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EEG coherence in girls with Attention-Deficit/Hyperactivity Disorder: Stimulant effects in good responders

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ABSTRACT

This study investigated the effects of stimulants on EEG coherence in girls with Attention-Deficit/Hyperactivity Disorder (AD/HD). Twenty girls with AD/HD (aged 7–12) and 20 age- and sex-matched controls had an eyes-closed resting electroencephalogram (EEG) recorded from 21 electrode sites. Coherence was calculated from eight intrahemispheric electrode pairs (four in each hemisphere), and eight interhemispheric electrode pairs, for the delta, theta, alpha and beta frequency bands. AD/HD participants were tested twice: first, prior to medication being prescribed, and second, six months later on a therapeutic dose of a stimulant. With intrahemispheric coherences at short-medium inter-electrode distances, AD/HD girls off-medication had reduced lateralisation in the delta, theta and alpha bands. They also had reduced lateralisation in the theta band for longer inter-electrode distances, and increased frontal interhemispheric coherences in all frequency bands. Medication had no impact on the laterality anomalies, but produced novel increases in intrahemispheric coherences at short-medium inter-electrode distances, which reached significance in the delta band and approached significance in the alpha band. However, these increased coherences remained indistinguishable from control levels. Reduced hemispheric lateralisations found in these AD/HD participants illustrate cortical abnormalities consistent with maturational lag explanations. The widespread elevated frontal interhemispheric coherences found in these AD/HD girls could reflect the narrow profile of female medication responders identified in clinical settings. The lack of substantial coherence medication effects in good clinical responders supports a previous medication study with AD/HD boys, and suggests that these coherence anomalies reflect structural, rather than solely functional, differences in brain development in AD/HD.

1. Introduction

Attention-Deficit/Hyperactivity Disorder (AD/HD) is a debilitating and persistent childhood condition, characterised by symptoms of inattention, hyperactivity and impulsivity and affects between 4% and 6% of school-aged children (American Psychiatric Association, 1994; Pelham et al., 1992). Without appropriate treatment, AD/HD can interrupt normal childhood development and functioning, and often persists into adulthood (Barkley, 1997b; Mannuzza et al., 1993).

Prevalence rates indicate that AD/HD is more common in boys than girls (American Psychiatric Association, 1994; James and Taylor, 1990; Pelham et al., 1992; Sawyer et al., 2001; Volkow and Swanson, 2003). Clinical samples have reported ratios of boys to girls as high as 9:1, while epidemiological studies have found 4:1 ratios (American Psychiatric Association, 1994; Gaub and Carlson, 1997). The high prevalence in boys has resulted in AD/HD research predominantly focusing on males. However, the literature developed from this research cannot always directly transfer to females with the same disorder. Compared to boys, girls with AD/HD are more likely to show symptoms of inattention, hyper-talkativeness and high emotional reactivity, rather than physical hyperactivity (Gaub and Carlson, 1997; Quinn, 2005). As hyper-talkativeness and emotional reactivity (symptoms often found in girls) are not currently listed in the DSM-IV diagnostic criteria (American Psychiatric Association, 1994), girls who display these behaviours may not be identified or referred for treatment. This may help explain the ratio discrepancies between clinical and epidemiological prevalence estimates (Gaub and Carlson, 1997; Quinn, 2005). For this reason, it is important for AD/HD research to investigate girls and boys separately.

1.1. Coherence

Electroencephalogram (EEG) coherence measures the similarity in cortical electrical activity between two electrode sites (Lubar et al., 1999) and has been conceptualised as the correlation in the time domain between two signals in a given frequency band (Shaw, 1981). Coherence provides information about the degree of connectivity between structures underlying a pair of recording electrodes (Clarke

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et al., 2005). High coherence between any two EEG signals is interpreted as indicating strong structural or functional connection between cortical areas (Fein et al., 1988).

Normal cortical development involves periods of cell proliferation and pruning, proposed to result in systematic (but not necessarily linear) fluctuations in EEG coherence (Barry et al., 2004; Thatcher et al., 1987). Thatcher's two-compartment coherence model proposed that short and long neuronal fibres contribute differently to coherence as a function of inter-electrode distance. Long-distance coherence increases with development of long axonal connections; in contrast, coherence at shorter inter-electrode distances decreases with development due to increases in complexity and competition of interactions within cell populations (Thatcher et al., 1986). There has been substantial support for this model's relevance in children with AD/HD (Barry et al., 2002, 2004, 2005, 2006; Clarke et al., 2005, 2007b).

Barry et al. (2004, 2005, 2006) investigated developmental trends in normal and AD/HD children (aged 8–12) to help develop age- and sex-related coherence norms, and found that cortical coherences develop in a systematic non-linear pattern with age, broadly supporting Thatcher's coherence model. Barry et al. (2004) found significant hemispheric lateralisation over short-medium inter-electrode distances in all frequency bands, which suggest hemispheric differentiation with increasing age. Children also had increased coherences over long inter-electrode distances in all frequency bands, except beta (Barry et al., 2004). This was suggested to indicate long axonal connection development with increasing age, consistent with Thatcher's model (Barry et al., 2004; Thatcher et al., 1986). Girls appeared to have a general lag in development of cortico-cortical connections, compared with aged-matched males, illustrating characteristic coherence development differences between sexes (Barry et al., 2004).

Developmental or maturational lag is represented by cortical activity similar to that of a normal younger child. Elevated delta and theta power, with reduced alpha and beta activity, has been found to be characteristic of normal young children in power studies (Clarke et al., 1998). Children with AD/HD have been found to have increased theta and decreased in alpha power, suggesting a maturational lag (Clarke et al., 1998, 2001b, 2001c). Reduced hemispheric lateralisation or specialisation has also been implicated in developmental lags. As cortico-cortical connections refine and develop, the cortical hemispheres become more specialised. A developmental lag is evident if hemispheric differentiation is similar to that of a younger normal child, indicating a delay in specialisation.

1.2. Intrahemispheric coherence

In relation to AD/HD populations, Montagu (1975) found that hyperkinetic children had significantly higher intrahemispheric coherences compared to normal controls. Chabot et al. (1996) and Chabot and Serfontein (1996) found that intrahemispheric coherences were much higher in the frontal and central cortical regions of children with attention disorders. Barry et al. (2002) found that boys and girls with AD/HD had elevated short-medium intrahemispheric coherences in the delta, theta and alpha bands, which indicated reduced cortical specialisation of short axonal connections in AD/HD. The children with AD/HD also had reduced longer intrahemispheric coherences in the alpha band, suggested as due to less-developed long axonal connections (Barry et al., 2002; Thatcher et al., 1986). Barry et al. (2005) investigated coherence development in boys with and without AD/HD, and found that boys with AD/HD (aged 8–12 years) did not display the same coherence development pattern as normal control boys. The boys with AD/HD showed evidence of smaller left-hemisphere elevations in short-distance coherences and greater elevations in some longer distance coherences, which Barry et al. (2005) suggested was due to a developmental lag.

1.3. Interhemispheric coherence

Chabot et al. (1996) and Chabot and Serfontein (1996) found that between-hemispheric (interhemispheric) coherences were much higher in the frontal and central cortical regions of children with attention disorders. Barry et al. (2002) found that interhemispheric coherences in the frontal regions were greater in children with AD/HD within delta and theta activity, and lower within beta, indicating frontal deficiencies in cortical specialisation in delta, theta and beta band activity. The boys' coherence development study found that boys with AD/HD showed atypical development frontally and in the temporal regions — indicating that boys with AD/HD have some abnormal cortico-cortical connectivity (Barry et al., 2005).

The female counter-part of Barry et al.'s, (2005) study is the only published female AD/HD coherence study to date, and it found coherence anomalies considerably different to those reported in boys with AD/HD. Barry et al. (2006) found that 80 girls with AD/HD (age 8–12) had elevations in interhemispheric coherences in frontal and temporal regions, which the authors suggested were due to abnormal cortico-cortical connectivity in girls with AD/HD. The girls with AD/HD also had enhanced laterality in delta and theta bands for short-medium intrahemispheric coherences, which suggested a maturational lag in cortical development. The complex age and sex effects reported by Barry et al. (2004, 2005, 2006) illustrate the importance of comparing children with AD/HD separately with age- and sex-matched controls to avoid unnecessary variability within participant populations.

1.4. Medication effects on coherence

For over 50 years stimulant medications such as methylphenidate (MPH) and dexamphetamine have been the most commonly-used treatment for AD/HD in Australia and North America (Barkley, 1990; Clarke et al., 2002; Erk, 2004). These medications are reported to improve behavioural, academic and social functioning in 50 to 90% of children treated (Lubar et al., 1999). Other clinical and empirical studies have found that 80% of patients prescribed these psycho-stimulants showed significant improvements in their core AD/HD symptoms (Clarke et al., 2002; Swanson et al., 1993; Wilens and Biederman, 1992).

Clarke et al. (2005) was the first study to specifically examine the effects of stimulant medication on EEG coherence in boys with AD/HD. Although the data confirmed characteristic abnormal coherences in AD/HD, the study failed to find any significant coherence changes attributable to medication. This led Clarke et al. (2005) to suggest that resting-state coherence indicates structural rather than functional aspects of brain dysfunction. From that perspective, the absence of stimulant effects in coherence, in the context of known normalisation of symptoms and EEG power measures, implies that the coherence anomalies reported in AD/HD reflect differences in brain *structure*. This is compatible with the fact that stimulant medication does not cure AD/HD, but rather provides a temporary amelioration of symptoms which remains only while medication continues (Swanson et al., 1993).

1.5. Hypotheses

This study investigated the effects of stimulant medication on intrahemispheric and interhemispheric coherences in AD/HD girls, in order to establish the generality of conclusions from Clarke et al. (2005), and illuminate brain functioning in girls with AD/HD.

2. Materials and methods

2.1. Participants

Twenty girls diagnosed with AD/HD Combined type or AD/HD Predominantly Inattentive type, according to the DSM-IV criteria (American Psychiatric Association, 1994), were selected from new