

EEG coherence and symptom profiles of children with Attention-Deficit/Hyperactivity Disorder

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HIGHLIGHTS

- Smaller left-lateralized coherences in AD/HD were negatively correlated with inattention.
- A smaller frontal interhemispheric coherence correlated negatively with hyperactivity/impulsivity.
- Negative correlations suggest that anomalies reflect compensatory brain function.

ABSTRACT

Objective: We compared EEG coherence in children with and without AD/HD, and sought to relate observed anomalies to AD/HD symptoms.

Methods: Forty children with AD/HD and 40 age- and sex-matched controls had eyes-closed resting EEG coherence calculated for eight interhemispheric electrode pairs and eight intrahemispheric pairs (four within each hemisphere) in the delta, theta, alpha, beta and “40 Hz” gamma bands.

Results: At short-medium inter-electrode distances, the AD/HD group had increased intrahemispheric coherence in delta and theta, and reduced (L > R) laterality in delta, alpha, beta and gamma. Over longer inter-electrode distances, the AD/HD group had reduced intrahemispheric coherence in alpha. In inter-hemispheric comparisons, the AD/HD group had reduced frontal coherence in delta, alpha and gamma, increased temporal theta and reduced temporal alpha coherences, and increased central/parietal/occipital coherence in theta. Smaller left-lateralized coherences in AD/HD correlated negatively with DSM Inattentive and DSM Total scores, and smaller frontal interhemispheric coherence in alpha correlated negatively with DSM Hyperactive/Impulsive score.

Conclusions: The negative correlations between AD/HD coherence anomalies and symptoms suggest that several anomalies reflect compensatory brain function.

Significance: Coherence differences in AD/HD may reflect anomalous frontal right-hemisphere linkages that help compensate functional brain anomalies in the left frontal regions in this disorder.

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1. Introduction

Attention-Deficit/Hyperactivity Disorder (AD/HD), a debilitating and persistent childhood developmental condition, is characterised by inappropriate symptoms of inattention, hyperactivity and impulsivity (American Psychiatric Association (APA), 1994; Pelham et al., 1992). This disorder can interrupt normal childhood development and functioning, and will often persist into adolescence and adulthood (Mannuzza et al., 1993). Prevalence studies have estimated that AD/HD affects around 3–5% of school children, making it one of the most common childhood conditions (APA, 1994; Cantwell, 1996).

Electroencephalogram (EEG) coherence measures similarities in electrical cortical activity between 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. High coherence between two EEG signals has been interpreted as reflecting a strong structural or functional connection between the underlying cortical regions (Fein et al., 1988), although Thatcher's two-process model of coherence (Thatcher et al., 1986) distinguishes short-medium range coherences as being reduced by competition within small local neural networks.

Previous EEG coherence studies typically report that children with AD/HD (including ADD and hyperkinesia) have increased intrahemispheric coherences (Montagu, 1975), particularly fron-

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tally and centrally (Chabot et al., 1996; Chabot and Serfontein, 1996). At short-medium inter-electrode distances in typical predominantly-male AD/HD samples, this elevation has been reported in the delta band, but is more evident in the theta and beta bands (Barry et al., 2002, 2005; Clarke et al., 2005, 2007). Values at short-medium inter-electrode distances are elevated in the left hemisphere in control children (Barry et al., 2002, 2004, 2005, 2006, 2007, 2009a,b; Clarke et al., 2005, 2007, 2009; Dupuy et al., 2008, in press) and this left-lateralization is generally reduced in typical AD/HD children, particularly in the theta and alpha bands (Barry et al., 2002, 2005; Clarke et al., 2005, 2007). At longer inter-electrode distances, intrahemispheric coherence has sometimes been reported reduced in AD/HD in the theta and alpha bands. Typical children with AD/HD have increased frontal inter-hemispheric coherence in the delta and theta bands (Barry et al., 2002, 2005; Clarke et al., 2005, 2007). Within the temporal region, such children have reduced interhemispheric alpha coherence (Barry et al., 2002, 2005; Clarke et al., 2005), and, in the central/parietal/occipital regions, elevated interhemispheric theta coherence (Barry et al., 2002; Clarke et al., 2005). This overall pattern is less apparent in females with AD/HD (Barry et al., 2006; Dupuy et al., 2008), and those children with comorbid behavioural or reading disorders (Barry et al., 2007, 2009b), and is not apparent in adults with AD/HD (Clarke et al., 2008). There has been little attempt to explain the frequency differences in the coherences anomalies noted above. A recent attempt to relate functional aspects of neural integration to different frequencies proposed that higher frequencies are involved in short-range integration, while lower frequencies are involved with longer-range integration (von Stein and Sarnthein, 2000). These authors related the different types of integration to brain functioning in different cognitive and perceptual tasks. This could provide a useful integrative perspective, but the proposal has not been explored in the AD/HD context.

Our previous work mentioned above used only the delta, theta, alpha, and beta frequency bands. The gamma band is found between approximately 30 and 80 Hz, with low amplitude, and is thought to reflect mental activity (Andreassi, 2000; Kakizaki, 1990). Recent EEG research has seen an increased focus on gamma activity and its association with cognitive functioning (Engel et al., 1992). Although most published studies on the gamma band focus on cognitive processing in response to specific tasks (e.g., DePascalis and Ray, 1998), Njokiktjen et al. (2001) examined intrahemispheric gamma coherence in a resting condition in children with nonverbal (NLD) versus verbal learning disabilities (VLD). The study found relative reductions in long distance gamma band coherence in the right hemisphere of children with NLD. While there are a few studies reporting gamma activity in AD/HD (e.g., Barry et al., 2009a, 2010; Yordanova et al., 2001), we are not aware of any studies on gamma coherence in an eyes-closed resting state in children with this condition. Hence the aim of this study was to investigate the nature of resting state EEG coherence differences in gamma in children with and without AD/HD. To place the study within the previous literature on coherence in AD/HD, we also assessed coherence in the four standard lower frequency bands. Finally, we aimed to relate any observed AD/HD coherence differences from controls to the major symptom profiles of the disorder, in terms of scores on the DSM Inattention, DSM Hyperactive-Impulsive, and DSM Total scales of Conners (1997).

2. Material & methods

2.1. Participants

Participants included 40 children who met DSM-IV (APA, 1994) criteria for AD/HD (25 with the Combined type and 15 with the

Inattentive type) and 40 aged- and sex-matched controls. All 80 participants were aged from 8 to 13 years ($M = 10.08$ years, $SD = 1.30$) and each group was made up of 29 males and 11 females. Both the AD/HD and control participants had a full scale WISC-III (Wechsler, 1992) IQ score of 85 or higher. The EEG power data from these subjects were reported in Barry et al. (2010).

The AD/HD participants were selected from new patients presenting at a Sydney-based paediatric practice for an AD/HD assessment. They had not been diagnosed with the disorder previously, had no history of medication use for the disorder, and were tested before being prescribed any medication. Inclusion in the AD/HD group was based on clinical assessments made by a paediatrician and a psychologist and required their agreement on diagnosis. Clinical interviews were used to assess the child and incorporated information from as many sources as were available. These included history given by a parent/guardian, school reports from the previous 12 months, scores on the Conners' Parent Rating Scale – Revised (L) (Conners, 1997), reports from other health professionals, and behavioural observations during the assessment. Children were excluded from the AD/HD group if they had a history of a problematic prenatal, perinatal or neonatal period, a head injury resulting in a loss of consciousness, CNS disorders with seizures or loss of consciousness, a paroxysmal headache or tics.

The control children were recruited from local school and community groups. Inclusion criteria for the control group were based on interviews with parent(s)/guardian(s), using the same procedure as the AD/HD participants, described above. Control children 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 other psychiatric condition described in the DSM-IV. Participants displayed no deviation from normal physical development. Finally, if any participant (AD/HD or control) displayed spike wave EEG activity, they were not included in the study.

2.2. Procedure

The parent/guardian of all participants gave their informed consent prior to the release of any clinical records or testing, and each child assented to participate in the study. Ethics approval for this study was obtained from the combined Illawarra Area Health/University of Wollongong Human Research Ethics Committee. All AD/HD participants were assessed and received standard medical care at the paediatric practice of RM and MS.

All participants were tested in a single session lasting approximately 2.5 h. Participants were first assessed by a paediatrician (physical examination and clinical history). Then participants had a psychometric assessment followed by an EEG assessment. After approx. 2 h, the EEG was recorded for five minutes during an eyes-closed resting condition, with participants seated on a reclining chair with dimmed lighting. Recording was interrupted by a rest period if there were any signs of fatigue, boredom, or restlessness. Electrode placement followed the international 10–20 system, using an electrode cap. A single electro-oculogram (EOG) electrode beside the right eye was referenced to Fpz, with a ground lead on the left cheek. Physically-linked ears were used as a reference, and impedance levels were less than 5 k Ω . Care was taken to match ear impedances. The EEG was recorded using a Lexicor NRS-24 with a sampling rate of 256 Hz. The sensitivity was set at 150 μ V/cm, a low frequency filter was set at 0.5 Hz, a high frequency filter was set at 70 Hz, with a notch filter at 50 Hz. Data were stored electronically for off-line analysis. The Lexicor data

were converted to allow analysis using Neuroscan software version 4.3.

The data were segmented into 2 s epochs. An experienced technician visually appraised every epoch to remove artefact. The EOG rejection was set at 50 μ V. Accepted epochs were baselined and their Fast Fourier Transforms (FFTs) were averaged in five selected frequency bands: Delta (1.5–3.5 Hz), Theta (4–7.5 Hz), Alpha (8–13 Hz), Beta (13.5–25 Hz) and Gamma (35–45 Hz). We used these classic fixed frequency ranges for the lower bands, rather than individually-defined ranges (Klimesch, 1999), to allow our data to be compared with existing coherence data in the AD/HD field, which has used only the stated ranges. The 30–80 Hz gamma range includes the usual mains frequency of 50 or 60 Hz, commonly removed in EEG recording by a notch filter at that frequency, and this needs to be considered in choosing a practical frequency range. A gamma peak around 40 Hz has been found to be dominant throughout childhood (Takano and Ogawa, 1998), and hence we defined our “40 Hz” gamma band using a bandwidth of 35–45 Hz, avoiding mains-frequency problems.

Coherence between an electrode pair for a particular frequency band was defined at the cross-spectral power between the sites normalised by dividing by the square root of the product of the power at each site within that band, following John et al. (1987). Coherence estimates were derived for each band for eight intrahemispheric (F3-O1, F4-O2, Fp1-F3, Fp2-F4, T3-T5, T4-T6, C3-P3, C4-P4) and eight interhemispheric (Fp1-Fp2, F7-F8, F3-F4, C3-C4, T3-T4, T5-T6, P3-P4, O1-O2) electrode pairs, in order to match data from our previous coherence studies in AD/HD.

2.3. Statistical analysis

Prior to any statistical analysis, in order to normalise the distributions, all coherence values were Fisher's z-transformed, and means were inverse-transformed for reporting. Following our previous work in this area, the 16 sets of coherence pairs were grouped for analysis into regions of interest – 2 for intrahemispheric coherences (either shorter or longer inter-electrode distances), and 3 for interhemispheric coherences (in different cortical regions). For each region of interest, an analysis of variance was used to examine the effects of group in each frequency band.

For intrahemispheric coherences, the means within the two hemispheres were compared in each band for (i) short-medium inter-electrode distances (left: Fp1-F3, T3-T5, C3-P3 versus right: Fp2-F4, T4-T6, C4-P4) and (ii) long inter-electrode distances (left: F3-O1 versus right: F4-O2); laterality was also examined within these analyses. The interhemispheric coherences were separately examined in the (iii) frontal (Fp1-Fp2, F7-F8, F3-F4), (iv) temporal (T3-T4, T5-T6), and (v) central/parietal/occipital (C3-C4, P3-P4, O1-O2) cortical regions. For these last three regional analyses, no within-region contrasts were examined. As all these within-subject orthogonal contrasts are planned, and there are no more of them than the degrees of freedom for effect (available $df = N - 1$, where N is the number of dependent variables in the analysis), no Bonferroni-type adjustment to alpha is required (Tabachnick and Fidell, 1989). All reported F values have (1, 78) degrees of freedom.

Pearson correlations were examined in the patient group for each significant between-group coherence effect with IQ and Conners' scores on the DSM Inattentive, DSM Hyperactive-Impulsive, and DSM Total scales. These analyses were treated as exploratory, and alpha was not adjusted for multiple tests.

3. Results

The groups did not differ significantly on mean age (controls: 10.2 years, c.f. AD/HD: 10.0 years; $F < 1$). Mean IQ was significantly

lower in the AD/HD group (95.7) than controls (105.6: $F = 16.63$, $p < .001$). Table 1 shows a summary of obtained effects.

3.1. Intrahemispheric coherences

At short-medium inter-electrode distances, the AD/HD group, compared with controls, had increased intrahemispheric coherence in the delta ($F = 5.29$, $p < .05$) and theta ($F = 8.69$, $p < .005$) bands (see Fig. 1A and “AD/HD vs. Control” row in Table 1 part (i)). In general, while controls showed greater coherence in the left hemisphere, the AD/HD group had significantly reduced left-lateralization in the delta ($F = 8.23$, $p < .005$), alpha ($F = 19.14$, $p < .001$), beta ($F = 11.83$, $p < .001$), and gamma bands ($F = 6.14$, $p < .05$); see “L > R \times AD/HD vs. Control” row in Table 1 part (i). Across groups, this resulted in significantly higher coherence in the left compared with the right hemisphere in the delta ($F = 210.08$, $p < .001$) and alpha ($F = 709.41$, $p < .001$) bands, and higher coherence in the right compared with the left hemisphere in the theta ($F = 405.68$, $p < .001$), beta ($F = 221.45$, $p < .001$), and gamma ($F = 46.70$, $p < .001$) bands; see “Left vs. Right” row in Table 1 part (i).

At longer inter-electrode distances, across groups, there was somewhat higher coherence in the left compared with the right hemisphere in theta ($F = 3.78$, $p = .055$). The AD/HD group had reduced intrahemispheric coherence in the alpha band compared with controls ($F = 4.41$, $p < .05$) (see Fig. 1B).

3.2. Interhemispheric coherences

As shown in Fig. 1C, the AD/HD group had reduced frontal interhemispheric coherence in the delta ($F = 9.45$, $p < .005$), alpha ($F = 8.04$, $p < .01$), and gamma ($F = 5.79$, $p < .05$) bands. In the temporal region; the AD/HD group had increased coherence in the theta band ($F = 6.66$, $p < .05$), and reduced coherence in the alpha band ($F = 8.04$, $p < .01$; see Fig. 1D). As shown in Fig. 1E, the AD/HD group had increased theta coherence in the central/parietal/occipital regions ($F = 10.42$, $p < .005$).

3.3. Correlations between coherence effects and patient characteristics

None of the significant AD/HD effects correlated with IQ in the AD/HD group. The reduced left-lateralization of short-range coherence was correlated with Conner's DSM Inattentive score and DSM Total score for delta ($r = -.415$, $p < .01$ and $r = -.371$, $p < .05$ respectively), alpha ($r = -.398$, $p < .05$ and $r = -.424$, $p < .01$ respectively), beta ($r = -.446$, $p < .01$ and $r = -.390$, $p < .05$ respectively), and gamma ($r = -.387$, $p < .05$ and $r = -.442$, $p < .01$ respectively). Note the negative sign of all these correlations. Interhemispheric frontal alpha coherence level was correlated positively with Conner's DSM Hyperactive/Impulsive score ($r = .363$, $p < .05$).

4. Discussion

The AD/HD group had a significantly-lower mean IQ level than the controls. Our previous work (Clarke et al., 2001, 2006, 2008) demonstrated that IQ differences do not contribute to observed group EEG coherence differences. This was confirmed here by the absence of any significant correlations within the AD/HD group between the observed AD/HD coherence effects and IQ. Thus in this study we can relate observed EEG coherence differences between the groups solely to the existence or otherwise of AD/HD.

Before turning to a detailed consideration of the AD/HD coherence anomalies, it is useful to consider some of the possible confounds involved here. Foremost with any study of gamma is the possible intrusion of muscle artefact into the gamma frequency range. This is most likely to occur at frontal and temporal sites,

Table 1
Summary of obtained coherence effects.

Effect	Frequency Band				
	Delta	Theta	Alpha	Beta	Gamma
<i>Intrahemispheric Coherences</i>					
<i>(i) Short-Medium</i>					
Left vs. Right	L > R****	L < R****	L > R****	L < R****	L < R****
AD/HD vs. Control	AD/HD↑*	AD/HD↑**			
L > R × AD/HD vs. Control	AD/HD↓****		AD/HD↓****	AD/HD↓****	AD/HD↓*
<i>(ii) Long</i>					
Left vs. Right		L > R ⁰⁵⁵			
AD/HD vs. Control			AD/HD↓*		
L > R × AD/HD vs. Control					
<i>Interhemispheric Coherences</i>					
<i>(iii) Frontal</i>					
AD/HD vs. Control	AD/HD↓**		AD/HD↓**		AD/HD↓*
<i>(iv) Temporal</i>					
AD/HD vs. Control		AD/HD↑*	AD/HD↓*		
<i>(v) Central/Parietal/Occipital</i>					
AD/HD vs. Control		AD/HD↑**			

↑ = Significantly increased; ↓ = significantly reduced; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.005$, **** $p < 0.001$; near-significant probabilities are also indicated.

and could lead to enhanced coherences between electrode pairs in these regions. The short-range intrahemispheric comparison covers both frontal and temporal pairs (plus a central-parietal pair) in each hemisphere. Fig. 1A indicates that there is no enhancement of gamma compared with beta coherence in these electrode pairs. Little gamma enhancement is apparent with the interhemispheric frontal data in Fig. 1C, but there is some elevation in the temporal region (1D); this is of little difference from the gamma enhancement shown in the central/parietal/occipital region (1E). These data thus argue against substantial muscle involvement in the gamma data reported here. On another point, we mentioned in Section 2.2 that we used the traditional fixed frequency ranges rather than individual alpha-defined ranges. Replication of this study with individually-defined bandwidths would yield results different to these, but the relationship between the two sets is unspecifiable at our present level of knowledge.

Similar to reports from our previous work, the present AD/HD group had increased short-medium intrahemispheric coherence in the delta and theta bands, and lower alpha coherence in long-distance intrahemispheric coherences. We have previously noted in several studies, following Thatcher's two-process model of coherence (Thatcher et al., 1986), that increased short-medium and decreased longer range coherences are both compatible with reduced cortical differentiation and maturity. The same interpretation can apply here, suggesting that the AD/HD group shows widespread signs of cortical immaturity.

Reduced left-lateralization in intrahemispheric coherences at shorter inter-electrode distances was also expected, and our results indicated that the AD/HD group had significantly reduced left-lateralization in the delta, alpha, beta, and gamma bands. We have previously interpreted this as suggesting that children with AD/HD have less hemispheric specialization than their age- and gender-matched controls; we will return to this point later.

The present AD/HD group also had reduced frontal interhemispheric coherences in the delta, alpha and gamma bands. While the alpha reduction was previously noted by Barry et al. (2005), the delta reduction is contrary to the usual increase reported from typical AD/HD groups (e.g., Barry et al., 2002; Clarke et al., 2005). This may reflect the relatively large proportion of females used here, and/or the inclusion of children with comorbid behavioural or reading disorders (see Section 1); this requires further research to resolve. This study found one interesting new result within the "40 Hz" gamma band: compared with controls, the AD/HD group had reduced frontal interhemispheric coherence. Although their

study lacked normal controls, Njokiktjen et al. (2001) found reduced frontal interhemispheric gamma coherences in children with NLD compared to children with VLD. Njokiktjen and colleagues thought the frontal coherence decrease reflected a defective interhemispheric interaction between cortical regions in NLD. It can be assumed that coherence in different frequency bands reflects different neuronal networks and neuronal processing, which can be involved in cortico-cortical and thalamo-cortical circuits (Wang, 2010). The present frontal results across the bands suggest broad interhemispheric disconnection in the frontal regions, and the gamma reduction suggests that these may be linked to cognitive processes associated with learning or language function. Temporal coherences were increased in theta but reduced in alpha, and central/parietal/occipital coherences were increased in theta, all in line with our previous studies of typical AD/HD samples. These have been considered previously to reflect widespread deficits in hemispheric specialization (e.g., Barry et al., 2002). Previous and current findings demonstrate increased as well as decreased coherence in AD/HD patients, indicating alterations in functional connectivity between brain regions. In line with these observations, a recent fMRI study demonstrated atypical default network connectivity in AD/HD patients, indicating both greater and lesser functional connectivity (Fair et al., in press). In addition to the well-characterized alterations in the frontal lobes, current structural and functional imaging studies attribute a key contribution of temporal lobe to abnormalities in AD/HD (Kobel et al., 2010).

A schematic summary of the present coherence results in the AD/HD brain is shown in Fig. 2. This allows some comparison with the proposal of von Stein and Sarnthein (2000) that different scales of cortical integration involve different frequencies. In their formulation, gamma underlies short-range integration, while lower frequencies are involved with longer-range integration. The intrahemispheric results, indicated on the left in Fig. 2, contradict this thesis, as short-range anomalies are apparent in lower frequencies than the long-range anomalies. In the interhemispheric coherence anomalies indicated on the right in Fig. 2, gamma is involved only in the frontal regions, which include the smallest inter-electrode distance (FP1-FP2). That comparison also included larger inter-electrode distances (F3-F4 and F7-F8), which are compatible with the lower-frequency anomalies obtained. However, the temporal comparison, which revealed an alpha anomaly, has no inter-electrode distance smaller than those in the central/occipital/parietal grouping, which generated only a theta anomaly. Thus the von

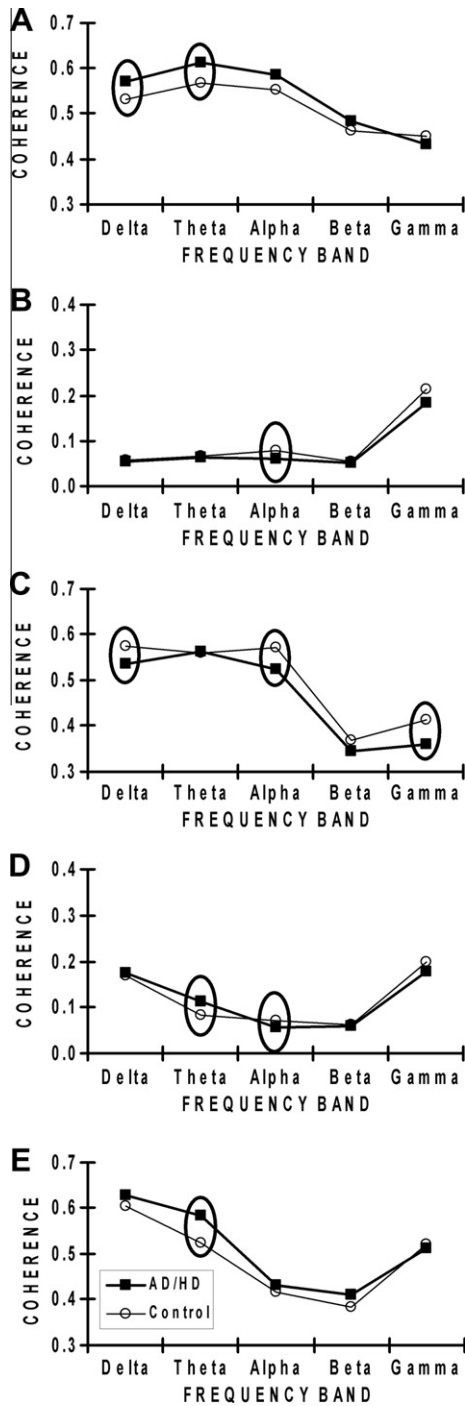


Fig. 1. Average coherences for the AD/HD and control groups, as a function of frequency band (delta, theta, alpha, beta and gamma). Data are shown for the five coherence groupings analysed here: intrahemispheric coherences at short (A), and long (B) inter-electrode distances, and interhemispheric coherences in the frontal (C), temporal (D), and central/parietal/occipital regions (E). Data pairs linked by ellipses are significantly different.

Stein and Sarnthein (2000) proposal does not offer much assistance in resolving the frequency distribution of the coherence anomalies in AD/HD. This question clearly needs further research.

Altered cortical EEG coherence in various neurological and psychiatric disorders has been reported. In the resting state, coherence has been found reduced in the theta band in schizophrenics (Uhlhaas and Singer, 2010), reduced in the alpha band in Alzheimer's disease patients (Rossini et al., 2007), and enhanced in theta, beta and gamma bands in parkinsonian patients

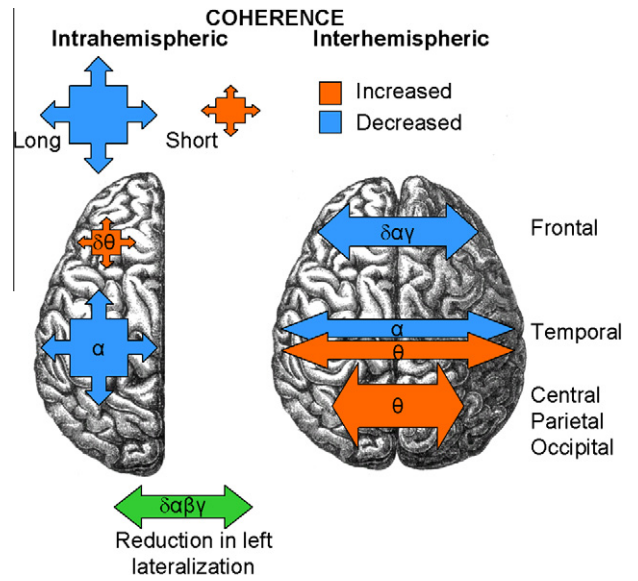


Fig. 2. Main alterations in EEG coherence in AD/HD brain.

(Moazami-Goudarzi et al., 2008). One of the most intriguing questions about these observations is how these alterations in neuronal network synchrony correlate with symptoms, and whether they contribute to the pathology of the disorder, or rather serve as compensatory mechanisms of the brain.

Exploratory correlations between the present significant coherence effects and AD/HD symptoms, as measured by the Conners' AD/HD scales, were most illuminating. Smaller left-lateralized coherences in AD/HD were correlated negatively with Conners' DSM Inattentive and DSM Total scores, and small frontal interhemispheric coherence in alpha was correlated negatively with Conners' DSM Hyperactive/Impulsive scores. That is, greater anomalies in reduced short-medium range intrahemispheric lateralization, and reduced frontal coherence, were both associated with lower symptom scores. In other words, greater coherence deviations from normality were associated with reduced symptoms, suggesting that these deficiencies are not the cause of the symptoms, but serve to reduce them.

In relation to the anomalous short-range lateralizations, increased AD/HD right-hemisphere dominance (compared with the left-hemisphere dominance in controls) was associated with reduced scores on Conners' DSM Inattentive and Total scales. This suggests that in children with AD/HD, the impact of a left-hemisphere deficit (associated with symptoms of inattention) may be functionally reduced by atypical right-hemisphere development of circuits involving short-medium range neuronal networks. These appear to utilise a broad range of frequencies, ranging from delta to gamma.

The only AD/HD coherence deficit associated with symptom levels on the Conners' Hyperactive/Impulsive scale was the reduced frontal interhemispheric coherence in the alpha band. In this case, lower levels of alpha coherence (greater deviation from controls) were associated with lower levels of hyperactivity/impulsivity in our AD/HD children. The direction of the correlation suggests that this coherence anomaly is associated with reduced impulsive/hyperactive symptoms in this sample. This finding was restricted to the alpha band, and frontal coherence reductions have not been reliably reported in previous studies – indeed, elevated coherences across a range of bands is more commonly noted. This suggests the need for caution in extrapolating this phenomenon beyond the present sample. Nevertheless, the link between anomalous coherences in the frontal lobes – the seat of inhibitory processing – and

impulsivity is intuitively appealing, and further work focussed on this area could be especially productive.

In summary, our sample of 40 typical AD/HD children, predominantly male with a mix of DSM-IV subtypes, showed broad reductions of left-lateralized coherences at short-medium inter-electrode distances, and a range of other coherence anomalies, that were relatively consistent with previous literature on the four lower EEG bands, and reduced left-lateralization and frontal inter-hemispheric coherences in gamma. Correlations observed between AD/HD symptoms and these coherence anomalies were opposite in direction to simple expectations, suggesting that several coherence anomalies may be associated with compensatory normalising brain function rather than AD/HD deficits. This was the first study to examine resting EEG coherence within the “40 Hz” gamma band in children with AD/HD, and the first to systematically relate observed coherence anomalies to symptom profiles. The findings suggest that coherence differences in this AD/HD sample may reflect anomalous frontal right-hemisphere linkages that help overcome functional brain anomalies in the left frontal regions in this disorder. The generalizability of these findings to other AD/HD samples is worth exploring in future research.

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References

- American Psychiatric Association (APA), editor. Diagnostic, statistical manual of mental disorders. Washington, DC: American Psychiatric Association; 1994. fourth edition. DSM-IV.
- Andreassi JL. Psychophysiology; human behavior & physiological response. Mahwah, NJ: Lawrence Erlbaum Associates; 2000. fourth edition.
- Barry RJ, Clarke AR, Hajos M, McCarthy R, Selikowitz M, Dupuy FE. Resting state EEG gamma activity in children with Attention-Deficit/Hyperactivity Disorder. *Clin Neurophysiol* 2010;121:1871–7.
- Barry RJ, Clarke AR, Hajos M, McCarthy R, Selikowitz M, Bruggemann JM. Acute atomoxetine effects on the EEG of children with Attention-Deficit/Hyperactivity Disorder. *Neuropharmacology* 2009a;57:702–7.
- Barry RJ, Clarke AR, McCarthy R, Selikowitz M. EEG coherence in children with Attention-Deficit/Hyperactivity Disorder and comorbid reading disabilities. *Int J Psychophysiol* 2009b;71:205–10.
- Barry RJ, Clarke AR, McCarthy R, Selikowitz M. EEG coherence in children with Attention-Deficit/Hyperactivity Disorder and comorbid oppositional defiant disorder. *Clin Neurophysiol* 2007;118:356–62.
- Barry RJ, Clarke AR, McCarthy R, Selikowitz M. Age and gender effects in EEG coherence. III. Girls with Attention-Deficit/Hyperactivity Disorder. *Clin Neurophysiol* 2006;117:243–51.
- Barry RJ, Clarke AR, McCarthy R, Selikowitz M, Johnstone SJ, Hsu C, Bond D, Wallace M, Magee C. Age and gender effects in EEG coherence. II. Boys with Attention-Deficit/Hyperactivity Disorder. *Clin Neurophysiol* 2005;116:977–84.
- Barry RJ, Clarke AR, McCarthy R, Selikowitz M, Johnstone SJ, Rushby JA. Age and gender effects in EEG coherence. I. Developmental trends in normal children. *Clin Neurophysiol* 2004;115:2252–8.
- Barry RJ, Clarke AR, McCarthy R, Selikowitz M. EEG coherence in Attention-Deficit/Hyperactivity Disorder: a comparative study of two DSM-IV subtypes. *Clin Neurophysiol* 2002;113:579–85.
- Cantwell D. Attention deficit disorder; a review of the past 10 years. *J Am Acad Child Adolesc Psychiatr* 1996;35:978–87.
- Chabot R, Merkin H, Wood L, Davenport T, Serfontein G. Sensitivity and specificity of QEEG with attention deficit or specific developmental learning disorders. *Clin Electroencephalogr* 1996;27:26–34.
- Chabot R, Serfontein G. Quantitative electroencephalographic profiles of children with attention deficit disorder. *Biol Psychiatry* 1996;40:951–63.
- Clarke AR, Barry RJ, Dupuy FE, McCarthy R, Selikowitz M, Heaven PCL. Childhood EEG coherence as a predictor of adult Attention-Deficit/Hyperactivity Disorder. *Acta Neuropsychol* 2009;7:182–92.
- Clarke AR, Barry RJ, McCarthy R, Selikowitz M. Age and sex effects in the EEG: differences in two subtypes of Attention-Deficit/Hyperactivity Disorder. *Clin Neurophysiol* 2001;112:806–14.
- Clarke AR, Barry RJ, McCarthy R, Selikowitz M, Johnstone SJ. The effects of imipramine hydrochloride on the EEG of children with Attention-Deficit/Hyperactivity Disorder. *Int J Psychophysiol* 2008;68:186–92.
- Clarke AR, Barry RJ, McCarthy R, Selikowitz M, Johnstone SJ, Hsu C, Magee C, Lawrence C, Croft R. Coherence in children with Attention-Deficit/Hyperactivity Disorder and excess beta activity in their EEG. *Clin Neurophysiol* 2007;118:1472–9.
- Clarke AR, Barry RJ, McCarthy R, Selikowitz M, Johnstone S, Abbott I, Croft R, Magee C, Hsu C, Lawrence C. Effects of methylphenidate on EEG coherence in Attention-Deficit/Hyperactivity Disorder. *Int J Psychophysiol* 2005;58:4–11.
- Clarke AR, Barry RJ, McCarthy R, Selikowitz M, Magee C, Johnstone SJ, Croft R. The EEG in low IQ children with Attention Deficit Hyperactivity Disorder. *Clin Neurophysiol* 2006;117:1708–14.
- Conners KC. Conners' Rating Scales – Revised. New York: Multi-Health Systems Inc.; 1997.
- DePascalis V, Ray WJ. Effects of memory load on event-related patterns of 40-Hz EEG during cognitive and motor tasks. *Int J Psychophysiol* 1998;28:301–15.
- Dupuy FE, Clarke AR, Barry RJ, McCarthy R, Selikowitz M. EEG coherence in children with Attention-Deficit/Hyperactivity Disorder: differences between good and poor responders to methylphenidate. *Psychiatry Res*, in press.
- Dupuy FE, Clarke AR, Barry RJ, McCarthy R, Selikowitz M. EEG coherence in girls with Attention-Deficit/Hyperactivity Disorder: stimulant effects in good responders. *Int J Psychophysiol* 2008;70:151–7.
- Engel AK, Konig P, Kreiter AK, Schillen TB, Singer W. Temporal coding in the visual cortex: new vistas on integration in the nervous system. *Trends Neurosci* 1992;15:218–26.
- Fair DA, Posner J, Nagel BJ, Bathula D, Dias TG, Mills KL, Blythe MS, Giwa A, Schmitt CF, Nigg JT. Atypical default network connectivity in youth with Attention-Deficit/Hyperactivity Disorder. *Biol Psychiatry*, in press.
- Fein G, Raz J, Brown F, Merrin E. Common reference coherence data are confounded by power and phase effects. *EEG Clin Neurophysiol* 1988;69:581–4.
- John ER, Pritchep L, Easton P. Normative data banks and neurometrics. In: Gevins A, Remond A, editors. Basic concepts, methods, and results of norm constructions. Methods of analysis of brain electrical and magnetic signals (handbook of electroencephalography and clinical neurophysiology, review series), vol. 1. New York: Elsevier; 1987.
- Kakizaki T. Transient lowering of mental activity during performance of a mental task. *Industrial Health* 1990;28:85–96.
- Klimesch W. EEG alpha and theta oscillations reflect cognitive and memory performance. A review and analysis. *Brain Res Rev* 1999;29:169–95.
- Kobel M, Bechtel N, Specht K, Klarhöfer M, Weber P, Scheffler K, Opwis K, Penner IK. Structural functional imaging approaches in attention deficit/hyperactivity disorder: does the temporal lobe play a key role? *Psychiatry Res* 2010;183:230–6.
- Lubar J, White N, Swartwood M, Swartwood J. Methylphenidate effects on global and complex measures of EEG. *Paediatr Neurol* 1999;21:633–7.
- Mannuzza S, Klein R, Bessier A, Malloy P, LaPadula M. Adult outcome of hyperactive boys; educational achievement, occupational rank and psychiatric status. *Arch Gen Psychiatry* 1993;50:565–76.
- Montagu J. The hyperkinetic child: a behavioural, electrodermal and EEG investigation. *Dev Med Child Neurol* 1975;17:299–305.
- Moazami-Goudarzi M, Sarnthein J, Michels L, Moukhtieva R, Jeanmonod D. Enhanced frontal low and high frequency power and synchronization in the resting EEG of parkinsonian patients. *NeuroImage* 2008;41:985–97.
- Njokiiktjen C, de Rijke W, Jonkman E. Children with nonverbal learning disabilities (NLD): coherence values in the resting state may reflect hypofunctional long distance connections in the right hemisphere. *Hum Physiol* 2001;27:523–8.
- Pelham W, Gnagy E, Greenslade K, Milich R. Teacher rating of DSM-III-TR symptoms for the disruptive behaviour disorders. *J Am Acad Child Adolesc Psychiatry* 1992;31:210–8.
- Rossini PM, Rossi S, Babiloni C, Polich J. Clinical neurophysiology of aging brain: from normal aging to neurodegeneration. *Prog Neurobiol* 2007;83:375–400.
- Shaw J. An introduction to the coherence function and its use in the EEG signal analysis. *J Med Eng Technol* 1981;5:279–88.
- Tabachnick B, Fidell L. Using multivariate statistics. New York: Harper Collins; 1989. second edition.
- Thatcher RW, Krause P, Hrybyk M. Cortico-cortical associations and EEG coherence. A two-compartmental model. *EEG Clin Neurophysiol* 1986;64:123–43.
- Takano T, Ogawa T. Characterization of developmental changes in EEG-gamma band activity during childhood using the autoregressive model. *Acta Paediatr Jpn* 1998;40:448–52.
- Uhlhaas PJ, Singer W. Abnormal neural oscillations and synchrony in schizophrenia. *Nat Rev Neurosci* 2010;11:100–13.
- von Stein A, Sarnthein J. Different frequencies for different scales of cortical integration: from local gamma to long range alpha/theta synchronization. *Int J Psychophysiol* 2000;38:301–13.
- Wang XJ. Neurophysiological and computational principles of cortical rhythms in cognition. *Physiol Rev* 2010;90:1195–268.
- Wechsler D. Wechsler intelligence scale for children – Manual. New York: Harcourt Brace Jovanovich Inc.; 1992. third edition.
- Yordanova J, Banaschewski T, Kolev V, Woerner W, Rothenberger A. Abnormal early stages of task stimulus processing in children with attention-deficit hyperactivity disorder – Evidence from event-related gamma oscillations. *Clin Neurophysiol* 2001;112:1096–108.