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EEG differences between good and poor responders to methylphenidate and dexamphetamine in children with attention-deficit/hyperactivity disorder

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Abstract

Objectives: This series of studies investigated (1) electroencephalographic (EEG) differences between good and poor responders to methylphenidate, (2) EEG differences between good and poor responders to dexamphetamine, and (3) differences in the EEGs of good responders to methylphenidate versus dexamphetamine, within samples of children with the combined type of attention-deficit/hyperactivity disorder (ADHD).

Methods: Twenty good and 20 poor responders to each of methylphenidate and dexamphetamine, based on the results of a continuous performance task, and 20 age-matched control subjects, participated in this study. EEG was recorded from 21 sites during an eyes-closed resting condition and Fourier transformed to provide estimates for total power, and absolute and relative power in the delta, theta, alpha and beta bands, and for the theta/alpha and theta/beta ratios.

Results: EEG differences were found between the good and poor responders to each medication. Good responders to methylphenidate had EEG profiles that suggested that they were more cortically hypoaroused than poor responders. In contrast, the good responders to dexamphetamine appeared to be more maturationally lagged than the poor responders. The two good-responder groups had EEG

profiles which suggested that there were two different underlying central nervous system (CNS) dysfunctions.

Conclusions: Children with the combined type of ADHD do not constitute a homogeneous clinical group, as different types of CNS dysfunction are present within this population. These results also indicate the need for medication testing to be undertaken before a child is prescribed stimulant medication for ADHD.

Author Keywords: Attention-deficit/hyperactivity disorder; Children; Electroencephalogram; Medication; Methylphenidate; Dexamphetamine

Article Outline

1. Introduction

For over 50 years, attention-deficit/hyperactivity disorder (ADHD) has been treated with stimulant medications such as methylphenidate and dexamphetamine. These drugs increase

catecholamines, mainly dopamine and norepinephrine, in the synaptic cleft, which accounts for the clinical effects in ADHD (Zametkin and Rapoport, 1987). Numerous controlled trials (Wilens and Biederman, 1992) and clinical and empirical reports (Swanson et al., 1993) have established that about 80% of patients have clinically significant benefits from medication, with 20% having no benefit or aversive side effects. Despite this high level of successful treatment with medication, there is still considerable controversy regarding possible over-diagnosis of ADHD and the inappropriate use of stimulant medications in children (Swanson; Jensen and Safer), especially in the popular press.

Electroencephalographic (EEG) studies of children with ADHD, relative to those without, have primarily found increased theta activity (Satterfield; Janzen; Clarke and Clarke, 2001d) which occurs primarily in the frontal regions (Mann; Chabot and Lazzaro), increased posterior delta (Matousek; Clarke and Clarke, 2001d) and decreased alpha and beta activity (Dykman et al., 1982; Callaway et al., 1983), also most apparent in the posterior regions (Mann; Clarke; Clarke; Clarke and Lazzaro). An increase in the theta/alpha (Matousek; Ucles; Clarke; Clarke and Clarke) and theta/beta ratios (Lubar; Janzen; Clarke; Clarke and Clarke) has also been found in children with ADHD compared to normal children.

Following these studies, a number of researchers have investigated the utility of discriminant function analysis of such EEG measures in the diagnosis of ADHD (Lubar; Mann; Chabot; Chabot; Hughes and Hoffman). However, this procedure has been criticized on the basis of poor sensitivity and specificity and is not recommended for use in clinical practice (Binnie; Levy; Rey and Nuwer). Levy and Ward (1995), in their review of brain imaging and ADHD, did concede that if EEG measures could reliably be used to predict medication response, then the importance of the technique would be established.

Few studies have investigated the use of EEG measures in discriminating between good and poor responders to medications. Princep and John (1990) found that discriminant function analysis of EEG data could discriminate between responders and non-responders to methylphenidate with 82% accuracy. Chabot et al. (1996) investigated the sensitivity and specificity of quantitative electroencephalograhic (QEEG) measures in determining good and poor responders to methylphenidate and dexamphetamine. Results indicated that discriminant function analysis using 6 QEEG measures could correctly classify 75.6% of good methylphenidate responders and 75.8% of good dexamphetamine responders. The limitation of these results is that the 6 QEEG factors found significant in the analysis consist of a mixture of monopolar and bipolar coherence, inter-hemispheric asymmetries and relative power in specific sites. This combination of measures makes the results difficult to translate into a functional procedure for the average clinician without requiring use of that specific testing package. In this context, the present series of studies aimed to further investigate EEG differences between good and poor responders to stimulant medications.

2. Study 1

This study aimed to further the investigation of EEG differences between good and poor responders to methylphenidate.

2.1. Method

2.1.1. Subjects

Three groups of 20 children, with 18 boys and two girls in the ADHD good-responder group (ADHDg-M) and the control group, and 17 boys and 3 girls in the ADHD poor-responder group (ADHDp-M), participated in this study. All children were between the ages of 8 and 12 years and right-handed and -footed. Subjects had a full-scale WISC-III IQ score of 85 or higher. Both clinical groups of children were drawn from new patients referred to a Sydney-based pediatric practice for an assessment of ADHD. The ADHD subjects had not been diagnosed as having ADHD previously, had no history of medication use for the disorder, and had their pediatric, psycho-educational and electrophysiological assessments before being tested on or prescribed any medication. The control group consisted of children from local schools and community groups.

Inclusion in the ADHD groups was based on a clinical assessment by a pediatrician and a psychologist; children were included only where both agreed on the diagnosis. DSM-IV criteria were used and children were included in the two ADHD groups if they met the full diagnostic criteria for the ADHD combined type. Clinical interviews incorporated information from as many sources as were available. These included a history given by a parent or guardian, school reports for the past 12 months, reports from any other health professionals and behavioral observations during the assessment. Children were excluded from the ADHD groups 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 central nervous system (CNS) diseases, convulsions or a history of convulsive disorders, paroxysmal headache or tics.

Inclusion in the control group was based on: an uneventful prenatal, perinatal and neonatal period; no disorders of consciousness, head injury with cerebral symptoms, history of CNS diseases, obvious somatic diseases, convulsions, history of convulsive disorders, paroxysmal headache, enuresis or encopresis after the 4th birthday, tics, stuttering, pavor nocturnes or excessive nail-biting, obvious mental diseases, conduct disorders, and no deviation with regard to mental and physical development. Assessment for inclusion as a control was based on a clinical interview with a parent or guardian similar to that of the ADHD subjects, utilising the same sources of information.

Handedness was assessed by ascertainment of the hand used for writing, catching and throwing a ball, holding a bat, and the foot used to kick a ball. Children were excluded from all groups if spike wave activity was present in the EEG.

2.1.2. Procedure

All subjects were tested in two sessions lasting approximately 3.5 h. Subjects were first assessed by a pediatrician, where a physical examination was performed and a clinical history taken. Subjects then had a psychometric assessment consisting of a WISC-III, Neale Analysis of Reading and Wide Range Achievement Test-R spelling. After this assessment, subjects had an electrophysiological assessment consisting of evoked potentials followed by an EEG. Subjects then had a lunch break for approximately 2 h and returned for medication testing.

The EEG was recorded in an eyes-closed resting condition, while subjects were seated on a reclining chair. Electrode placement was in accordance with the international 10-20 system, using an electrode cap produced by Electrocap International. The activity in 21 derivations was divided into 9 regions by averaging in each region. These regions 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). 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. A linked ear reference was used with all EEG channels; reference and ground leads were 9 mm tin disk electrodes. 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 QEEG. The sensitivity was set at 150 μV per cm, 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 2.5 s epochs.

Thirty 2.5 s epochs were selected from the live trace and stored in a 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 template was based on a recorded epoch, which the technician initially appraised as being artefact free. An epoch was rejected if the maximum amplitude from any electrode was greater than that of the template, and the technician considered this to have resulted from artefact. Epochs were always rejected if the EOG amplitude was greater than 50 μV. The technician also visually appraised every epoch and decided to accept or reject it. These were further reduced to 24 epochs (1 min) for Fourier analysis by a second technician. The EEG was analyzed in 4 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 both absolute and relative power, as well as the total power of the EEG (1.5–25 Hz). Theta/alpha and theta/beta ratio coefficients were also calculated between the frequency bands by dividing the power of the slower frequency band by the power of the faster frequency band.

The medication test consisted of the Vigilance Task of the Gordon Diagnostic System (Gordon, 1986). Subjects viewed a series of numbers which were sequentially displayed, and had to respond to a target number which followed another target number, by pressing a button. Numbers were presented for 200 ms, with an 800 ms inter-stimulus interval. Each test consisted of 3 identical blocks, which contained 180 stimuli in each block. Within each block, there were 15 random presentations of the paired target stimuli. The total number of correct responses and commission errors were recorded. The child was then given 10 mg of methylphenidate. The subject was retested, 1 h after the initial test, with a second vigilance task which used different target numbers. Percentage changes in correct responses and commission errors were calculated, and subjects were included in the ADHDg-M group if they had an increase in correct responses and a decrease in commission errors. Subjects also had to show an improvement in behavior, as reported by their parents, at their first follow-up clinical appointment (6 months after the initial assessment). Inclusion in the ADHDp-M group was based on: no change or a decrease in correct responses and an increase in commission errors.

The decision to test the child on methylphenidate partly reflected economic factors. In Australia, greater government subsidies are available for the cost of dexamphetamine than for methylphenidate, which meant that some children were not tested on methylphenidate, preventing their inclusion in this study. Thus methylphenidate was tested if the child's family could better afford the medication or the child had previously shown an adverse response to dexamphetamine on the vigilance task.

2.1.3. Statistical analysis

Analysis of variance (ANOVA) was performed examining the effects of region and group for each band in absolute and relative power, the total power, and ratio coefficients. The effects of region were examined in two orthogonal 3-level repeated-measures factors. The first of these was a sagittal factor, within which planned contrasts compared the frontal region with the posterior region, and their mean with the central region. The second factor was laterality, within which planned contrasts compared activity in the left hemisphere with that in the right hemisphere, and their mean with the midline region. These planned contrasts allow optimal clarification of site effects within the regions studied. Within the Group factor, planned contrasts compared the patient groups with the control group (to establish ADHD differences from normals) and the ADHDg-M group with the ADHDp-M 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 (Tabachnick and Fidell, 1989). Only between-group effects and interactions are reported here for space reasons.

2.1.4. Results

The ADHDg-M group had a significantly greater increase in correct responses ($F(1,38)=59.29$, $P<0.001$) and a reduction in commission errors ($F(1,38)=28.21$, $P<0.001$) compared to the ADHDp-M group (Table 1). A summary of the mean EEG characteristics of each group is shown in Table 2, with the significant EEG differences between the ADHD and control groups in Table 3, and differences between the two ADHD groups in Table 4.

Table 1. Percentage changes in correct responses and commission of errors for good and poor responders to methylphenidate and dexamphetaminea

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Table 2. Age and EEG means (SD) for the ADHD and control groups in Studies 1 and 2

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Table 3. Summary of significant differences between the ADHD groups and the control group, for studies 1 and 2[a]

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Table 4. Summary of significant ADHD group differences for studies 1, 2 and 3[a]

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The two ADHD groups had greater absolute theta ($F(1,57)=7.15$, $P<0.05$), relative theta ($F(1,57)=35.45$, $P<0.001$), theta/alpha ($F(1,57)=18.29$, $P<0.001$) and theta/beta ratios ($F(1,57)=9.65$, $P<0.01$) than the control group (see Fig. 1). The two ADHD groups had less power than the control group in relative alpha ($F(1,57)=16.32$, $P<0.001$) and beta ($F(1,57)=16.32$, $P<0.001$). The difference between the ADHD groups and the control group was greater in the frontal regions than the posterior regions for the theta/alpha ratio ($F(1,57)=12.69$, $P<0.001$), and greater in the posterior regions than the frontal regions for absolute beta ($F(1,57)=4.10$, $P<0.05$) and relative delta ($F(1,57)=6.73$, $P<0.05$). The difference between the mean of the frontal and posterior regions and the central region was less in the two ADHD groups than the control group in relative alpha ($F(1,57)=6.52$, $P<0.05$), and relative beta ($F(1,57)=6.52$, $P<0.05$).

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Fig. 1. EEG and ratio coefficient differences between the control group and the good and poor responders to methylphenidate.

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The midline had greater power than the two hemispheres, and this difference was greater in the ADHD groups than the control group in absolute theta ($F(1,57)=7.19$, $P<0.01$), the theta/alpha ($F(1,57)=10.40$, $P<0.01$) and the theta/beta ($F(1,57)=7.99$, $P<0.01$) ratios. This difference in power between the two hemispheres and the midline was maximal at the central regions in absolute theta ($F(1,57)=7.70$, $P<0.01$), with the difference being greater in the two ADHD groups than the control group.

In the comparison of the two ADHD groups, the ADHDg-M group had greater total power ($F(1,57)=4.53$, $P<0.05$), absolute theta ($F(1,57)=6.21$, $P<0.05$), and a higher theta/beta ratio ($F(1,57)=8.36$, $P<0.01$) across all sites. In absolute delta, a group difference approaching significance was found, with the ADHDg-M group having greater activity than the ADHDp-M group ($F(1,57)=3.79$, $P=0.056$). The difference between the two ADHD groups was greater in the posterior regions than the frontal regions for total power ($F(1,57)=4.46$, $P<0.05$), absolute theta ($F(1,57)=6.44$, $P<0.05$), absolute delta ($F(1,57)=6.41$, $P<0.05$) and the theta/beta ratio ($F(1,57)=5.42$, $P<0.05$). The difference between the mean of the frontal and posterior regions and the central region was greater in the ADHDg-M group than the ADHDp-M group for total power ($F(1,57)=5.54$, $P<0.05$), absolute theta ($F(1,57)=6.93$, $P<0.05$) and absolute delta ($F(1,57)=6.17$, $P<0.05$). In the ADHDp-M group, the theta/beta ratio was lower in central regions than the mean of the frontal and posterior regions, but in the ADHDg-M group the ratio in central regions was higher than the frontal/posterior mean ($F(1,57) =9.21$, $P<0.01$).

Laterally, the difference between the two ADHD groups was greater in the right hemisphere than the left hemisphere for the theta/alpha ratio, with the ADHDg-M having a higher ratio than the ADHDp-M group ($F(1,57)=4.88$, $P<0.05$). The difference between the two hemispheres and the midline was greater in the ADHDg-M group than the ADHDp-M group for absolute theta ($F(1,57)=4.43$, $P<0.05$) and the theta/beta ratio ($F(1,57)=6.52$, $P<0.05$), with the midline having a greater ratio than the two hemispheres.

3. Study 2

Study 2 aimed to replicate Study 1 in a sample of children who showed good and poor response to dexamphetamine.

3.1. Method

3.1.1. Subjects

Three groups of 20 children, with 19 boys and one girl in the ADHD good-responder group (ADHDg-D) and the control group, and 18 boys and two girls in the ADHD poor-responder group (ADHDp-D), participated. Six patients from Study 1 were included in this study: 5 from the ADHDp-M group in the ADHDg-D group, and one from the ADHDg-M group in the ADHDp-D group. All children in this study met the same age, IQ and inclusion criteria as those in Study 1.

3.1.2. Procedure

The procedure and statistical analyses used in Study 1 were used in this study, except that subjects were given 5 mg of dexamphetamine instead of 10 mg of methylphenidate. An additional comparison was also made between the ADHD children in Study 1 and this study, to determine if the patient groups were similar.

3.1.3. Results

The ADHDg-D group had a significantly greater increase in correct responses ($F(1,38)=45.29$, $P<0.001$) and a greater reduction in commission errors ($F(1,38)=68.49$, $P<0.001$) compared to the ADHDp-D group (Table 1). A summary of the mean EEG characteristics of each group is shown in Table 2, with the significant EEG differences between the ADHD and control groups in Table 3, and differences between the two ADHD groups in Table 4.

The two ADHD groups had more relative theta ($F(1,57)=13.46$, $P<0.001$), less relative alpha ($F(1,57)=7.45$, $P<0.01$), and less posterior absolute beta ($F(1,57)=8.55$, $P<0.01$) than the control group (Fig. 2). The two ADHD groups also had a higher theta/alpha ratio coefficient ($F(1,57)=8.35$, $P<0.01$) than the control subjects, and this was greater in the frontal regions than the posterior regions ($F(1,57)=4.80$, $P<0.05$). A difference approaching significance was also found for the theta/beta ratio, with the two ADHD groups having a higher ratio coefficient than the control group ($F(1,57)=3.77$, $P=0.057$).

Full-size image (26K)

Fig. 2. EEG and ratio coefficient differences between the control group and the good and poor responders to dexamphetamine.

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Laterally, the difference between the two ADHD groups and the control group was greater in the left hemisphere than the right hemisphere for absolute alpha ($F(1,57)=4.64$, $P<0.05$). The two ADHD groups had a decrease in left posterior total power ($F(1,57)=4.68$, $P<0.05$) and absolute alpha ($F(1,57)=5.21$, $P<0.05$) compared to the control group.

The ADHDg-D group had less relative alpha ($F(1,57)=5.11$, $P<0.05$) and relative beta ($F(1,57)=4.24$, $P<0.05$) than the ADHDp-D group across all sites, with the maximal group difference occurring in the frontal regions for relative beta ($F(1,57)=11.06$, $P<0.01$). The ADHDg-D group had greater total power ($F(1,57)=4.23$, $P<0.05$), and relative delta ($F(1,57)=5.3$, $P<0.05$) in the posterior regions than the ADHDp-D group. This difference approached significance in absolute alpha, with the ADHDg-D group having less posterior power than the ADHDp-D group ($F(1,57)=3.71$, $P=0.059$). For total power, the difference between the mean of the frontal and posterior regions, compared to the central regions, was greater in the ADHDg-D group than the ADHDp-D group ($F(1,57)=4.64$, $P<0.05$), and for absolute alpha, this difference was smaller in the ADHDg-D group ($F(1,57)=4.64$, $P<0.05$).

For absolute beta, the difference between the midline and the two hemispheres was smaller in the ADHDg-D group than the ADHDp-D group ($F(1,57)=4.42$, $P<0.05$). The ADHDg-D group had a smaller enhancement of posterior midline power compared to the ADHDp-D group for total power ($F(1,57)=6.06$, $P<0.05$), and absolute alpha ($F(1,57)=5.21$, $P<0.05$). The ADHDg-D group had a smaller enhancement of frontal midline relative theta ($F(1,57)=4.85$, $P<0.05$) than the ADHDp-D group. No significant differences were found for absolute delta or theta.

In the comparison of the ADHD groups from Study 1 and this study, the only difference found was that the patients in this study had slightly less relative theta globally ($F(1,78)=5.51$, $P<0.05$).

4. Study 3

Study 3 aimed to determine whether good responders to methylphenidate and dexamphetamine have different EEG profiles.

4.1. Method

Subjects from the ADHD good-responder groups in Studies 1 and 2 were used in this study. The same sagittal and lateral contrasts as in Studies 1 and 2 were examined within frequency bands.

4.2. Results

As indicated in Table 4, the good responders to methylphenidate (ADHDg-M) had a greater theta/beta ratio ($F(1, 38)=4.25$, $P<0.05$), and less relative delta ($F(1,38)=5.04$, $P<0.05$) across all regions, than the good responders to dexamphetamine (ADHDg-D). In the posterior regions compared to the frontal regions, the ADHDg-M group had greater total power ($F(1, 38)=4.29$, $P<0.05$), absolute delta ($F(1, 38)=4.80$, $P<0.05$), and absolute theta ($F(1, 38)=4.97$,

$P<0.05$), than the ADHDg-D group (Fig. 3). In absolute theta, the difference between the mean of the frontal/posterior regions and the central region was greater in the ADHDg-M group than the ADHDg-D group ($F(1, 38)=4.14$, $P<0.05$). The ADHDg-M group had greater absolute beta in the left hemisphere than the ADHDg-D group, but this was reversed in the right hemisphere ($F(1, 38)=4.19$, $P<0.05$). In absolute alpha, the comparison of the two hemispheres in the frontal and posterior regions indicated that the ADHDg-M group had greater left posterior power than the ADHDg-D group ($F(1, 38)=4.56$, $P<0.05$).

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Fig. 3. EEG and ratio coefficient differences between good responders to methylphenidate and dexamphetamine.

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No significant group differences were found for relative theta, alpha and beta, or the theta/alpha ratio.

5. Discussion

EEG studies of children with ADHD have typically found increased theta activity (Satterfield; Mann; Janzen; Chabot; Lazzaro; Clarke; Clarke and Clarke), increased posterior delta (Matousek; Clarke; Clarke and Clarke), decreased alpha and beta activity (Dykman; Callaway; Mann; Clarke; Clarke; Clarke and Lazzaro), and an increase in the theta/alpha (Clarke and Clarke) and theta/beta ratios (Lubar; Janzen; Clarke; Clarke and Clarke) compared to normal children.

Study 1 found that the two ADHD groups had greater absolute and relative theta, lower relative alpha and beta, and greater theta/alpha and theta/beta ratios than the control group. These results are consistent with previous studies of children with ADHD. In Study 2, the number of significant differences between the ADHD and control groups was less, but the most consistent findings of increased relative theta and decreased relative alpha, decreased posterior absolute beta, and a higher theta/alpha and theta/beta ratio, were replicated. As has been reported previously (John and Clarke), relative power differences appear to be more

stable than absolute power, and differences in ratio coefficients remain good indicators of group differences (Lubar and Clarke).

Despite the fact that stimulant medication remains the major form of treatment for ADHD, and the number of EEG studies that have investigated electrophysiological abnormalities in ADHD, only a relatively small number of studies have investigated differences between good and poor responders to medication. Satterfield et al. (1972) compared good and poor responders to methylphenidate on measures of skin conductance level (SCL), EEG and auditory evoked potentials (ERP). Results indicated that good responders had low SCL, excessive EEG slow wave activity, characterized by high power delta and theta, and an increased P2 amplitude. This was further investigated in subsequent studies (Satterfield and Satterfield), which again found increased EEG abnormality in good responders to methylphenidate. While Satterfield et al. (1973a) interpreted the greater slow wave activity as possibly representing a maturational lag, these results were ultimately believed to indicate that good responders to methylphenidate are cortically hypoaroused (Satterfield and Cantwell, 1974).

The results of Study 1 are highly consistent with the above studies. The good responders to methylphenidate had higher total power than the poor responders, which primarily resulted from increased power in the delta and theta bands. An increased theta/beta ratio was also found in the ADHDg-M group, which is supportive of the hypoarousal theory. With increasing age, slow wave activity is replaced by faster waveforms (Wada and Clarke) during normal maturation of the EEG, with a strong complementary replacement being found between decreased activity in the theta band and increasing alpha power (Gasser et al., 1988b). As a result of this, a number of researchers have used the theta/alpha ratio to measure maturational changes in childhood (Matthis; Matousek and Clarke). In contrast to this, the theta/beta ratio has been proposed as a reliable measure of differences between children with and without ADHD. Lubar (1991) proposed this based on findings from normal children. During resting conditions, the dominant activity in the EEG is in the theta and alpha bands. When a person becomes aroused, activity reduces in the theta band and begins to shift towards the beta band. The hypothesis was that, if children with ADHD are underaroused, they may have problems reaching normal levels of arousal, which would be reflected in lower levels of beta activity, and higher theta. In Study 1, the ADHDg-M group had a higher theta/beta ratio than the ADHDp-M group, but no significant differences were found between groups on the theta/alpha ratio. This profile would suggest that they differ on measures of arousal, not maturation.

Within the literature, the majority of studies that have investigated differences between good and poor responders to stimulant medication have used methylphenidate, even though dexamphetamine is commonly prescribed for ADHD. An underlying assumption in much of the literature appears to be that the two medications are essentially similar, which results in discussions of the medications together under the collective title of ‘stimulants’. However, dexamphetamine has been found to have more side effects than methylphenidate (Efron et al., 1997), and not all children who respond to one medication will respond to the other (Chabot et al., 1996).

Study 2 compared good and poor responders to dexamphetamine. In all the significant differences found in this study, the good-responder group had more extreme EEG differences from the control group than did the poor responders. The results indicated that good responders had less relative alpha and beta activity across all sites. In posterior regions, the

good responders had greater total power, and less absolute and relative alpha. Unlike the differential responding to methylphenidate, differences in the EEG profiles of the good and poor responders to dexamphetamine suggest that the good responders have features of greater maturational lag than the poor responders. The increased posterior total power and relative delta, and the decreased posterior alpha are consistent with the regional topographic differences expected in younger normal children (Gasser, T., Jennen-Steinmetz, C., Sroka, L., Verleger, R. and Mocks, J., 1988. Development of the EEG of school age children and adolescents. II. Topography. *Electroenceph clin Neurophysiol* **69**, pp. 100–109. Abstract |

PDF (695 K) | View Record in Scopus | Cited By in Scopus (64)Gasser et al., 1988a). With normal development of beta activity, the difference between the midline and the two hemispheres increases with age (Clarke et al., 2001a). In this study, the difference in absolute beta between the midline and the two hemispheres was less in the ADHDg-D group than the ADHDp-D group, which would further suggest that the good responders are more maturationally lagged.

From Studies 1 and 2, the EEG profiles in the good-responder groups appear more abnormal than the poor responders to both methylphenidate and dexamphetamine. However, the EEG profiles of the good-responder groups appear to be qualitatively different. In Study 3, these EEG profiles were compared to determine exactly how the groups differed. In all the significant differences obtained, except for relative delta, the good responders to methylphenidate had greater EEG abnormalities than the responders to dexamphetamine. The good responders to methylphenidate (ADHDg-M) had a greater theta/beta ratio across all regions, greater posterior total power, and greater absolute delta and theta. These results suggest that the two groups differ primarily on measures of cortical arousal, with the methylphenidate good responders being more hypoaroused than the dexamphetamine good responders.

These results indicate that there is substantial heterogeneity within children with a diagnosis of ADHD of the Combined type. Clarke et al. (2001c) found 3 distinct subtypes of ADHD based on EEG profiles rather than behavior. These appeared to be a hypoaroused group, a small hyperaroused group, and a maturationally lagged group. The present study identified two groups, a hypoaroused group, and a maturationally lagged group, based on differences in their responses to medication. A hyperaroused group was not identified in the present study. However, a review of individual subjects found that two children in the ADHDp-D group had a hyperaroused EEG profile. This is compatible with our expectations, as cortical stimulation of an over-aroused child should not result in behavioral improvement. Together, these results suggest that, within the ADHD Combined type diagnosis, there are a number of distinct groups of children with different types of CNS dysfunction (see also Clarke et al., 2001e), and different responses to treatment regimes.

These results have implications for clinical practice. Much of the literature on medication use in ADHD treats the various stimulants as being similar and largely inter-changeable. This may not be accurate, as they appear to affect different groups of children differently. This indicates that it would be preferable if the efficacy of each medication with an individual was evaluated before treatment is commenced.

While the use of EEG measures in the diagnosis of ADHD has been widely criticised, primarily on the grounds of it still being experimental (Binnie; Rey and Nuwer), the procedure has also been identified as having enormous potential clinical value if it could be

used to identify good responders to medication (Levy and Ward, 1995). A small number of researchers have investigated the use of EEG measures in discriminant function analysis, to differentiate good and poor responders to methylphenidate (Princep and Chabot), and good responders to methylphenidate and dexamphetamine (Chabot et al., 1999). Results from these studies have shown a high degree of discriminability between good and poor responders to methylphenidate, as well as between good responders to either methylphenidate or dexamphetamine. While the present series of studies did not investigate differences at the individual level, the results indicate that there are distinct EEG group differences between good and poor responders to both methylphenidate and dexamphetamine, and between good responders to the two medications. These results also suggest that the two groups of good medication responders have different underlying electrophysiological abnormalities. Together these data have the potential to develop into valid and reliable tools to aid in the assessment of medication response in children with ADHD.

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