SUMMARY

Attention-Deficit/Hyperactivity Disorder (AD/HD) is a common psychiatric disorder of childhood that continues to affect many people as adults. At present it is not possible to determine in childhood who will have the disorder as an adult. The aim of this study was to determine whether EEG coherence differences exist between children who outgrow the disorder and those who continue to be symptomatic as adults.

Pre-treatment EEGs were recorded during an eyes-closed resting condition from 38 boys diagnosed with AD/HD and 38 age-matched control subjects. Coherence was calculated for 8 intra-hemispheric electrode pairs (4 in each hemisphere), and 8 inter-hemispheric electrode pairs, within each of the delta, theta, alpha and beta bands. A second assessment was performed on the AD/HD subjects 11 years after the initial assessment to determine whether subjects met criteria for adult AD/HD.

Across the entire AD/HD sample, increased frontal delta and theta coherences were found compared with controls. Both interhemispheric and intraintrahemispheric coherence differences were found in the delta and theta bands between those who outgrew the disorder and those who continued to have AD/HD as adults.

Increased frontal delta and theta coherences appear to be the most reliable coherence markers of childhood AD/HD. Children who later outgrow the disorder have coherence anomalies different from those who continue to have AD/HD as adults. These results suggest that coherence measures might serve as a marker that can be used clinically in childhood to predict adult AD/HD.

Key words: attention-deficit/hyperactivity disorder, AD/HD, adults, EEG, coherence
BACKGROUND

Attention-Deficit/Hyperactivity Disorder (AD/HD) is one of the most common psychiatric conditions of childhood, affecting between 4% and 6% of school-age children (APA, 1994; Lindgren et al., 1990; Pelham et al., 1992). Between 40% and 70% of children with the disorder will continue to manifest AD/HD as adults (Bellack & Black, 1992). However, at present there is no reliable childhood marker of who will outgrow the disorder and who will continue to be symptomatic as an adult. Standard clinical practice involves regular assessments of the child over a number of years to monitor changes in the presentation of the disorder. The development of a reliable diagnostic test, which could be administered at the initial assessment in childhood, would be useful in the development of a long term treatment regime.

One measure that has been used to investigate CNS dysfunctions in children with the disorder is EEG coherence. EEG coherence is conceptualised as the correlation in the time domain between two signals in a given frequency band (Shaw, 1981), providing information about the degree of connectivity between structures underlying the pair of electrodes used to calculate the coherence measure. With normal brain development, synaptic connections both proliferate and are pruned over time, and this has been hypothesised to cause fluctuations in coherence (e.g., Thatcher et al., 1987; Thatcher, 1994). The increase in myelination with age has also been hypothesised to impact on coherence (e.g., Barry et al., 2004).

A few studies have investigated the coherence of children with AD/HD using an eyes-closed resting condition, the dominant paradigm in EEG studies of this disorder. Montague (1975) found that hyperkinetic children had significantly elevated intrahemispheric coherences compared to controls. Chabot and Serfontein (1996), and Chabot et al. (1996), reported that children with an attention disorder had increased interhemispheric and intrahemispheric coherence in frontal and central regions, but did not report in which bands these abnormalities were found. Barry et al. (2002) found substantial increases in theta coherence and reductions in alpha coherence for most interhemispheric and short distance intrahemispheric measures, with an alpha reduction also apparent at longer inter-electrode distances. Frontally, AD/HD children also had interhemispheric coherences elevated in the delta and theta bands, and reduced in the alpha band. Clarke et al. (2005) found that AD/HD children had lower theta intrahemispheric coherences than controls at long inter-electrode distances, and reduced lateralisation at both long and short-medium inter-electrode distances. For interhemispheric comparisons, AD/HD children showed increased coherences in the frontal regions for the low frequency bands (delta and theta), and reduced coherences in the alpha band. In the central/parietal/occipital regions, interhemispheric coherences in the alpha band were again lower in AD/HD children than in controls. These studies indicate the presence of substantial frontal lobe dys-
function, with increased slow wave coherence commonly being found in studies of children with AD/HD.

The aims of this study were to further investigate EEG coherence differences between children with and without AD/HD, and to determine whether coherence differences exist between children who later outgrow the disorder and those who continue to be symptomatic as adults.

MATERIAL AND METHODS

Participants

Seventy six males participated in this study. Thirty eight participants met criteria for AD/HD according to the DSM-IV (APA, 1994) as children (aged 8 to 12 years), and of these, 24 continued to meet DSM-IV criteria for AD/HD as young adults (aged 18 to 25 years). Thirty eight children also participated as control subjects in this study. The AD/HD participants were all childhood patients of the pediatric practice of RM and MS, where they were assessed and treated for AD/HD Combined type as children. The control group consisted of children who were drawn from the local community, and who were age- and gender-matched to the AD/HD subjects at their initial assessment for AD/HD as children. Informed consent was obtained from all participants prior to inclusion in this study.

The childhood assessment for AD/HD was based on a clinical assessment by a paediatrician and a psychologist, and children were included in this study only where both agreed on the diagnosis. Clinical interviews incorporated information from as many sources as were available. These included a history given by a parent or guardian, school reports for a minimum of the past 12 months, reports from any 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 disorder of consciousness, a head injury with cerebral symptoms, a history of CNS diseases, convulsions or a history of convulsive disorders, paroxysmal headache or tics. Subjects were also excluded if they met DSM criteria for conduct or oppositional defiant disorder, a depressive or anxiety disorder, Asperger’s or Tourette’s syndromes.

The assessment of adult AD/HD was based on published criteria for the diagnosis of AD/HD in adults (Adler & Cohen, 2004; Fargason & Ford, 1994; Montano, 2004), which requires the determination of AD/HD during childhood, and the existence of AD/HD symptoms in adulthood as determined by a clinical interview and AD/HD rating scales. The second assessment included a clinical interview, an assessment of IQ, reading ability, current AD/HD symptoms, depression level, and general mental health status. The Conners Adult AD/HD rating scale was also used to determine the presence of AD/HD symptoms, with a T-Score > 70 on the DSM-IV inattentive, hyperactive-impulsive or total subscales being used as the clinical cut off.
Inclusion in the control group was based on the same assessment as that used to assess the AD/HD group as children, except that these participants had to have an IQ greater than 85, and perform in the normal range or better for reading. The IQ and Reading criteria were used because people with low IQs (Katada et al., 1981) and reading problems (Lubar et al., 1985) are known to have abnormalities in their EEGs.

Procedure

Initial Assessment in Childhood

All subjects had an initial assessment that lasted approximately 2.5 hours, with the EEG being recorded after 1.5 hours of testing. Subjects were first assessed by a paediatrician, where a physical examination was performed and a clinical history taken. A semistructured clinical interview was used as part of this assessment to aid in the determination of the psychiatric diagnosis. Subjects then had a psychometric assessment consisting of a WISC-III, Neale Analysis of Reading and the South Australian Spelling Test. After this assessment, subjects had an electrophysiological assessment consisting of evoked potentials followed by an EEG. This assessment was conducted between January 1994 and July 1996.

Second Assessment in Adulthood

All participants were tested in a single 4 hour session. During this assessment, a comprehensive clinical history was taken, which included treatment history for any mental illness, participant’s present living arrangements, any history of problems at school including suspensions and expulsions, highest educational level attained, current employment and number of jobs held, as well as periods of unemployment, legal problems/criminality both before and after the age of 18, and present drug use (covering both legal and illegal drugs). A psychometric assessment was then performed. This consisted of the Weschler Adult Intelligence Scale and the Woodcock Reading Mastery Test-Revised. Participants also completed the General Health Questionnaire (GHQ-60), the Conners Adult AD/HD rating Scale, and the Center for Epidemiological Studies Depression scale. This assessment was conducted on average 11 years after the initial assessment.

Electrophysiological Assessment

The data used in this study are from the EEGs recorded at the initial childhood assessment of these subjects for AD/HD. The EEGs were recorded during an eyes-closed resting condition, while subjects were seated on a reclining chair. All subjects were instructed to make them selves comfortable and to stay as still as possible. Subjects were also instructed to try to keep their eyes as still as possible. If subjects started to become overly active, or the technician had concerns that they were becoming drowsy, the recording was stopped and subjects had a short rest before continuing.
Electrode placement was in accordance with the international 10-20 system, using an electrode cap. The activity in 21 derivations was recorded using a linked-ear reference. A single electro-oculogram (EOG) electrode referenced to Fpz was placed beside the right eye and a ground lead was placed on the left cheek. Reference and ground leads were 9 mm tin disk electrodes, and impedance levels were set at less than 5 kOhm.

The EEG was recorded and Fourier transformed by a Cadwell Spectrum 32, software version 4.22, using test type EEG, montage Q-EEG. The sensitivity was set at 150 microvolts per centimetre, low frequency filter 0.53 Hz, high frequency filter 70 Hz, and 50 Hz notch filter. The sampling rate of the EEG was 200 Hz and the Fourier transformation used 2.56 second epochs.

Thirty 2.56 second epochs were selected from the live trace and stored to floppy disk. Epoch rejection was based on both visual and computer selection. Computer reject levels were set using a template recorded at the beginning of the session and all subsequent epochs were compared to this. The EOG rejection was set at 50 microvolts. The technician also visually appraised every epoch and decided to accept or reject it. As part of this appraisal, the technician sought low amplitude muscle artefact and rolling eye movements, which may not be identified by the computer reject procedure. These were further reduced to 24 epochs (~1 min) for Fourier analysis by a second technician. 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). Coherence between an electrode pair for a particular band was defined as 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 intra-hemispheric (F3-O1, F4-O2, Fp1-F3, Fp2-F4, T3-T5, T4-T6, C3-P3, C4-P4) and eight inter-hemispheric (Fp1-Fp2, F7-F8, F3-F4, C3-C4, T3-T4, T5-T6, P3-P4, O1-O2) electrode pairs, following Barry et al. (2002).

**Statistical analysis of the EEG coherence measures**

Prior to analysis, in order to normalise the distribution of the correlation measures, each coherence value was transformed using Fisher’s z-transform, and means obtained were inverse-transformed for reporting. The 16 sets of coherences were grouped for analysis into regions of interest – 2 for intra-hemispheric coherences (involving either short/medium or long inter-electrode distances), and 3 for inter-hemispheric coherences (involving different brain regions), following Barry et al. (2002). For the intra-hemispheric coherences, the means within hemisphere were compared for each band for (i) the short/medium inter-electrode distances (left: Fp1-F3, T3-T5, C3-P3 and right: Fp2-F4, T4-T6, C4-P4) and (ii) long inter-electrode distances (left: F3-O1 and right: F4-O2). Within each of these two sets of analyses, laterality (left vs. right) was examined as a planned contrast on the electrode pairs listed. The inter-hemispheric coherences were separately examined within (iii) the
For each of the 5 regions of interest, an analysis of variance was used to examine the effects of group on coherences in each frequency band. For the first 2 groups of electrode pairs, both hemispheric and group differences were examined. However, for the last 3 regional analyses, only group differences were examined, with no within-region contrasts. Within the group factor, the AD/HD group was compared with the control group to determine whether the AD/HD group had a childhood coherence profile typical of the literature, and then the AD/HD subjects who outgrew the disorder were compared to those who continued to meet diagnostic criteria for AD/HD as adults. As all these orthogonal 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). All F values reported have (1, 73) degrees of freedom.

**RESULTS**

**Clinical data**

At the adult assessment, 14 subjects failed to meet criteria for the disorder. Of those who did meet criteria, 14 were diagnosed as having AD/HD combined type, 2 with predominantly hyperactive/impulsive type, and the remaining 8 showed symptoms only of the inattentive type of the disorder.

**Coherence**

**AD/HD versus Control**

The mean coherence values from each electrode pair and frequency band are shown in Table 1.

For intrahemispheric coherences at short-medium inter-electrode distances, the AD/HD group had a significantly increased laterality compared to controls in the delta band ($F = 6.06, p < 0.05$), and the theta band ($F = 23.25, p < 0.001$).

For interhemispheric coherences, in the frontal regions, the AD/HD group displayed significant greater coherences than controls in the delta ($F = 5.89, p < 0.05$) and theta ($F = 15.13, p < 0.001$) bands.

**Adult AD/HD versus Outgrew Disorder**

For short-medium intrahemispheric inter-electrode distances, the Adult AD/HD group had significantly greater coherences than the Outgrew group in the delta ($F = 10.22, p < 0.005$) and theta ($F = 10.51, p < 0.005$) frequency bands.

For short-medium intrahemispheric coherences, the Adult AD/HD group had a significantly reduced effect of laterality compared with the Outgrew group in the delta band ($F = 6.64, p < 0.05$).
The Adult AD/HD group had significantly higher interhemispheric coherences than the Outgrew group in the delta band, for both the temporal regions ($F = 6.74, p < 0.05$), and central/parietal/occipital regions ($F = 4.84, p < 0.05$).

Table 1. Mean coherence across subjects for each electrode pair (standard deviation in brackets)

<table>
<thead>
<tr>
<th></th>
<th>Delta</th>
<th>Theta</th>
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<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Adult AD/HD</td>
</tr>
<tr>
<td>Fp1-Fp2</td>
<td>0.88 (0.26)</td>
<td>0.91 (0.24)</td>
</tr>
<tr>
<td>F7-F8</td>
<td>0.39 (0.18)</td>
<td>0.46 (0.16)</td>
</tr>
<tr>
<td>F3-F4</td>
<td>0.78 (0.13)</td>
<td>0.81 (0.17)</td>
</tr>
<tr>
<td>C3-C4</td>
<td>0.72 (0.13)</td>
<td>0.76 (0.13)</td>
</tr>
<tr>
<td>T3-T4</td>
<td>0.22 (0.20)</td>
<td>0.26 (0.14)</td>
</tr>
<tr>
<td>T5-T6</td>
<td>0.43 (0.19)</td>
<td>0.47 (0.12)</td>
</tr>
<tr>
<td>P3-P4</td>
<td>0.74 (0.18)</td>
<td>0.77 (0.21)</td>
</tr>
<tr>
<td>O1-O2</td>
<td>0.81 (0.32)</td>
<td>0.84 (0.23)</td>
</tr>
<tr>
<td>Fp1-F3</td>
<td>0.75 (0.21)</td>
<td>0.79 (0.18)</td>
</tr>
<tr>
<td>Fp2-F4</td>
<td>0.73 (0.18)</td>
<td>0.75 (0.20)</td>
</tr>
<tr>
<td>T3-T5</td>
<td>0.60 (0.17)</td>
<td>0.60 (0.14)</td>
</tr>
<tr>
<td>T4-T6</td>
<td>0.57 (0.16)</td>
<td>0.61 (0.18)</td>
</tr>
<tr>
<td>C3-P3</td>
<td>0.77 (0.19)</td>
<td>0.78 (0.13)</td>
</tr>
<tr>
<td>C4-P4</td>
<td>0.76 (0.16)</td>
<td>0.78 (0.18)</td>
</tr>
<tr>
<td>F3-O1</td>
<td>0.22 (0.17)</td>
<td>0.19 (0.09)</td>
</tr>
<tr>
<td>F4-O2</td>
<td>0.22 (0.17)</td>
<td>0.21 (0.09)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Alpha</th>
<th>Beta</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Adult AD/HD</td>
</tr>
<tr>
<td>Fp1-Fp2</td>
<td>0.89 (0.23)</td>
<td>0.90 (0.32)</td>
</tr>
<tr>
<td>F7-F8</td>
<td>0.49 (0.25)</td>
<td>0.46 (0.20)</td>
</tr>
<tr>
<td>F3-F4</td>
<td>0.80 (0.23)</td>
<td>0.80 (0.21)</td>
</tr>
<tr>
<td>C3-C4</td>
<td>0.58 (0.25)</td>
<td>0.59 (0.27)</td>
</tr>
<tr>
<td>T3-T4</td>
<td>0.22 (0.15)</td>
<td>0.19 (0.12)</td>
</tr>
<tr>
<td>T5-T6</td>
<td>0.31 (0.23)</td>
<td>0.24 (0.19)</td>
</tr>
<tr>
<td>P3-P4</td>
<td>0.60 (0.32)</td>
<td>0.56 (0.31)</td>
</tr>
<tr>
<td>O1-O2</td>
<td>0.69 (0.40)</td>
<td>0.70 (0.28)</td>
</tr>
<tr>
<td>Fp1-F3</td>
<td>0.88 (0.24)</td>
<td>0.87 (0.27)</td>
</tr>
<tr>
<td>Fp2-F4</td>
<td>0.86 (0.26)</td>
<td>0.85 (0.24)</td>
</tr>
<tr>
<td>T3-T5</td>
<td>0.58 (0.23)</td>
<td>0.58 (0.19)</td>
</tr>
<tr>
<td>T4-T6</td>
<td>0.56 (0.19)</td>
<td>0.58 (0.25)</td>
</tr>
<tr>
<td>C3-P3</td>
<td>0.71 (0.25)</td>
<td>0.73 (0.21)</td>
</tr>
<tr>
<td>C4-P4</td>
<td>0.69 (0.25)</td>
<td>0.70 (0.31)</td>
</tr>
<tr>
<td>F3-O1</td>
<td>0.22 (0.15)</td>
<td>0.23 (0.15)</td>
</tr>
<tr>
<td>F4-O2</td>
<td>0.26 (0.16)</td>
<td>0.23 (0.21)</td>
</tr>
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</table>
DISCUSSION

AD/HD is a disorder that goes through significant changes from childhood to adulthood. While many with childhood AD/HD will outgrow the disorder, between 40% and 70% will continue to have AD/HD as adults (Bellack & Black, 1992), although their symptom profile tends to change. All participants in this study were initially diagnosed as children with the combined type of AD/HD. Results of the second clinical assessment indicated that 63% of subjects continued to meet criteria for AD/HD as adults. These subjects met criteria for AD/HD combined type (14), predominantly hyperactive/impulsive type (2), and inattentive type (8). These results are generally in line with past research that has found that hyperactive components of the disorder reduce with increasing age, but the impulsive and inattentive components are more likely to continue into adulthood (Hallowell & Ratey, 1994; Hechtman et al., 1984).

In the first stage of the present data analysis, we compared the total AD/HD sample to the control group. This analysis was performed to aid in identifying the most robust childhood coherence abnormalities found across studies. Past coherence research in AD/HD children has found elevated intrahemispheric coherences (Montague, 1975) especially in the frontal and central regions (Chabot and Serfontein, 1996; Chabot et al., 1996). In the theta band, both intrahemispheric and interhemispheric abnormalities in theta coherence are also found (Barry et al., 2002; Clarke et al., 2005; Barry et al., 2005). In the alpha band, AD/HD children have also been found to have reduced differences between the hemispheres, and lower intrahemispheric alpha coherences at longer inter-electrode distances than controls (Barry et al., 2005).

For short-medium intrahemispheric coherences, the AD/HD group in the present study had significantly greater differences between coherences in the left and right hemispheres, in the delta and theta bands, compared to controls. This is not a common finding, as most AD/HD studies have found greater hemispheric differences in control subjects.

The present study also found that the AD/HD group had significantly increased interhemispheric coherences in the frontal regions compared to the controls in both the delta and theta bands. Increased frontal theta coherence is the most consistent finding within the childhood AD/HD coherence literature, with this abnormality being found in most studies (Montague, 1975; Chabot et al., 1996; Chabot & Serfontein, 1996; Barry et al., 2002; Barry et al., 2005, 2006; Clarke et al., 2005). Increased delta coherence has also been found in some of these studies (Barry et al., 2002; Clarke et al., 2005). One of the dominant theories of coherence is that coherence values reflect the degree of structural connection between regions of the brain (Fein et al., 1988; Dupuy et al., 2008). Hence the common finding of elevated frontal lobe coherence suggests the presence of structural frontal lobe abnormalities in children with AD/HD. This is consistent with many of the present models of AD/HD, which place frontal-lobe mediated executive function deficits at the core of the AD/HD
Within both the lay and professional press, there is considerable concern over the issue of misdiagnosis of AD/HD, as such a diagnosis often leads to a child being placed on long-term medication for the disorder. Part of this problem arises because there are no independent diagnostic tests for the disorder, with most diagnoses being based on behavioural information provided by the child’s parents. As elevated frontal theta coherence is consistently found within the literature, that might be one component of the EEG that can be incorporated into an independent diagnostic test for this disorder.

While it is well recognised that some, but not all, children with AD/HD will outgrow the disorder, at present it is not possible to identify in childhood who will or will not outgrow the disorder. Being able to accurately predict the developmental path of the disorder in childhood would have substantial clinical benefits for the development of long-term treatment plans. For this reason, the second aim of the study was to determine whether EEG coherence differences exist between children who outgrow the disorder and those who continue to have the disorder as adults. The results of the present study indicated a number of coherence differences in the childhood EEGs of those who outgrew the disorder compared to those who continued to have AD/HD as an adult. Overall, those who continue to have AD/HD as adults had increased delta coherence in a number of interhemispheric and intrahemispheric comparisons as children, relative to those who outgrew the disorder.

Thatcher et al. (1986) proposed a two-process model of cortico-cortical associations in which short and long neuronal fibres contribute differentially to coherence as a function of inter-electrode distance. At larger distances, coherence is mainly dependent on the longer fibres alone, increases with their density/development, and falls off systematically with increasing inter-electrode distance. In contrast, increased density/development of short fibres in specialised neuronal populations reduces coherence by increasing the complexity and competition of interactions within the cell population. According to this model, the present results suggest the presence of decreased cortical differentiation in those children who continue to have the disorder as adults, compared with those who outgrow the disorder. They also suggest that increased delta coherence may be associated with a more permanent structural abnormality, rather than representing a maturational delay in CNS development, or a functional abnormality that corrects with age.

The results of this study indicate the existence of childhood central nervous system abnormalities that may be able to predict the developmental path of AD/HD. However, for these observed differences to be turned into a reliable test, their sensitivity and specificity needs to be tested at the individual level. Even if these measures do not have sufficient reliability and validity at the individual level, this study indicates that further research into childhood markers of adult AD/HD is warranted.

This study investigated EEG coherence differences between children with...
AD/HD, who would and would not later outgrow the disorder. Across the entire AD/HD sample, increased frontal delta and theta coherences were found, and these appear to be the most reliable coherence markers of AD/HD. Coherence differences, in both intrahemispheric and interhemispheric linkages, were also found in the delta and theta bands between those children who outgrew the disorder and those who continued to have AD/HD as adults. These results indicate that coherence measures might provide a marker that could be used clinically in childhood to predict adult AD/HD.

ACKNOWLEDGEMENT

This research was supported under the Australian Research Council’s Discovery funding scheme (project number DP0987232).

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