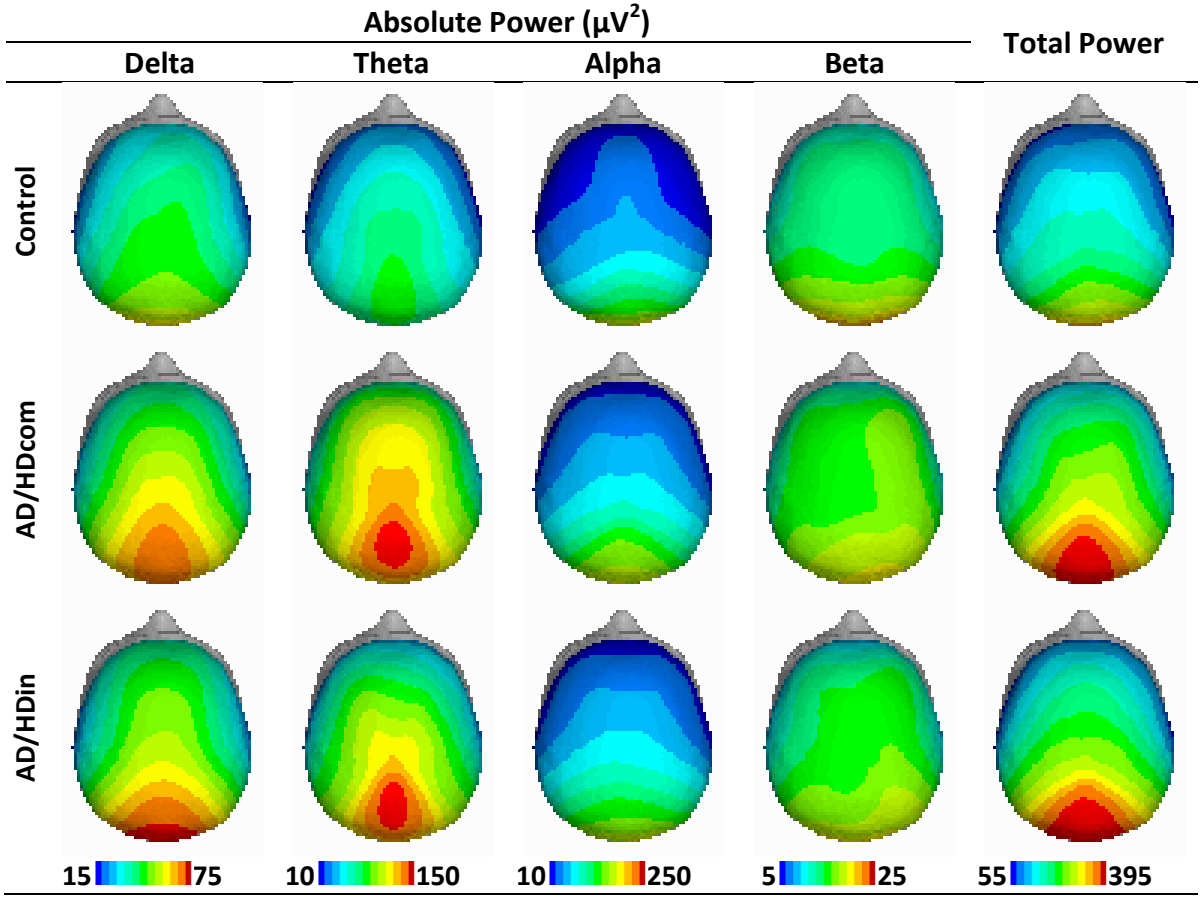

Figure 3.3 Topographic maps for absolute power for the girl AD/HD and control groups.

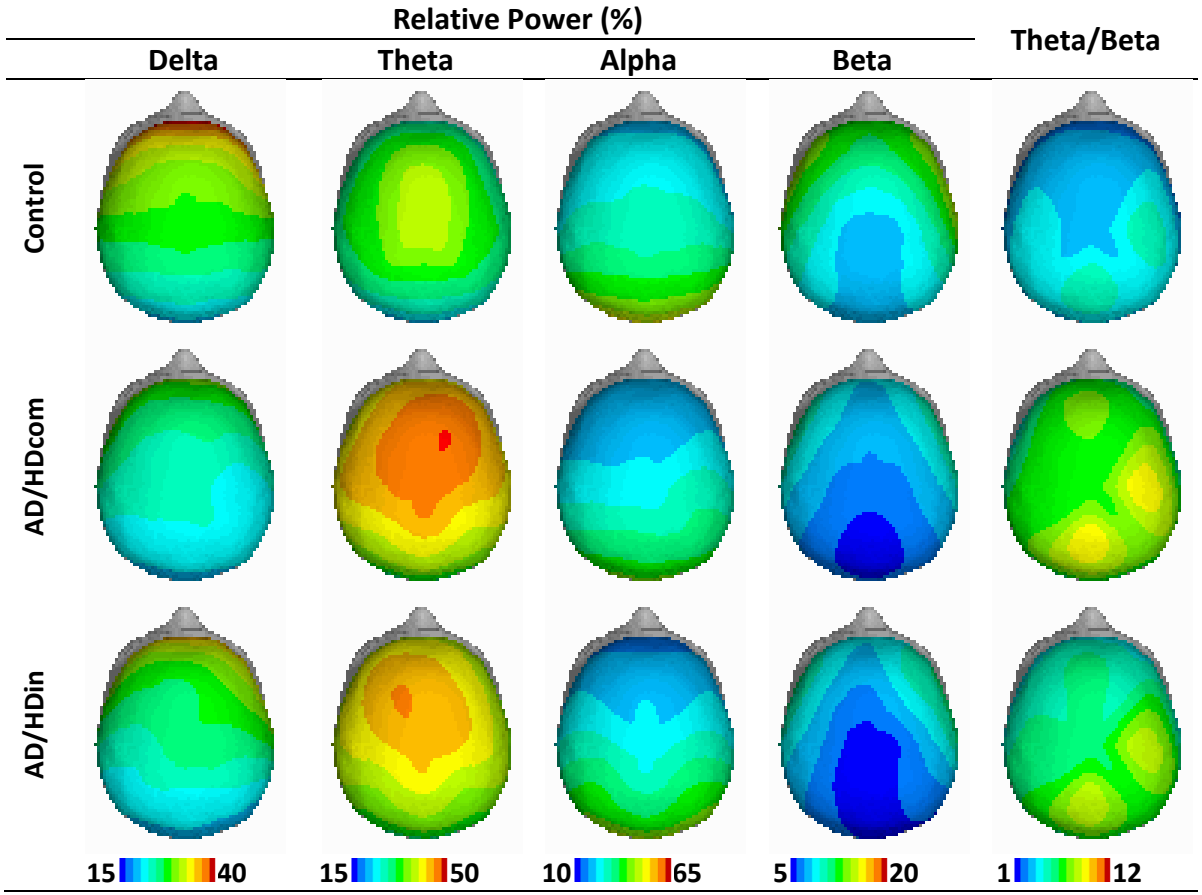

Figure 3.4 Topographic maps for relative power and theta/beta ratio for the girl AD/HD and control groups.

3.3.2.2 Relative Power

Figure 3.4 shows that the AD/HD girl groups, compared with controls, had globally reduced relative delta activity (AD/HD-g < CON-g: $F = 7.71$, $p = .006$, $\eta_p^2 = .06$), more so in the frontal region (AD/HD-g < CON-g x F > P: $F = 9.70$, $p = .002$, $\eta_p^2 = .08$). This effect was more evident in the left hemisphere (AD/HD-g < CON-g x F > P x L > R: $F = 4.61$, $p = .034$, $\eta_p^2 = .04$). Figure 3.4 shows that the AD/HD girl groups had globally elevated relative theta activity across the scalp (AD/HD-g > CON-g: $F = 72.25$, $p < .001$, $\eta_p^2 = .38$). Relative alpha activity was lower in the posterior region of the right hemisphere in the AD/HD girl groups c.f. controls (AD/HD-g < CON-g x F < P x L < R: $F = -4.60$, $p = .034$, $\eta_p^2 = .04$). Relative beta activity was globally lower in the AD/HD girl groups than in controls (AD/HD-g < Con-g: $F = 30.39$, $p < .001$, $\eta_p^2 = .21$). This beta reduction was more evident in the frontal region (AD/HD-g < CON-g x F > P: $F = 6.88$, $p = .010$, $\eta_p^2 = .06$) and in the hemispheres (AD/HD-g < CON-g x L/R > M: $F = 7.22$, $p = .008$, $\eta_p^2 = .06$). This last effect was more apparent in the central region (AD/HD-g < CON-g x F/P < C x L/R > M: $F = 11.38$, $p = .001$, $\eta_p^2 = .09$). Finally, Figure 3.4 shows that, similar to boys, the AD/HD girl group had a larger theta/beta ratio across the scalp (AD/HD-g > CON-g: $F = 23.50$, $p < .001$, $\eta_p^2 = .17$); this elevation was larger at the midline (AD/HD-g > CON-g x L/R < M: $F = 12.64$, $p = .001$, $\eta_p^2 = .10$). See Table 3.3 for a summary of these results.

Table 3.3 Results for girl AD/HD and control groups.

	Delta	Theta	Alpha	Beta	Total Power
Main Effect	AD/HD-g↑**	**AD/HD-g↑*** **			AD/HD-g↑**
F < P					
F/P > C		AD/HD-g↑*			
L < R					
L/R < M	AD/HD-g↑**	**AD/HD-g↑*** **		AD/HD-g↑*	**AD/HD-g↑*** **
F < P x L < R					
F < P x L/R < M				AD/HD-g↑*	AD/HD-g↑*
F/P > C x L < R					
F/P > C x L/R < M	AD/HD-g↑**	**AD/HD-g↑*** **			AD/HD-g↑**

*p < .05, **p < .01, ***p < .001 (**bold** – comparable effect between sexes)

Note. The direction arrow is reversed where group x topography results are opposite to that stated in the Results section.

Table 3.3 cont. Results for girl AD/HD and control groups.

	Rel Delta	Rel Theta	Rel Alpha	Rel Beta	Theta/Beta
Main Effect	AD/HD-g↑**	**AD/HD-g↑*** **	AD/HD-g↓**	**AD/HD-g↑*** **	
F < P			**AD/HD-g↑****		
F/P > C		AD/HD-g↑*			
L < R					
L/R < M	AD/HD-g↑**	**AD/HD-g↑*** **			
F < P x L < R			AD/HD-g↑*		AD/HD-g↓*
F < P x L/R < M					
F/P > C x L < R					
F/P > C x L/R < M	AD/HD-g↑**	**AD/HD-g↑*** **			

*p < .05, **p < .01, ***p < .001 (**bold** – comparable effect between sexes)

Note. The direction arrow is reversed where group x topography results are opposite to that stated in the Results section.

3.3.3 Boys – AD/HDcom vs. AD/HDin

3.3.3.1 Absolute Power

Figure 3.1 shows that the AD/HDcom boys, compared with the AD/HDin boys, had globally elevated absolute theta activity (AD/HDcom-b > AD/HDin-b: $F = 3.97$, $p = .049$, $\eta_p^2 = .03$), less so in the central region (AD/HDcom-b > AD/HDin-b x F/P > C: $F = 5.12$, $p = .025$, $\eta_p^2 = .04$). Table 3.4 summarises these results.

3.3.3.2 Relative Power

Figure 3.2 shows that relative delta activity was reduced in the posterior region of the right hemisphere in the AD/HDcom boy group c.f. the AD/HDin boy group (AD/HDcom-b < AD/HDin-b x F < P x L < R: $F = 5.94$, $p = .016$, $\eta_p^2 = .05$) and at the midline compared with the hemispheres (AD/HDcom-b < AD/HDin-b x F < P x L/R < M: $F = 5.34$, $p = .023$, $\eta_p^2 = .04$). Figure 3.2 shows that, compared with AD/HDin boys, the AD/HDcom boys had globally elevated relative theta activity (AD/HDcom-b > AD/HDin-b: $F = 6.26$, $p = .014$, $\eta_p^2 = .05$). This elevation was more evident in the frontal midline regions (AD/HDcom-b > AD/HDin-b x F > P x L/R < M: $F = 3.91$, $p = .050$, $\eta_p^2 = .03$). The AD/HDcom boys had globally reduced relative alpha activity (AD/HDcom-b < AD/HDin-b: $F = 8.59$, $p = .004$, $\eta_p^2 = .07$) and this reduction was more dominant in the posterior region (AD/HDcom-b < AD/HDin-b x F < P: $F = 7.21$, $p = .008$, $\eta_p^2 = .06$) but less so in the central region (AD/HDcom-b < AD/HDin-b x F/P > C: $F = 6.26$, $p = .014$, $\eta_p^2 = .05$). The final column of Figure 3.2 shows that the theta/beta ratio across the scalp was elevated in the AD/HDcom boys (AD/HDcom-b > AD/HDin-b: $F = 6.50$, $p = .012$, $\eta_p^2 =$

.05), particularly at the midline (AD/HDcom-b > AD/HDin-b x L/R < M: $F = 5.67$, $p = .019$, $\eta_p^2 = .05$). These results are summarised in Table 3.4.

Table 3.4 Results for boy AD/HDcom and AD/HDin groups.

	Delta	Theta	Alpha	Beta	Total Power
Main Effect		AD/HDcom-b↑*			
F < P					
F/P > C		AD/HDcom-b↑*			
L < R					
L/R < M					
F < P x L < R					
F < P x L/R < M					
F/P > C x L < R					
F/P > C x L/R < M					

*p < .05, **p < .01, ***p < .001 (**bold** – comparable effect between sexes; greyscale– previously reported in literature)
Note. The direction arrow is reversed where group x topography results are opposite to that stated in the Results section.

Table 3.4 cont. Results for boy AD/HDcom and AD/HDin groups.

	Rel Delta	Rel Theta	Rel Alpha	Rel Beta	Theta/Beta
Main Effect		AD/HDcom-b↑*	AD/HDcom-b↓**		AD/HDcom-b↑*
F < P			AD/HDcom-b↓**		
F/P > C			AD/HDcom-b↓*		
L < R					
L/R < M					AD/HDcom-b↑*
F < P x L < R	AD/HDcom-b↓*				
F < P x L/R < M	AD/HDcom-b↓*	**AD/HDcom-b↓***			
F/P > C x L < R					
F/P > C x L/R < M					

*p < .05, **p < .01, ***p < .001 (**bold** – comparable effect between sexes; greyscale– previously reported in literature)
Note. The direction arrow is reversed where group x topography results are opposite to that stated in the Results section.

3.3.4 Girls – AD/HDcom vs. AD/HDin

3.3.4.1 Absolute Power

Figure 3.3 shows that the AD/HDcom girl group, compared with the AD/HDin girl group, had elevated absolute theta activity in the right hemisphere (AD/HDcom-g > AD/HDin-g x L < R: $F = 5.23$, $p = .024$, $\eta_p^2 = .04$). Table 3.5 summarises absolute power results for the girl clinical groups.

3.3.4.2 Relative Power

Figure 3.4 shows that the AD/HDcom girls, c.f. the AD/HDin girls, had elevated relative delta activity in posterior regions (AD/HDcom-g > AD/HDin-g x F < P: $F = 6.93$, $p = .010$, $\eta_p^2 = .06$) and in the right hemisphere (AD/HDcom-g > AD/HDin-g x L < R: $F = 8.00$, $p = .006$, $\eta_p^2 = .06$). The AD/HDcom girls also had elevated relative delta activity in the right hemisphere of the central (AD/HDcom-g > AD/HDin-g x F/P < C x L < R: $F = 6.08$, $p = .015$, $\eta_p^2 = .05$) and posterior regions (AD/HDcom-g > AD/HDin-g x F < P x L < R: $F = 5.08$, $p = .026$, $\eta_p^2 = .04$). Figure 3.4 shows that, compared with the AD/HDin girls, the AD/HDcom girls had elevated relative theta activity in the left hemisphere (AD/HDcom-g < AD/HDin-g x L > R: $F = 6.18$, $p = .014$, $\eta_p^2 = .05$) and at the midline (AD/HDcom-g < AD/HDin-g x L/R < M: $F = 5.94$, $p = .016$, $\eta_p^2 = .05$). This last effect was greater in the posterior region (AD/HDcom-g < AD/HDin-g x F < P x L/R < M: $F = 4.68$, $p = .033$, $\eta_p^2 = .04$) but reduced in the central region (AD/HDcom-g < AD/HDin-g x F/P > C x L/R < M: $F = 4.68$, $p = .033$, $\eta_p^2 = .04$). Finally, relative beta activity in the central region of the hemispheres was reduced in the AD/HDcom girls (AD/HDcom-g <

AD/HDin-g x F/P < C x L/R > M: $F = 4.39$, $p = .038$, $\eta_p^2 = .04$). See Table 3.5 for a summary of these results.

Table 3.5 Results for girl AD/HDcom and AD/HDin groups.

	Delta	Theta	Alpha	Beta	Total Power
Main Effect					
F < P					
F/P > C					
L < R		AD/HDcom-g↑*			
L/R < M					
F < P x L < R					
F < P x L/R < M					
F/P > C x L < R					
F/P > C x L/R < M					

*p < .05, **p < .01, ***p < .001 (**bold** – comparable effect between sexes)

Note. The direction arrow is reversed where group x topography results are opposite to that stated in the Results section.

Table 3.5 cont. Results for girl AD/HDcom and AD/HDin groups.

	Rel Delta	Rel Theta	Rel Alpha	Rel Beta	Theta/Beta
Main Effect					
F < P	AD/HDcom-g↑**				
F/P > C					
L < R	AD/HDcom-g↑**	AD/HDcom-g↓*			
L/R < M		AD/HDcom-g↓*			
F < P x L < R	AD/HDcom-g↑*				
F < P x L/R < M		**AD/HDcom-g↓***			
F/P > C x L < R	AD/HDcom-g↓*				
F/P > C x L/R < M		AD/HDcom-g↓*		AD/HDcom-g↑*	

*p < .05, **p < .01, ***p < .001 (**bold** – comparable effect between sexes)

Note. The direction arrow is reversed where group x topography results are opposite to that stated in the Results section.

3.4 Discussion

There were no significant IQ differences between the Combined and Inattentive types, in either the boy or girl groups. Although the boy and girl AD/HD type groups had lower mean IQ scores compared with the boy and girl control groups, they remained in the average range (see Table 3.1). The pattern of IQ differences is similar within each sex and as they are within normal range, IQ is not expected to impact EEG power results. Previous studies have found that IQ scores did not contribute significantly to EEG power measures suggesting that observed EEG group differences relate solely to the presence of AD/HD (Barry et al., 2009; Chabot & Serfontein, 1996; Clarke et al., 2001c, 2006).

Despite the wealth of AD/HD literature, the majority of it is based on school-aged boys, with little known of sex differences (Rucklidge & Tannock, 2001). Those authors found that the combination of being female and having AD/HD places girls at a higher risk of psychological distress, and that the disorder is more impairing psychologically for females than males. Girls with AD/HD tend to be more inattentive rather than hyperactive-impulsive (Biederman et al., 2002; Lahey et al., 1994), more often showing behaviours such as daydreaming, poor school performance and depressive affect (Quinn, 2005; Quinn & Wigal, 2004). As a result, girls with AD/HD may not be captured by the current diagnostic criteria that focus primarily on excess motor activity and disruptiveness, which is more common in boys (Biederman et al., 2002; Quinn & Wigal, 2004). Without accurate diagnosis and proper treatment for the disorder, the mental health and wellbeing of females with AD/HD are jeopardised (Quinn, 2005; Rucklidge, 2010). The current diagnostic assessments for AD/HD rely heavily on subjective

observations of the child's behaviour by parents (usually the mother), teachers and medical practitioners (Barkley, 1997; Dulcan et al., 1997; Root & Resnick, 2003). Information obtained from EEG recordings offers additional independent support, aiding in the diagnostic process (Magee et al., 2005). However, EEG profiles are only useful if they are accurate and valid. Applying information from male-dominant EEG profiles to all potential patients with AD/HD may no longer be appropriate as discrepancies in EEG abnormalities have been found between boys and girls with AD/HD (for an overall review, see Dupuy, Clarke & Barry, 2013). This suggests that there is a need to develop separate EEG profiles for the separate groups (i.e., boys, girls and AD/HD types).

Previous studies have reported significant global EEG effects between the Combined and Inattentive types in boys or mixed-sex groups (Barry & Clarke, 2009; Chabot & Serfontein, 1996; Clarke et al., 1998, 2001c, 2001d; Lubar, 1991), but in exclusive girl subject groups, Dupuy et al. (2011) could not replicate results from these past studies. This intriguing finding suggested that sex may substantially influence the EEG profiles of AD/HD types. The aim of the current study was to explore the EEG activity between AD/HD types with a particular focus on sex effects.

An initial comparison of the AD/HD groups with healthy controls in boys and girls was conducted to ensure that the EEG data in the present study was comparable with past studies. Although relying heavily on boys, previous studies have found that children with AD/HD generally have globally elevated increased posterior absolute delta activity (Clarke et al., 2001b, 2001c), elevated absolute frontal theta activity (Chabot & Serfontein, 1996; Clarke et al., 2002; Mann et al., 1992) and reduced global absolute alpha and beta activity (Clarke et al., 2001b, 2001c; Lazzaro et al., 1998) and a

larger theta/beta ratio (Barry et al., 2009; Clarke et al., 2001c, 2001d; Clarke, Barry, Dupuy, et al., 2011; Clarke, Barry, McCarthy, et al., 2011; Janzen et al., 1995; Lansbergen et al., 2011; Lubar, 1991; Monastra et al., 1999, 2001).

In the present study, Figures 3.1 and 3.2 show that the boy AD/HD groups, compared with boy controls, had globally elevated absolute and relative theta, globally reduced absolute and relative alpha, reduced relative beta activity and a larger theta/beta ratio. Figures 3.3 and 3.4 show that the girl AD/HD groups, compared with girl controls, had globally elevated absolute delta, absolute and relative theta, total power, and globally reduced relative delta and beta activity, and a larger theta/beta ratio. Elevated slow wave (delta and theta) activity, reduced relative beta activity and a larger theta/beta ratio is similar to the literature (mentioned above), indicating that the EEG activity from our AD/HD subjects is representative of the disorder. It is worth noting that girls with AD/HD have previously been found to have globally elevated absolute delta activity and total power, which is not commonly reported in boys (Clarke et al., 2003, Clarke, Barry, McCarthy, Selikowitz & Johnstone, 2007; Dupuy et al., 2011).

The main aim of this study was to explore the influence of sex on the EEGs of AD/HD types. The current study found that boys with AD/HD of the Combined type, compared with boys of the Inattentive type, had globally elevated absolute and relative theta activity, globally reduced relative alpha activity and a larger theta/beta ratio. All these differences have been found previously by Clarke et al. (2001c, 2001d) in mixed-sex groups. The girl clinical groups in this study had results different from the boys. Girls of the Combined type, compared with girls of the Inattentive type, had greater absolute theta in the right hemisphere, greater right posterior relative delta

activity, and reduced relative theta activity in the left hemisphere. There were no significant global EEG differences found between the girl AD/HD types groups in theta, alpha, or the theta/beta ratio – as found in boys (compare Tables 3.4 and 3.5). However, these results are broadly comparable to the sole published girl study on AD/HD types (Dupuy et al., 2011). These results show that the EEG profiles of AD/HD types are dissimilar for boys and girls (only one result matched across the sexes; note bold font in Tables 3.4 and 3.5).

Some of the most interesting findings are the global EEG differences between the two AD/HD types in boys that were not found in girls (see Tables 3.4 and 3.5): the Combined type had elevated absolute and relative theta, reduced relative alpha and a larger theta/beta ratio than the Inattentive type. Previous studies of EEG differences between AD/HD types in boys have suggested that the Combined type is associated with greater abnormalities than the Inattentive type (Barry & Clarke, 2009; Chabot & Serfontein, 1996; Clarke et al., 1998, 2001c, 2001d). Some have even suggested that the Combined and Inattentive types may reflect activity in different and independent neuroanatomical systems (Clarke et al., 2001c, 2001d). However, girls' EEG activity has been found to be rather homogenous, regardless of AD/HD type (Clarke et al., 2003; Dupuy et al., 2011). The results from this study show that the EEG profiles differ more in nature, rather than just extent, between AD/HD types in boys and girls.

It is also noteworthy that Figures 3.1 – 3.4 show differing topographical patterns between the boy and girl control groups. Differences in EEG maturation have been found previously between boys and girls (Benninger, Matthis & Scheffner, 1984; Clarke, Barry, McCarthy & Selikowitz, 2001a; Harmony, Marosi, Diaz de Leon, Becker & Fernández, 1990; Matthis, Scheffner & Benninger, 1980). Although not discussed in

detail here, these studies have generally found that girls, compared with boys, have maturationally-delayed EEG development, but this lag tends to disappear by adolescence. This suggests that, although male EEG activity matures earlier, females catch up in adolescence. Over an age range of 7-12 years (as in the current groups), the EEG maturation patterns that differ between boys and girls are likely to cloud AD/HD abnormalities. Because they differ normally, grouping boys and girls together in AD/HD-EEG research makes it very difficult to understand the effects that are directly attributable to the disorder. To control for sex effects, separate male and female EEG profiles should be used. This study shows that the EEG differences between AD/HD types and controls are not identical between boys and girls, partly because the EEGs of healthy boys and girls are not the same.

With mounting evidence that sex differences exist within AD/HD, it is now apparent that the dominant male-based literature is no longer appropriate for understanding EEG abnormalities in females with AD/HD. This study has found dissimilar EEG profiles between boys and girls with the Combined and Inattentive types of AD/HD. A clinical implication of these results is that those who include EEG recordings as part of their diagnostic procedure ought to use separate male and female profiles to compare with their patient's data. This study has also reiterated that the EEG activity of healthy boys and girls differs. Further replication of these results across different subject groups is important to add to their generality. Although it is accepted that boys and girls have different EEG maturation patterns, many AD/HD investigations have continued to pool males and females together. These maturational sex differences confound AD/HD-related EEG abnormalities and obscure outcomes. Future research should be mindful of this and avoid excessive overgeneralizations based on male results; rather, it is time

to pursue sex-specific research. This idea of the necessity of sex-specific research is not limited to AD/HD, but may be important in other disorders where the literature is predominately based on males, such as in Autism, Asperger's, Conduct Disorder, Oppositional Defiant Disorder, and Tourette's Syndrome.

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4 GIRLS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: EEG DIFFERENCES BETWEEN DSM-IV TYPES

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4.1 Introduction

Attention-Deficit/Hyperactivity Disorder (AD/HD) is characterised by behaviourally-inappropriate symptoms of hyperactivity, impulsivity and inattention (APA, 2000). Prevalence estimates suggest that AD/HD is evident in 3-5% of school children (APA, 2000), and clinical populations have estimated male to female ratios as high as 9:1 (Arnold, 1996). Girls with AD/HD are more likely to show symptoms of inattention, hyper-talkativeness and emotional reactivity, which are largely ignored by teachers, and subsequently they may not be referred for treatment (DuPaul et al., 2006; Gaub & Carlson, 1997; Gershon, 2002; Quinn, 2005). As a result of unequal prevalence ratios, referral biases, and male-directed diagnostic criteria, male subjects have dominated AD/HD research. The literature developed from male AD/HD research cannot always directly apply to females, as significant sex differences have been found (Gaub & Carlson, 1997; Gershon, 2002; Graetz, Sawyer & Baghurst, 2005; Gross-Tsur et al., 2006; Ohan & Johnstone, 2005).

There are three types of AD/HD recognised in the DSM-IV; predominantly Inattentive, predominantly Hyperactive-Impulsive, and the Combined type. Each type is based on the dominant observed symptoms (APA, 2000). The Inattentive type is linked more with internalizing behaviours, which are largely displayed by females, and the Combined type is overwhelmingly present in clinical settings regardless of gender (Gershon, 2002; Nigg, 2006; Quinn, 2005).

Children with AD/HD display consistent EEG abnormalities. Research has shown that these children typically have increased posterior absolute delta activity (Clarke, Barry, McCarthy & Selikowitz, 2001a, 2001b; Matousek, Rasmussen & Gillberg, 1984),

and elevated frontal absolute theta activity (Chabot & Serfontein, 1996; Clarke, Barry, McCarthy & Selikowitz, 2002; Lazzaro et al., 1998; Satterfield, Cantwell, Lesser & Podsin, 1972), and reduced relative alpha and relative beta activity (Clarke et al., 2001a, 2001b; Lazzaro et al., 1998). However, most of these studies were conducted on male or mixed-sex samples, with minimal, if any, female representation.

Clarke et al. (2001a) found qualitative EEG differences between the Combined and Inattentive types within a heavily male sample (64 boys and 16 girls), resulting in little interpretation for females. Clarke et al. (2001b) investigated sex and AD/HD-type differences in children using equal numbers; 40 boys and 40 girls, and found that the Combined type group had greater absolute and relative theta and less relative alpha than the Inattentive type group. However, the statistical design in Clarke et al. (2001b) used a mixed-sex sample to investigate AD/HD types, grouping both males and females together, and there was no explicit analysis of AD/HD types in females alone.

There are no published studies that *directly* examine EEG differences between AD/HD types in girls. The aim of this study is to address that gap by investigating EEG differences between girls with the Combined and Inattentive types of AD/HD.

4.2 Method

4.2.1 Participants

Ninety girls, aged 8–12 years (M = 10.0, SD = 1.4 years), participated in this study. These girls are a subset of subjects used by Clarke et al. (2001b). Of these, there were 30 females in the AD/HD Combined type group (AD/HDcom), 30 females in the AD/HD Inattentive type group (AD/HDin) and 30 controls. Clinical participants were selected from new patients presenting for an AD/HD assessment at a paediatric practice, with

no previous AD/HD diagnosis. The 30 controls were recruited from local schools and community groups. All participants had full-scale WISC-III (Wechsler, 1992) IQ scores of 85 or higher. Participants had no history of medication use for any psychiatric disorder, and AD/HD participants were tested before being prescribed any medication.

Inclusion in the AD/HD groups was based on independent clinical assessments made by a paediatrician and a psychologist, and both agreed on the diagnosis. Both clinicians used behavioural observations, a comprehensive history taken from parent(s)/guardian(s), school reports from the past 12 months, and any reports from other health professionals, to make their diagnoses. Participants were excluded if they had a history of problematic prenatal, perinatal or neonatal periods, a history of CNS diseases, convulsions or convulsive disorders. They were also excluded if there was evidence of a consciousness disorder, head injury with cerebral symptoms, paroxysmal headaches or tics, or if they met criteria for Conduct Disorder, Oppositional Defiant Disorder, an anxiety or depressive disorder, Asperger's or Tourette's Syndrome.

Inclusion for controls was based on assessments involving parent(s)/guardian(s), using the same procedure as AD/HD participants, described above. Controls had no problems during their prenatal, perinatal or neonatal periods, no disorders of consciousness, no head injuries resulting in cerebral symptoms, and no history of CNS diseases or obvious somatic diseases, no history of convulsive disorders or convulsions, tics, stuttering, paroxysmal headaches, enuresis or encopresis after their fourth year, and no other psychiatric condition. Participants displayed no deviation from normal physical development. Participants were excluded from all groups if spike wave or excess beta activity (Clarke, Barry, McCarthy & Selikowitz, 2001c) was found in their EEG.

4.2.2 Procedure

Ethics approval for this study was obtained from the combined Illawarra Area Health/University of Wollongong Human Research Ethics Committee. Parent(s)/Guardian(s) of participants gave informed consent, and participants assented.

Participants were tested in a single morning over approximately 2.5 hours. A clinical history and physical examination was conducted first for subjects. Participants then completed the WISC-III, the Neale Analysis of Reading (Neale, 1999) and the Wide Range Achievement Test - Revised (WRAT-R) spelling test (Jastak, 1984). Participants then had an eyes-closed, resting EEG recorded. An electrode cap ensured International 10–20 electrode placement, and activity was recorded from 21 electrodes: Fp1, Fpz, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, Oz, O2.

Using 9 millimetre (mm) tin disk electrodes, a single electrooculogram (EOG) electrode referenced to Fpz was placed beside the participant's right eye, and a ground lead was placed on the left cheek. A linked ear reference was used for all EEG sites, and impedance levels were all below 5 KiloOhm. The EEG was recorded and analysed on a Cadwell Spectrum 32, software version 4.22, using test type EEG, montage Q-EEG (Cadwell Laboratories Inc., Kennewick, WA, USA). The sensitivity was set at 150 microvolt (μV) per centimetre with a high frequency filter set at 70 Hertz (Hz), a notch filter set at 50 Hz, and a low frequency filter set at 0.53 Hz. The sampling rate was set at 200 Hz and the Fast Fourier Transformation (FFT) used 2.56 second (s) epochs.

Thirty 2.56 s epochs were selected from the live EEG trace and stored electronically. Epoch rejections were based on both computer and visual selections. The EOG rejection level was set at 50 µV. An EEG lab technician visually evaluated every epoch for acceptance. The 30 selected epochs were further reduced to 24 epochs (~1 min) for Fourier analysis. The recorded EEG was analysed in four frequency bands: delta (1.5–3.5 Hz), theta (3.5–7.5 Hz), alpha (7.5–12.5 Hz), and beta (12.5–25 Hz), for absolute and relative power, and total power (1.5–25 Hz). Relative power (%) was calculated by dividing absolute power in the frequency band by the total power and multiplying by 100.

Activity from the 21 electrodes was grouped into nine cortical regions by averaging in each region: left frontal (Fp1, F7, F3), midline frontal (Fpz, Fz), right frontal (Fp2, F8, F4), left central (T3, C3), midline central (Cz), right central (T4, C4), left posterior (T5, P3, O1), midline posterior (Pz, Oz) and right posterior (T6, P4, O2).

4.2.3 Statistical Analysis

The effects of region and group for each frequency band in total, absolute and relative powers were examined. The effects of region were examined in two orthogonal three-level repeated-measures factors. The first of these was a sagittal factor, where planned contrasts compared the frontal (F) region with the posterior (P) region, and their mean (F/P) with the central (C) region. The second factor was laterality, within which planned contrasts compared activity in the left (L) hemisphere with that in the right (R) hemisphere, and their mean (L/R) with the midline (M) region.

Within the group factor, planned contrasts compared the two clinical groups (AD/HD) with the control group (CON). The second group analysis compared the

AD/HDcom group with the AD/HDin group. All reported *F* values have (1, 87) degrees of freedom. As all these contrasts are planned and there are no more of them than the degrees of freedom for effect, no Bonferroni-type adjustment to α is required (Tabachnick & Fidell, 1989). An α level of .05 was used for statistical significance.

4.3 Results

Head maps showing scalp topography of the control and two clinical groups for each absolute and relative power band are shown in Figures 4.1 and 4.2.

4.3.1 AD/HD vs. Control

4.3.1.1 Absolute Power

As shown Figure 4.1, the AD/HD groups had greater total power across the scalp than controls (AD/HD > CON: $F = 8.01$, $p < .01$). The greater total power was more apparent at the midline than the two hemispheres (AD/HD > CON x L/R < M: $F = 5.70$, $p < .05$) and this effect was enhanced in the central region compared with the frontal/posterior regions (AD/HD > CON x F/P < C x L/R < M: $F = 8.80$, $p < .005$).

The AD/HD groups had greater absolute power across the scalp than controls in the delta (AD/HD > CON: $F = 4.59$, $p < .05$) and theta (AD/HD > CON: $F = 17.16$, $p < .001$) bands. The greater global theta power was more evident at the midline compared with the two hemispheres (AD/HD > CON x L/R < M: $F = 9.87$, $p < .005$), and this effect was greater in the central region than the frontal/posterior region (AD/HD > CON x F/P < C x L/R < M: $F = 9.94$, $p < .005$). The AD/HD groups had relatively less absolute beta activity in the two hemispheres compared with the midline than controls (AD/HD < CON x L/R < M: $F = 4.43$, $p < .05$).

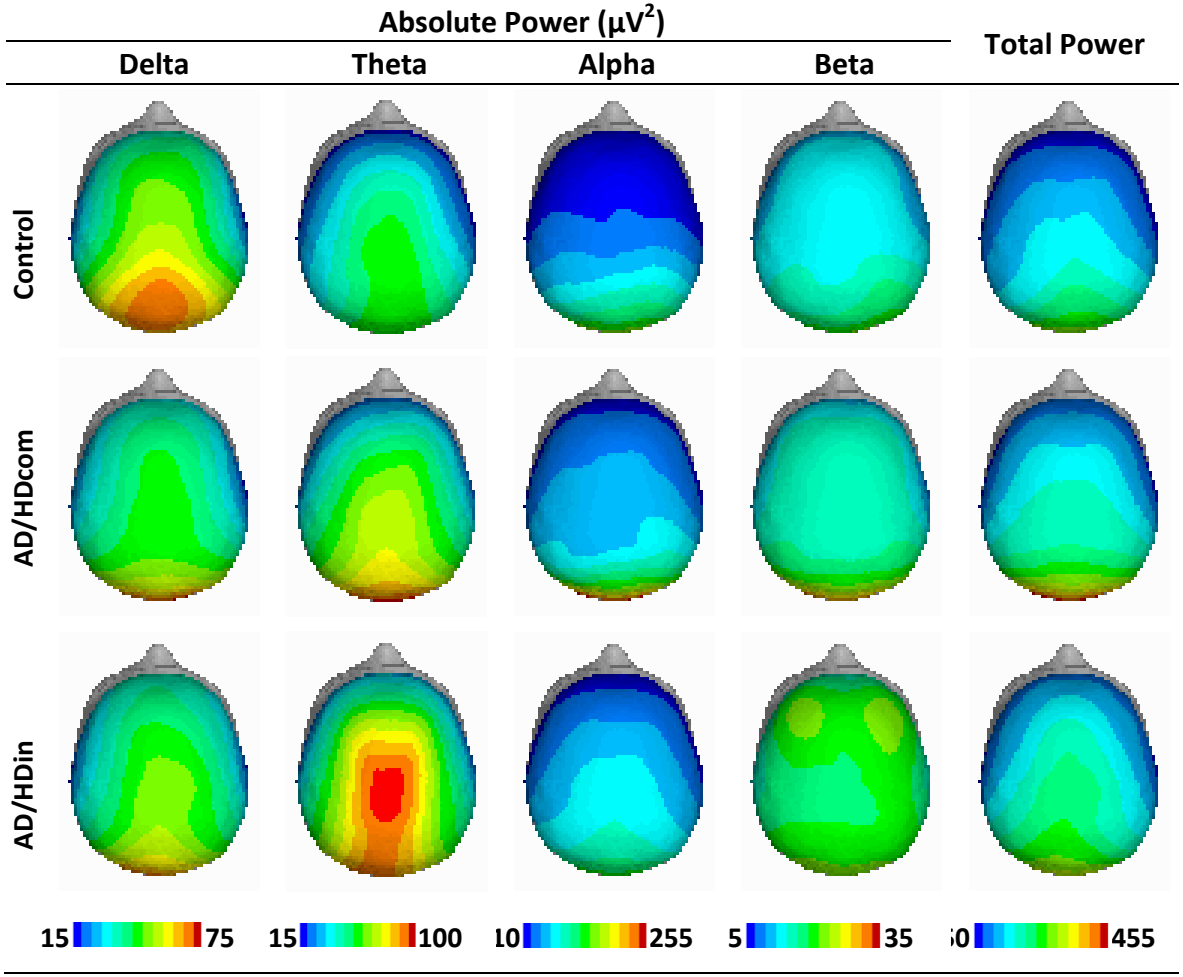

Figure 4.1 Topographic maps for absolute power for the control and two AD/HD groups.

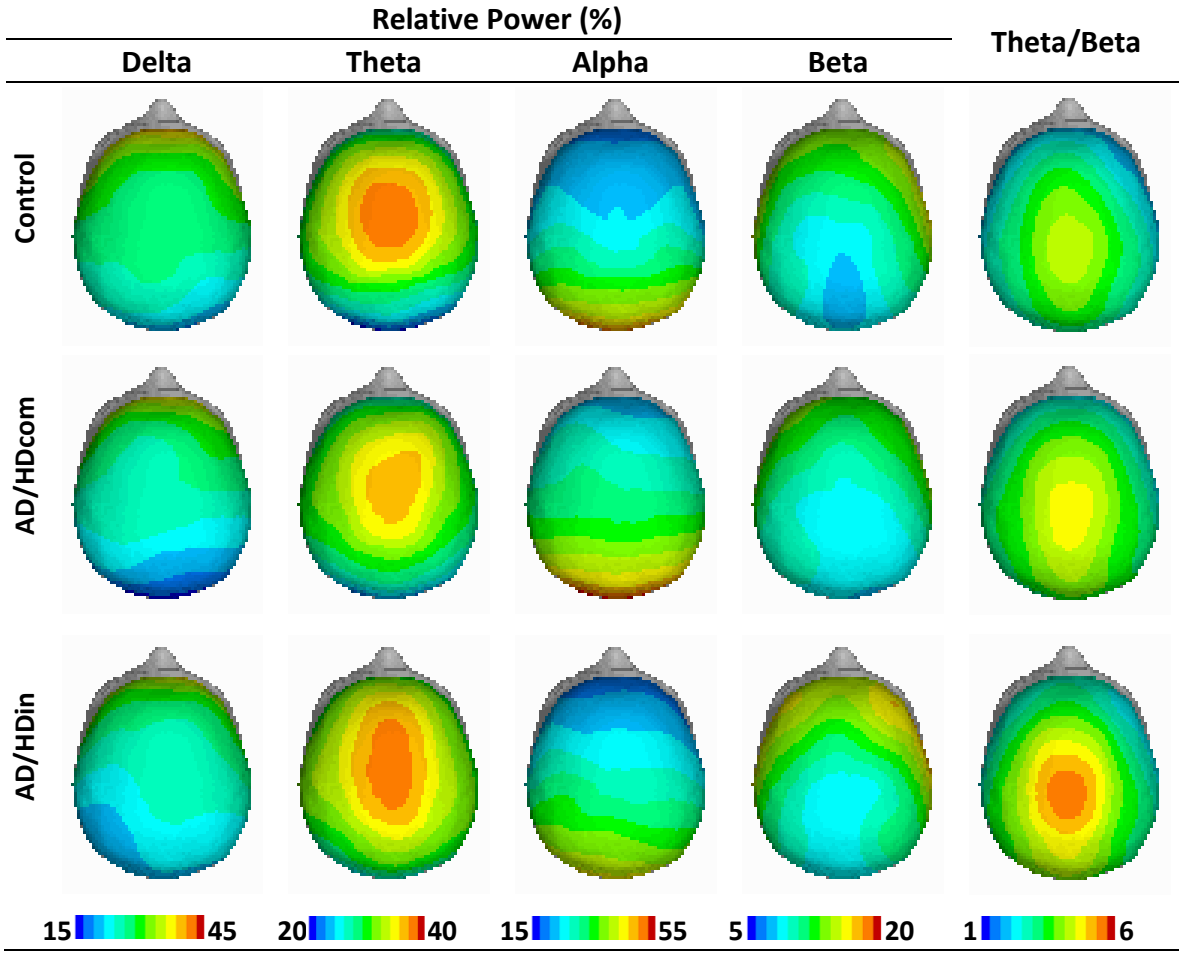

Figure 4.2 Topographic maps for relative power for the control and two AD/HD groups.

4.3.1.2 Relative Power

As shown in Figure 4.2, the AD/HD groups had reduced relative delta activity across the scalp than controls (AD/HD < CON: $F = 9.18$, $p < .005$). The frontal elevation in relative delta was less in the AD/HD groups than the control group (AD/HD < CON x F > P: $F = 8.40$, $p < .005$). The central reduction in the midline compared with the two hemispheres was smaller in the AD/HD groups than controls (AD/HD < CON x F/P > C x L/R > M: $F = 4.00$, $p < .05$). Together, these results indicate that relative delta in the AD/HD groups is reduced and more equipotential across the scalp.

Compared with controls, the AD/HD groups had greater global relative theta activity (AD/HD > CON: $F = 53.10$, $p < .001$).

The AD/HD groups had less relative alpha at midline compared with the two hemispheres than controls (AD/HD < CON x L/R < M: $F = 5.03$, $p < .05$). A frontal reduction of relative alpha was less evident in the right than left hemisphere in the AD/HD groups compared with controls (AD/HD < CON x F < P x L < R: $F = 5.34$, $p < .05$).

The AD/HD groups had reduced relative beta activity across the scalp compared with controls (AD/HD < CON: $F = 21.06$, $p < .001$), particularly in the hemispheres (AD/HD < CON x L/R > M: $F = 10.14$, $p < .005$). This effect was reduced in the frontal compared with the posterior region (AD/HD < CON x F < P x L/R > M: $F = 3.98$, $p < .05$) and in the central compared with the frontal/posterior region (AD/HD < CON x F/P < C x L/R > M: $F = 5.02$, $p < .05$). Together, these results indicate that relative beta in the AD/HD groups is reduced, particularly in non-vertex regions.

4.3.2 AD/HDcom vs. AD/HDin

4.3.2.1 Absolute Power

As can be seen in Figure 4.1, the AD/HDcom group had greater absolute theta activity in the right than left hemisphere compared with the AD/HDin group (AD/HDcom > AD/HDin x L < R: $F = 5.30$, $p < .05$). Compared with the AD/HDcom group, the AD/HDin group had reduced midline beta activity in the posterior region compared with the frontal region (AD/HDcom > AD/HDin x F < P x L/R < M: $F = 4.86$, $p < .05$).

4.3.2.2 Relative Power

Figure 4.2 shows that the AD/HDcom group had reduced relative delta activity in the right compared with the left hemisphere than the AD/HDin group (AD/HDcom < AD/HDin x L < R: $F = 15.68$, $p < .001$), and this effect was largest centrally (AD/HDcom < AD/HDin x F/P < C x L < R: $F = 7.13$, $p < .01$). The AD/HDcom group also had less relative delta in the frontal hemispheric regions compared with the midline than the AD/HDin group (AD/HDcom < AD/HDin x F > P x L/R > M: $F = 5.23$, $p < .05$).

The AD/HDin group had less relative theta activity in the right than left hemisphere compared with the AD/HDcom group (AD/HDcom < AD/HDin x L > R: $F = 6.62$, $p < .05$).

Compared with the AD/HDin group, the AD/HDcom group had greater relative alpha activity at the midline than the two hemispheres in the posterior compared with the frontal region (AD/HDcom > AD/HDin x F < P x L/R < M: $F = 5.92$, $p < .05$).

The AD/HDcom group had less relative beta activity in the central region compared with the frontal/posterior region than the AD/HDin group (AD/HDcom < AD/HDin x F/P

< C: $F = 4.26$, $p < .05$). This effect was enhanced in the hemispheres compared with the midline (AD/HDcom < AD/HDin x F/P < C x L/R > M: $F = 7.46$, $p < .01$).

4.4 Discussion

This study investigated EEG differences between the Combined and Inattentive types of AD/HD in girls. Previous research has found consistent EEG abnormalities in AD/HD. Typically, AD/HD children have increased posterior absolute delta (Clarke et al., 2001a, 2001b), elevated frontal absolute theta (Chabot & Serfontein, 1996; Clarke et al., 2002; Satterfield et al., 1972), and reduced relative alpha and relative beta activity (Clarke et al., 2001a, 2001b; Lazzaro et al., 1998).

The present study found that the two AD/HD groups had greater absolute delta, theta and total power across the scalp compared with controls. The increased absolute theta and total power were greater at the midline compared with the two hemispheres in the AD/HD groups than in controls. They also had relatively less midline absolute beta activity than controls. The AD/HD groups had reduced relative delta and beta activity, but increased relative theta activity across the scalp. Compared with controls, the AD/HD groups had reduced relative delta at the midline central regions, suggesting relative delta is more equipotential across the scalp. The AD/HD groups also had reduced and more equipotential relative alpha and beta activity than controls, particularly at the midline compared with the hemispheres.

Elevated total power, absolute delta and theta activity across all regions, as reported in this study, have been found in previous AD/HD studies (Clarke et al., 2001a, 2001b, 2003; Clarke, Barry, McCarthy, Selikowitz & Johnstone, 2007). Increased relative theta and reduced relative beta across all regions has been reported

in both female and male AD/HD populations (Clarke et al., 2001a, 2001b, 2003, 2007; Lazzaro et al., 1998). Although there is minimal published literature on EEG activity in AD/HD girls, the current results are consistent with this literature, and suggest this female AD/HD sample has an EEG profile that is similar to other AD/HD girls. As mentioned earlier, reported significant sex differences between AD/HD males and females suggests that male AD/HD research cannot always apply to females, warranting sex-specific research in this field.

Clarke et al.'s (2003) EEG investigation of AD/HD girls suggested that the primary EEG deficit, a reduced relative beta activity with a reciprocal increase in relative theta activity, reflected a 'cortical hypoarousal' profile. The current female AD/HD group had increases in relative theta and reductions of relative beta activity consistent with the 'hypoarousal' profile. However, recent research has found that although this theta/beta profile is robust within the AD/HD literature, it does not reflect CNS arousal levels as originally thought. Barry, Clarke, Johnstone, McCarthy and Selikowitz (2009) found no correlation between the theta/beta profile and skin conductance level (SCL), a well-respected marker of CNS arousal. Instead, the theta/beta profile has been suggested to underlie deficits in attentional processing (Barry et al., 2009); however, further research is needed.

Global EEG differences have been found previously between the Combined and Inattentive types of boys with AD/HD (Clarke, Barry, McCarthy & Selikowitz, 1998, 2001a, 2001b). Clarke et al. (2001a) even suggested that the two AD/HD types may reflect different and independent neuroanatomical systems. However, those global EEG differences were not replicated in this female study. Clarke et al. (2003) found that girls with AD/HD had very similar EEG profiles regardless of AD/HD type; whereas

Clarke et al. (2001c) found three distinct EEG-defined profiles in boys with AD/HD. The homogenous nature of female AD/HD groups could partially explain the lack of results. The results of Clarke et al. (2003) are supported by the present study with a lack of significant global differences between the AD/HD types in girls.

Focus turns to *why* global EEG differences have been found in AD/HD boys, but not in AD/HD girls. An AD/HD diagnosis relies heavily on referrals, and if teachers do not perceive females to be problematic and/or displaying AD/HD behaviours/symptoms, girls are less likely to be referred for assessment and treatment. DuPaul et al. (2006) found that teachers perceived boys to be more disruptive and exhibit more AD/HD-type behaviours than girls. This suggests that only girls who are identified as being highly disruptive are referred for treatment, which could explain the homogenous nature of female AD/HD clinical groups.

Although AD/HD girls are less likely to display disruptive hyperactive behaviours, like their male AD/HD counterparts, they do present with more inattentive and internalising symptoms (Quinn, 2005). Consequently, common AD/HD rating scales, such as the Conners' Parent Rating Scale (Conners, 1997), have lower thresholds for clinical hyperactive/impulsive behaviours displayed by girls than those set for boys. This suggests that girls do not have to display as many, or as severe, hyperactive/impulsive behaviours to reach the thresholds for AD/HD Hyperactive/Impulsive or Combined types, than are needed for boys to reach the same thresholds. This could explain the homogenous EEG results reported in the current study, as girls do not have the same behavioural gap between AD/HD types as do boys.

It may be that girls do have significant AD/HD type EEG differences, but the female thresholds for these behaviours are so low that the AD/HD types are not clearly

distinct from each other. This could be investigated by creating AD/HD Combined and Inattentive type groups using abnormally high AD/HD type scores on behavioural scales and re-examining EEG differences between the two AD/HD types.

This was the first study to directly examine EEG differences in girls with the Combined and Inattentive types of AD/HD. The EEG results between AD/HD females and age-matched controls are consistent with the published literature. The current results have the robust theta/beta abnormality, although further research is needed for a full explanation of this AD/HD profile. The lack of global differences between the AD/HD types in girls is curious, as differences have been found previously in boys. The EEG activity in AD/HD females is homogenous, regardless of AD/HD type, and this is reflected in the current results. Sex-biased referrals and diagnostic criteria thresholds may account for the homogeneity found in the current study. This study supports the pursuit of further female-specific AD/HD investigations. Future research in this area should be mindful of these results and take efforts to address overgeneralisations of male AD/HD research.

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5 EEG DIFFERENCES BETWEEN THE COMBINED AND INATTENTIVE TYPES OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN GIRLS: A FURTHER INVESTIGATION

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5.1 Introduction

This study is a follow-up to a previously published article that examined EEG differences between two types of Attention-Deficit/Hyperactivity Disorder (AD/HD) in girls (Dupuy, Clarke, Barry, McCarthy & Selikowitz, 2011). The complex AD/HD condition is characterised by behaviourally-inappropriate symptoms of inattention and/or hyperactivity-impulsivity (APA, 2000). Prevalence estimates suggest that AD/HD affects 3-7% of school children (APA, 2000; Pastor & Reuben, 2008), showing that AD/HD is one of the most common childhood disorders. Dupuy et al. (2011) addressed a gap in the AD/HD literature where there had been no direct investigation of EEG differences between two common types of AD/HD exclusively in girls. There is a general consensus that more boys than girls have AD/HD; boy-to-girl ratios range from 3:1 to 9:1 (APA, 2000; Arica & Conners, 1998; Gaub & Carlson, 1997; Hartung & Widiger, 1998; Rutter, Caspi & Moffitt, 2003). The AD/HD types have slightly different boy-to-girl ratios; 2.6:1 for the AD/HD Combined type, 2.2:1 for the Inattentive type and 2.0:1 for the Hyperactive-Impulsive type (Willcutt, 2012). Although these studies (and the current study) relied on DSM-IV criteria for an AD/HD diagnosis; the proposed changes to the AD/HD symptom criteria in the DSM-V, particularly the 'Inattentive Presentation' (Hechtman, French, Mongia & Cherkasova, 2011) may include girls that otherwise would not meet the criteria threshold, which may change these prevalence rates.

Although AD/HD is one of the most widely researched disorders, the literature is overwhelmingly based upon studies with school-aged boys, with comparatively little focus on females and sex differences (Arnold, 1996). This is shifting, and more

attention is now focussing on sex differences and female profiles that are separate to males; one such area is the EEG activity of children with AD/HD. The majority of this literature suggests that children with AD/HD have relatively consistent EEG abnormalities: increased posterior absolute delta activity (Clarke, Barry, McCarthy & Selikowitz, 2001a, 2001b; Matousek, Rasmussen & Gillberg, 1984), globally elevated absolute and relative theta activity, dominant frontally (Barry & Clarke, 2009; Barry, Clarke, Johnstone, McCarthy & Selikowitz, 2009; Chabot & Serfontein, 1996; Clarke, Barry, McCarthy & Selikowitz, 2002; Lazzaro et al., 1998; Satterfield, Cantwell, Lesser & Podsin, 1972), and reduced relative alpha and relative beta activity (Clarke et al., 2001a, 2001b; Clarke, Barry, Dupuy et al., 2011; Clarke, Barry, McCarthy & Selikowitz, 2011; Lazzaro et al., 1998). A larger theta/beta ratio has also been found consistently in AD/HD children, compared with healthy controls (Barry & Clarke, 2009; Clarke et al., 2001a, 2001b; Clarke, Barry, Dupuy et al., 2011; Clarke, Barry, McCarthy et al., 2011; Janzen, Graap, Stephanson, Marshall & Fitzsimmons, 1995; Lansbergen, Arns, van Dongen-Boomsma, Spronk & Buitleaar, 2011; Lubar, 1991; Monastra et al., 1999; Monastra, Lubar & Linden, 2001). However, most of these studies were conducted on males or mixed-sex samples with minimal female inclusion.

Although discussed in greater detail in our previous paper (Dupuy et al., 2011), the few investigations into EEG differences between AD/HD types have found that the Combined type is more often associated with greater EEG abnormalities than the Inattentive type, particularly in the absolute theta and alpha bands (Barry & Clarke, 2009; Chabot & Serfontein, 1996; Clarke, Barry, McCarthy & Selikowitz, 1998, 2001a, 2001b). Three studies on subtype EEG differences by Clarke et al. (1998, 2001a, 2001b) showed such significant widespread/global differences (in absolute and relative

theta, relative alpha, theta/alpha & theta/beta ratios) that the authors suggested the EEG results reflected neuroanatomical anomalies that differed between AD/HD types. However, as mentioned above, these studies included either a majority of, or exclusively male cohorts, with few or no females included. Dupuy et al. (2011) was the first to examine EEG differences between AD/HD types in an exclusive female sample (90 girls, aged 7-12 years) and did not replicate the global results found in past studies. While this reinforces the argument for sex-specific EEG research in AD/HD, our focus in this follow-up paper is on explanations for this disparity between males and females.

Girls with AD/HD are less likely than boys to display disruptive hyperactive-impulsive behaviours (Berry, Shaywitz & Shaywitz, 1985; Carlson, Tamm & Gaub, 1997; DuPaul et al., 2006; Gaub & Carlson, 1997; Gershon, 2002; Quinn, 2005; Rucklidge & Tannock, 2001). Consequently, there are lower thresholds for clinically significant hyperactive-impulsive behaviours displayed by girls than those set for boys (Conners, 1997). This suggests that girls do not have to display as many (or as disruptive) hyperactive-impulsive behaviours to reach thresholds for AD/HD Combined or Hyperactive-Impulsive types, than are needed for boys to reach the same thresholds. There may be global EEG differences between AD/HD types in girls, but perhaps the female thresholds for anomalous behaviours are so low that the AD/HD types are not clearly distinct from one another, resulting in the homogenous EEG results found by Dupuy et al. (2011). The aim of this study is to further explore the EEGs of girls with AD/HD using behaviourally exaggerated Combined and Inattentive type groups.

5.2 Method

5.2.1 Participants

Sixty girls, aged 7−12 years (*M* = 10.1, *SD* = 1.5 years), participated in this study. Of these, 20 were in the AD/HD Combined type group (AD/HDcom), 20 in the AD/HD Inattentive type group (AD/HDin) and 20 controls (CON). Clinical participants were selected from a pool of patients at a paediatric practice and controls were recruited via local schools and community groups. All participants had a full-scale WISC-III IQ score of 80+. Participants had no history of medication use for any psychiatric disorder, and AD/HD participants were tested prior to being placed on any medication. Data from these subjects have not been published previously.

Inclusion in the AD/HD groups was based on independent clinical assessments made by a paediatrician and a psychologist (both agreed on AD/HD type diagnosis). Both clinicians used behavioural observations, a comprehensive history taken from parent(s)/guardian(s), school reports from the past 12 months, and any other relevant health reports to make their diagnoses. Participants were excluded if they had a history of problematic prenatal, perinatal or neonatal periods, a history of CNS diseases, convulsions or convulsive disorders. They were also excluded if there was evidence of a consciousness disorder, head injury with cerebral symptoms, paroxysmal headaches or tics, or if they met criteria for Conduct Disorder, Oppositional Defiant Disorder, an anxiety or depressive disorder, Asperger's or Tourette's Syndrome.

Additional inclusion criteria for the AD/HD type groups included scores from the Conners Parent Rating Scale-Revised: Long Version (Conners, 1997). All girls with AD/HD scored above the clinical range (over the 66th percentile) on the DSM-IV

inattentive and DSM-IV total subscales. These subscales are based on DSM-IV criteria for AD/HD and are strongly linked to AD/HD symptom behaviours and are sex normed (Conners, 1997). Girls with the Combined type were included if their raw scores on the DSM-IV hyperactive-impulsive subscale were *above* the 71st percentile (within the clinical range). Girls with the Inattentive type were included if their raw scores on the same subscale (DSM-IV hyperactive-impulsive) were *below* the 55th percentile (average range), ensuring they did not have clinically significant hyperactive-impulsive behaviours. These additional selection criteria were used to exaggerate the hyperactive-impulsive distinction between the Inattentive and Combined type groups. Note that clinical subjects were diagnosed with the specified AD/HD type, independently of their Conners' rating scale scores.

Inclusion for controls was based on assessments involving parent(s)/guardian(s), using the same procedure as AD/HD participants, described above. Controls had no problems during their prenatal, perinatal or neonatal periods, no disorders of consciousness, no head injuries resulting in cerebral symptoms, and no history of CNS diseases or obvious somatic diseases, no history of convulsive disorders or convulsions, tics, stuttering, paroxysmal headaches, enuresis or encopresis after their fourth year, and no other psychiatric condition. Participants displayed no deviation from normal physical development. Participants were excluded if spike waves were evident in their EEG.

5.2.2 Procedure

Participants were tested in a single morning over approximately 2.5 hours. A clinical history and physical examination were conducted first. Participants then

completed the WISC-III, the Neale Analysis of Reading and the South Australian Spelling Test. After, participants had a five minute eyes-closed, resting EEG recorded. An electrode cap ensured International 10–20 electrode placement, and activity was recorded from 19 electrodes: Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, O2. These electrodes were divided in to nine regions by averaging each region. These were the left frontal (Fp1, F7, F3), midline frontal (Fz), right frontal (Fp2, F8, F4), left central (T3, C3), midline central (Cz), right central (T4, C4), left posterior (T5, P3, O1), midline posterior (Pz) and right posterior (T6, P4, O2) regions. A linked ear reference was used, with a cap ground placed between Fpz and Fz. Impedance levels were all below 5 kOhm. The EEG was recorded using a Lexicor NRS-24 with a sampling rate of 256 Hz and a gain of 32,000. A low frequency filter was set at 0.5 Hz and a high frequency filter at 70 Hz, with a notch filter at 50 Hz. The EEG was initially visually artefacted by a trained technician for a minimum of 75 s of artefact-free trace and then Fourier transformed using NxLink software (version 4.3.1). The recorded EEG was analysed in four frequency bands: delta (1.5–3.5 Hz), theta (3.5–7.5 Hz), alpha (7.5–12.5 Hz), and beta (12.5–25 Hz), for absolute and relative power, and total power (1.5–25 Hz). The theta/beta ratio was also calculated by dividing theta activity by beta activity at each electrode site before averaging into regions.

5.2.3 Statistical Analysis

The clinical data were tested in one-way analyses of variance (ANOVAs) comparing the scores of the AD/HD groups with controls and the Combined type group with the Inattentive type group.

The effects of region and group for each frequency band in total, absolute and relative powers, and the theta/beta ratio, were examined. The effects of region were examined in two orthogonal three-level repeated-measures factors. The first of these was a sagittal factor, where planned contrasts compared the frontal (F) region with the posterior (P) region, and their mean (F/P) with the central (C) region. The second factor was laterality, within which planned contrasts compared activity in the left (L) hemisphere with that in the right (R) hemisphere, and their mean (L/R) with the midline (M) region. These factors allow identification of regional topography, and their difference between groups.

Within the group factor, planned contrasts compared the two clinical groups together (AD/HDcom and AD/HDin) with the control group (CON). The second group analysis compared the AD/HDcom group with the AD/HDin group. As all these contrasts are planned and there are no more of them than the degrees of freedom for effect, no Bonferroni-type adjustment to α is required. An α level of .05 was used for statistical significance. All reported *F* values have (1, 57) degrees of freedom.

5.3 Results

5.3.1 Clinical Data

Table 5.1 shows mean age and test scores for the two AD/HD groups and controls. No significant differences were found within age, IQ, reading or spelling age. Scores from the Conners' parent-rating AD/HD scale were significantly different between the AD/HD and control groups on measures of inattention ($F = 378.15$, $p < .001$) and hyperactivity-impulsivity ($F = 23.18$, $p < .001$; see Table 5.1). Between the clinical groups; the AD/HDcom group, compared with the AD/HDin group, had higher scores

on symptoms of inattention (F = 12.14, p = .001) and hyperactivity-impulsivity (F = 954.41, p < .001).

Table 5.1 Mean age and psychometric test scores for the two AD/HD groups and controls.

	AD/HDcom	AD/HDin	Control
Mean Age in years *(SD)*	9.60 *(1.39)*	10.00 *(1.84)*	10.60 *(1.14)*
IQ score	98.50	99.00	103.60
Reading Age in years	9.07	9.77	10.48
Spelling Age in years	9.90	9.95	10.15
Inattention	87.80	81.45	49.25
Hyperactive/Impulsive	87.95	50.45	47.80

5.3.2 AD/HD vs. Control

Figure 5.1 shows that the AD/HD groups, compared with controls, had reduced absolute delta activity at the midline (AD/HD < CON x L/R < M: F = 6.76, p = .012, η_p^2 = .11). Absolute theta was globally elevated in the AD/HD groups, compared with controls, which neared significance (AD/HD > CON: F = 3.93, p = .052, η_p^2 =.06).

Compared with controls, the AD/HD groups had elevated power in the central regions of the midline in absolute alpha (AD/HD > CON x F/P < C x L/R < M: F = 6.40, p = .014, η_p^2 = .10), absolute beta (AD/HD > CON x F/P < C x L/R < M: F = 4.58, p = .037, η_p^2 = .07), and total power (AD/HD > CON x F/P < C x L/R < M: F = 6.23, p =.015, η_p^2 = .10).

Figure 5.2 shows that the AD/HD groups had a reduced relative theta in the central region (AD/HD < CON x F/P < C: F = 4.22, p =.045, η_p^2 = .07).

The AD/HD groups had reduced relative alpha activity in the left hemisphere (AD/HD < CON x L > R: F = 4.60, p =.036, η_p^2 = .07) and a smaller central reduction (AD/HD < CON x F/P > C: F = 11.01, p =.002, η_p^2 = .16).

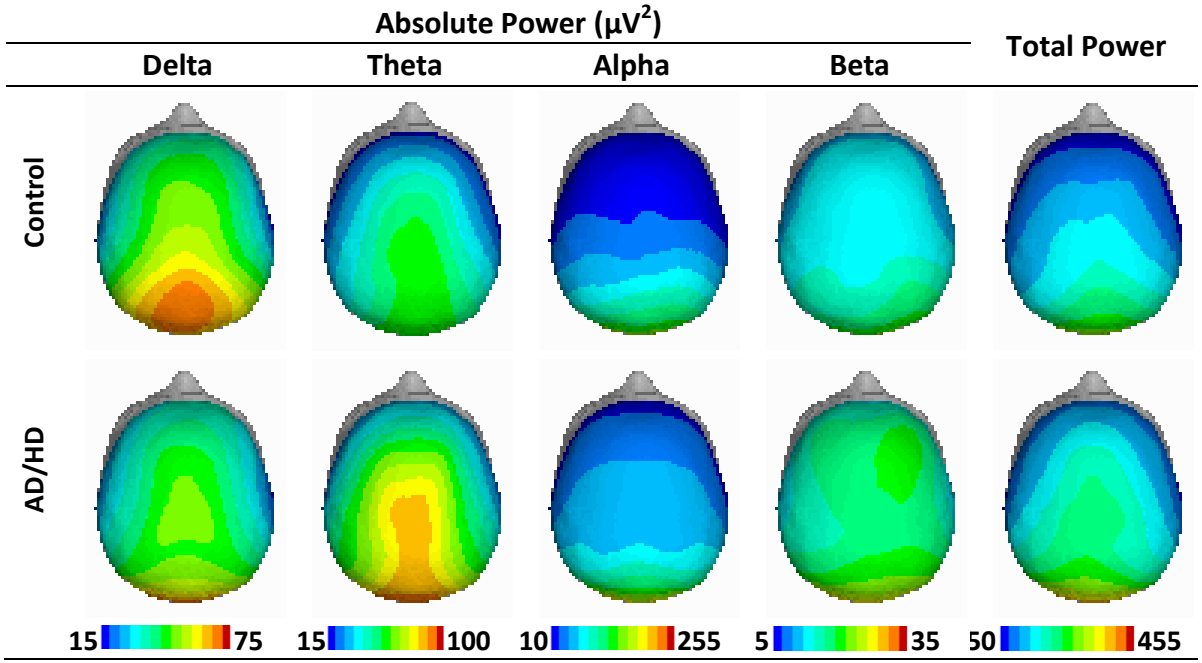

Figure 5.1 Topographic maps for absolute power for the control and the average of the two AD/HD groups

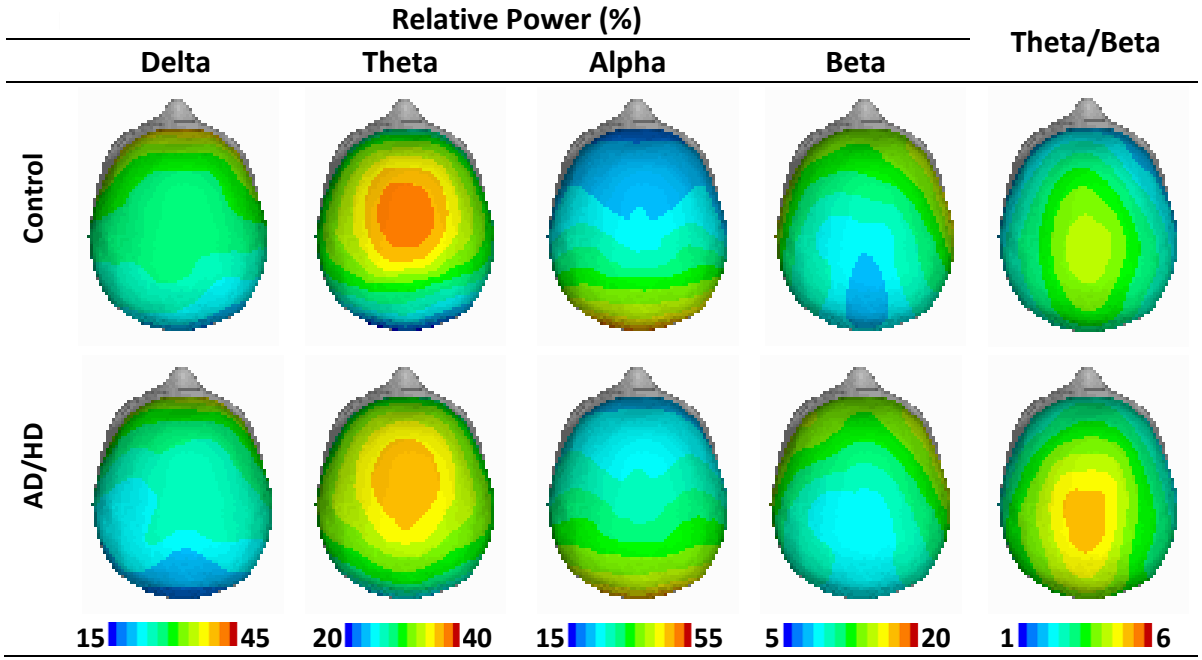

Figure 5.2 Topographic maps for relative power for the control and the average of the two AD/HD groups.

5.3.3 AD/HDcom vs. AD/HDin

Figure 5.3 shows that the AD/HDcom group, compared with AD/HDin group, had reduced absolute theta activity in the left posterior region (AD/HDcom < AD/HDin x F < P x L > R: $F = 4.35$, $p = .042$, $\eta_p^2 = .07$), and left central region (AD/HDcom < AD/HDin x F/P < C x L > R: $F = 4.67$, $p = .035$, $\eta_p^2 = .08$).

Compared with the AD/HDin group, the AD/HDcom group had a larger central reduction of absolute alpha activity (AD/HDcom > AD/HDin x F/P > C: $F = 4.91$, $p = .031$, $\eta_p^2 = .08$). Absolute alpha was elevated temporally in the AD/HDcom group (AD/HDcom > AD/HDin x L/R > M: $F = 5.12$, $p = .027$, $\eta_p^2 = .08$) and this was more evident in the posterior region (AD/HDcom > AD/HDin x F < P x L/R > M: $F = 6.75$, $p = .012$, $\eta_p^2 = .11$).

Figure 5.3 shows that the AD/HDcom group had elevated absolute beta activity in the posterior region (AD/HDcom > AD/HDin x F < P: $F = 5.30$, $p = .025$, $\eta_p^2 = .09$) and this was more evident in the midline (AD/HDcom > AD/HDin x F < P x L/R < M: $F = 5.10$, $p = .028$, $\eta_p^2 = .08$). The midline elevation was greater in the central region (AD/HDcom > AD/HDin x F/P < C x L/R < M: $F = 4.39$, $p = .041$, $\eta_p^2 = .07$).

The AD/HDcom group had less total power at the midline (AD/HDcom < AD/HDin x L/R < M: $F = 5.99$, $p = .018$, $\eta_p^2 = .10$) and this difference was greater in the frontal region (AD/HDcom < AD/HDin x F > P x L/R < M: $F = 7.20$, $p = .010$, $\eta_p^2 = .11$).

Figure 5.4 shows that the AD/HDcom group had less relative delta activity in the right than left hemisphere (AD/HDcom < AD/HDin x L < R: $F = 7.26$, $p = .009$, $\eta_p^2 = .11$). Relative theta activity was elevated in the right frontal region of the AD/HDcom group (AD/HDcom > AD/HDin x F > P x L < R: $F = 5.24$, $p = .026$, $\eta_p^2 = .08$).

Compared with the AD/HDin group, the AD/HDcom group had less relative alpha activity in the left than right hemisphere (AD/HDcom < AD/HDin x L > R: $F = 8.38$, $p = .005$, $\eta_p^2 = .13$) and this was more apparent in the posterior region (AD/HDcom < AD/HDin x F < P x L > R: $F = 4.06$, $p = .019$, $\eta_p^2 = .07$). The AD/HDcom group had less relative beta activity in the right hemisphere (AD/HDcom < AD/HDin x L < R: $F = 5.86$, $p = .019$, $\eta_p^2 = .09$).

Figure 5.4 shows that the AD/HDcom group, compared with the AD/HDin group, had a lower theta/beta ratio in the left hemisphere (AD/HDcom < AD/HDin x L > R: $F = 5.63$, $p = .021$, $\eta_p^2 = .09$).

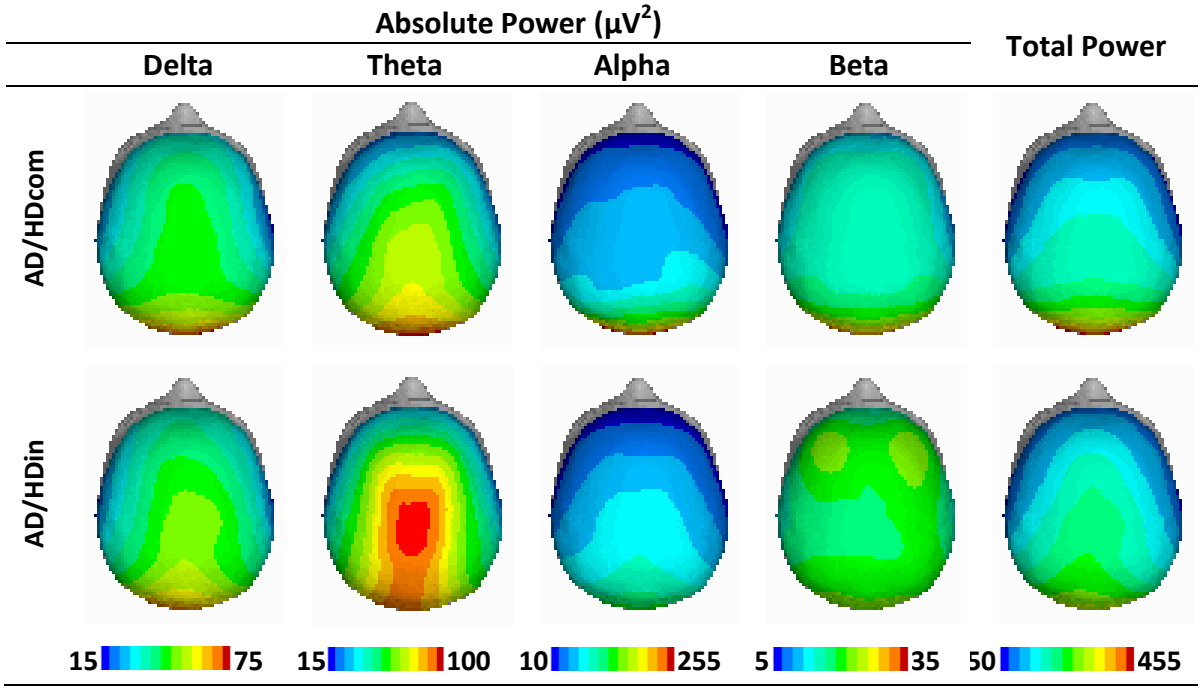

Figure 5.3 Topographic maps for absolute power for the Combined and Inattentive type groups.

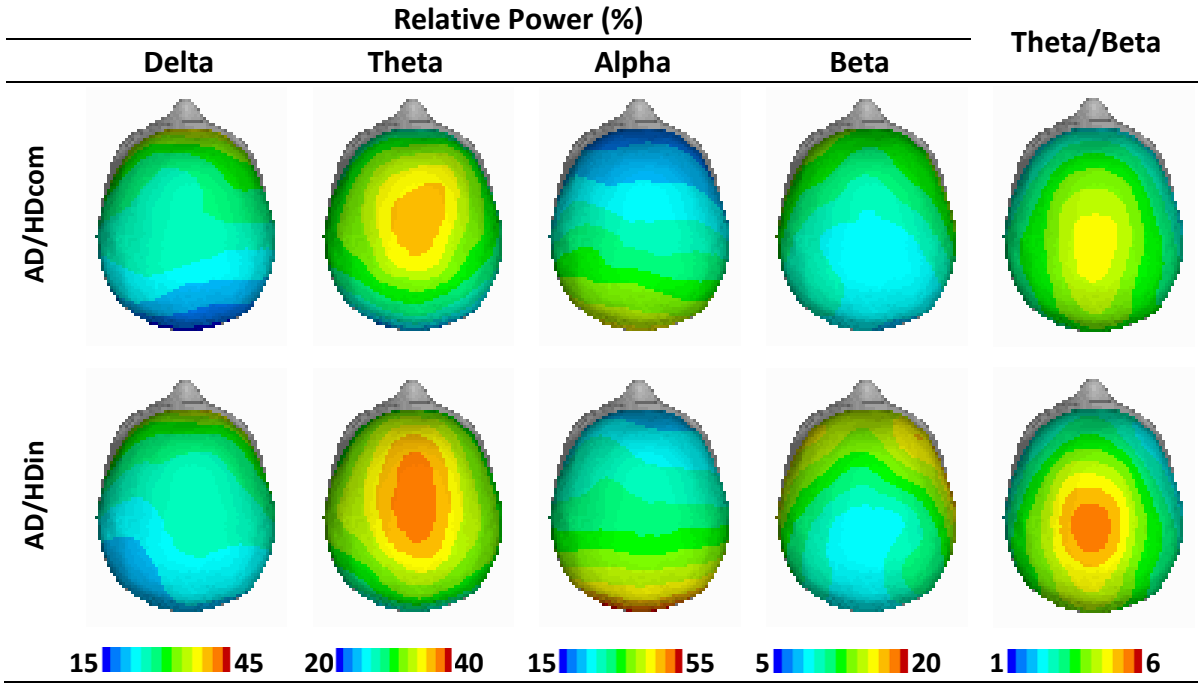

Figure 5.4 Topographic maps for relative power and the theta/beta ratio for the Combined and Inattentive type groups.

5.4 Discussion

This study investigated the EEGs of girls with Combined and Inattentive types of AD/HD. A lack of global EEG differences between these types in girls was initially reported by Dupuy et al. (2011), which was in contrast to results from previous studies using boys and mixed-sex groups (Barry & Clarke, 2009; Chabot & Serfontein, 1996; Clarke et al., 1998, 2001a, 2001b). Dupuy et al. (2011) suggested that global EEG effects may exist between these AD/HD types (as has been reported previously) but have not been found due to lower behavioural thresholds set for girls than for boys. Girls, compared with boys, do not have to display as severe or as many clinically significant hyperactive-impulsive behaviours, suggesting that the Combined and Inattentive types may not be as clearly distinct from one another in girls as in boys. This study inflated the behavioural gap between girls with the Combined and Inattentive types, in an attempt to detect EEG differences that have been previously reported between these types.

There were no significant differences between the two clinical groups and controls on age, IQ score, or reading and spelling age (see Table 5.1). The AD/HD groups, compared with controls, had (as expected) significantly greater scores on symptoms of inattention and hyperactivity-impulsivity. As this study created artificially exaggerated AD/HD type groups, it is no surprise that their symptom behaviour scores significantly differ between the two AD/HD groups. The Combined type group shows significantly elevated scores of inattention and hyperactivity-impulsivity (compared with the AD/HDin), consistent with the

Combined type behavioural profile (see Table 5.1). The AD/HDin group had significantly elevated scores on inattention and non-clinical scores on hyperactivity-impulsivity (see Table 5.1). If male thresholds had been used on these female clinical groups, the Combined type group would have clinically significant scores on hyperactivity-impulsivity and inattention, but at the lower end of the clinical range (rather than in the high female range) and the Inattentive type group would have below average (normal) scores on hyperactivity-impulsivity symptom behaviours. Both groups would have clinically significantly inattentive scores (but close to borderline rather than in the high female range). These differences in Conners' sex-normed behavioural thresholds reflect the fact that girls with AD/HD do not have to show as many or as severe AD/HD symptom behaviours as boys to reach the clinical thresholds.

An initial comparison of EEG activity between the AD/HD groups and controls was done to verify that the current sample is comparable with past studies. Past studies have found that children with AD/HD often have increased posterior absolute delta activity (Clarke et al., 2001a, 2001b; Matousek et al., 1984), elevated global absolute and relative theta activity, commonly in the frontal region (Barry & Clarke, 2009; Barry et al., 2009; Chabot & Serfontein, 1996; Clarke et al., 2002; Lazzaro et al., 1998; Satterfield et al., 1972), and reduced relative alpha and relative beta activity (Clarke et al., 2001a, 2001b; Clarke, Barry, Dupuy et al., 2011; Clarke, Barry, McCarthy et al., 2011; Lazzaro et al., 1998) and a larger theta/beta ratio (Barry & Clarke, 2009; Clarke, Barry, Dupuy et al., 2011; Clarke, Barry, McCarthy et al., 2011; Janzen et

al., 1995; Lansbergen et al., 2011; Lubar, 1991; Monastra et al., 1999, 2001). However, these EEG abnormalities are based heavily on male-normed data, with minimal, if any, female representation. The few studies that have examined EEG profiles exclusively in girls with AD/HD have found that, compared with age- and sex-matched controls, girls have globally elevated absolute delta, theta and total power (Clarke et al., 2003; Dupuy et al., 2011; Dupuy, Clarke & Barry, 2013), greater relative theta (Dupuy et al., 2011, 2013) and reduced relative beta (Clarke, Barry, McCarthy, Selikowitz & Johnstone, 2007; Dupuy et al., 2011, 2013). Although these female results are fairly comparable to the literature (in that there is an elevation of slow wave activity and reduction of fast wave activity), there are discrepancies between the profiles of boys and girls with AD/HD and highlights the need for further research in this area (for a review see Dupuy et al., 2013).

This study found that the AD/HD groups, compared with controls, had reduced absolute delta activity at the midline compared with the hemispheres, suggesting that delta power was more equipotential in girls with AD/HD (see Figure 5.1). Absolute theta activity was greater across the scalp in the AD/HD groups compared with controls, which neared significance. The AD/HD groups had a central-midline elevation in absolute alpha, beta and total power. The AD/HD groups also had reduced relative theta activity in the central region, and reduced relative alpha activity in the left hemisphere. Globally elevated absolute theta is robust in a variety of AD/HD samples (Barry & Clarke, 2009; Barry et al., 2009; Bresnahan, Anderson & Barry, 1998; Chabot & Serfontein, 1996; Clarke et al., 2001a, 2001b; Dupuy et al., 2011; Janzen et al., 1995;

Lansbergen et al., 2011; Lazzaro et al., 1998; Lubar, 1991; Monastra et al., 1999; Satterfield et al., 1972). Excess slow-wave activity is an enduring AD/HD characteristic, and increased theta activity is thought to be linked with impulsive behaviours, as both impulsivity and elevated theta activity persist across the lifespan (Barry & Clarke, 2009). Clarke et al. (2003) conducted a cluster analysis on AD/HD females and suggested that the primary EEG deficit in AD/HD girls is elevated relative theta activity with a reciprocal reduction of relative beta activity. Although Dupuy et al. (2011) showed results similar to this profile, it is not replicated in these more extreme AD/HD type groups. While there is evidence of elevated theta activity, which neared significance, there is no reciprocal beta result (see Figure 5.2). However, this is a non-typical AD/HD sample; it is a female AD/HD group made up of exaggerated AD/HD types in an attempt to exaggerate EEG abnormalities, and this may explain why results vary from past female AD/HD studies.

The focus of this study is an attempt to obtain global EEG effects between AD/HD types in groups of girls with exaggerated behavioural profiles. This study found that the Combined type group, compared with Inattentive type group, had lower absolute theta activity in the left posterior region, and more absolute alpha in the temporal-posterior region (see Figure 5.3). Absolute beta activity was elevated in the Combined type group in the midline-posterior region, also reported by Dupuy et al. (2011). Total power was less in the Combined type group compared with the Inattentive type group, more so in the midline-posterior region. The Combined type group, c.f. Inattentive type group, had reduced relative delta (also found by Dupuy et al., 2011), and

relative beta activity in the right hemisphere. The Combined type group had reduced theta/beta ratio in the left hemisphere. While it is difficult to profile these topographical results, it is interesting to note that they differ from what has been found between AD/HD types in boys and mixed-sex groups (Clarke et al., 2001a, 2001b). What is most important is the lack of global EEG effects between these manipulated AD/HD type groups, reiterating that there is less EEG variance between AD/HD types in girls and that their EEGs are markedly different from the predominantly male literature.

The lack of global effects between these widely disparate AD/HD type groups is surprising as the behavioural profiles between the two AD/HD type groups are significantly different; the Combined type had clinically significant levels of hyperactive-impulsive symptom behaviours while the Inattentive type had non-clinical (average) range scores. Based on this large behavioural gap, it would seem reasonable to expect global EEG differences between these groups, as has been found in previous studies (Barry & Clarke, 2009; Chabot & Serfontein, 1996; Clarke et al., 1998, 2001a, 2001b). Although topographical differences were found, no global effects emerged, further supporting previous conclusions that girls with AD/HD have indistinct EEG profiles, regardless of diagnosed type (Dupuy et al., 2011, 2013). Clarke et al. (2001b) found that the EEG differences between AD/HD groups and controls were smaller in girls than in boys. Also, a female medication study found that EEGs of medicated girls with AD/HD normalized more than boys, suggesting that their pre-treatment EEGs may have been less abnormal to start with (Clarke et al., 2007).

Rucklidge (2010) acknowledged that while there has been increasing interest in the development and use of separate standards when rating AD/HD behaviours (the Conners' rating scales include sex and age normed data; Conners, 1997), the DSM-IV does not consider sex in the diagnostic criteria (APA, 2000). The same is true for EEG profiles within AD/HD; sex is rarely considered or accounted for. Based on the disparity in EEG results between the well-documented and largely male-normed data and the emerging female-normed data (Clarke et al., 2001b, 2003, 2007; Dupuy et al., 2011, 2013), if EEG profiles are to be valid and reliable in this disorder then separate male and female data pools are necessary.

A possible limitation of this study is the reliance on parent-rating scales. This study created behaviourally exaggerated AD/HD type groups based on the Conners' parent rating scale for AD/HD. Although clinical subjects were diagnosed with a specified AD/HD type, they were selected for their high/low scores on particular symptoms behaviours as indicated by a parent rating scale. It may have been helpful to include other information to help strengthen the behavioural gap between the Combined and Inattentive groups. Although the Conners' rating scales have become one of the standard measures of AD/HD (Collett, Ohan & Myers, 2003), they still rely on the child's behaviour as observed by the parent. Although parents are the best informants of external behaviours (Loeber, Green, Lahey & Strouthamer-Loeber, 1991) they can provide only limited information on the internal states. These are best described by self-report measures; children and adolescents are best able to report on their subjective experiences (Collett et al., 2003). Subjective

information on symptom behaviours used in conjunction with the parent-rating scales may have helped further differentiate the two AD/HD type groups. A second limitation is the appropriateness of DSM-IV criteria for diagnosing AD/HD in girls. It is well-known that the DSM-IV criteria for AD/HD were primarily developed with males. It remains contentious whether these male-based AD/HD symptoms apply to females or not; some researchers have offered other descriptions that may capture AD/HD in females better than the DSM-IV (Ohan & Johnston, 2005; Quinn & Nadeau, 2005). With the release of the DSM-V due, updated symptom criteria may better suit females than previous editions.

Even by inflating AD/HD type group differences, significant global EEG effects between the Combined and Inattentive AD/HD types in girls remain elusive. It appears that the EEG profiles of the Combined and Inattentive types are not as different in girls as in boys. Barry and Clarke (2009) suggested that girls with AD/HD have different EEG profiles and follow a different developmental path than AD/HD boys. This is becoming increasingly evident, especially between AD/HD types; the nature of EEG in girls with AD/HD is fundamentally different from what has been observed in boys. Dupuy et al. (2011) and this study demonstrate that the current male-based AD/HD literature is no longer appropriate for understanding the disorder in females, and EEG profiles based on female-normed data are necessary.

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6 EEG AND ELECTRODERMAL ACTIVITY IN GIRLS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

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6.1 Introduction

Attention-Deficit/Hyperactivity Disorder (AD/HD) is a neurodevelopmental disorder characterised by inappropriate behaviours of inattention and/or hyperactivity-impulsivity (APA, 2000). The disorder is estimated to affect 3-7% of school children and is diagnosed more often in boys than girls; boy-to-girl ratios range from 3:1 to 9:1 (APA, 2000; Arcia & Conners, 1998; Gaub & Carlson, 1997; Hartung & Widiger, 1998; Pastor & Ruben, 2008; Rutter, Capsi & Moffitt, 2003; Willcutt, 2012). With the preponderance of AD/HD being diagnosed in boys, it is no surprise that our understanding of the disorder is based heavily on research with male cohorts. However, there is increasing interest in sex differences and female profiles that are separate from male profiles (Arnold, 1996; Briscoe-Smith & Hinshaw, 2006; Dupuy, Clarke & Barry, 2013; Gaub & Carlson, 1997; Quinn, 2005; Rucklidge, 2010).

While boys are more likely to have AD/HD, girls with AD/HD are more likely to experience greater levels of peer rejection (Arnold, 1996; Berry, Shaywitz & Shaywitz, 1985) and abuse (Briscoe-Smith & Hinshaw, 2006), and are at a higher risk for psychological problems than boys with AD/HD (Rucklidge & Tannock, 2001). Girls with AD/HD are also less hyperactive, but more inattentive, and have higher rates of depressive and anxiety disorders than boys with AD/HD (Carlson, Tamm & Gaub, 1997; DuPaul et al., 2005; Gaub & Carlson, 1997; Gershon, 2002; Quinn, 2005). Quinn (2005) suggested that in place of excess motor activity (the hallmark of hyperactivity), girls with AD/HD will more often display behaviours such as high emotional reactivity and excessive talking. These sex differences suggest that separate male and female profiles offer better understanding of the nature of AD/HD.

The EEG activity of the majority of children with AD/HD is characterised by a deviant baseline cortical pattern (Lansbergen, Arns, van Dongen-Boomsma, Spronk & Buitleaar, 2011). These children tend to have increased posterior absolute delta activity (Clarke, Barry, McCarthy & Selikowitz, 2001a, 2001b; Matousek, Rasmussen & Gilberg, 1984), globally elevated absolute and relative theta activity, most often frontally (Barry & Clarke, 2009; Barry, Clarke, Johnstone, McCarthy & Selikowitz, 2009; Chabot & Serfontein, 1996; Clarke, Barry, McCarthy & Selikowitz, 2002; Lazzaro et al., 1998; Satterfield, Cantwell, Lesser & Podsin, 1972), and reduced relative alpha and relative beta activity (Clarke et al., 2001a, 2001b; Clarke, Barry, Dupuy, et al., 2011; Clarke, Barry, McCarthy & Selikowitz, 2011; Lazzaro et al., 1998). The gamma frequency band, although not as extensively researched as the four traditional bands, has been found to be significantly reduced in groups of AD/HD children, in both absolute and relative power (Barry, Clarke, Hajos, McCarthy, Selikowitz & Bruggemann, 2009; Barry et al., 2010). A larger, aberrant theta/beta ratio has also been consistently found in AD/HD children (Barry, Clarke, Johnstone, et al., 2009; Clarke, Barry, Dupuy, et al., 2011; Clarke et al., 2001a, 2001b; Clarke, Barry, McCarthy, et al., 2011; Janzen, Graap, Stephanson, Marshall & Fitzsimmons, 1995; Lansbergen et al., 2011; Lubar, 1991; Monastra, Lubar & Linden, 2001; Monastra et al., 1999; Synder & Hall, 2006). It is important to note that these studies are based largely on male-normed data, with minimal, if any, female inclusion.

There have been few studies that have examined resting EEG profiles exclusively in girls with AD/HD (for a review, see Dupuy, Clarke, et al., 2013). One of the first, Baving, Laught and Schmidt (1999), found that 15 AD/HD girls (aged 4 and 8 years) had greater frontal alpha activation in the left than right hemisphere, suggested to

represent a left frontal deficit, compared with aged-matched control girls. Other studies have found that girls with AD/HD, compared with girl controls, had globally elevated absolute delta, theta and total power, greater relative theta and reduced relative beta (Clarke et al., 2001b, 2003; Clarke, Barry, McCarthy Selikowitz & Johnstone, 2007; Dupuy, Barry, Clarke, McCarthy & Selikowitz, 2013; Dupuy, Clarke, Barry, McCarthy & Selikowitz, 2011). Although these initial studies are broadly comparable to the male-based AD/HD literature (with an elevation of slow wave activity and reduction of fast wave activity), there are EEG differences between boys and girls with AD/HD. These discrepancies should not be overlooked and separate male and female profiles should be utilized as part of standard EEG-AD/HD research.

Despite our knowledge of characteristic EEG abnormalities within AD/HD, we are yet to fully understand the exact causes of the disorder. It is generally accepted that a dysfunction of the Central Nervous System (CNS) is involved, although the underlying mechanisms are not well known (Fonseca, Tedrus, Bianchini & Silva, 2013). The hypoarousal model proposes that the CNS is underaroused in children with AD/HD, which in turn causes symptoms of inattention and hyperactivity-impulsivity (Satterfield & Cantwell, 1974). This model has been widely used to explain the seemingly-paradoxical effect that stimulant medications have on AD/HD behaviours. In small doses, psychostimulants act by increasing arousal to normal levels, resulting in improved behaviour. Satterfield, Cantwell and Satterfield (1974) found that stimulant medications improved hyperactivity and raised CNS arousal to a more optimal level. Satterfield et al. (1974) also found that hyperactive children who had low CNS arousal levels (measured by skin conductance level; SCL) also had a negative correlation between their arousal level and the severity of their behaviour: the lower SCL, the

greater behavioural disturbances (distractibility and inattention). SCL is an electrodermal measure that reflects output from the sympathetic branch of the autonomic nervous system (Boucesin, 1992; El-Shiekh, 2007; Hoeldtke, Davis, Hshieh, Gaspar & Dworkin, 1992; Wallis, 1981) and is a reliable marker of CNS or physiological arousal (Barry & Sokolov, 1993; Raine, Veneables & Williams, 1990; Raskin, 1973; Rosenthal & Allen, 1978; van Lang, Tulen, Kallen, Rosbergen, Dieleman & Ferdinand, 2007).

Initial attempts to support the hypoarousal model using electrodermal measures resulted in mixed findings; some supported underarousal in AD/HD (Satterfield & Dawson, 1971; Satterfield et al., 1974) and others found no difference in CNS arousal between AD/HD and non-AD/HD subjects (Cohen & Douglas, 1972; Montagu, 1975; Spring, Greenberg, Scott & Hopwood, 1974). However, this disparity was suggested to be a methodological issue due to the use of Cambridge electrode jelly, which is specifically formulated to increase skin conductance (Montagu, 1975), as the contact medium. Subsequent investigations of the hypoarousal model (with inert contact media) have found more consistent results; AD/HD is associated with significantly lower SCL (Barry, Clarke, Johnstone, et al., 2009, 2012; Broyd et al., 2005; Hermens et al., 2004; Lazzaro et al., 1999). Again, it is important to note that these studies included only males, except for Barry et al. (2012). Barry et al. (2012) included mixed-sex subject groups (26 males and 10 females), but sex was not included as a factor within their analyses. Only Hermens et al. (2004) and Hermens, Kohn, Clarke, Gordon and Williams (2005) included mixed-sex groups of adolescents and adults in their studies of CNS arousal in AD/HD, but their SCL measure reflected SCL changes over

time or 'rate of EDA decrement', which is not commonly reported in the literature, making it difficult to draw comparisons with other studies.

There are no published studies that directly explore CNS arousal or the hypoarousal model exclusively in girls with AD/HD. To date, it has been assumed that girls with AD/HD would have lower SCL, as boys with AD/HD appear to have, yet there has been no direct investigation of SCL in girls with AD/HD. The aim of this study is to address this gap and investigate differences in CNS arousal and EEG activity in girls with AD/HD.

6.2 Methods

6.2.1 Participants

The study included 80 Caucasian girls aged 7-12 years (*M* = 9.43, *SD*= 1.73). Of these, 40 were healthy controls and 40 girls were diagnosed with AD/HD (30 were diagnosed with the Inattentive type and 10 were diagnosed with the Combined type – AD/HD types are not referred to in this study as our previous research found that girls with the Combined and Inattentive AD/D types have indistinct EEG profiles – see Clarke et al., 2003; Dupuy et al., 2011; Dupuy, Barry, et al., 2013). The clinical participants were selected from patients at a paediatric practice and controls were recruited via the local community. All participants had an IQ score of 80+. Participants had no history of medication use for any psychiatric disorder, and AD/HD participants were tested nil medication.

Inclusion in the AD/HD group was based on clinical assessments made by a paediatrician and a psychologist, and both agreed on the diagnosis. Both clinicians used behavioural observations, a comprehensive history taken from

parent(s)/guardian(s), school reports from the past 12 months, and any other relevant reports, to make their diagnoses.

Participants were excluded if they had a history of problematic prenatal, perinatal or neonatal periods, a history of CNS diseases, convulsions or convulsive disorders. They were also excluded if there was evidence of a consciousness disorder, head injury with cerebral symptoms, paroxysmal headaches or tics. Participants were excluded if they met criteria for Conduct Disorder, Oppositional Defiant Disorder, an anxiety or depressive disorder, Asperger's or Tourette's Syndrome.

Controls were included based on clinical interviews with parent(s)/guardian(s), similar to the AD/HD participants, described above. Control subjects scored in the normal range on measures of accuracy and comprehension on the Neale Analysis of Reading, the South Australian Spelling Test, and behavioural questionnaires (Conners' Parent Rating Scale, Child Behavior Checklist and Depression and Anxiety Youth Scale). Controls had no problems during their prenatal, perinatal or neonatal periods, no disorders of consciousness, no head injuries resulting in cerebral symptoms, and no history of CNS diseases or obvious somatic diseases, no history of convulsive disorders or convulsions, tics, stuttering, paroxysmal headaches, and no other psychiatric condition. Participants displayed no deviation from normal physical development. Participants were not included if spike waves were found in the EEG.

6.2.2 Procedure

Ethics approval for this study was obtained from the combined Illawarra Area Health/University of Wollongong Human Research Ethics Committee. Prior to the

release of any clinical records or testing, the parent(s)/guardian(s) of each participant gave written informed consent and all participants assented.

Participants were tested in a single session over approximately 2.5 hrs. A clinical history and physical examination were conducted first. Participants then completed the WISC-III, the Neale Analysis of Reading and the South Australia Spelling Test. Then, each participant had an eyes-closed resting EEG recorded during a five-minute stimulus-free period. This was the only EEG task participants had to complete and fatigue did not influence the frequency characteristics of the EEG. An electrode cap ensured International 10–20 electrode placement, and activity was recorded from 19 electrodes: Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, O2. These electrodes were divided in to nine regions by averaging each region. These were the left frontal (Fp1, F7, F3), midline frontal (Fz), right frontal (Fp2, F8, F4), left central (T3, C3), midline central (Cz), right central (T4, C4), left posterior (T5, P3, O1), midline posterior (Pz) and right posterior (T6, P4, O2) regions. Electrode sites were referenced to linked ears and a cap ground was placed between Fpz and Fz.

The EEG was recorded on a Neuroscan NuAmps using software version 4.3.1 with a sampling rate of 500 Hz. A gain of 30,000 was used, with a high pass filter of 1 Hz, low pass filter of 52 Hz, and a 50 Hz notch filter. The EEG trace was then visually artefacted by a technician. A minimum of 75 seconds of artefact-free EEG was selected for analysis, from which 2 second epochs were Fourier transformed using Scan 4.3.1 software. The 75 seconds of artefact-free EEG was selected over the five-minute eyes-closed recording period across all subjects. EEG estimates were calculated for five frequency bands: delta (1.5-3.5 Hz), theta (3.5-7.5 Hz), alpha (7.5-12.5 Hz), beta (12.5-25 Hz), and gamma (35-45 Hz) for absolute and relative power, total power and the

theta/beta ratio. The theta/beta ratio was calculated as the ratio of theta to beta relative power at each site. Total power is the sum of all included frequency bands. A gamma peak around 40 Hz has been found to be dominant throughout childhood (Takano & Ogawa, 1998), and our defined gamma range is a bandwidth of 35-45 Hz, avoiding the mains frequency of 50 Hz.

Electrodermal activity was recorded simultaneously and continuously during the five-minute resting EEG recording period (described above). Participants' SCLs were recorded at 10 Hz from two Ag/AgCl electrodes placed on the ventral surfaces of the medial phalanges of the second and third digits of their non-dominant hand. Electrodes were filled with an electrolyte of 0.05 M NaCl in an inert ointment base, and secured with small Velcro bands. A voltage of 0.5 V was applied across the electrode pair using a constant-voltage device (UFI Bioderm 2701). This system outputs two data streams: tonic DC-coupled skin conductance level (SCL) and AC-coupled skin conductance fluctuations (SCR); only SCL was used in this study (measured in microSiemens; µS). After exclusion of movement artefacts, the mean SCL was calculated for each subject.

6.2.3 Statistical Analysis

The clinical data were tested in one-way analyses of variance (ANOVAs) comparing the scores of the AD/HD group with controls (CON). For the EEG data, the effects of region and group for each frequency band in total, absolute and relative powers and theta/beta ratio were examined. The effects of region were examined in two orthogonal three-level repeated-measures factors. The first of these was a sagittal factor, where planned contrasts compared the frontal (F) region with the posterior (P)

region, and their mean (F/P) with the central (C) region. The second factor was laterality, within which planned contrasts compared activity in the left (L) hemisphere with that in the right (R) hemisphere, and their mean (L/R) with the midline (M) region.

For the electrodermal activity, a separate one-way ANOVA tested mean SCL differences between the AD/HD and control groups. Additionally, two-tail Pearson *r* correlations were calculated to explore relationships between SCL and EEG frequency bands and between SCL and symptom behaviours. To reduce the number of comparisons, only symptom behaviours from the DAYS and two subscales from the Conners' rating scale that related directly to AD/HD (DSM-IV inattention and DSM-IV hyperactive-impulsive subscales) were included. Scores from the CBCL correlated highly with scores from the Conners' and DAYS, and were not included. No alpha correction was made for these exploratory correlations. An α level of .05 was used for statistical significance. All reported *F* values have (1, 78) degrees of freedom.

In addition, five exploratory stepwise regressions were carried out to further examine the relationship between physiological measures and symptom behaviours in the clinical and control groups together.

6.3 Results

6.3.1 Clinical Data

Mean age, psychometric results and symptom behaviour scores are shown in Table 6.1. The AD/HD and control groups did not differ significantly on chronological or reading age. The AD/HD group had significantly lower mean IQ scores than controls (see Table 6.1), but all IQ scores were within the normal range. The AD/HD symptom behaviours as reported by the Conners' scales were significantly elevated in the AD/HD

group compared with controls. Anxiety, depression and social maladjustment scores, as measured by the DAYS, were also all significantly elevated in the AD/HD group compared with controls (see Table 6.1).

Table 6.1 Mean age, psychometric tests and symptom behaviour scores for the AD/HD and control groups.

	AD/HD	Control	*F*	*p*
Age in years *(SD)*	9.18 *(1.77)*	9.68 *(1.68)*	1.68	.199
IQ	100.6	113.10	28.16	**< .001**
Reading Age in years	11.03	13.23	0.70	.404
Conners' - Inattention	76.05	48.85	158.86	**< .001**
Conners' - Hyperactivity-Impulsivity	68.13	46.93	52.39	**< .001**
DAYS - Anxiety	65.95	47.73	9.14	**.003**
DAYS - Depression	60.18	40.48	12.29	**.001**
DAYS - Social Maladjustment	54.23	38.18	10.04	**.002**

Significant values are shown in bold.

6.3.2 EEG Results

Figure 6.1 displays the frequency distribution for each group, averaged across all sites. The top panel shows a frequency range of 0-25 Hz. The AD/HD group have lower delta, theta, alpha (although not globally significant) and beta activity compared with controls. The bottom panel (note the reduced power scale) shows a higher frequency range of 25-50 Hz containing the gamma band (35-45 Hz). Note that the control group shows a gamma peak at 40.5 Hz and this peak is not evident in the AD/HD group.

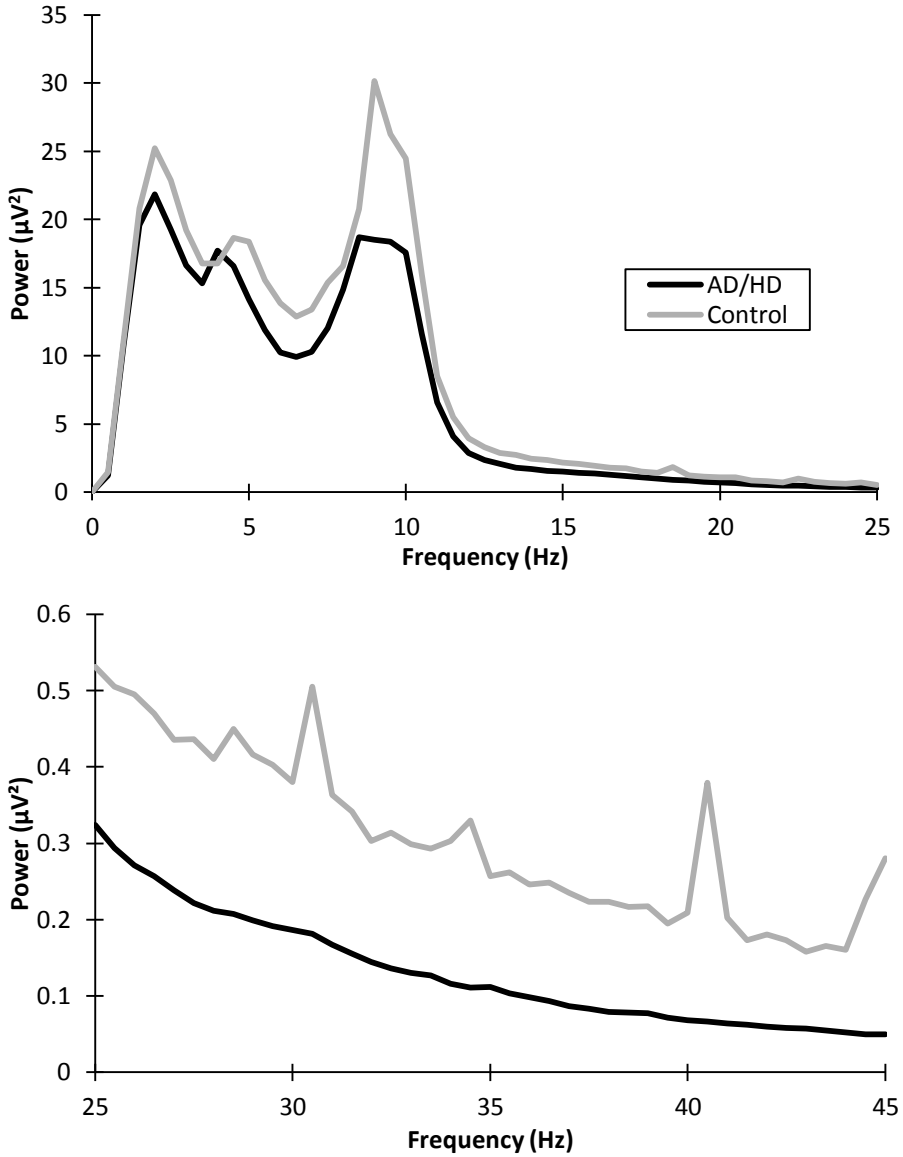

Figure 6.1 EEG frequency distribution for the AD/HD and control groups, averaged across all sites. Top: a frequency range of 0-25 Hz. Bottom: a higher frequency range (25-45 Hz) containing the gamma band.

6.3.2.1 Absolute Power

Figure 6.2 displays headmaps that indicate scalp topography for the two groups for each frequency band. Figure 6.2 shows that the AD/HD group, compared with controls, had reduced absolute delta in the posterior compared with the frontal region (AD/HD < CON x F < P: $F = 7.43$, $p = .008$, $\eta_p^2 = .09$). The central reduction of absolute

alpha activity, evident at the midline, was less in the AD/HD girl group, compared with controls (AD/HD < CON x F/P > C x L/R < M: $F = 4.38$, $p = .040$, $\eta_p^2 = .05$). Figures 6.1 and 6.2 show that absolute beta activity was globally reduced in the AD/HD group c.f. controls (AD/HD < CON: $F = 10.69$, $p = .002$, $\eta_p^2 = .12$), particularly in the posterior region (AD/HD < CON x F < P: $F = 6.94$, $p = .010$, $\eta_p^2 = .08$). Figures 6.1 and 6.2 also show that absolute gamma activity was reduced across the scalp in the AD/HD group c.f. controls (AD/HD < CON: $F = 10.83$, $p = .002$, $\eta_p^2 = .12$), more so in the posterior region (AD/HD < CON x F < P: $F = 8.09$, $p = .006$, $\eta_p^2 = .09$). This gamma reduction was also more evident in the central region (AD/HD < CON x F/P < C: $F = 4.05$, $p = .048$, $\eta_p^2 = .05$) and in the hemispheres (AD/HD < CON x L/R > M: $F = 5.25$, $p = .025$, $\eta_p^2 = .06$).

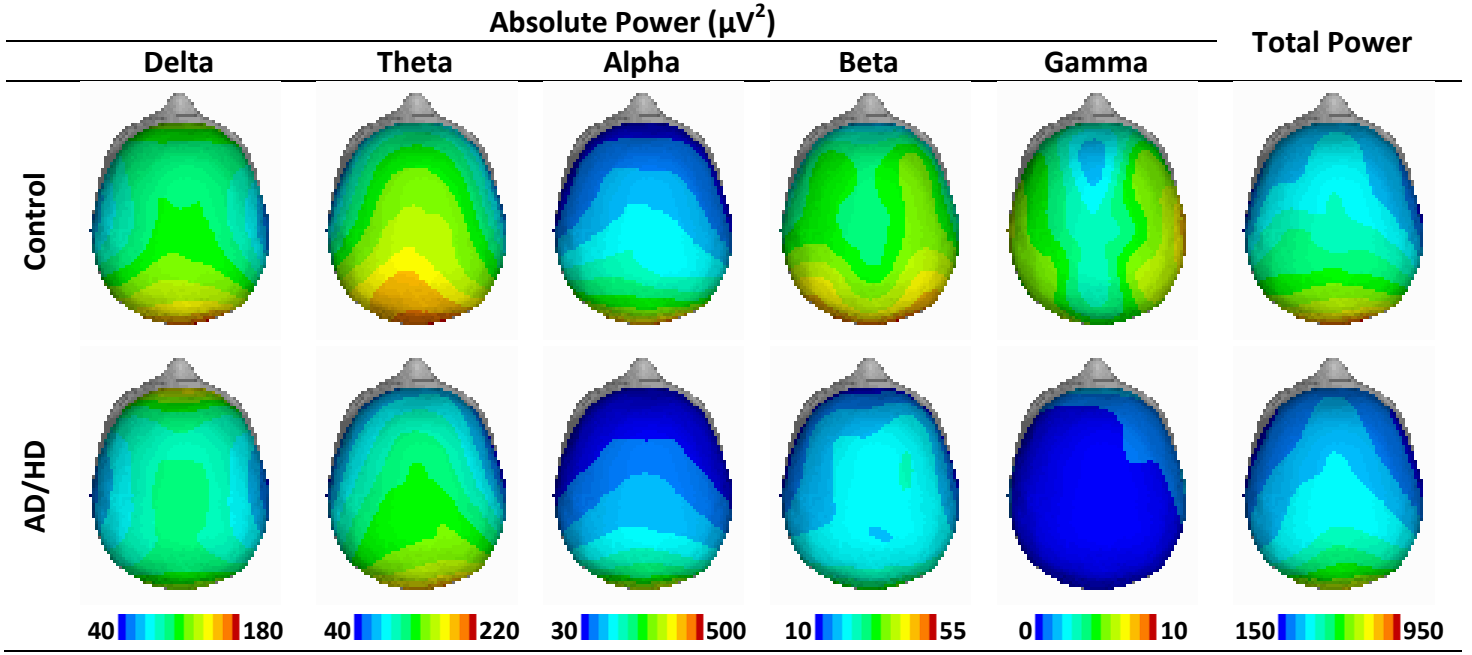

Figure 6.2 Topographic maps for absolute power for the AD/HD and control groups.

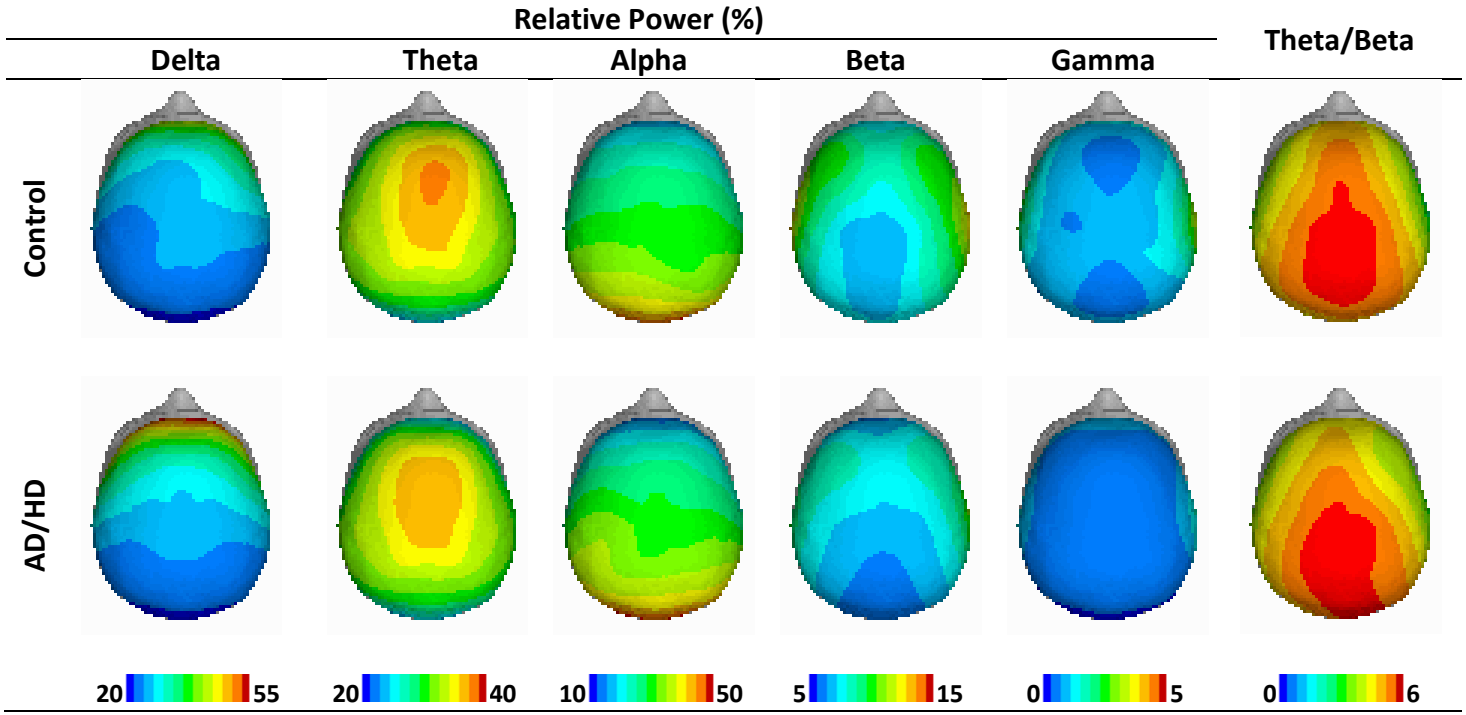

Figure 6.3 Topographic maps for relative power and the theta/beta ratio for the AD/HD and control groups.

6.3.2.2 Relative Power

Figure 6.3 shows that the AD/HD girl group, compared with controls, had globally elevated relative delta activity (AD/HD > CON: $F = 4.62$, $p = .035$, $\eta_p^2 = .06$). This elevation was larger in the frontal region (AD/HD > CON x F > P: $F = 26.33$, $p = .001$, $\eta_p^2 = .25$) and in the left hemisphere (AD/HD > CON x L > R: $F = 5.82$, $p = .018$, $\eta_p^2 = .07$). Relative delta was also elevated in the hemispheres in the AD/HD group c.f. controls (AD/HD > CON x L/R > M: $F = 13.59$, $p = .001$, $\eta_p^2 = .15$), more so frontally (AD/HD > CON x F > P x L/R > M: $F = 6.39$, $p = .014$, $\eta_p^2 = .08$). The AD/HD group had elevated relative theta activity in the central region of the left hemisphere (AD/HD > CON x F/P < C x L > R: $F = 5.09$, $p = .027$, $\eta_p^2 = .06$). The AD/HD group had elevated relative alpha in the posterior compared with frontal region (AD/HD > CON x F < P: $F = 5.43$, $p = .022$, $\eta_p^2 = .07$). The central reduction of relative alpha was greater at the midline in the AD/HD group (AD/HD > CON x F/P > C x L/R < M: $F = 6.99$, $p = .010$, $\eta_p^2 = .08$). Figure 6.3 shows that in relative beta activity, the AD/HD group compared with controls had reduced activity in the hemispheres (AD/HD < CON x L/R > M: $F = 12.51$, $p = .001$, $\eta_p^2 = .14$), particularly in the central region (AD/HD < CON x F/P < C x L/R > M: $F = 9.35$, $p = .003$, $\eta_p^2 = .11$). Relative beta was also reduced in the frontal region of the left hemisphere in the AD/HD group (AD/HD < CON x F > P x L > R: $F = 5.39$, $p = .023$, $\eta_p^2 = .06$). Figure 6.2 shows that relative gamma activity was reduced across the scalp in the AD/HD group (AD/HD < CON: $F = 8.67$, $p = .004$, $\eta_p^2 = .10$), more so in the central region (AD/HD < CON x F/P < C: $F = 9.17$, $p = .003$, $\eta_p^2 = .11$) and in the hemispheres (AD/HD < CON x L/R > M: $F = 14.73$, $p = .001$, $\eta_p^2 = .16$), which created a significant interaction (AD/HD < CON x F/P < C x L/R > M: $F = 9.27$, $p = .003$, $\eta_p^2 = .11$).

6.3.3 SCL Results

Figure 6.4 shows that the AD/HD group, compared with controls, had significantly lower mean SCL levels (AD/HD < CON: $F = 19.95$, $p < .001$, $\eta_p^2 = .20$). Table 6.2 shows correlations between EEG frequency bands and SCL in the AD/HD and control groups, and the groups together. Within the AD/HD group, SCL was positively correlated with absolute delta ($r = .35$, $p = .01$), absolute alpha ($r = .30$, $p = .03$), absolute beta ($r = .32$, $p = .02$), absolute gamma ($r = .34$, $p = .01$) and total power ($r = 31$, $p = .03$). Within controls, Table 6.2, shows a negative correlation between SCL and absolute beta ($r = -.27$, $p = .04$).

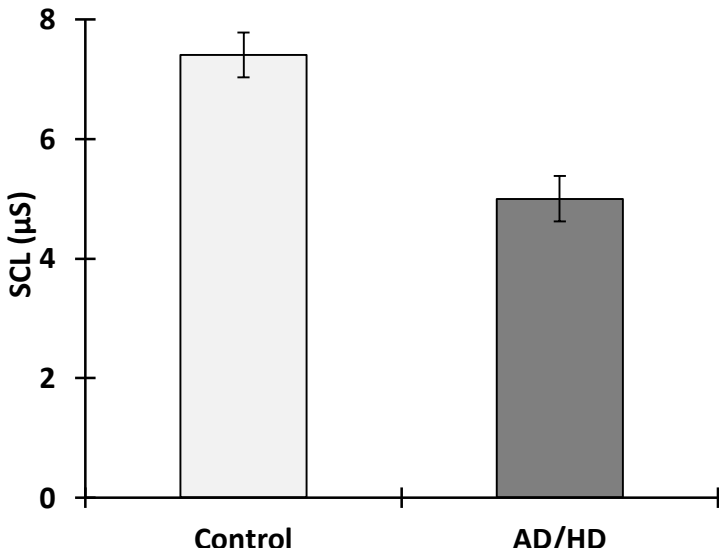

Figure 6.4 Mean SCL for the AD/HD and control groups, with standard error bars.

Table 6.2 Correlation results between mean SCL and frequency band data for the AD/HD and control groups.

	AD/HD SCL		Control SCL		Together SCL	
	r	*p*	*r*	*p*	*r*	*p*
Absolute Delta	**.35**	**.01**	-.21	.10	.12	.14
Absolute Theta	.20	.10	-.14	.19	.09	.21
Absolute Alpha	**.30**	**.03**	-.19	.12	.09	.22
Absolute Beta	**.32**	**.02**	**-.27**	**.04**	.09	.22
Absolute Gamma	**.34**	**.01**	-.21	.09	.05	.33
Total Power	**.31**	**.03**	-.22	.09	.11	.17
Relative Delta	.03	.43	.13	.21	-.07	.26
Relative Theta	.04	.41	.23	.08	.16	.07
Relative Alpha	.03	.43	.19	.12	-.09	.22
Relative Beta	.09	.29	.13	.20	.00	.49
Relative Gamma	.01	.50	.21	.10	.04	.36
Theta/Beta Ratio	.08	.31	.02	.45	.03	.39

Significant values are shown in bold.

Table 6.3 shows correlations between SCL and symptom behaviours for each group and the patient and control groups together. Within AD/HD, there was a negative correlation between SCL and scores of depression (r = -.53, p = .01) and scores of social maladjustment (r = -.31, p = .02). That is, elevated symptoms of depression and social maladjustment correlates with reduced SCL. No significant correlations were found within the control group; however Table 6.3 shows significant correlations between SCL and symptom behaviours when the two groups are put together. There were negative correlations between SCL of both groups together and symptoms of inattention (r = -.45, p < .001), hyperactivity-impulsivity (r = -.23, p = .004), depression (r = -.41, p < .001), anxiety (r = -.26, p = .01) and social maladjustment (r = -.31, p = .002).

Table 6.3 Correlation results between SCL and symptom behaviours

	AD/HD SCL		Control SCL		Together SCL	
	r	*p*	*r*	*p*	*r*	*p*
Inattention	-.19	.12	-.12	.24	**-.45**	**< .001**
Hyperactivity-Impulsivity	.01	.48	.01	.49	**-.23**	**.004**
Anxiety	-.18	.14	-.08	.31	**-.26**	**.01**
Depression	**-.53**	**.01**	.05	.37	**-.41**	**< .001**
Social Maladjustment	**-.31**	**.02**	.09	.29	**-.31**	**.002**

Significant values are shown in bold.

6.3.4 Regression Results

Five stepwise regressions were conducted on the AD/HD and control groups together to examine whether significant EEG effects and SCL could help explain AD/HD symptoms and co-morbid behaviours (anxiety and depression), as reported by parent-rating questionnaires. For inattention, a significant model of best fit emerged with three variables that explained 35.5% of variance ($F = 15.51$, $p < .001$). Shown in Table 6.4, the significant predictor variables were: elevated frontal relative delta activity (which was positively correlated with inattentive symptoms), SCL (which was negatively correlated) and reduced relative gamma activity in temporal regions (which was negatively correlated). That is, increased frontal relative delta, reduced SCL and reduced temporal relative gamma correlated with increasing symptoms of inattention, across girls with AD/HD and controls. For hyperactivity-impulsivity, the significant model of best fit had one variable that explained 13.9% of the variance ($F = 13.74$, $p < .001$). Table 6.4 shows that the significant predictor was elevated frontal relative delta (which was positively correlated), indicating that increased frontal relative delta activity correlated with increasing symptoms of hyperactivity-impulsivity, across patient and control groups.

The significant model of best fit for Anxiety had one variable that explained 5.3% of the variance ($F = 5.46$, $p = .022$). Table 6.4 shows the significant predictor was SCL (which was negatively correlated), indicating that reduced SCL is correlated with increasing symptoms of anxiety. For Depression, a significant model of best fit emerged with two variables that explained 22.6% of the variance ($F = 12.56$, $p < .001$). The significant predictors were SCL and reduced posterior midline absolute alpha activity (both predictors were negatively correlated). That is, reduced SCL and reduced absolute alpha activity are correlated with increasing symptoms of depression. The final regression analysis for Social Maladjustment found the model of best fit had two variables that explained 13.1% of the variance ($F = 6.96$, $p = .002$). Table 6.4 shows the significant predictors were SCL (which was negatively correlated) and reduced posterior relative alpha activity (which was positively correlated). That is, reduced SCL and reduced posterior relative alpha are correlated with increasing symptoms of social maladjustment.

Table 6.4 Summary of stepwise regressions for predicting symptom behaviours for the AD/HD and control groups together.

Behaviours	ΔR^2 *(SE)*	Variables	*β*	*t*	*p*
Inattention	.355 *(13.42)*	Rel Delta (F > P)	.365	3.85	**<.001**
		SCL	-.319	-3.36	**.001**
		Rel Gamma (F/P < C x L/R > M)	-.251	-2.76	**.007**
Hyperactivity-Impulsivity	.139 *(15.62)*	Rel Delta (F > P)	.387	3.71	**<.001**
Anxiety	.053 *(27.19)*	SCL	-.256	-2.34	**.022**
Depression	.226 *(26.63)*	SCL	-.359	-3.57	**.001**
		Alpha (F/P > C x L/R < M)	-.287	-2.86	**.005**
Social Maladjustment	.131 *(22.29)*	SCL	-.268	-2.51	**.014**
		Rel Alpha (F < P)	.236	2.21	**.030**

Significant values are shown in bold.

6.4 Discussion

This study found that the current group of girls with AD/HD had lower mean IQ scores compared with female controls, although both groups were in the average range. Although the relationship between intelligence and EEG activity is unresolved, previous studies have found that IQ scores do not contribute significantly to EEG power measures (Barry, Clarke, Johnstone, et al., 2009; Clarke et al., 2006; Chabot & Serfontein, 1996), and we suggest that the current observed EEG group differences relate solely to the presence of AD/HD.

This study investigated CNS arousal and EEG activity in girls with AD/HD. Children with AD/HD show a relatively consistent deviant EEG profile: elevated absolute and relative theta activity, reduced relative alpha and relative beta activity, and a larger theta/beta ratio. However, this profile is based predominantly on male cohorts and it is no longer considered appropriate to apply this profile to girls (Dupuy, Clarke, et al., 2013). Girls with AD/HD have been found to have elevated absolute delta and relative theta activity, elevated absolute alpha, more total power, and reduced relative alpha and absolute beta activity relative to female controls (Clarke et al., 2001b, 2003, 2007; Dupuy et al., 2011; Dupuy, Barry, et al., 2013; Dupuy, Clarke, et al., 2013).

The current study found that girls with AD/HD, compared with controls, had reduced posterior absolute delta, reduced midline absolute alpha, globally reduced absolute beta and gamma activity, dominant in the posterior region (see Figure 6.2). Within relative power, the AD/HD girl group had globally elevated relative delta activity, dominant in the frontal-temporal region, elevated left-central relative theta, elevated posterior relative alpha, reduced fronto-temporal relative beta and globally

reduced relative gamma, which was dominant in the central-temporal region (see Figure 6.3). These results support the literature that suggests AD/HD is profiled by elevated slow-wave activity and reduced fast-wave activity. However, these results are different to EEG profiles of boys with AD/HD - most notably, globally elevated delta has rarely been reported among boys with AD/HD, yet has been found fairly consistently in girls (Clarke et al., 2007; Dupuy et al., 2011; Dupuy, Barry, et al., 2013). The current AD/HD girls had global elevations of relative delta activity and global reductions of absolute beta, which have been reported previously in girls with AD/HD (Clarke et al., 2001b, 2003; Dupuy et al., 2011).

The AD/HD girl group also had globally reduced absolute and relative gamma activity. Figure 6.2 shows that within absolute gamma, reductions were larger in the temporal-posterior regions compared with controls. For relative gamma activity, Figure 6.3 shows the reductions were larger in the temporal-central regions. The gamma frequency band has not been as extensively investigated as the four traditional bands within childhood AD/HD populations, so there is limited literature to compare with. Barry, Clarke, Hajos, et al. (2009) found that 50 children with AD/HD (mixed-sex, aged 8-12 years) had globally reduced absolute and relative gamma activity, which was more evident in the temporal-posterior regions, compared with controls. In a separate subject group, Barry et al. (2010) found that 40 children (mixed-sex, aged 8-12 years) also had significantly lower absolute and relative gamma, more so in the temporal-posterior regions, than controls. It is interesting to note that globally reduced absolute and relative gamma activity has also been found in this exclusive female AD/HD subject group (see Figures 6.1-6.3). Although replication is needed, this finding of reduced gamma power in AD/HD reinforces its presence within the disorder.

The main focus of this study is investigating the hypoarousal model exclusively within girls who have AD/HD. This model suggests that children with AD/HD have an underaroused CNS which results in the core symptoms of the disorder (Satterfield & Cantwell, 1974). The SCL is established as a valid and reliable measure of CNS arousal (Barry & Sokolov, 1993; Raine et al., 1990; Raskin, 1973; Rosenthal & Allen, 1978). El-Shiekh (2007) reported that baseline SCL in healthy children (aged 6-13 years) remained stable over a two-year period. Within AD/HD children, SCL has been found to be significantly lower relative to controls and has been found to be significantly lower in children with AD/HD compared with controls (Barry, Clarke, Johnstone, et al., 2009, 2012; Broyd et al., 2005; Lazzaro et al., 1999; Satterfield & Dawson, 1971; Satterfield et al., 1974). Studies of psychostimulant effects on SCL have supported the notion that the CNS and ANS are under-aroused in children with AD/HD and stimulant medications are beneficial as they act to increase or normalize these low levels (Broyd et al., 2005; Satterfield & Dawson, 1971; Satterfield et al., 1974). While low SCL/CNS arousal appears to be a defining feature of AD/HD, until now it has never been investigated exclusively in female patients. The current results support previous studies and the hypoarousal model. As shown in Figure 6.4; girls with AD/HD had significantly lower mean SCL compared with controls. This suggests that girls with AD/HD have a disturbance in their CNS arousal systems demonstrated by hypoarousal.

Interestingly, the current study found a significant *positive* correlation between SCL and absolute alpha activity in AD/HD girls (controls had a negative trend; see Table 6.2). A negative correlation between SCL and alpha activity has been found previously in AD/HD and control boys (Barry et al., 2004, 2009). At rest, dominant alpha wave activity indicates an awake yet relaxed cortical state and is usually negatively

associated with CNS arousal (Loo & Makeig, 2012). Dominant alpha wave activity during eyes-closed conditions has been noted among boys (Barry, Clarke, McCarthy, Selikowitz, Rushby & Ploskova, 2004), and a group of mixed-sex children (Barry, Clarke, Johnstone & Brown, 2009). The present data is compatible with these results and Figure 6.1 shows an alpha peak at 9 Hz in both subject groups. Alpha blocking is traditionally viewed as an indicator of arousal increase (Sharpless & Jasper, 1956). The positive correlation between SCL and alpha activity found in the current sample of girls with AD/HD contradicts this expectation and indicates an anomaly in the arousal mechanisms of girls with AD/HD, which differs from boys. Although Barry et al. (2012) focussed on the effects of caffeine on SCL in children with AD/HD (mixed-sex); the study suggested that a straightforward low SCL level may not fully encapsulate the CNS dysfunction associated with AD/HD. Rather, Barry et al. (2012) suggested that an arousal *mechanism* dysfunction may better portray the underlying nature of CNS arousal dysfunction in AD/HD. Girls with AD/HD do exhibit hypoarousal with lower mean SCL, but their positive relationship between SCL and alpha activity shows that their arousal mechanism is qualitatively different to that found in boys with AD/HD.

There are two possible explanations for the positive link between alpha and arousal in girls with AD/HD. One, as elevated anxiety can reduce alpha activity (Ellingson, 1954; Slatter, 1960; Stauss, 1945), it is possible that anxiety may influence the alpha-SCL relationship in girls with AD/HD. Girls with AD/HD are more likely to be anxious than boys with AD/HD (Gershon, 2002) and girls without AD/HD (Quinn, 2005). The current female AD/HD group had significantly greater mean anxiety scores (based on DAYS) than controls (see Table 6.1; note that all subjects were screened for a diagnosed anxiety disorder). It may be that girls with AD/HD are more anxious by

nature and therefore more likely to have less alpha activity when compared with their control counterparts. This anxiety, which is likely to lower alpha activity, will then impact on the relationship with SCL, resulting in a positive relationship, opposite to that found in previous studies. The second possible explanation is based on the notion that there are two distinct deficits within AD/HD; 1. an arousal deficit, and 2. an alpha deficit. The first, an arousal deficit, is indicated by significantly lower SCL, which is commonly reported in AD/HD (Barry et al., 2009, 2012; Broyd et al., 2005; Lazzaro et al., 1999; Satterfield & Dawson, 1971; Satterfield et al., 1974). The second, an alpha deficit, is not uncommon, as the EEG profile of AD/HD is often characterised by elevated slow-wave (delta, theta) and reduced fast-wave (alpha, beta, gamma) (Barry & Clarke, 2009; Barry et al., 2003, 2004, 2010; Chabot & Serfontein, 1996; Clarke et al., 2001a, 2001b, 2002, 2003; Clarke, Barry, Dupuy, et al., 2011; Clarke, Barry, McCarthy, et al., 2011; Dupuy et al., 2011; Dupuy, Barry, et al., 2013; Hermens et al., 2004; Lansbergen et al., 2011; Lazzaro et al., 1998, 1999; Monastra et al., 1999, 2001). Recognition of these two deficits within the disorder would dissolve any link between arousal and alpha in AD/HD, suggesting that it is inappropriate to relate one to the other. These two explanations (anxiety versus twin deficits) are speculative, and need to be examined in further research.

Exploratory stepwise regressions were conducted to investigate the relationship between EEG effects, SCL, and symptom behaviours based on parent rating scales in the AD/HD and control groups together. Only scales from the Conners' and DAYS rating scales were included in the regression analyses as the scores from the CBCL were highly correlated with scores from the Conners' and DAYS. The regression analyses found that increasing inattentive symptoms were linked with elevated frontal

relative delta activity, reduced SCL, and reduced temporal relative gamma activity in the clinical and control groups together (see Table 6.4). Elevated hyperactivity-impulsivity symptoms were correlated with elevated frontal relative delta activity. Clarke, Barry, McCarthy, et al. (2011) found that elevated frontal relative theta significantly correlated with symptoms of inattention, and even suggested that frontal relative theta could be a specific marker of inattention, but that was not replicated in this study with girls. Elevated frontal relative theta, a common EEG profile in boys with AD/HD, has been less reliable among females with AD/HD (Clarke et al., 2003, 2007; Dupuy et al., 2011), while absolute and relative delta increases are more often found among girls with AD/HD (Clarke et al., 2003, 2007; Dupuy et al., 2011; Dupuy, Barry, et al., 2013). The current correlations of relative delta with inattention and hyperactivity-impulsivity may indicate a relationship between EEG and core AD/HD symptom behaviours that is unique to girls. Reduced relative gamma was negatively correlated with inattention, and Barry et al. (2010) found a similar negative relationship with absolute gamma in a mixed group of children with AD/HD. Benasich et al. (2008) and Barry et al. (2010) suggested that reduced gamma activity indicates a developmental lag, and the current negative relationship between relative gamma and inattention may indicate an element of developmental delay in girls with AD/HD. As mentioned earlier, low SCL has been found among children with AD/HD and the hypoarousal model predicts that those with AD/HD symptoms will have low SCL (Satterfield & Cantwell, 1974), so it is no surprise that low SCL correlates positively with core AD/HD symptom behaviours. This correlation helps reinforce the relationship between AD/HD symptom behaviours and physiology.

The regression analyses also found that elevated anxiety symptoms were predicted by reduced SCL. Increasing depressive symptoms were also predicted by reduced SCL and reduced midline posterior absolute alpha activity. Lastly, increasing social maladjustment symptoms, which indicate a child's inability to adjust socially, was predicted by a reduction of SCL, and reduced posterior relative alpha. These results suggest that increased symptoms of depression and social maladjustment are predicted by hypoarousal.

As mentioned earlier, the nature of CNS arousal as indicated by SCL appears more complex than simple low or high levels in this disorder. An anomalous arousal mechanism may better describe the nature of CNS arousal within AD/HD (Barry et al., 2012) and this arousal dysfunction may play a role in the relationship with symptom behaviours in girls with AD/HD. There is limited literature on the physiology of social maladjustment. El-Sheikh and Arsiwalla (2011) found that lower SCL levels correlated with elevated externalizing symptoms, and van Goozen, Matthys, Cohen-Kettenis, Buitelaar and van Engeland (2000) found that children with disruptive behaviour disorder had abnormally low baseline SCL. These results have been explained in relation to sensation seeking (Zuckerman, 1969, 1974), suggesting that children with abnormally low SCL may engage in antisocial behaviour (indicating high levels of social maladjustment) to increase their arousal levels (Zuckerman, 1974).

Reduced SCL has been found among adults with depression (Dawson, Schell & Catania, 1977; Iacono et al., 1983; Storrie, Doerr & Johnson, 1981; Thorell, 2009; Ward, Doerr & Storrie, 1983) and the current correlation between elevated depressive symptoms and reduced SCL and alpha may represent this relationship. However, the literature on electrodermal activity and depression is less consistent in children

(Lorber, 2004; Scarpa & Raine, 1997), suggesting further research and clarification is needed. While anxiety has been linked with elevated skin conductance (Pruneti, Fontana & Bicchieri, 2006), the relationship between anxiety and electrodermal activity also remains unclear in children (El-Shiekh & Arsiwalla, 2011; Wallien, van Goozen & Cohen-Kettenis, 2007). Although it is difficult to draw firm conclusions from the current exploratory results, these relationships between symptom/behaviours and physiological results offer insights for future research directions in linking EEG and physiological measures with specific behaviours.

This is the first study to investigate hypoarousal exclusively in girls with AD/HD. The EEG results are comparable to previous results in girls with AD/HD, with the finding of globally elevated relative delta and globally reduced absolute beta, absolute gamma and relative gamma activity. Although the gamma frequency band is fairly new in AD/HD research, results are consistent with the previous study in AD/HD children. Girls with AD/HD are underaroused, as indicated by a lower mean SCL compared with controls. However, a positive correlation between SCL and absolute alpha activity in girls with AD/HD suggests an anomalous arousal mechanism that is different to that in boys with AD/HD. The significant correlations reported between physiology and symptom behaviours should be replicated, as these were purely exploratory in this study. Nevertheless, these relationships offer insights for further research directions in girls with AD/HD.

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7 DSM-5 ADULT ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: SEX DIFFERENCES IN EEG ACTIVITY

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7.1 Introduction

Attention-Deficit/Hyperactivity Disorder (AD/HD) is characterised by developmentally-inappropriate levels of inattention and/or hyperactivity and impulsivity (APA, 2013). Although initially conceptualised as a childhood condition, it is now widely acknowledged that AD/HD often persists into adulthood (<18 years) (Polanczyk & Rohde, 2007; Wilens, Faraone & Biederman, 2004). Prevalence rates of adult AD/HD have been estimated at 2.5-5%, suggesting that it is a relatively common adult disorder (APA, 2013; Faraone & Biederman, 2005; Kessler et al., 2005, 2006; Nutt et al., 2007; NICE, 2008; Polanczyk & Jensen, 2008; Willcutt, 2012). Children with AD/HD are much more likely to be boys than girls; with boy-to-girl ratios ranging from 2:1 up to 9:1 (APA, 2013; Arcia & Conners, 1998; Gaub & Carlson, 1997; Hartung & Widiger, 1998; Pastor & Ruben, 2008; Rutter, Caspi & Moffitt, 2003; Willcutt, 2012). However, this ratio difference within adults is less pronounced with male-to-female ratios estimated at 1-2:1 (APA, 2013; Willcutt, 2012). These ratios show that AD/HD is more common in males than females across the lifespan, although the discrepancy between males and females is not as wide in adulthood as it is in childhood.

For the first time, specific criteria for adult AD/HD have been included in the DSM-5 (APA, 2013). The DSM-5 states that older adolescents and adults (aged 17 and older) must have a minimum of five inattentive and/or five hyperactive-impulsive symptoms to meet adult AD/HD criteria (APA, 2013). Although symptoms have not changed from the previous edition, the DSM-5 has included more adult-appropriate symptom descriptions (APA, 2013). The symptom age-of-onset was changed from seven years in the DSM-IV-TR (APA, 2000) to 12 years in the DSM-5 (APA, 2013).

Electroencephalography (EEG) is valuable in exploring the underlying neural substrates associated with AD/HD (Becker & Holtmann, 2006). Children with AD/HD tend to have increased posterior absolute delta activity (Clarke, Barry, McCarthy & Selikowitz, 2001a, 2001b Matousek, Rasmussen & Gillberg, 1984), globally elevated absolute and relative theta activity, most often frontally (Barry & Clarke, 2009; Barry, Clarke, Johnstone, McCarthy & Selikowitz, 2009; Chabot & Serfontein, 1996; Clarke, Barry, McCarthy & Selikowitz, 2002; Lazzaro et al., 1998; Satterfield, Cantwell, Lesser & Podosin, 1972), and reduced relative alpha and relative beta activity (Clarke et al., 2001a, 2001b; Clarke, Barry, Dupuy, McCarthy, Selikowitz & Heaven, 2011; Clarke, Barry, McCarthy & Selikowitz, 2011; Lazzaro et al., 1998). A larger theta/beta ratio across the scalp has also been found consistently in AD/HD children, compared with controls (Barry, Clarke, Johnstone, et al., 2009; Clarke et al., 2001a, 2001b; Clarke, Barry, Dupuy, et al., 2011; Clarke, Barry, McCarthy, et al., 2011; Janzen, Graap, Stephanson, Marshall & Fitzsimmons, 1995; Lansbergen et al., 2011; Lubar, 1991; Monastra et al., 1999; Monastra, Lubar & Linden, 2001; Synder & Hall, 2006). Global reductions of absolute and relative gamma have been found among children with AD/HD, relative to controls (Barry, Clarke, Hajos, et al., 2009; Barry, Clarke, Hajos, McCarthy, Selikowitz & Dupuy, 2010; Dupuy, Clarke, Barry, McCarthy & Selikowitz, in press).

The EEG activity of adults with AD/HD is a comparatively less well investigated. So far, adults with AD/HD have shown globally elevated absolute and relative delta, globally elevated absolute and relative theta activity, and a larger theta/beta ratio across the scalp relative to controls (Bresnahan, Anderson & Barry, 1999; Bresnahan & Barry, 2002; Bresnahan, Barry, Clarke & Johnstone, 2006; Clarke, Barry, Heaven,

McCarthy, Selikowitz & Bryne, 2008; Hermens, Williams, Lazzaro, Whitmont, Melkonian & Gordon, 2004; Woltering, Jung, Liu & Tannock, 2012). There have been inconsistent reports on activity within absolute and relative alpha and beta bands (Bresnahan & Barry 2002; Bresnahan et al. 2006; Clarke et al., 2008; Hermens et al., 2004; Woltering et al., 2012). Gamma power has yet to be examined within adults with AD/HD. A limitation of this EEG profile is the incompatibility of eyes-open versus eyes-closed recording conditions. The above mentioned studies include a mix of eyes-open (Bresnahan & Barry 2002; Bresnahan et al., 1999, 2006) and eyes-closed (Hermens et al., 2004; Clarke et al., 2008; Koehler et al., 2009; Woltering et al., 2012) recording conditions. There are significant differences in power levels and topography between these two conditions (Barry, Clarke, Johnstone, Magee & Rusby, 2007; van Dongen-Boomsma et al., 2010; Woltering et al., 2012).

Importantly, none of the adult AD/HD-EEG studies investigated female profiles separately to males. One study excluded females (Clarke et al., 2008), while others included mixed-sex subject groups (Bresnahan & Barry, 2002; Bresnahan et al., 1999, 2006; Hermens et al., 2004; Koehler et al., 2009; van Dongen-Boomsma et al., 2010; Woltering et al., 2012). While Hermens et al. (2004) and Koehler et al. (2009) reported on sex differences, sex was only included as a variable within a wider statistical analysis. Hermens et al. (2004) concluded that adult males with AD/HD had more aberrant EEG profiles than females with AD/HD, particularly in the theta band, and Koehler et al. (2009) did not find any sex effects in comparisons between the AD/HD and control groups. However, there are no female-only comparisons of EEG activity between adult subjects with and without AD/HD.

The aim of this study was to investigate sex differences in the EEGs of adult males

and females with AD/HD. This study is unique as is it the first to implement the new DSM-5 adult AD/HD criteria and the first to report on gamma power within this population. It is also unique in that all adults with AD/HD had an initial childhood diagnosis.

7.2 Method

7.2.1 Participants

Sixty-four adults (aged 20-29 years; *M* = 24.56, *SD* = 2.42) participated in this study. Two groups of adults with AD/HD included 16 males (AD/HD-m) and 16 females (AD/HD-f), and these were matched against 16 male and 16 female controls (CON-m and CON-f). All AD/HD subjects are past patients of Dr. Rory McCarthy and Dr. Mark Selikowitz and were clinically diagnosed and treated for AD/HD as children based on DSM-IV criteria (APA, 1994). The AD/HD subjects were reassessed here as adults and diagnosed with adult AD/HD based on DSM-5 criteria (APA, 2013). All adults who were medicated during childhood for the disorder were unmedicated for a minimum period of five years prior to this study.

The control group consisted of age-matched adults selected from a research participation pool of university students. Controls were included if they had an IQ score of at least 85 and they performed in the normal range or better on reading ability and scored below clinical levels on symptom checklists. The control subjects had no history of childhood AD/HD and no indications of psychopathology.

7.2.2 Procedure

Ethics approval for this study was obtained from the combined Illawarra Area

Health/University of Wollongong Human Research Ethics Committee. All participants gave informed consent for this study.

Subjects were tested in a single four hour session, with breaks taken as necessary to control for fatigue. During this assessment, a comprehensive clinical history was taken which included treatment history for any mental illness, present living arrangements, history of problems at school (including suspensions and expulsions), highest educational level, current employment and number of past jobs (including periods of unemployment), legal problems/criminality as a minor and as an adult, and present use of drugs (legal and illegal). Subjects then completed the Weschler Adult Intelligence Scale (WAIS-III) and the Woodcock Reading Mastery Test - Revised. They also completed the General Health Questionnaire (GHQ-60), the Conners' Adult ADHD rating scale-self-report: long version (CAARS-S:L), and the Center for Epidemiological Studies-Depression scale (CES-D). The CAARS helped determine the presence of AD/HD symptoms, with a *T*-score greater than 60 on AD/HD related subscales (DSM-IV inattentive, DSM-IV hyperactive; DSM-IV AD/HD total; AD/HD index) used as the clinical cut off. These CAARS subscales are based upon DSM-IV criteria and include nine inattentive and nine hyperactive-impulsive symptoms on their respective subscales and 18 total AD/HD symptoms on the DSM-IV AD/HD total subscale (Conners et al., 1999).

Then, an eyes-closed EEG was recorded over a five-minute, task-free, resting condition. An electrode cap was fitted to ensure International 10–20 electrode placement and EEG activity was recorded from 19 electrodes: Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, O2. These electrodes were divided into nine regions for analysis by averaging each region. These included the left frontal (Fp1,

F7, F3), midline frontal (Fz), right frontal (Fp2, F8, F4), left central (T3, C3), midline central (Cz), right central (T4, C4), left posterior (T5, P3, O1), midline posterior (Pz) and right posterior (T6, P4, O2) regions. Electrode sites were referenced to one ear lobe and data were then re-referenced to the average of digitally-linked ears. A cap ground was placed between Fpz and Fz. Two electrodes were placed 1 cm above and 1 cm below the right eye to record vertical eye-movement and two electrodes were placed 1 cm from the outer canthus of each eye to record horizontal eye-movement. Impedance levels on all electrodes were kept below 5 kΩ.

The EEG was recorded using a Neuroscan NuAmps, software version 4.3.1, with a sampling rate of 500 Hz. A gain of 30,000 was used, with a high pass filter of 1 Hz, low pass filter of 52 Hz, and a 50 Hz notch filter. A minimum of 75 seconds of artefact-free EEG was selected for analysis, from which 2 second epochs were Fourier transformed using Scan 4.3.1 software. The 75 seconds of artefact-free EEG was selected over the five-minute eyes-closed recording period across all subjects. EEG estimates were calculated for five frequency bands: delta (1.5-3.5 Hz), theta (3.5-7.5 Hz), alpha (7.5-12.5 Hz), beta (12.5-25 Hz), and gamma (35-45 Hz) for absolute and relative power, total power, and the theta/beta ratio. Total power is the sum of all included frequency bands. The theta/beta ratio was calculated by dividing theta power by beta power at each site.

7.2.3 Statistical Analysis

The clinical data were tested in one-way analyses of variance (ANOVAs) comparing the scores of the male AD/HD group with male controls, and the female AD/HD group with female controls. For the EEG data, the effects of region and group for each

frequency band in absolute and relative power, total power, and the theta/beta ratio were examined. Within region, two orthogonal three-level repeated-measures factors, and their interactions were examined. The first of these was a sagittal factor, within which planned contrasts compared the frontal (F) region with the posterior (P) region, and their mean (F/P) with the central (C) region. The second factor was laterality, within which planned contrasts compared the left (L) and right (R) hemispheres, and their mean (L/R) with the midline (M) region. Within the group factor, planned contrasts compared the clinical group with the control group. These analyses were conducted separately for males and females, and all these *F* values have (1, 30) degrees of freedom.

Additional analyses were conducted to examine sex by group interactions based on significant effects reported from the separate male and female analyses, described above. These additional analyses were done to directly compare two effects and allow for accurate reporting on the statistical significance of their difference (Nieuwenhuis, Forstmann & Wagenmakers, 2011). These examined the sex factor, comparing differences between the EEGs of the patient and control in male (Male) and female (Fem) groups. All these *F* values have (1, 60) degrees of freedom. As all contrasts are planned and there are no more of them than the degrees of freedom for effect, no Bonferroni-type adjustment to α is required (Tabachnick & Fidell, 2007). An α level of .05 was used for statistical significance.

7.3 Results

7.3.1 Clinical Data

Mean age and clinical scale scores for each group are presented in Tables 7.1-7.4.

No significant differences were found for age or IQ between the male and female AD/HD and control groups. The male groups did not significantly differ on reading age, but the female AD/HD group had significantly lower mean reading age than the female controls. However, all scores were in the average range (see Tables 7.1 and 7.2). The mean general health score (measured via GHQ-60) and mean depression score (measured via CES-D) differed significantly between the AD/HD and control groups for both males and females (see Tables 7.1 and 7.2). However, scores were in the non-clinical range in all groups. Tables 7.3 and 7.4 show mean subscale scores from the self-reported AD/HD questionnaire, the CAARS. All subscales on the CAARS were significantly elevated in the male and female AD/HD groups compared with male and female controls (see Tables 7.3 and 7.4).

Table 7.1 Mean age (in years) and psychometric test result for the male AD/HD and control groups.

	Male AD/HD	Male Control	*F*	*p*
Age *(SD)*	25.38 *(2.03)*	22.63 *(2.22)*	1.48	.233
IQ	110.25	112.31	0.14	.711
Reading Age	25.5	27.31	0.23	.647
General Health	6.62	5.94	4.76	**.037**
Depression Score	14.69	2.69	6.81	**.014**

Significant values in bold.

Table 7.2 Mean age (in years) and psychometric test result for the female AD/HD and control groups.

	Female AD/HD	Female Control	*F*	*p*
Age *(SD)*	28.51 *(1.38)*	24.38 *(2.67)*	0.38	.542
IQ	105.94	112.38	2.06	.162
Reading Age	25.69	32.63	7.29	**.011**
General Health	9.31	6.25	4.76	**.037**
Depression Score	13.56	2.65	6.12	**.019**

Significant values in bold.

Table 7.3 Mean CAARS subscale scores for the male AD/HD and control groups.

	Male AD/HD	Male Control	*F*	*p*
Inattention/Memory Problems	57.50	45.31	17.18	**< .001**
Hyperactivity/Restlessness	56.00	43.13	27.48	**< .001**
Impulsivity/Emotional Lability	52.16	42.25	10.26	**.003**
Problems with self-concept	53.19	44.50	7.07	**.012**
DSM-IV Inattentive	68.88	50.19	34.38	**< .001**
DSM-IV hyperactive	63.38	46.94	35.15	**< .001**
DSM-IV AD/HD total	71.00	49.00	61.79	**< .001**
AD/HD Index	56.69	42.25	29.25	**< .001**

Significant values in bold.

Table 7.4 Mean CAARS subscale scores for the female AD/HD and control groups.

	Female AD/HD	Female Control	*F*	*p*
Inattention/Memory Problems	61.50	45.69	42.64	**< .001**
Hyperactivity/Restlessness	54.00	42.69	20.59	**< .001**
Impulsivity/Emotional Lability	58.75	43.19	39.99	**< .001**
Problems with self-concept	55.81	44.38	11.41	**.002**
DSM-IV Inattentive	63.31	45.875	51.86	**< .001**
DSM-IV hyperactive	58.19	40.94	37.52	**< .001**
DSM-IV AD/HD total	62.75	43.13	83.52	**< .001**
AD/HD Index	60.56	42.69	60.70	**< .001**

Significant values in bold.

7.3.2 EEG in Males – AD/HD vs. Control

Figure 7.1 shows that, compared with male controls, the male AD/HD group had elevated absolute theta activity in the frontal compared with posterior region of the right compared with the left hemisphere (AD/HD-m > CON-m x F > P x L < R: $F = 5.57$, $p = .025$, $\eta_p^2 = .16$). Within absolute alpha activity, the male AD/HD group c.f. male controls had less alpha in the right than in the left hemisphere (AD/HD-m < CON-m x L < R: $F = 6.85$, $p = .014$, $\eta_p^2 = .19$) and Figure 7.1 shows that this was particularly evident in the posterior region (AD/HD-m < CON-m x F < P x L < R: $F = 5.07$, $p = .032$, $\eta_p^2 = .14$). Figure 7.1 shows that the male AD/HD group, compared with controls, had globally reduced absolute beta activity (AD/HD-m < CON-m: $F = 6.27$, $p = .018$, $\eta_p^2 = .17$). Within absolute gamma activity, the male AD/HD group c.f. male controls had less gamma power in the posterior regions (AD/HD-m < CON-m x F < P: $F = 7.47$, $p = .010$, $\eta_p^2 = .20$), particularly within the hemispheres (AD/HD-m < CON-m x F < P x L/R > M: $F = 4.61$, $p = .040$, $\eta_p^2 = .13$). Figure 7.1 shows that total power was reduced in the posterior region of the right hemisphere in the male AD/HD group c.f. male controls (AD/HD-m < CON-m x F < P x L < R: $F = 5.15$, $p = .031$, $\eta_p^2 = .15$).

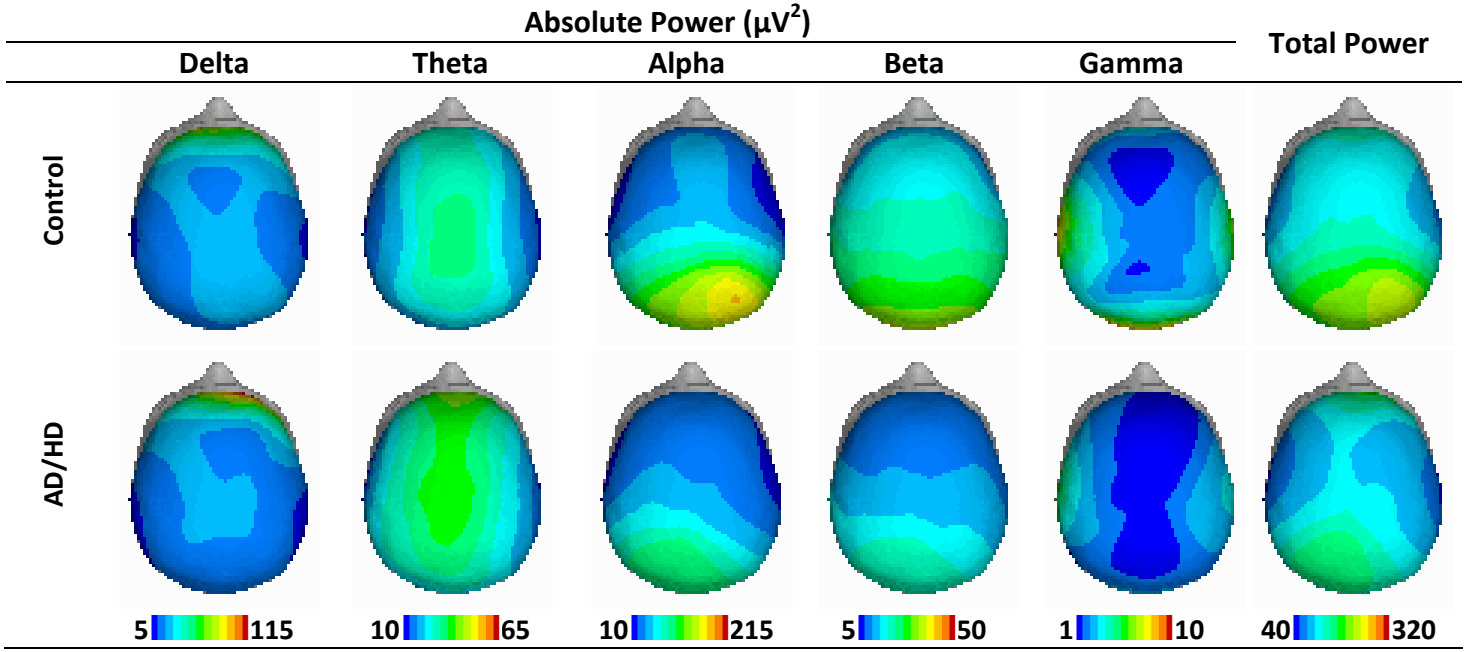

Figure 7.1 Topographic maps for absolute power for the male AD/HD and control groups.

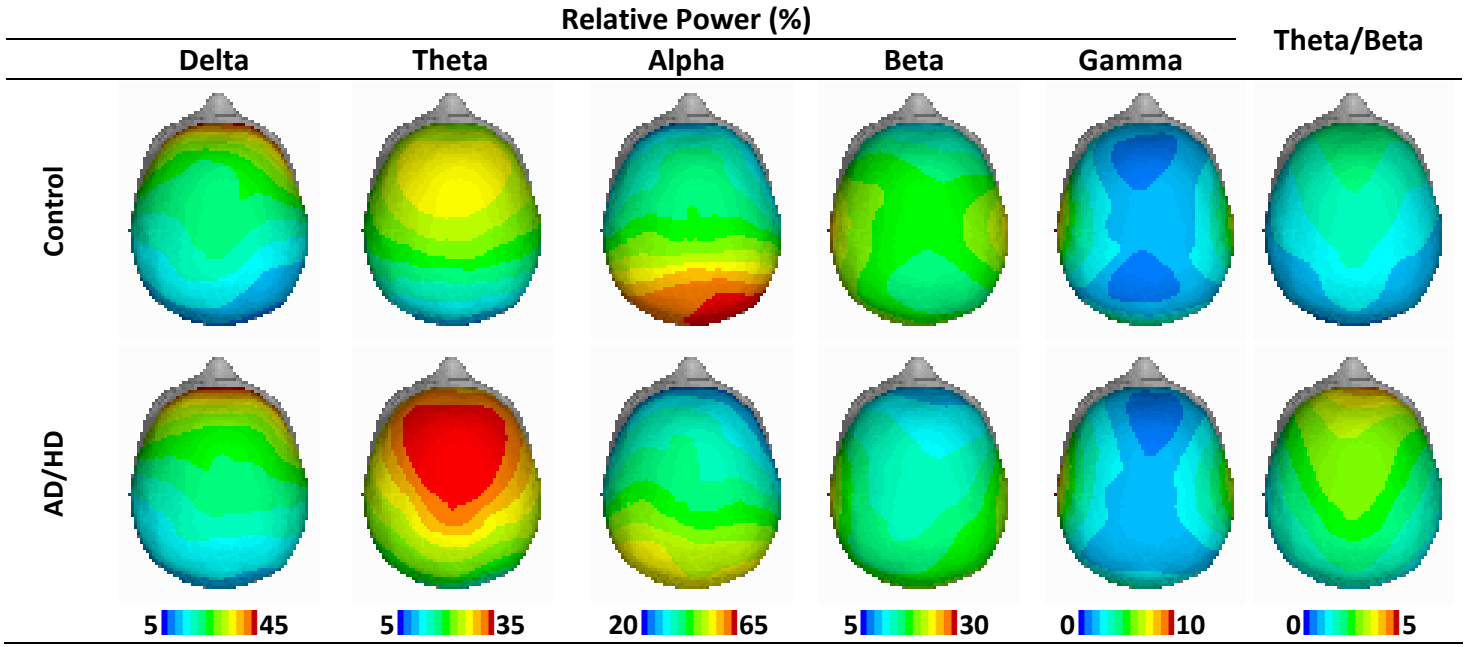

Figure 7.2 Topographic maps for relative power and theta/beta ratio for the male AD/HD and control groups.

Figure 7.2 shows that compared with male controls, the male AD/HD group had globally elevated relative theta activity (AD/HD-m > CON-m: $F = 6.24$, $p = .018$, $\eta_p^2 = .17$). This elevation was more evident in the central region of the right hemisphere (AD/HD-m > CON-m x F/P < C x L < R: $F = 5.45$, $p = .027$, $\eta_p^2 = .15$). The male AD/HD group c.f. male controls had less relative alpha activity in the right hemisphere (AD/HD-m < CON-m x L < R: $F = 5.79$, $p = .023$, $\eta_p^2 = .16$). Figure 7.2 shows that the theta/beta ratio was elevated across the scalp in the male AD/HD group (AD/HD-m > CON-m: $F = 5.06$, $p = .032$, $\eta_p^2 = .14$). This elevated theta/beta ratio in the male AD/HD group was greater in the frontal compared with posterior region, which neared significance (AD/HD-m > CON-m x F > P: $F = 4.03$, $p = .054$, $\eta_p^2 = .12$), and there was a central reduction (AD/HD-m > CON-m x F/P > C: $F = 7.10$, $p = .012$, $\eta_p^2 = .19$) that was more dominant at the midline (AD/HD-m > CON-m x F/P > C x L/R < M: $F = 7.64$, $p = .010$, $\eta_p^2 = .20$).

7.3.3 EEG in Females – AD/HD vs. Control

Compared with female controls, the female AD/HD group had elevated relative delta activity in the frontal region of the left hemisphere (AD/HD-f > CON-f x F > P x L > R: $F = 4.80$, $p = .036$, $\eta_p^2 = .14$). No other significant effects were found between the female AD/HD group and controls.

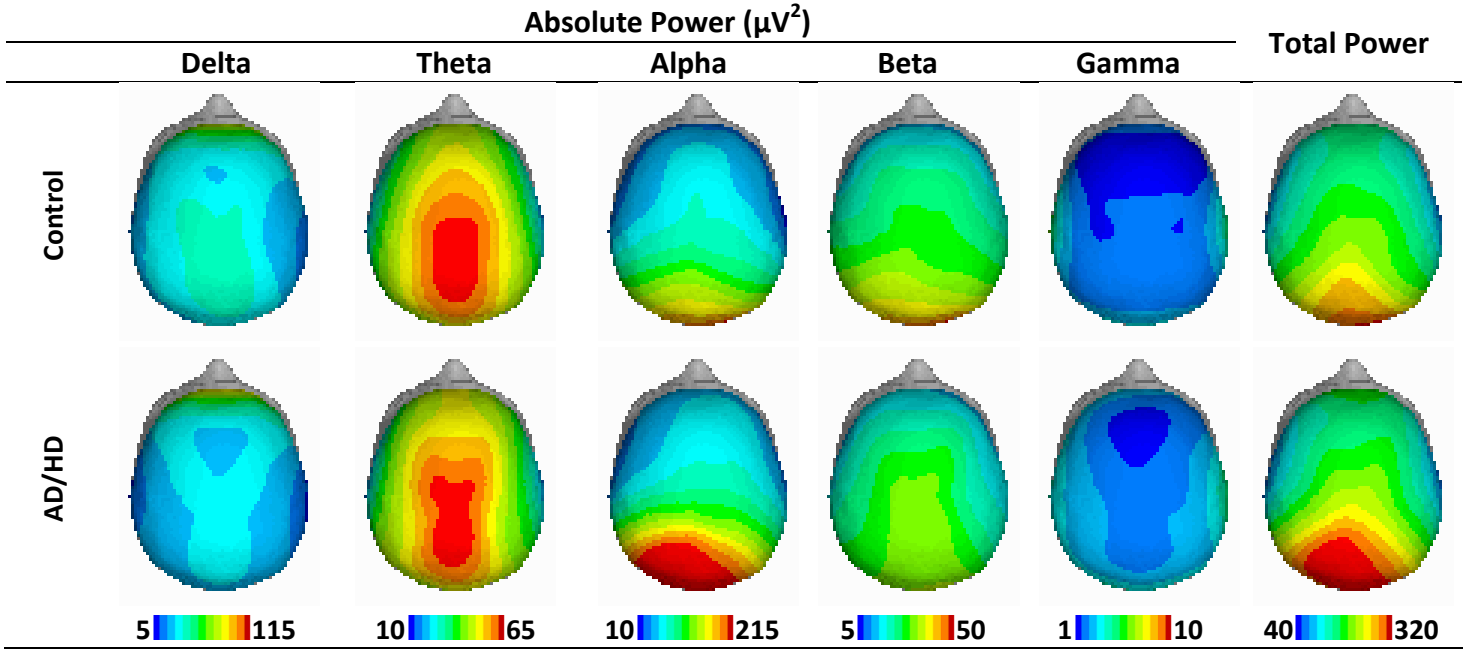

Figure 7.3 Topographic maps for absolute power for the female AD/HD and control groups.

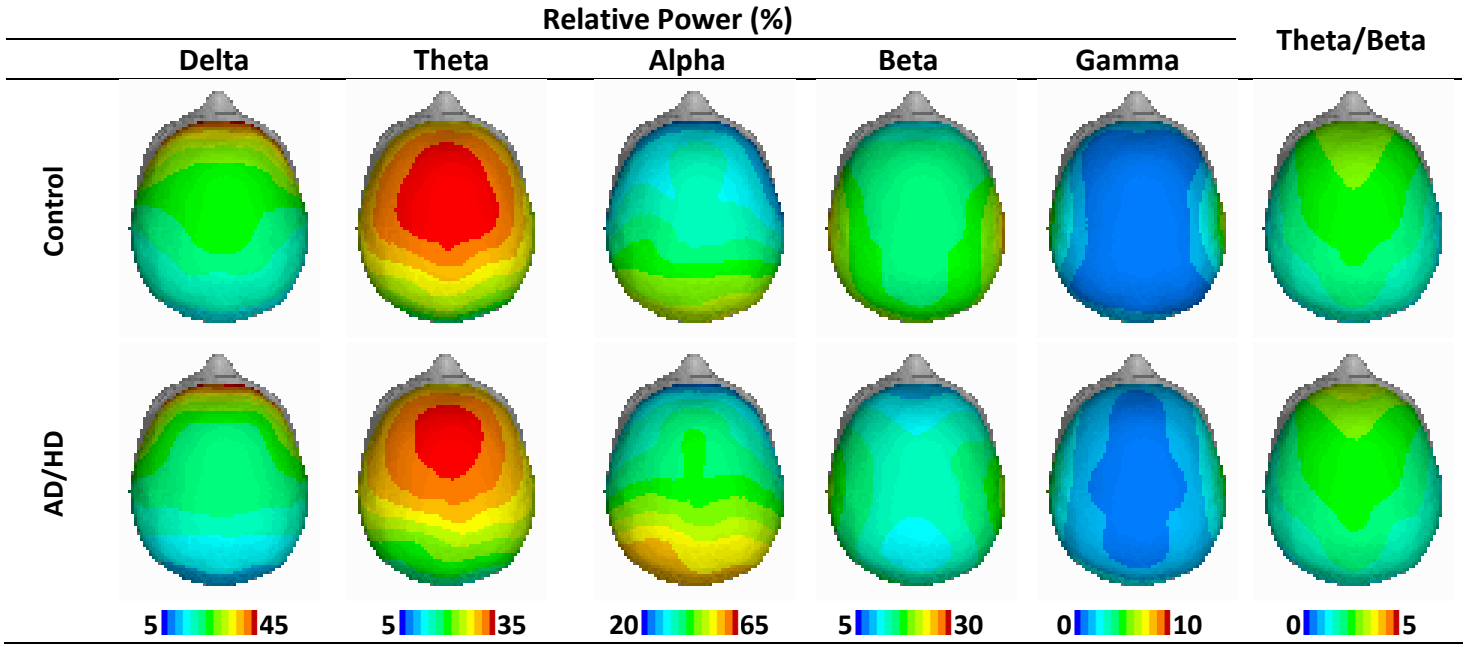

Figure 7.4 Topographic maps for relative power and theta/beta ratio for the female AD/HD and control groups.

7.3.4 EEG in Males vs. Females – Significant sex by group interactions

Table 7.5 summarizes the significant EEG effects found in the separate male and female analyses (reported above), and results from group interaction analyses. There were 14 effects noted in males but not in females. Only three of these were found to differ significantly in the interaction analyses. First, Figure 7.2 shows that the male AD/HD group, c.f. male controls, had globally elevated relative theta activity, while Figure 7.4 suggests that the female AD/HD group had less relative theta than female controls, but this was not significant (AD/HD-f < CON-f: $F = 0.13$, $p = .724$). The comparison of this global relative theta anomaly was significantly different between males and females (Male > Fem x AD/HD > CON: $F = 4.09$, $p = .048$, $\eta_p^2 = .06$). This suggests a substantial difference of globally elevated relative theta in patients compared with controls between the male and female groups, with this anomaly present only in males with AD/HD.

The second and third significant group interactions were found within the theta/beta ratio (see Table 7.5). Males with AD/HD, c.f. male controls, had a larger theta/beta ratio in the frontal/posterior compared with central region; with a frontal dominance (see Figure 7.2), but this anomaly was not significant in the female groups (AD/HD-f > CON-f x F/P > C: $F = 0.10$, $p = .749$). This theta/beta elevation differed significantly between the male and female groups (Male > Fem x AD/HD > CON x F/P > C: $F = 4.27$, $p = .043$, $\eta_p^2 = .07$). The male AD/HD group also had a significant frontal-midline dominance of the theta/beta ratio, but this was not significant in the female groups (AD/HD-f > CON-f x F/P > C x L/R < M: $F = 0.91$, $p = .349$). This elevated frontal-

midline theta/beta ratio differed significantly between males and females (Male > Fem x AD/HD > CON x F/P > C x L/R < M: $F = 6.22$, $p = .015$, $\eta_p^2 = .09$). These two group interactions suggest that there is a substantial difference in elevated frontal-midline theta/beta ratio in AD/HD patients relative to controls, with these anomalies present only in males with AD/HD.

Table 7.5 Summary of results from the separate male and female analyses and the group interactions

	Males		Females		Group Interaction	
Male Results	*F*	*p*	*F*	*p*	*F*	*p*
Theta						
AD/HD > Con x F > P x L < R	**5.57**	**.025**	.839	.367	0.98	.327
Alpha						
AD/HD < Con x L < R	**6.85**	**.014**	1.53	.226	0.26	.615
AD/HD < Con x F < P x L < R	**5.07**	**.032**	2.33	.138	0.00	.976
Beta						
AD/HD < Con x Main effect	**6.27**	**.018**	0.24	.625	0.67	.416
Gamma						
AD/HD < Con x F < P	**7.47**	**.010**	0.12	.733	3.37	.071
AD/HD < Con x F < P x L/R > M	**4.61**	**.040**	0.64	.429	1.07	.304
Total Power						
AD/HD < Con x F < P x L < R	**5.15**	**.031**	1.78	.193	0.55	.460
Relative Theta						
AD/HD > Con x Main effect	**6.24**	**.018**	0.13	.724	**4.09**	**.048**
AD/HD > Con x F/P < C x L < R	**5.45**	**.027**	0.43	.519	1.66	.203
Relative Alpha						
AD/HD < Con x L < R	**5.79**	**.023**	0.61	.439	2.18	.145
Theta/Beta						
AD/HD > Con x Main effect	**5.06**	**.032**	0.00	.974	2.30	.135
AD/HD > Con x F > P	**4.03**	**.054**	0.37	.550	1.02	.317
AD/HD > Con x F/P > C	**7.10**	**.012**	0.10	.749	**4.27**	**.043**
AD/HD > Con x F/P > x L/R < M	**7.64**	**.010**	0.91	.349	**6.22**	**.015**
Female Results						
Relative Delta						
AD/HD > Con x F > P x L > R	0.32	.577	**4.80**	**.036**	3.13	.082

Significant values are shown in bold.

There was only one AD/HD effect noted in females but not in males, but this did not differ significantly in the interaction analysis (see Table 7.5). This suggests that effects

similar to those present in females were also present in males, but did not reach significance.

7.4 Discussion

The aim of this study was to investigate the EEG activity of adults, particularly females, with AD/HD based on the new DSM-5 diagnostic criteria (APA, 2013). There is relatively little known about adult AD/HD compared with the vast literature on children, or specifically, boys with AD/HD. This study is novel also as the adult subjects with AD/HD were clinically assessed and diagnosed with the disorder *as children* (based on DSM-IV criteria; APA, 1994) and then reassessed here as unmedicated adults. The majority of the adult AD/HD-EEG literature has relied on retrospective accounts of childhood to diagnose the disorder in their adult subjects (Bresnahan & Barry, 2002; Bresnahan et al., 1999, 2006; Hermens et al., 2004; Koehler et al., 2009; van Dongen-Boomsma et al., 2010). A new diagnosis of AD/HD in adulthood is based upon information reported retrospectively, and research in this area has found that many adults are unable to accurately report on AD/HD symptoms in their childhood (Mannuzza, Klein, Bessler, Malloy & LaPadula, 1993; Mannuzza, Klein, Donald, Bessler, Shrout, 2002; Miller, Newcorn & Halperin, 2010). An initial childhood AD/HD diagnosis (as used in this study) helps confirm that the current adult AD/HD subjects satisfy all diagnostic requirements for the disorder.

There were no significant differences between the male groups for age, IQ and reading age (see Table 7.1). There were no significant differences between the female groups for age or IQ, and although the reading age was significantly lower in the female AD/HD group, all scores were in the normal range (see Table 7.2). Although

both the male and female AD/HD groups had higher scores on the general health questionnaire (GHQ-60) and the depression scale (CES-D) compared with their sex-matched controls, all these scores were in the non-clinical range (see Tables 7.1 and 7.2). Tables 7.3 and 7.4 show that all subscales on the adult AD/HD rating scale (CAARS) were significantly elevated in both the male and female AD/HD groups compared with their sex-matched controls. Together these data illustrate that the male and female AD/HD groups had clinically significant AD/HD symptoms, and did not differ on any other variables likely to contribute to EEG differences – that is, they differ only on sex.

The few available published EEG studies have found that adults with AD/HD had globally elevated absolute and relative delta, globally elevated absolute and relative theta and a larger theta/beta ratio across the scalp relative to controls (Bresnahan & Barry 2002; Bresnahan et al., 1999, 2006; Clarke et al., 2008; Hermens et al., 2004; Koehler et al., 2009; Woltering et al., 2012). Results within absolute and relative alpha and beta activity have been inconsistent (Bresnahan & Barry 2002; Bresnahan et al., 2006; Clarke et al., 2008; Hermens et al., 2004; Woltering et al., 2012). Differences between eyes-open and eyes-closed recording conditions can partially explain these inconsistencies (Barry et al., 2007; van Dongen-Boomsma et al., 2010; Woltering et al., 2012). Adding to this problem is the reliance on mixed-sex subject groups. The greatest novelty of the current study is thus the specific analysis of EEG activity exclusively within a group of adult females with AD/HD.

This study found that the male AD/HD group had elevated right frontal absolute theta activity, reduced right posterior absolute alpha activity, globally reduced absolute beta, reduced frontal absolute gamma activity and reduced right posterior

total power compared with controls (see Figure 7.1). Figure 7.2 shows that within relative power, the male AD/HD group had globally elevated relative theta, which was dominant in the right-frontal region, reduced right hemisphere relative alpha activity. Also, the theta/beta ratio was elevated across the scalp, with a central reduction at the midline. Global elevations of relative theta and the theta/beta ratio are the two most prevalent EEG anomalies found across AD/HD subject groups (for overall reviews see Barry & Clarke, 2009; Barry et al., 2003; Dupuy, Barry, et al., 2013) and both have been suggested to be reliable EEG markers of AD/HD (Clarke et al., 2008; Loo & Makeig, 2012; Snyder & Hall, 2006).

Figure 7.1 also shows that the AD/HD male group, c.f. controls, had reduced absolute gamma activity in the temporal-posterior region. There were no significant differences in either absolute or relative gamma activity between females with and without AD/HD. The gamma frequency band has not been widely researched within AD/HD populations, and has not previously been reported in adults with AD/HD. Barry, Clarke, Hajos, et al. (2009) found that a mixed-sex sample of children with AD/HD had globally reduced absolute and relative gamma activity, which was more evident in the temporal-posterior regions, compared with controls. In a separate mixed-sex subject group, Barry et al. (2010) found that children also had significantly lower absolute and relative gamma, more so in the temporal-posterior regions, than controls. Recently reduced gamma power has been noted among girls with AD/HD (Dupuy et al., in press). Within an eyes-closed resting state, girls with AD/HD, compared with controls, had significantly lower absolute and relative gamma activity, particularly in the temporal-posterior regions (Dupuy et al., in press). The current gamma results from the adult males with AD/HD are similar to findings reported in

children with AD/HD (Barry, Clarke, Hajos, et al., 2009; Barry et al., 2010; Dupuy et al., in press), in which absolute gamma was significantly lower, notably in the posterior regions, relative to age- and sex-matched controls. Including gamma power in future EEG studies would be beneficial to understand and profile this high frequency band among AD/HD populations.

In stark contrast to males, no significant global differences were found between the female AD/HD and control groups. Only a single topographic effect emerged: relative delta activity was elevated in the left frontal region in the female AD/HD group c.f. female controls. These differing results between males and females are compatible with results from Hermens et al. (2004), who reported that their sample of males with AD/HD had more aberrant EEG profiles than females with AD/HD, particularly in the theta band. These findings suggest that there is less EEG variance among adult females, than among adult males, with and without AD/HD.

The additional group interaction analyses aided interpretation of the initial separate male and female analyses by determining if there were statistically significant differences in the AD/HD groups relative to controls between males and females (Nieuwehhuis et al., 2011). The male AD/HD group, c.f. male controls, had a globally elevated relative theta anomaly, but this was not found in females. The sex by group interaction analysis found that this relative theta anomaly is substantially different between males and females (see Table 7.5). Males with AD/HD, c.f. male controls also had a larger theta/beta ratio, more so in the frontal and midline regions, and these effects were not significant in the female groups. The group interaction analyses noted in Table 7.5 show that this frontal-midline theta/beta anomaly is substantially different between males and females, being present only in males with AD/HD. This

statistical method confirms that there are significant sex differences between men and women with and without AD/HD, namely in relative theta and the theta/beta ratio, which are consistent EEG markers of AD/HD. The adult male AD/HD-EEG profile in this study is compatible with the literature (globally elevated relative theta, reduced absolute beta and a larger theta/beta ratio). Clarke et al. (2008) suggested that this profile in adults may indicate a processing deficit that has persisted from childhood in to adulthood. However, adult *females* with AD/HD do not show this AD/HD-EEG profile. The current results further indicate that AD/HD affects the cortical activity of males and females differently (Clarke et al., 2001b, 2003, 2007; Dupuy et al., 2011; Dupuy, Barry, et al., 2013; Dupuy, Clarke, et al., 2013; Hermens et al., 2004, 2005;), and it is important to examine males and female independently across all ages.

This study examined the EEG activity of adult men and women diagnosed with the new DSM-5 adult AD/HD criteria. This group of adults is distinctive as they were all diagnosed with the disorder as children, whereas the majority of adult AD/HD-EEG studies have relied on retrospective accounts for inclusion in their AD/HD subject groups. The current study found that adult males with AD/HD, compared with male controls, had significant global elevations of relative theta activity, and the theta/beta ratio and global reductions of absolute beta activity. This is also the first study to report on gamma power within an adult AD/HD sample. The male AD/HD group had lower posterior absolute gamma activity than controls, which is relatively compatible to results in children. However, no significant global differences or gamma results were found between adult females with and without AD/HD. The additional group interaction analyses confirmed that there are statistically significant sex differences between males and females with and without AD/HD, in relative theta and the

theta/beta ratio. From these results it is evident that the EEG profiles of males and females with AD/HD differ, warranting further independent examinations of AD/HD with females.

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8 CONCLUSION

This chapter summaries the major findings from the experimental studies and discusses the implications these results have for understanding EEG activity in females with AD/HD. Future research directions for building upon these conclusions will also be discussed.

8.1 Summary of Studies

Chapter 2 commenced the thesis with a published literature review that explored the scope of existing knowledge on the resting EEG profiles of females with AD/HD. From this knowledge based on four decades of research, children with AD/HD (aged 7-13 years) show a relatively consistent EEG profile. This profile is characterised by elevated slow wave activity and reduced fast wave activity. Specifically, relative to non-AD/HD controls, children with AD/HD have shown elevations in posterior absolute delta activity (Clarke, Barry, McCarthy & Selikowitz, 2001c, 2001d; Matousek, Rasmussen & Gilberg, 1984), global elevations of absolute and relative theta activity (Barry & Clarke, 2009; Barry, Clarke, Johnstone, McCarthy & Selikowitz, 2009; Chabot & Serfontein, 1996; Clarke, Barry, McCarthy & Selikowitz, 2002; Lazzaro et al., 1998; Satterfield, Cantwell, Lesser & Podosin, 1972), and global reductions of relative alpha, and relative beta activity (Clarke et al., 2001c, 2001d; Clarke, Barry, Dupuy, et al., 2011; Clarke, Barry, McCarthy & Selikowitz, 2011; Lazzaro et al., 1998). A larger theta/beta ratio across the scalp has also been reported within AD/HD children (Barry, Clarke, Johnstone, et al., 2009; Clarke et al., 2001c, 2001d; Clarke, Barry, Dupuy, et al., 2011; Clarke, Barry, McCarthy, et al., 2011; Janzen, Graap, Stephanson, Marshall & Fitzsimmons, 1995; Lansbergen, Arns, van Dongen-Boomsma, Spronk & Buitleaar, 2011; Lubar, 1991; Monastra et al., 1999; Monastra, Lubar & Linden, 2001; Synder &

Hall, 2006). Although gamma power has only recently been included within AD/HD-EEG research, absolute and relative gamma activity have been reduced across the scalp among AD/HD children, relative to controls (Barry, Clarke, Hajos, et al., 2009; Barry et al., 2010). However, this EEG profile is problematic as it has relied heavily on research with male and mixed-sex subject groups. The Chapter 2 review highlighted that, relative to the amount of knowledge on males, there is little understanding of females and sex differences within the current EEG-AD/HD literature.

Although a small number of published studies have included exclusive female subject groups (Baving, Laucht & Schmidt, 1999; Clarke, Barry, McCarthy & Selikowitz, 2001d; Clarke, Barry, McCarthy, Selikowitz, Clarke, et al., 2003; Clark, Barry, McCarthy, Selikowitz & Johnstone, 2007; Hermens et al., 2004; Hermens, Kohn, Clarke, Gordon & Williams, 2005), these are dwarfed by the numbers available on males and mixed-sex groups (for reviews see Barry & Clarke, 2009; Barry, Clarke & Johnstone, 2003; Snyder & Hall, 2006). So far, these EEG studies have indicated that girls with AD/HD (aged 7-12 years), compared with girl controls, have globally elevated absolute delta, absolute theta, and total power, greater relative theta, and reduced relative beta during rest (Clarke et al., 2001d; Clarke, Barry, McCarthy, Selikowitz, Clarke, et al., 2003; Clarke et al., 2007; Dupuy, Clarke, Barry, McCarthy & Selikowitz, 2011). Although these results are broadly comparable to the current AD/HD literature (with an elevation of slow wave activity and reduction of faster wave activity), differences are noted in total power, absolute delta activity, and relative alpha activity. Estimates of the theta/beta ratio and gamma power have been unexplored within females with AD/HD.

Chapter 2 also reviewed the research literature on EEG differences *between t*ypes of AD/HD, based on the DSM-IV criteria (APA, 1994). Among boys and mixed-sex

subject groups, children with the Combined type of AD/HD show global elevations of absolute theta and alpha activity, as well as a larger theta/beta ratio, relative to children with the Inattentive type (Chabot & Serfontein, 1996; Clarke, Barry, McCarthy & Selikowitz, 1998, 2001c, 2001d; Lubar, 1991; Mann, Lubar, Zimmerman, Miller & Muenchen, 1992). Although Clarke et al. (2001d) included a separate girl AD/HD group (equal to the number of included boys), there was no explicit comparison of AD/HD type differences within girls. Exploration of EEG differences between AD/HD types in girls has been overlooked in the literature.

Using archival data, Chapter 3 directly investigated sex differences between the resting EEG profiles of boys and girls with the Combined and Inattentive types of AD/HD within three groups of 80 children (aged 8-12 years; 40 boys and 40 girls in each of the Combined type, Inattentive type and control groups). This study was novel as the statistical design allowed for a direct comparison of EEG activity of AD/HD types between single-sex subject groups and this type of comparison had not been done before.

Between the two AD/HD types, the boy Combined type group, compared with the boy Inattentive type group, had globally elevated absolute and relative theta activity, globally reduced relative alpha activity, and a larger theta/beta ratio, supporting previous literature. However, only topographical differences and no global effects, were found between the girl type groups. These findings show that there are considerable differences in the EEG profiles of the Combined and Inattentive types of AD/HD between boys and girls. In boys, the Combined type has been associated with greater EEG anomalies than the Inattentive type (Barry & Clarke, 2009; Chabot & Serfontein, 1996; Clarke et al., 1998, 2001c, 2001d). However, this is not the case in

girls; a lack of significant global effects implies that the EEG profiles between these two AD/HD types are largely indistinct.

Interestingly, Figures 3.1-3.4 show dissimilar topographical patterns between the boy and girl control groups. Despite knowledge that sex influences EEG maturational trajectories (Benninger, Matthis & Scheffner, 1984; Clarke, Barry, McCarthy & Selikowitz, 2001a; Harmony, Marosi, Diaz de Leon, Becker & Fernández, 1990; Matthis, Scheffner & Benninger, 1980), many research studies have pooled boys and girls together into mixed-sex subject groups (i.e., Barry et al., 2010; Bresnahan, Anderson & Barry, 1999; Bresnahan & Barry, 2002; Bresnahan, Barry, Clarke & Johnstone, 2006; Chabot & Serfontein, 1996; El-Sayed, Larsson, Persson & Rydelius, 2002; Hale et al., 2010; Hermens et al., 2004; Monastra et al., 1999, 2001). Utilizing mixed-sex subject groups in children is problematic as sex-specific EEG maturation may cloud genuine AD/HD-EEG anomalies; making it difficult to establish effects that are directly attributable to the disorder.

Chapter 4 examined resting EEG differences between AD/HD types *exclusively* in girls (aged 8-12 years, with 30 girls in each of the Combined type, Inattentive type and control groups). This chapter used archival data to conduct a female-only comparison of EEG activity between the Combined and Inattentive types of AD/HD. Similar to Chapter 3, although topographical effects emerged, there were no significant global differences between the two AD/HD groups.

This disparity between boys and girls was puzzling and it was suggested that the AD/HD types are not as clearly distinct in females as in males. Girls with AD/HD, compared with boys with AD/HD, show less hyperactive symptoms (Gaub & Carlson, 1997; Gershon, 2002; Quinn, 2005), and thus there are lower thresholds for clinically

significant hyperactive-impulsive behaviours set for girls than for boys (Conners, 1997). This suggests that the behavioural gap between AD/HD types is smaller in girls than in boys, which may partially explain a lack of significant global EEG effects in girls.

To explore this hypothesis, Chapter 5 again investigated EEG differences (unpublished archival data) between AD/HD types in girls, but this time with an inflated behavioural gap. Twenty girls with an initial diagnosis of the Combined type of AD/HD were included if their behavioural profile showed highly-clinically significant scores on the DSM-IV Hyperactive-Impulsive subscale of the Conners' Parent AD/HD rating scale, and 20 girls with the Inattentive type of AD/HD were included if they scored in the average/non-clinical range on the same subscale. All AD/HD subjects, from both AD/HD type groups, had highly-clinically significant scores on the DSM-IV Inattentive subscale. This extra inclusion criterion helped artificially exaggerate the distinction of hyperactive-impulsive behaviours between the AD/HD type groups. Although topographical differences were found, once again, no significant global EEG effects were found between AD/HD types in girls.

The lack of significant global effects was somewhat surprising, as the behavioural profiles of the two AD/HD type groups were deliberately manipulated to be clinically different, and the Combined type group had significantly greater levels of hyperactive-impulsive behaviours than the Inattentive type group. With a large (and statistically significant) behavioural gap between the type groups, it was expected that global EEG differences would emerge, as found previously in boys and mixed-sex subject groups (even without such a behavioural gap).

Chapter 6 collected new subject data to explore the hypoarousal model of AD/HD (Satterfield & Cantwell, 1974), in girls. This is a dominant model within the EEG

literature for AD/HD and proposes that the CNS is underaroused in children with AD/HD, resulting in the core symptoms of inattention, hyperactivity, and impulsivity (Satterfield & Cantwell, 1974). This model has been previously investigated with relatively consistent results; children with AD/HD have significantly lower skin conductance level (SCL), indicating a hypoarousal component in the disorder (Barry, Clarke, Johnstone, McCarthy & Selikowitz, 2009; Barry et al., 2012; Broyd et al., 2005; Hermens et al., 2004; Lazzaro et al., 1999). However, to date, this model had never been empirically examined exclusively in girls. In a group of 80 girls (aged 7-12 years, 40 with AD/HD and 40 controls), resting EEG and SCL were recorded and analysed. Gamma power was also included in the EEG analysis within this chapter as it had not been previously reported in exclusive girl subject groups.

The results from Chapter 6 indicated that girls with AD/HD had globally elevated slow wave (elevated relative delta), and globally reduced fast wave (reduced absolute beta) activity, relative to controls. Similar to gamma results reported by Barry, Clarke, Hajos, et al. (2009), and Barry et al. (2010), the girls with AD/HD within this study also had globally reduced absolute and relative gamma activity, relative to controls. Girls with AD/HD had significantly reduced mean SCL, relative to controls. This is (interestingly) consistent with the hypoarousal literature in AD/HD. Reduced SCL indicates that there is a hypoarousal component in both boys and girls with AD/HD. However, a significant *positive* correlation was reported between SCL and absolute alpha activity in girls with AD/HD. This positive relationship contrasts with previous *negative* correlations between SCL and alpha reported among boys with AD/HD (Barry et al., 2004; Barry, Clarke, Johnstone, et al., 2009). At rest, dominant alpha activity indicates an awake yet relaxed state and is negatively associated with CNS arousal (Loo

& Makeig, 2012). The positive relationship between SCL and alpha contradicts this expectation, and indicates that the arousal anomaly in girls with AD/HD is different from that in boys. This novel positive SCL-alpha correlation also implies that a simple straightforward arousal reduction cannot fully explain the underlying CNS deficits associated with this disorder within girls. Instead, as Barry et al. (2012) suggested, an anomalous arousal *mechanism* better describes the CNS arousal dysfunction that is associated with AD/HD.

Higher ratings of anxiety, which are commonly reported among girls with AD/HD (Elkins, Malone, Keyes, Iacono & McGue, 2011; Gershon, 2002; Quinn, 2005) may offer insights for understanding this female-specific SCL-alpha relationship. Girls with AD/HD have reported more anxiety symptoms than boys with AD/HD (Gershon, 2002), and girls without AD/HD (Quinn, 2005). It is possible that girls with AD/HD, who are more anxious by nature, are more likely to have less alpha activity at rest, relative to their control counterparts. Anxiety lowers alpha activity (Loo & Makeig, 2012), and the elevated anxiety levels that were noted within this girl AD/HD group (see Table 6.1) may have impacted the SCL-alpha relationship, resulting in a positive, instead of an expected negative, correlation.

Chapter 6 also incorporated exploratory regression analyses to generate novel relationships between physiology and symptoms. These correlations indicated that increasing inattentive symptoms were predicted by elevated frontal relative delta activity, reduced SCL, and reduced temporal gamma activity. Elevated hyperactive-impulsive symptoms correlated with elevated frontal relative delta activity. These relationships imply that girls with AD/HD have an element of a developmental delay. As elevated delta activity is more often found in girls than in boys with AD/HD, the

correlations between AD/HD symptoms and relative delta activity may be uniquely female.

The regression analyses also indicated that reduced SCL predicted increased anxiety symptoms. Increasing symptoms of depression were predicted by reduced SCL and reduced midline posterior absolute alpha activity. Lastly, increasing symptoms of social maladjustment, which indicates a child's inability to adjust socially, were predicted by a reduction of SCL, and reduced posterior relative alpha. These correlations implied that elevated symptoms of anxiety, depression, and social maladjustment may be linked with hypoarousal.

There is minimal literature on the physiology of social maladjustment. What has been published suggests that children with low SCL may engage in antisocial behaviours, which can indicate social maladjustment, to increase their arousal levels (El-Sheikh & Arsiwalla, 2011; van Goozen et al., 2000; Zuckerman, 1969, 1974). The literature on the relationship between physiology and symptoms of depression and anxiety in children is unclear so it is difficult to draw firm conclusions. Nevertheless, these relationships indicate that there are links between specific symptoms and physiology and are worthy of further investigation.

Chapter 7, the final experimental chapter, implemented the new DSM-5 (APA, 2013) adult AD/HD criteria to examine sex differences in the EEG activity of adult males and females with AD/HD. The majority of adult AD/HD-EEG studies (of which there are few) have relied on subject's retrospective accounts of childhood to base a new diagnosis (Bresnahan et al., 1999, 2006; Bresnahan & Barry, 2002; Hermens et al., 2004; Koehler et al., 2009; van Dongen-Boomsma et al., 2010). This study was unique in that the new data were collected from adults with AD/HD who had been clinically

assessed and diagnosed with AD/HD *as children* (based on DSM-IV criteria; APA, 1994) and then reassessed as unmedicated adults. This was also the first adult AD/HD-EEG study to include a female-only comparison of EEG activity within adults, and the first to include estimates of gamma power within an adult AD/HD sample. Eyes-closed resting EEGs were recorded from 16 men and 16 women with AD/HD (aged 20-29 years), and were matched with controls.

The adult males with AD/HD, relative to male controls, had globally reduced absolute beta activity, globally elevated relative theta, and a larger theta/beta ratio. In stark contrast, there were no significant global differences between adult women with and without AD/HD, only a single topographical effect: the adult female AD/HD group had elevated relative delta activity in the left frontal region relative to controls. In gamma power, the AD/HD male group, compared with male controls, had reduced absolute gamma activity in the temporal-posterior region, but there were no significant differences in either absolute or relative gamma activity between females with and without AD/HD.

Extra analyses were performed to validily report on statistically significant differences, rather than difference between significance levels, between males and females in the AD/HD groups relative to sex-appropriate controls (Nieuwenhuis, Forstmann & Wagenmakers, 2011). The male AD/HD group, c.f. male controls, had a globally elevated relative theta anomaly, but this was not found in females. The group interaction analysis found that this relative theta AD/HD anomaly was significantly different between males and females. Males with AD/HD, c.f. male controls, also had a larger theta/beta ratio, more so in the frontal-midline region, which was not significant in the female groups. These effects were also significantly different

between males and females. These results confirm that there are differences between men and women with and without AD/HD.

The EEG profile of adult males with AD/HD in this study is similar to the existing AD/HD literature (globally elevated relative theta, globally reduced absolute beta, and a larger theta/beta ratio). Reduced temporal-posterior absolute gamma activity in the male AD/HD group is compatible with results in children with AD/HD (Barry et al., 2009, 2010; Chapter 6). However, this profile was not found in the adult female AD/HD group. Females with AD/HD do not have the same cortical anomalies as have been found in males with AD/HD. This chapter concluded that AD/HD affects the cortical activity of adult males and females differently across the lifespan.

8.2 Major Findings

8.2.1 EEG Activity in Girls with AD/HD

As males, particularly school-aged boys, have been the most commonly researched subject groups in AD/HD-EEG research, there has been little focus on female-specific EEG anomalies. The experimental studies within this thesis have consistently shown that the EEG activity of girls with AD/HD is different to the existing AD/HD-EEG literature that is based on boys and mixed-sex subject groups. Although both boys and girls with AD/HD generally show global elevations of slow wave activity, and global reductions of fast wave activity, relative to controls, there are noteworthy differences. While boys and girls with AD/HD show global elevations of absolute and relative theta, and global reductions of relative beta activity, *girls* with AD/HD also show global elevations of absolute delta activity and total power, and these results are not typically found within boys with AD/HD. Also, girls with AD/HD do not display deficiencies

within alpha activity, whereas global reductions of relative alpha activity are part of the male-based AD/HD-EEG profile (Clarke et al., 2001c, 2001d; Clarke, Barry, Dupuy, et al., 2011; Clarke, Barry, McCarthy & Selikowitz, 2011; Lazzaro et al., 1998).

This thesis also investigated EEG differences between AD/HD types. The current literature lists significant global differences between the Combined and Inattentive types of AD/HD according to DSM-IV criteria. Children with the Combined type of AD/HD show elevated absolute theta, reduced alpha and a larger theta/beta ratio relative to children with the Inattentive type, but these global effects were not reproduced in exclusive groups of girls with AD/HD. The consistent lack of global effects between female AD/HD types confirms that there is less EEG variance within girls with AD/HD than within boys with AD/HD. There is a consistent theme that girls with AD/HD (across types) have EEG anomalies that differ from the current AD/HD-EEG profile. A major conclusion of this thesis is that the existing literature that supports this AD/HD-EEG profile does not apply to females. Boys and girls should be researched separately. If mixed-sex subject groups are unavoidable, sex must be included as a statistical variable.

Developmental aspects of the EEG are also important to consider when researching children. Although each frequency band follows its own maturational trajectory, there is a general consensus that with increasing age, low frequency band (delta and theta) activity decreases while higher frequency band (alpha and beta) activity increases (Clarke et al., 2001a; Cragg et al., 2011; Gasser, Jennen-Steinmetz, et al., 1988; Gasser, Verleger, et al., 1988; John et al., 1980; Matousek & Petersen, 1973; Matsuura et al., 1985). Within this general consensus, it is known that the alpha frequency initially speeds up before reaching maturity around 10 years of age (Niedermeyer & Da Silva,

2004). To account for these maturational changes to the EEG, some researchers rely on individual alpha peak frequency ranges (e.g., Lansbergen et al., 2010). However, the chapters within this thesis relied on fixed-frequency ranges as used by the majority of the AD/HD-EEG literature. The key finding in this thesis is that the EEG activity of females with AD/HD is significantly different to the EEG activity of males with AD/HD. This finding is strengthened by the use of similar methodologies between the experimental chapters in this thesis and the current literature.

8.2.2 EEG Activity in Women with AD/HD

Compared to the focus on children, the EEG activity of adults with AD/HD is largely unexplored. This is no surprise as AD/HD is characterised as a childhood neurodevelopmental disorder (APA, 2013). However, the increasing recognition and prevalence of AD/HD persisting into adolescences and adulthood (Faraone & Biederman, 2005; Kessler et al., 2005, 2006; Nutt et al., 2007; NICE, 2008; Polanczyk & Jensen, 2008; Wilens, Faraone & Biederman, 2004; Willcutt, 2012) necessitates the exploration of EEG activity in adult AD/HD populations.

The few published studies have found that adults with AD/HD have global elevations of absolute and relative delta, global elevations of absolute and relative theta activity, and a larger theta/beta ratio across the scalp relative to controls (Bresnahan & Barry, 2002; Bresnahan et al., 1999, 2006; Clarke, Barry, Heaven, McCarthy, Selikowitz & Bryne, 2008; Hermens et al., 2004; Woltering, Jung, Liu & Tannock, 2012). There have been inconsistent results on absolute and relative alpha and beta activity (Bresnahan & Barry 2002; Bresnahan et al. 2006; Clarke et al., 2008; Hermens et al., 2004; Woltering et al., 2012).

Equivalent to the limitation within the childhood AD/HD-EEG literature, this adult AD/HD literature is based on male-only and mixed-sex subject groups. No female-specific comparisons of EEG activity have been conducted prior to the study in this thesis. Adult females with AD/HD show distinctive differences in their EEG activity (relative to controls) compared with adult males with AD/HD. While adult males with AD/HD, compared with male controls, show global elevations of slow wave (elevated relative theta), reduced fast wave activity (reduced absolute beta), and a larger theta/beta ratio, the EEG profiles of adult females with and without AD/HD are globally indistinct.

Chapters 2, 3, 4 and 6 showed that *girls* with AD/HD have an EEG profile characterised by elevated slow wave activity (absolute and relative delta, absolute and relative theta) and reduced fast wave activity (absolute and relative beta, absolute gamma), compared with girl controls, but this was not found in *adult women* with the disorder. The change of EEG activity over time in females with AD/HD differs from that in males with AD/HD. Boys and adult males with AD/HD have comparable EEG profiles; elevated slow-wave, reduced fast-wave and larger theta/beta ratio, suggesting a continuing deficit from childhood to adulthood. While girls with AD/HD show a similar profile, adult women do not, suggesting a substantial change in female patient EEG activity from childhood to adulthood. This is a major finding carried through from childhood to adult studies; AD/HD affects the cortical activity of males and females differently across the lifespan. The female-specific EEG profiles generated in this thesis emphasize important and significant differences between males and females with AD/HD. These sex differences indicate that the AD/HD-EEG profiles that

are based upon research with males and mixed-sex subjects groups are not relevant to females. Males and female should be researched separately across ages.

8.2.3 Theta/Beta Ratio in Females with AD/HD

The proportion of theta to beta power makes up the theta/beta ratio. Given the consistent finding of elevated theta activity within AD/HD, and the general association of beta activity with concentration/attention, it is not surprising that global elevations of the theta/beta ratio are often reported within AD/HD populations (Barry, Clarke, Johnstone, et al., 2009; Bresnahan & Barry, 2002; Bresnahan et al., 2006; Clarke et al., 2001c, 2001d; Clarke, Barry, Dupuy, et al., 2011; Clarke, Barry, McCarthy, et al., 2011; Janzen et al., 1995; Lansbergen et al., 2011; Lubar, 1991; Monastra et al., 1999, 2001; Synder & Hall, 2006). The theta/beta ratio has also been found to distinguish between types of AD/HD: the Combined type has shown global elevations of the theta/beta ratio relative to the Inattentive type (Clarke et al., 2001c, 2001d). As such, the theta/beta ratio has become a consistent identifier of AD/HD, with recommendations that estimates of the theta/beta ratio are useful as part of the diagnostic process (Magee et al., 2005; Synder & Hall, 2006). Although some researchers have recently expressed concern over the ability of the theta/beta to serve as a diagnostic marker for AD/HD (Arns, Conners & Kraemer, 2013; Ogrim, Kropotov & Hestad, 2012), these articles relied on eyes-open (rather than eyes-closed) EEG data. It is well known that there are significant differences in topography and power level between eyes-open and eyes-closed recording conditions (Barry et al., 2007; van Dongen-Boomsma et al., 2010; Woltering et al., 2012). While the theta/beta ratio was once argued to be an indicator of arousal (Lubar, 1991), it is now suggested to represent a substrate of

activation (Barry et al., 2004). Barry, Clarke, Johnstone, et al. (2009) proposed that an elevated theta/beta ratio indicates an impaired capacity for attentional tasks, a defining characteristic of AD/HD.

Another possible interpretation could be that states of low vigilance and/or drowsiness underlie elevated theta activity (Sander, Arns, Olbrich, & Hegerl, 2010). According to the concept of vigilance stages, a state of low vigilance is indicated by a reduction of alpha and elevation of delta and theta wave activity and drowsiness has been defined by elevated delta and theta activity (Sander et al., 2010). Although it is possible that excess theta may indicate low levels of vigilance or drowsiness, according to these definitions, there needs to be evidence of reduced alpha (for low vigilance) and elevations of delta (for drowsiness). Although excess theta activity is a robust EEG characteristic among males with AD/HD (but not as consistent among females), alpha and delta results are not as reliably found in either males or females. It seems unlikely that drowsiness or low vigilance can fully explain the consistent existence of elevated theta activity within AD/HD populations.

Although the theta/beta ratio has been a consistent feature within the EEG literature, estimates of the theta/beta ratio have rarely been investigated in females with AD/HD. This thesis found that both girls and adult women with AD/HD do not show global elevations of the theta/beta ratio compared with sex-matched controls, nor are there any global theta/beta distinctions between AD/HD types in girls. The theta/beta ratio does not appear to be a reliable marker of the disorder within females, contrary to implications of the current general literature.

8.2.4 Gamma power in Females with AD/HD

Gamma activity lies above the four traditional bands and is considered to range between approximately 30 and 80 Hz (Engel, Fries & Singer, 2001; Fell, Fernandez, Klaver, Elger & Fries, 2003). Gamma power has been relatively unexplored in AD/HD populations and has only been reported by our research group, over two studies with mixed-sex subject groups of children with AD/HD (Barry, Clarke, Hajos, et al., 2009; Barry et al., 2010). Both studies found that absolute and relative gamma were significantly lower, notably in the posterior regions, relative to age- and sex-matched controls (Barry, Clarke, Hajos, et al., 2009; Barry et al., 2010). Two of the experimental studies within this thesis (Chapter 6 and 7) reported on estimates of absolute and relative gamma activity in girls (aged 7-12 years), and adult women (aged 20-29 years). Similar to Barry, Clarke, Hajos, et al. (2009) and Barry et al. (2010), in Chapter 6, girls with AD/HD had global reductions of absolute and relative gamma activity, dominant in posterior regions, compared with controls. In Chapter 7, no significant gamma distinctions were found between women with and without AD/HD. In contrast to the adult female results, adult males with AD/HD had reduced absolute gamma activity in the temporal-posterior region, relative to male controls. These gamma results, which are relatively consistent with results found in children, suggest an ongoing deficit of gamma power in males, but not in females. This indicates that there is a female-specific change in gamma power between childhood and adulthood within AD/JD.

8.2.5 CNS Arousal in Females with AD/HD

Despite recognition of AD/HD-related EEG anomalies, the exact underlying causes of the disorder remain unknown. A dysfunctional CNS is generally accepted to be

involved, although the mechanisms are not well understood (Fonseca, Tedrus, Bianchini & Silva, 2013). The Hypoarousal model proposes that the CNS is underaroused in children with AD/HD, resulting in core AD/HD symptoms (Satterfield & Cantwell, 1974). Studies using SCL, a reliable index for arousal (Barry & Sokolov, 1993; Raine, Veneables & Williams, 1990; Raskin, 1973; Rosenthal & Allen, 1978; van Lang, Tulen, Kallen, Rosbergen, Dieleman & Ferdinand, 2007), have linked AD/HD with low SCL (Barry, Clarke, Johnstone, et al., 2009, 2012; Broyd et al., 2005; Hermens et al., 2004; Lazzaro et al., 1999). While this model has received research attention, only males were included in research studies, except for Barry et al. (2012). Although Barry et al. (2012) included mixed-sex subject groups (26 males and 10 females); sex was not included as a statistical factor. This thesis has found that girls with AD/HD have significantly lower SCL, compared with controls. Both boys and girls with AD/HD are hypoaroused.

However, uniquely female, the significant positive correlation between SCL and absolute alpha activity complicates this hypoarousal concept in females. An anomalous arousal mechanism, as initially suggested by Barry et al. (2012), better describes the underlying nature of the dysfunction of CNS arousal in AD/HD. It is also likely that the higher incidence of anxiety noted among females with AD/HD influences alpha activity and impacts on the relationship between SCL and alpha. It would be beneficial to further explore the effect of anxiety on SCL and EEG measures within female AD/HD populations.

8.2.6 Symptom Correlations

Chapter 6 included novel relationships between physiology and AD/HD symptoms and comorbid behaviours. Elevated ratings of inattentive symptoms were predicted by increased frontal relative delta activity, reduced SCL, and reduced temporal relative gamma activity. Elevated ratings of hyperactive-impulsive symptoms were predicted by increased frontal relative delta activity. It is interesting to note that elevated frontal relative delta activity correlated with the core AD/HD symptoms in girls. Absolute and relative delta anomalies are more often reported in female-only comparisons of EEG activity relative to male and mixed-sex subject groups (Clarke, Barry, McCarthy, Selikowitz, Clarke, et al., 2003; Clarke et al., 2007; Chapters 3, 4 and 6). This implies that elevated frontal relative delta activity has a unique role within the EEG activity of girls with AD/HD, warranting further exploration. Barry et al. (2010) previously correlated reduced relative gamma with inattentive symptoms in a mixed-sex group of children. Reduced gamma power may indicate a developmental delay (Benasich et al., 2008; Barry et al., 2010). The negative correlation between inattention and relative gamma activity implies that girls with AD/HD have elements of a developmental lag within their EEG activity.

It has been noted that girls with AD/HD frequently have elevated scores of internalising behaviours, most commonly depression and anxiety (DuPaul et al., 2005; Elkins et al., 2011; Gershon, 2002; Graetz, Sawyer & Baghurst, 2005; Quinn, 2005). These behaviours correlated with SCL and significant EEG effects found in girls with AD/HD. High scores of anxiety behaviours were predicted by reduced SCL, and elevated scores of depressive behaviours were predicted by reduced SCL and reduced

absolute alpha activity. Stated earlier, anxiety has been linked with hypoarousal (reduced SCL), and this present relationship further implies the role of anxious behaviours on physiology. There is limited understanding of the role that anxiety and depression have on EEG activity within children with AD/HD. The significant relationships found between these behaviours and physiology implies that symptoms of anxiety and depression are likely to influence the EEG activity of girls with AD/HD and are worthy of further research.

8.3 Future Directions

This thesis indicates that the EEG profiles of girls and women with AD/HD are different to the profiles that are based on the existing literature. Established global EEG differences between the Combined and Inattentive types of AD/HD are not evident in exclusive female groups, implying that girls with AD/HD have relatively homogenous EEG profiles, regardless of diagnosed type. Chapter 5 suggested that the DSM's categorization of the AD/HD types may not necessarily apply to females. There have been concerns about the appropriateness of AD/HD diagnostic criteria for females in the past (Arnold, 1996; Nadeau & Quinn, 2002; Nassbaum, 2012; Ohan & Johnston, 1996). McGee and Feehan (1991) proposed that AD/HD diagnostic criteria should include gender-specific thresholds related to the degree of deviance from gender-referenced norms. It would be interesting to explore if the updated subtype 'presentations' in the DSM-5 (APA, 2013) addresses this proposal, and include girls that would have otherwise failed to meet criteria. It would be worthwhile to explore if global EEG differences emerge in females based on these new subtype presentation parameters.

This thesis focussed on the EEG activity of girls (aged 7-12 years), and adult women with AD/HD (aged 20-29 years). It would be useful to conduct a longitudinal study that includes the maturation of EEG activity within girls, adolescents and women with AD/HD across age groups. A female adolescent EEG profile would be useful to compare with research conducted with adolescent males (Hobbs, Clarke, Barry, McCarthy & Selikowitz, 2007). Additionally, the sample size of adult women with AD/HD (in Chapter 7) was small, and it would be benefical to replicate results within a larger subject group.

Chapter 6 explored the hypoarousal model of AD/HD within girls. Girls, like boys, with AD/HD are hypoaroused. However, a novel positive relationship between SCL and absolute alpha activity contrasts with a previously defined negative relationship between these factors. It is possible that anxiety has influenced this SCL-alpha correlation as elevated ratings of anxiety are noted among girls with AD/HD (Gershon, 2002; Quinn, 2005). It would be helpful to define the role of anxiety on arousal and EEG measures within this population.

The exploratory correlations between AD/HD symptoms, comorbid behaviours and physiology implied connections between anxiety, depression and the EEG activity of girls with AD/HD. It is important to replicate these relationships and explore the nature of these EEG-behaviour correlations within female AD/HD populations.

8.4 Conclusion

The aims of this thesis were to explore and define the resting EEG activity of females with AD/HD. The results from the experimental chapters have shown that the existing male-dominated EEG literature is not directly transferable to females with the

disorder, and single-sex subject and control groups must become standard practice for research within this area. If mixed-sex subject groups are to be used, sex should be included as a statistical variable to account for sex differences.

Although the results from these chapters were unexpected, based on the literature with boys and mixed-sex groups, they are consistent. Across the experimental studies, girls and women with AD/HD have reliably produced EEG profiles that differ from profiles based on males and mixed-sex subject groups. Specifically, Chapters 3, 4, and 5 found that girls with the Combined and Inattentive types of AD/HD have relatively homogenous EEG profiles, whereas global EEG differences have been found previously in boys and mixed-sex groups. Chapter 6 found that although girls with AD/HD are hypoaroused, a positive relationship between absolute alpha and SCL complicates the concept of a straightforward deficit of arousal levels within this disorder. Lastly, Chapter 7 found that the EEG profile of adult females with AD/HD is largely indistinct from women without AD/HD. There were also significant sex differences between males and females, with and without AD/HD. These sex differences were found in relative theta and the theta/beta ratio, both of which are the most commonly noted findings in the disorder.

The findings from this thesis demonstrate that a female-specific EEG research literature pool is needed. If baseline resting EEG profiles are uncharacteristic of the current literature, as found within this thesis, then it is likely that these sex differences carry over to other areas of EEG such as eyes-open EEG, event-related potentials (ERPs), and coherence, and possibly beyond AD/HD to other disorders with an high male prevalence rate (i.e., Oppositional defiant disorder, Conduct disorder, Asperger's Syndrome, Autism, etc.).

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