Event-related wave activity in the EEG provides new marker of ADHD

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Abstract

Objective: This study examines the utility of new measures of event-related spatio-temporal waves in the EEG as a marker of ADHD, previously shown to be closely related to the P3 ERP in an adult sample.

Methods: Wave activity in the EEG was assessed during both an auditory Oddball and a visual continuous performance task (CPT) for an ADHD group ranging in age from 6 to 18 years and comprising mostly Combined and Inattentive subtypes, and for an age and gender matched control group.

Results: The ADHD subjects had less wave activity at low frequencies (<1 Hz) during both tasks. For auditory Oddball targets, this effect was shown to be related to smaller P3 ERP amplitudes. During CPT, the ~1 Hz wave activity in the ADHD subjects was inversely related to clinical and behavioral measures of hyperactivity and impulsivity. CPT wave activity at ~1 Hz was seen to “normalise” following treatment with stimulant medication.

Conclusions: The results identify a deficit in low frequency wave activity as a new marker for ADHD associated with levels of hyperactivity and impulsivity.

Significance: The marker is evident across a range of tasks and may be specific to ADHD. While lower ~1 Hz activity partly accounts for reduced P3 ERPs in ADHD, the effect also arises for tasks that do not elicit a P3. Deficits in behavioral inhibition are hypothesized to arise from underlying dysregulation of cortical inhibition.

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Keywords: EEG; ADHD; Phase dynamics; Hyperactivity/Impulsivity; Stimulant medication

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1. Introduction

ADHD involves a number of symptoms that vary across individuals. The symptoms include hyperactivity, impulsivity and inattention and are often associated with conduct and emotional problems. Models of brain function in ADHD emphasize frontal/parietal interactions in deficits of attention (Pliszka et al., 1996; Silberstein et al., 1998; Levy and Farrow, 2001; Shaw et al., 2006) and anterior cingulate/lateral pre-frontal cortex interactions in behavioral disinhibition (Barbey, 1997; Quay, 1997; Williams, 2006). Mechanisms of large-scale coordination between cortical areas are explored in the present research via measures of global spatio-temporal waves in the EEG (hereafter termed ‘wave activity’). The present research focuses on delta-band wave activity, comparing ADHD subjects to matched controls on two distinct task conditions.

As reviewed by Barry et al. (2003b), the most robust ERP finding in relation to ADHD has been that of a reduced posterior P3 during an auditory Oddball task (see also Johnstone and Barry, 1996; Kemner et al., 1998; Lazzaro et al., 2001). However, this finding is not specific to ADHD, but arises for a variety of disorders of childhood and adolescence (Frank et al., 1994; Jeon and Polich, 2003). The P3 ERP has long been known to be associated with activity in the delta range (Basar-Eroglu et al., 1992; Demiralp et al., 1999; Heinrich et al., 2001; Quian Quiroga et al., 2001). In addition, delta-band spatio-temporal waves occurring at the time of the P3 ERP elucidate the spatio-temporal properties of these ERPs, when the latencies of the P3 are measured at multiple sites over the entire scalp (Alexander et al., 2006c). Specifically, for the P3-related peak in wave activity, the timing (300–400 ms) and frequency (2–3 Hz) matched known characteristics of the P3 ERP (Basar-Eroglu et al., 1992; Demiralp et al., 1999). In addition, the anterior to posterior pattern of P3 latencies across the scalp (Anderer et al., 1996; Alexander et al., 2006c) was matched by an anterior to posterior pattern of average wave motion at the P3-related peak in wave activity (Alexander et al., 2006c).

This electrical wave activity in the EEG can be described as the cortical equivalent to waves on a pond spreading from a dropped stone. A number of studies have shown wave activity in scalp EEG/MEG to be task/activity dependent, including working memory activation (Sauseng et al., 2002), listening to auditory tones (Ribary et al., 1991), resting states (Ito et al., 2005) and sleep (Massimini et al., 2004). The wave measures are at least as sensitive as EEG power measures or ERP amplitudes, as indicated from effect size statistics in studies involving child and adolescent populations. Wave measures have been used to differentiate first episode psychosis (FEP) subjects from controls and show moderate correlations with FEP symptom factors (Alexander et al., 2006d). They have also been used to demonstrate brain-functional differences during development in carriers of the apolipoprotein ε4 allele (Alexander et al., 2007). We have previously reported differences in ADHD children and adolescents on wave activity in abstract form (Alexander et al., 2006b). It was found that P3-related wave activity in children and adolescents peaks in the ~1 Hz range.

In addition to auditory Oddball targets, this study assessed subjects using CPT. The CPT is the most commonly used objective measure in discriminating ADHD (Corkum and Siegel, 1993) by tapping into an individual's ability to sustain attention. Several studies report moderate-to-high levels of sensitivity and poor-to-moderate specificity in identifying ADHD (Levy and Hobbes, 1997; Forbes, 1998; Riccio and Reynolds, 2001). Performance measures can be obtained from the CPT, including false positives, also referred to as errors of commission. False positives are more frequently displayed by children with ADHD than controls (Corkum and Siegel, 1993; Losier et al., 1996) and are believed to index impulsivity and hyperactivity when executed quickly after stimulus presentation, but to index inattention when delayed relative to stimulus presentation (Greenblatt et al., 1991; Halperin et al., 1988; Barkley, 1997).

When correlated with symptom scores, false positives have been found to correlate with all ADHD symptom domains in a child sample – most highly with hyperactivity (.59) followed by hyperactivity and impulsivity combined (.54) (Epstein et al., 2003). By definition, only the non-target condition of the CPT can elicit a false positive response, and is used in the present research to further test the hypothesis that low frequency wave activity may be related to Hyperactivity/Impulsivity symptoms in ADHD. Further, the non-target condition does not elicit a P3 ERP, enabling the generality of any wave activity differences in ADHD also to be tested.

Stimulant medications such as methylphenidate (MPH) and dexamphetamine (DEX) are thought to ameliorate symptoms of ADHD through the catecholamines dopamine and noradrenaline (Zametkin and Rapoport, 1986; Heilman et al., 1991; Volkow et al., 2001). These medications are thought to increase cortical arousal (Clarke et al., 2002b) and subsequently improve inhibitory functions, possibly via lateral pre-frontal cortex and associated anterior cingulate cortex circuits (Aston-Jones et al., 1999; Pliszka et al., 1996). These medications have been shown to be associated with changes (typically improvements) in ERPs componentry measured during CPT (Verbaten et al., 1994; Sunohara et al., 1999; Zillessen et al., 2001; Lawrence et al., 2005). Behaviorally, there appears no difference in their effects as measured by CPT performance (Efron et al., 1997). This study tested medication effects on CPT wave activity and its relationship to false positive responses and related clinical measure of Hyperactivity/Impulsivity.

This study sought to answer two questions. First, are the reported differences for ADHD in auditory Oddball P3 amplitude related to measures of wave activity? In particular, differences were expected for the delta-band components of wave activity, due to their association with the P3 ERP during auditory Oddball (Alexander et al., 2006c) and previous demonstration of low frequency effects on ERP differences in ADHD during auditory Oddball (Johnstone et al., 2003). Establishing a link between P3 ERP findings and wave activity in child/adolescent populations could further elucidate the meaning of reduced P3 amplitudes in ADHD.

Second, can equivalent wave activity differences be detected during tasks that do not elicit a P3 ERP? Visual CPT non-target trials were therefore analyzed because of their contrasting task characteristics to auditory Oddball targets, and reported sensitivity to ADHD clinical symptoms. A finding of related differences for both tasks would therefore help establish the generality of the measure of smoothly propagating wave activity as a marker for ADHD. To this end, the study compared ADHD subjects to controls on the measure of wave activity during CPT non-targets and related these results to clinical scales and behavioral measures of hyperactivity and impulsivity. In addition, this study explored the effects of stimulant medication on wave activity during CPT and its relationship to behavioral measures.

2. Methods

2.1. Subject selection

EEG data were acquired via the Brain Resource International Database from 175 ADHD participants (mean age = 12.29 ± 3.08 years; range 6–18 years; 40 females) and 175 age/gender matched controls (mean age = 12.23 ± 3.06 years; range 6–18 years). All ADHD participants were referred from pediatricians and psychologists (including SC, MK, CL) in Sydney and Adelaide according to DSM-IV-TR criteria (American Psychiatric Association, 1994) – 104 met the criteria for the Combined subtype of ADHD (24 females), 66 met the criteria for the Predominantly Inattentive subtype (15 females) and 5 were Hyperactive/Inattentive subtype (1 female) (Hermens et al., 2006). Secondary comorbid diagnoses within the ADHD group were accepted, and included learning disorder, conduct disorder, oppositional defiant, depression and anxiety.

Based on the opinion of the referring pediatrician, each patient was categorized according to broad comorbidity subgroups. Of the 175 ADHD patients, 11% were considered to show internalizing comorbidities, 35% with externalizing and 12% were diagnosed with comorbid learning disorders. All ADHD subjects were unmedicated at the first time of testing. One hundred and eighteen were medication naïve, 40 had washed-out from MPH for a minimum of 48 h and 17 had washed-out from DEX for a minimum of 48 h. Control participants were recruited through advertisements in school and community groups. All participants had an estimated IQ of 80 or above, assessed using the full-scale IQ (WISC-III or K-BIT) for ADHD participants and Spot the Real Word test (Baddeley et al., 1993) for controls. The Spot the Real Word test has been validated against the WAIS full-scale IQ (Paul et al., 2005).

All participants identified English as their primary language and except for a diagnosis of ADHD in the clinical groups (and any associated comorbid disorders listed above)
did not report experiencing a neurological disorder; physical brain injury; unconsciousness within the last 5 years; severe impediment to vision, hearing, or hand movement; or personal history of addiction to drugs. The control group also reported no family history of ADHD and no diagnosis of any psychological disorder. The subjects participated in the standardized testing procedures from the Brain Resource International Database (www.brainresource.com). All subjects gave written informed consent prior to participation, and local Ethics Committees for each participating laboratory approved all experimental procedures.

2.2. Medication treatment

A second, medicated testing session was carried out on 65 of the ADHD subjects (28 Inattentive type, 2 Hyperactive/Impulsive, 35 Combined, 13 female). All these ADHD subjects were taking their prescribed course of MPH \((n=46)\) or DEX \((n=19)\) for a period of at least 4 weeks, and were required to take their typical MPH/DEX dose 60 min before the testing session commenced. The average dose of MPH and DEX taken before the session was 22 mg and 10 mg, respectively. Importantly, two previous studies have reported no qualitative or efficacy differences between MPH and DEX (Elia et al., 1991; Efron et al., 1997).

2.3. Electroencephalographic data acquisition

Participants were seated in a sound and light attenuated room, controlled at an ambient temperature of 22 °C, and were assessed on a profile of cognitive domains. This battery of tests has good test-retest reliability (Williams, 2006) and established norms (Paul et al., 2005). A brief description of each test used in this study is provided below. EEG data were acquired from 26 channels: Fp1, Fp2, F7, F3, Fz, F4, F8, FC3, FCz, FC4, T3, T4, C3, Cz, C4, T4, CP3, CPz, CP4, T5, P3, Pz, P4, T6, O1, O2, using a Quikcap, NuAmps and according to the 10–20 electrode international system. Data were recorded relative to the average of A1 and A2 (mastoid) electrodes’ sites. Horizontal eye-movements were recorded with electrodes placed 1.5 cm lateral to the outer canthus of each eye. Vertical eye movements were recorded with electrodes placed 3 mm above the middle of the left eyebrow and 1.5 cm below the middle of the left bottom eye-lid. Skin resistance was \(<5\) and \(>1\ \text{kΩ}\) for all electrodes. A continuous acquisition system was employed and EEG data were EOG corrected offline (Gratton et al., 1983). The sampling rate of all channels was 500 Hz. A low pass filter with an attenuation of 40 dB per decade above 100 Hz was employed prior to digitization.

2.4. Experimental tasks

2.4.1. Auditory oddball task

Participants were presented with a series of high and low tones, at 75 dB and lasting for 50 ms (with rise and fall times of 5 ms). The inter-stimulus interval was 1.0 s. Participants were instructed to ignore the low (‘background’) tones (presented at 500 Hz) and to press, simultaneously with the index finger of each hand, a response button only when they heard high infrequent (‘target’) tones, which are presented at 1000 Hz. Speed and accuracy of response were equally stressed in the task instructions. The background and target tones were presented in a quasi-random order, with the constraint that two targets cannot appear consecutively. There were 60 targets and 280 backgrounds. The duration of the auditory oddball task was 6 min. This study examined the event-related EEG activity to Oddball target trials. Event-related EEG activity to Oddball targets provides robust electrophysiological information relating to the selection, evaluation and detection of significant auditory stimuli (e.g. Hillyard and Kutas, 1983), as well as eliciting a robust P3 ERP. Individual P3 ERP amplitudes were calculated as described elsewhere (Hermens et al., 2005a,b).

2.4.2. Visual continuous performance task

This task consisted of a series of letters (B, C, D or G) presented to the subject on the screen (for 200 ms), separated by an interval of 2.5 s. If the same letter appeared twice in a row, the subject was asked to press buttons simultaneously with the index finger of each hand. Speed and accuracy of response were equally stressed in the task instructions. There were 125 stimuli presented in total, 85 being non-target letters and 20 being target letters (i.e. repetitions of the previous letter). This study examined event-related EEG activity to CPT non-targets. The task condition allows assessment of the capacity to evaluate and detect visual target stimuli whilst continually updating target identity during task performance. CPT non-targets provide robust electrophysiological information relating to the selection and evaluation of visual stimuli and to the updating of working memory stores with newly relevant visual information (e.g. Clark et al., 1998; Weber et al., 2005). This task lasts approximately 6 min and also taps vigilance capacity. False positive responses during this task provide a direct behavioral index of impulsivity.

2.5. Phase gradient measures and global power

The EEG data from each of the tasks were analyzed using spatio-temporal wave measures and global power. In previous studies, spatio-temporal waves measured at the scalp had long spatial-wavelength and showed smooth changes in phase across the scalp – smooth phase gradients – at each time sample (Ribary et al., 1991; Sauseng et al., 2002; Massimini et al., 2004; Ito et al., 2005). These properties were explored in detail in Alexander et al. (2006c). Comparisons to surrogate data showed that during episodes of spatio-temporal waves measurable at the scalp, the waves have long spatial wavelength compared with the size of the scalp. Across multiple electrodes, the phase values at a given time-sample and frequency could therefore be assigned an unambiguous spatio-temporal ordering.
– the relative phases – from the phase-leading site to the most phase-lagged site. The presence of a smooth phase gradient in the pattern of relative phases was shown to coincide with the presence of spatio-temporal waves (Alexander et al., 2006c). The measure of spatio-temporal waves in the present study makes use of these properties of long spatial wavelength and smooth phase gradients to detect the waves.

The method for measuring long wavelength activity, via phase gradients, is discussed in detail elsewhere (Alexander et al., 2006c). In brief, the phases at each electrode site were estimated using two-cycle Morlet wavelets. The phases were estimated for 30 logarithmically spaced frequency bands between 0.2 and 32 Hz and at 10 ms intervals between –200 and 800 ms within each trial, where zero is the time of stimulus onset. For each time sample and at each frequency, the phases at each electrode were converted into relative phases by referencing the phases relative to the phase-leading electrode.

The spatial patterns of relative phases were assessed using three phase gradient basis functions. These basis functions are smoothly changing gradients across the scalp. The three basis functions consist of an anterior–posterior component (BAP), a peripheral–central component (BPC) and a right–left component (BRL). The phase gradient basis functions are illustrated in Alexander et al. (2006c), Fig. 2. Linear combinations of these phase gradient basis functions enable a wide range of smoothly changing patterns of phase gradient to be characterized, each having the property of exhibiting only one minimum or only one maximum; that is, having only one wave source or one wave sink. The amount of variance explained in the pattern of relative phases across the scalp by the phase gradient basis functions is given by

$$\sigma^2_{\Psi} = \rho(M\Psi, \Psi)^2$$

where $\Psi$ is the pattern of relative phases across the scalp, $\rho$ is the correlation function, $\sigma^2_{\Psi}$ and is the amount of variance explained (Alexander et al., 2006c). $M\Psi$ is the linear combination of basis functions that gives the best fit, given by

$$M\Psi = \rho(B_{AP}, \Psi)^2B_{AP} + \rho(B_{PC}, \Psi)^2B_{PC} + \rho(B_{RL}, \Psi)^2B_{RL}$$

The specific organization of patterns of phase gradient can be assessed by calculating the correlations of the relative phases with each of the individual basis functions at each time sample and frequency. The correlations of the relative phases with the anterior–posterior, peripheral–central and right–left basis functions are denoted as $r_{AP}$, $r_{PC}$ and $r_{RL}$, respectively.

The measure $\sigma^2_{\Psi}$ can be taken as the amount of spatio-temporal wave activity conforming to the properties described in the previous paragraphs, termed wave activity. The measure $M\Psi$ defines the overall shape (and hence direction) of the wave that best describes the EEG data, termed the wave map. These three measures, $r_{AP}$, $r_{PC}$ and $r_{RL}$ are used to quantify the amount that each direction-specific component contributes to the wave activity. These are termed the anterior–posterior component, the peripheral–central component and the right–left component, respectively.

Fig. 1 illustrates the method for calculating phase gradients, and the relationship of the method to spatio-temporal waves in the scalp EEG. Fig. 1a shows an individual’s EEG data filtered at ~10 Hz, during 130 ms of a single trial. The first six snapshots of scalp activity reveal a wave emerging from the top of the scalp (near Cz) and propagating to electrode sites at the periphery of the scalp. The last six snapshots of scalp activity show a wave moving from the anterior region of the scalp to the posterior (see Alexander et al., 2006c, supplementary material, for a movie of this time series). Fig. 1b shows these same phase values transformed into relative phases. The transformation of the data into relative phases shows a clear transition between two modes, from a central to peripheral phase gradient to an anterior to posterior one. The correlations of the relative phases with each of the phase gradient basis functions are shown in Fig. 1c. Initially, the relative phases have a strong peripheral–central component (reversed in direction) and there is a switch to a strong anterior–posterior component by the end of the time-series.

For the purpose of comparison to the wave measures, event-related global power in the EEG was measured at the same frequencies and times as the spatio-temporal wave measures of EEG. The power at each electrode was computed using the same Morlet wavelets, and the logarithm of this value averaged over electrodes to produce the mean log power (MLP) over the scalp at each time and frequency (Alexander et al., 2006c). A number of methodological issues arising from the wave measures are dealt with explicitly and in detail in Alexander et al. (2006c). These issues include the effects of volume conduction, choice of number of cycles in the Morlet wavelet and the relationship of the wave measures to power measures.

2.6. Calculation of band-pass filtered ERPs

For comparison with the results of Johnstone et al. (2003), the auditory Oddball EEG was band-pass filtered, and the filtered time series averaged for target trials to produce ERPs. Johnstone et al. (2003) used Fourier techniques to filter their ERP time-series between 0.01 and 2.0 Hz. In
the present research, a two-cycle, 1 Hz Morlet wavelet was used to extract the phase and amplitude at each time sample. This wavelet has a lower frequency resolution than standard Fourier techniques, essentially because it is equivalent to a Fourier transform using a very short time series window (Herrmann et al., 2005; Alexander et al., 2006c, Fig. 7). The half-power frequencies of a 1 Hz, two-cycle Morlet wavelet are at $1 \pm \frac{1}{\sqrt{2}}$ Hz. The filtered EEG data used to construct ERPs in the present research therefore contain components of the EEG signal from $\sim 0.5$ Hz to $\sim 1.5$ Hz. An additional $1 \pm 0.5$ Hz time series was constructed with the power information removed, that is, only phase information was retained. This additional time series was averaged for target trials to produce phase-only 0.5–1.5 Hz ERPs. Since, by definition, the range of values for the phase-only EEG time series is $\pm 1.0$, the amplitude of the phase-only 0.5–1.5 Hz ERPs is solely a function of phase jitter across trials at a given electrode. The maximum value of the phase-only 0.5–1.5 Hz ERP was also calculated for each subject, that is, the largest positive going component, called hereafter the phase-only 0.5–1.5 Hz ERP amplitude.

2.7. Statistical analysis of behavioral and EEG variables

All statistical analyses were made using the Statistical Package for Social Sciences (SPSS v.14). The results were analyzed in two stages. First, the wave activity for the two tasks at 1 Hz was averaged over the time interval 200–600 ms post-stimulus. This 1 Hz mean wave activity was compared across groups, for both tasks, within a single repeated measures ANOVA. ANCOVA, controlling for age, gave essentially identical results, so only the ANOVA results are reported here. Within the ADHD group, an ANOVA was conducted using comorbidity categories as the independent variable to test for the effects of comorbidity. The ANOVA examined four levels of comorbidity: ADHD with (1) none, (2) internalizing, (3) externalizing and (4) learning disorder; for the mean 1 Hz measures on both tasks. A separate ANOVA assessed the subset of ADHD subjects tested on two occasions, comparing their mean 1 Hz wave activity measures pre- and post-medication.

Within the control group, the mean 1 Hz wave activity for auditory Oddball target trials for each subject was correlated with P3 ERP amplitudes at Pz, and with the phase-only
0.5–1.5 Hz ERP amplitudes at Pz. Within the ADHD group, the mean 1 Hz wave activity for both tasks was correlated with clinical scales of Inattentiveness and Hyperactivity/Impulsivity, and behavioral measures of reaction time, false positive responses and false negative responses. The change in wave activity during CPT pre- vs. post-medication was correlated with the change in false positive responses during CPT pre- vs. post-medication. All correlations were made using the Spearman’s ρ statistic. Where variable distributions were normal, or could be transformed to normal, Pearson’s r and partial correlations controlling for age were also used, but in all cases gave similar results.

In the second stage of analysis, the first stage results were further explored over multiple times and frequencies. The differences between the ADHD and control groups on the EEG measures were tested for statistical significance at each time and frequency point sampled. This entails a large number of statistical tests (one for each of the 3000 time/frequency points for the EEG variables of global power and wave activity). To avoid type I errors, the multiple t-test results were only included as being statistically significant if they passed two hurdles. Only significant results from the first stage of analysis were analyzed in the second stage, and results were only included if they were significant at the p < 0.05 level, over 20 contiguous time and/or frequency points (Alexander et al., 2006a). One-way ANCOVA was also used to analyze each time and frequency point, with age as a covariate, but in all cases gave similar results to t-tests, so only the t-test results are reported here. Analogous to the between groups analysis, multiple paired-samples t-tests were used to explore pre- and post-medication changes in wave activity over the entire matrix of times and frequencies.

Wave activity within the ADHD group was compared to clinical and experimental measures by correlating the EEG measure at each time and frequency point with the behavioral variable. Within the medication re-test group, change in wave activity at each time and frequency point during CPT was correlated with change in false positive responses. This also entails a large number of statistical tests, so the same two inclusion hurdles applied to the between groups tests were also applied to all correlation analyses. A number of the clinical and behavioral variables had skewed distributions, so Spearman’s ρ was used for the correlation procedure. Where variables were normally distributed, or could be transformed to normal distributions, Pearson’s r and partial correlations controlling for age were also utilized. In all cases, these latter methods gave similar results to Spearman’s ρ, so only this latter statistic is reported in the results.

3. Results

3.1. Wave activity during auditory Oddball target trials and relationship to P3 ERP

Values of wave activity were compared for the ADHD group and their matched controls for auditory Oddball targets. Table 1 shows the ADHD group had lower mean 1 Hz wave activity than the control group. The detailed time by frequency analyses are shown in Fig. 2a. The control subjects showed a peak in wave activity, associated with the P3 ERP, at 470 ms, 1.2 Hz. The ADHD subjects had less wave activity at lower frequencies, with the largest differences occurring at ~1 Hz. Inspection of the plots for wave activity clearly indicates the group differences largely overlapped (in frequency and time) with the low frequency P3-related peaks in the control group. In other words, the ADHD subjects had less P3-related wave activity during auditory Oddball. The group difference was maximal at 600–800 ms.

<table>
<thead>
<tr>
<th>Group comparisons</th>
<th>Task</th>
<th>ANOVA</th>
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<tr>
<td></td>
<td>Oddball targets</td>
<td>CPT non-targets</td>
</tr>
<tr>
<td>Clinical vs. control comparison: mean wave activity (1 Hz, 200–600 ms)</td>
<td>ADHD mean (SD)</td>
<td>0.491 (0.0797)</td>
</tr>
<tr>
<td>Controls mean (SD)</td>
<td>0.527 (0.0772)</td>
<td>0.506 (0.0856)</td>
</tr>
<tr>
<td>ADHD comorbidity comparison: mean wave activity (1 Hz, 200–600 ms)</td>
<td>No comorbidity mean (SD)</td>
<td>0.492 (0.0842)</td>
</tr>
<tr>
<td>Internalizing mean (SD)</td>
<td>0.490 (0.0766)</td>
<td>0.473 (0.0900)</td>
</tr>
<tr>
<td>Externalizing mean (SD)</td>
<td>0.482 (0.065)</td>
<td>0.474 (0.0667)</td>
</tr>
<tr>
<td>Learning disorder mean (SD)</td>
<td>0.511 (0.103)</td>
<td>0.476 (0.122)</td>
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<tr>
<th>Group comparisons</th>
<th>Treatment condition</th>
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<tr>
<td>ADHD medication group pre- vs. post-treatment comparisons: CPT mean wave activity (1 Hz, 200–600 ms)</td>
<td>Pre-medication</td>
<td>0.469 (0.0835)</td>
</tr>
<tr>
<td></td>
<td>Post-medication</td>
<td>0.503 (0.0828)</td>
</tr>
</tbody>
</table>

Summary ANOVAs for mean wave activity (1 Hz, 200–600 ms). Repeated measures ANOVA showed that the ADHD group had significantly less mean wave activity than the control group during auditory Oddball and CPT. There were no group by task interactions. Repeated measures ANOVA on the ADHD group, divided into comorbidity sub-groups, showed no effect for comorbidity sub-group on mean wave activity for either tasks. Repeated measures ANOVA on the ADHD medication sub-group showed that there was a significant increase in mean wave activity from pre-medication to the post-medication condition during CPT.
a. Wave activity for auditory Oddball, target trials

b. Wave activity for Continuous Performance Task, non-target trials

c. Wave activity for Continuous Performance Task, non-target trials

d. Global power for auditory Oddball Task, targets

e. Global power for Continuous Performance Task, non-targets
The direction of wave propagation was quantified at the peak in wave activity via the grand-average wave map of the control group. The wave map for auditory Oddball was generated for the time/frequency point 470 ms, 1.2 Hz. Fig. 1d shows that the grand-average wave map had a posterior to anterior gradient. In order to confirm the relationship of the wave map to standard ERP components, grand-averaged ERP curves were generated for both groups using 0.5–1.5 Hz band-pass filtered time-series. Fig. 3a shows these low frequency ERP waveforms. There was a clear latency distribution to the positive and negative peaks. The ERPs for auditory Oddball targets have the posterior to anterior gradient in the latencies is indicated, confirming the results for the grand-average wave map given in Fig. 1. The ERP curves are plotted on a scale of ±9 μV. (b) The EEG data were band-pass filtered between 0.5 and 1.5 Hz, and amplitude information removed, before trial-averaging to produce ERPs. That is, the filtered ERPs contain information about phase only. The results, in terms of group differences and latency gradient, are visually identical to the band-pass filtered data in (a). Differences due to the presence of EEG amplitude information only become apparent at the single trial level. The ERP curves are plotted on a scale of ±0.6.

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Fig. 3. Grand-average ERPs derived from 0.5–1.5 Hz filtered time-series, for the auditory Oddball task, target trials. The control group ERPs are shown with an unbroken curve, the ADHD group ERPs with the broken curve. The dotted diagonal lines show the latencies of the initial negative going and later positive going ERPs across the scalp, in the control group grand-average. The time scale at bottom left is in milliseconds, with zero corresponding to stimulus delivery. The ERP data shown for the same electrodes and in that same format as Johnstone et al. (2003), Fig. 2, for ease of comparison. (a) The EEG data are band-pass filtered between 0.5 and 1.5 Hz before trial-averaging to produce ERPs. The control group has larger late, positive going ERP amplitude at most electrode sites. A clear posterior to anterior gradient in the latencies is indicated, confirming the results for the grand-average wave map given in Fig. 1. The ERP curves are plotted on a scale of ±9 μV. (b) The EEG data were band-pass filtered between 0.5 and 1.5 Hz, and amplitude information removed, before trial-averaging to produce ERPs. That is, the filtered ERPs contain information about phase only. The results, in terms of group differences and latency gradient, are visually identical to the band-pass filtered data in (a). Differences due to the presence of EEG amplitude information only become apparent at the single trial level. The ERP curves are plotted on a scale of ±0.6.

Fig. 2. Group comparisons for event-related wave activity \( \left( s^2_{\text{wav}} \right) \) and global power, for auditory Oddball and CPT. The left column shows the grand-average time by frequency plots of wave activity for the ADHD group, with the controls in the middle column, except for row C, which compares the ADHD medication treatment sub-group, pre- and post-medication. The right column shows the mean difference between the two groups, with significant regions \( (p < 0.05) \) bounded by black lines. For each of the plots, the scale of values for wave activity or global power is shown next to the plot. Frequency is displayed on the y-axis, on a logarithmic scale. Time during the trial is displayed on the x-axis, with zero being the time of stimulus delivery. The ERP data shown for the same electrodes and in that same format as Johnstone et al. (2003), Fig. 2, for ease of comparison. (a) For the auditory Oddball task, target trials, the ADHD subjects had significantly lower wave activity values at 1 Hz, which was closely related in time and frequency to the control group peak in wave activity in the same band. (b) For CPT, non-target trials, the ADHD subjects had significantly lower wave activity values at 1 Hz, which also was closely related in time and frequency to the control group peak in wave activity in the same band. (c) Medication response in ADHD subjects showing change in CPT wave activity for the treatment sub-group. Post-medication, the ADHD subjects showed an increase in 1 Hz wave activity. The magnitude of the mean difference was similar to the difference between the control and ADHD groups (seen in b), and the change was in the direction of the control group. (d) During the auditory Oddball task, target trials, ADHD subjects showed significantly lower global power in the beta-band \( (p < 0.05) \), which was apparent at most times, except between 300 and 600 ms. The ADHD subjects also showed increased power at very low frequencies; however, this may be due to recording artifact (see Section 3). There is an absence of a significant difference between the two groups in global power at 1 Hz. (e) During the CPT, non-target trials, ADHD subjects showed significantly lower global power in the beta-band \( (p < 0.05) \), which was apparent at all times, except 350 ms. There is an absence of a significant difference between the two groups in global power at 1 Hz.
appearance of a posterior to anterior wave in childhood/adolescence. At most electrode sites, the amplitude of the filtered ERPs was smaller in the ADHD group. This qualitatively confirms the quantitative differences found using the wave measure. Fig. 3b shows the grand-average phase-only 0.5–1.5 Hz ERPs. The shapes of the curves are essentially identical in the grand-average to the curves that include amplitude information.

The ADHD group was compared to the matched control group on the measure of global power, shown in Fig. 2d. The ADHD subjects showed a decrease in event-related beta power, consistent with previous research (Callaway et al., 1983). The main result of interest in the present research context is the lack of group differences in the ~1 Hz band.

Correlational analyses in the control sample were undertaken to quantitatively confirm the qualitative observations of a relationship between the P3 ERP and P3-related wave activity (Alexander et al., 2006c). Table 2 shows that 1 Hz mean wave activity for auditory Oddball target trials was significantly correlated with P3 amplitudes at Pz. Fig. 4a, left plot, shows the detailed time by frequency correlations for wave activity and P3 amplitudes at Pz. The peak correlations were in the ~1 Hz band, at 310 ms. By way of comparison, Fig. 4b, centre plot, shows that event-related global power was unrelated to P3 amplitude at Pz at P3-related times and frequencies. Table 2 also shows that 1 Hz mean wave activity for auditory Oddball target trials was significantly correlated with the phase-only 0.5–1.5 Hz ERP amplitude at Pz, and that this correlation was greater than for the P3 ERP. This result is confirmed in Fig. 4a, right plot, which shows the detailed time by frequency correlations for wave activity and phase-only 0.5–1.5 Hz ERP amplitude at Pz.

Values of wave activity were compared for the ADHD group and their matched controls for CPT non-targets. Table 1 shows the ADHD group had lower mean 1 Hz wave activity than the control group. The detailed time by frequency analyses are shown in Fig. 2b. The control subjects showed a peak in wave activity at 400 ms, 1.2 Hz for CPT. Inspection of the plots for wave activity clearly indicates the group differences largely overlapped (in frequency and time) with the low frequency peak in the control group. The group difference was maximal 100–400 ms. During the CPT task, the ADHD subjects also showed lower values of wave activity in the theta band at around the time of stimulus delivery and at ~700 ms post-stimulus.

The results for global power during CPT non-targets were consistent with the Oddball results. Fig. 2e shows the group comparisons on the measure of global power. Again there was a lack of group differences in the ~1 Hz band. For CPT, the effect sizes, given by $\eta^2_p$, were calculated at each time and frequency point for the measures of global power and wave activity. Effect sizes peaked for global power in the beta range at 2.9% of variance explained. By comparison, the effect size for the wave activity measure peaked in the ~1 Hz range at 5.0% of variance explained. These figures are for individual time/frequency points, for the purposes of direct comparison of measures, and do not reflect the combined explanatory power of the measures over a range of time and frequency points.

There were no significant effects of comorbidity group on either mean 1 Hz variable in the ANOVA conducted for comorbidity effects. For all comorbidity sub-groups, the ADHD means were lower than the control mean, for both task conditions.

3.3. Relationship between CPT wave activity, measures of Hyperactivity/Impulsivity and medication effects

The finding of a decrease in wave activity on the mean 1 Hz wave activity measure during CPT was consistently related to several behavioral variables and to medication effects (see Table 1). By way of contrast, while global power for auditory Oddball and CPT in the beta range was lower for the ADHD group, it was positively correlated with the DSM IV Hyperactivity/Impulsivity scale (results not shown). Correlations between mean 1 Hz wave activity and the number of false positive responses in the ADHD group were negative and statistically significant, for both auditory Oddball and CPT. However, the magnitude of these correlations was strongest for CPT, and additionally, the (negative) correlation between mean 1 Hz wave activity and Hyperactivity/Impulsivity scale was statistically significant for only CPT. Because of the strength and consistency of the results using the wave activity measure during CPT.
non-targets, and for brevity of exposition, the remainder of the results section focuses on this aspect of the findings.

Fig. 4b, left plot, shows the correlation of the wave activity measure during CPT with the Hyperactivity/Impulsivity scale from the DSM IV clinical assessment of the ADHD subjects. The same region of the plot that showed group differences between ADHD and controls, in the vicinity of ~1 Hz, also showed modest but significant correlations with the Hyperactivity/Impulsivity scale. The maximum correlation in this region was \( p = -0.23 \) and the peak correlation in this region occurred at approximately the same time and frequency as the maximal group difference between the ADHD and matched control groups on the wave activity measure. There were additional regions of negative correlation in the pre-stimulus theta band and in the alpha band. There were no significant correlations between wave activity and the DSM IV Inattentiveness scale (see Table 1).

Fig. 4b, centre plot, shows the correlation of the wave activity measure during CPT with false positive responses during CPT (that is, the number of button presses to non-target stimuli). Almost the entire region of the plot shows significant correlations between wave activity and false positives, but the strongest correlations were in the ~1 Hz region. The peak correlation was \( p = -0.46 \), and occurred at approximately the same time and frequency as the maximal group difference between the ADHD and matched control groups on the wave activity measure during CPT. There were no significant correlations with number of false negative responses. Within the sub-group of ADHD subjects treated with stimulant medication, the change in mean wave activity was negatively correlated with the change in false positive responses.

### Table 2

Summary correlations:

<table>
<thead>
<tr>
<th>Wave activity</th>
<th>P3 amplitude at Pz</th>
<th>Phase-only 0.5–1.5 Hz ERP amplitude at Pz</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oddball targets</td>
<td>0.281</td>
<td>0.374</td>
</tr>
<tr>
<td>( p ) (two-tailed)</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>( N )</td>
<td>151</td>
<td>158</td>
</tr>
</tbody>
</table>

ADHD group correlations:

<table>
<thead>
<tr>
<th>Wave activity</th>
<th>Inattentiveness</th>
<th>Hyperactivity/Impulsivity</th>
<th>Mean reaction time</th>
<th>False positives</th>
<th>False negatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oddball targets</td>
<td>0.014</td>
<td>-0.062</td>
<td>-0.082</td>
<td>-0.213</td>
<td>-0.145</td>
</tr>
<tr>
<td>( p ) (two-tailed)</td>
<td>0.868</td>
<td>0.456</td>
<td>0.336</td>
<td>0.011</td>
<td>0.086</td>
</tr>
<tr>
<td>( N )</td>
<td>145</td>
<td>145</td>
<td>141</td>
<td>141</td>
<td>141</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Wave activity</th>
<th>CPT non-targets</th>
<th>Mean reaction time</th>
<th>False positives</th>
<th>False negatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \Delta ) mean reaction time</td>
<td>0.072</td>
<td>-0.319</td>
<td>-0.052</td>
<td></td>
</tr>
<tr>
<td>( \Delta ) false positives</td>
<td>0.571</td>
<td>0.01</td>
<td>0.679</td>
<td></td>
</tr>
<tr>
<td>( \Delta ) false negatives</td>
<td>65</td>
<td>65</td>
<td>65</td>
<td></td>
</tr>
</tbody>
</table>

Summary correlations for mean wave activity (1 Hz, 200–600 ms) within the control group, P3 ERP amplitudes at the Pz electrode were positively correlated with mean wave activity during auditory Oddball targets. Similarly, the control group showed a significant positive correlation between phase-only 0.5–1.5 Hz ERP amplitude at Pz and the mean wave activity. Within the ADHD group, mean wave activity during auditory Oddball targets was negatively correlated with the number of false positive responses. Within the ADHD group, mean wave activity during CPT was negatively correlated with both Hyperactivity/Impulsivity score and number of false positive responses. Within the sub-group of ADHD subjects treated with stimulant medication, the change in mean wave activity was negatively correlated with the change in false positive responses.
In order to assess the relationship of these brain-functional changes to behavioral change, the change in false positive responses before and after medication was correlated with the change in wave activity before and after medication. The correlations between these two measures of change are shown in Fig. 4b, right plot. Again, there were moderate correlations in the ~1 Hz band. This meant that those subjects that had the biggest decrease in false positives post-medication also had the highest increases of wave activity in the ~1 Hz band post-medication. The strongest correlations in this band were observed prior to stimulus delivery ($\rho = -0.41$ at $\sim-100$ ms) but there were significant correlations in this frequency band at all times during the trial. There were additional negative correlations between change in false positive and change in wave activity in the pre-stimulus alpha and theta bands, and late (~600 ms) post-stimulus alpha and theta.

**4. Discussion**

The present research proposes that a decrease in wave activity in the ~1 Hz range is a novel marker for ADHD. Wave activity measures the amount of smoothly propagating, long wavelength activity across the scalp. This finding
was demonstrated for both selective (Oddball) and sustained (CPT) attention tasks, across two different sensory modalities (auditory and visual, respectively). Notably, the diminished ~1 Hz wave activity occurred in the absence of group differences in event-related global power in the same frequency range. A link between this reduced wave activity and previous findings of a reduced P3 ERP in ADHD during auditory Oddball was also demonstrated, while it was also shown that the decreased ~1 Hz wave activity is not specific to task conditions that elicit a P3 ERP.

During CPT, the diminished ~1 Hz wave activity in ADHD subjects was shown to be related to higher Hyperactivity/Impulsivity scores and higher numbers of false positive responses during CPT. Treatment with stimulant medication was shown to normalize the ~1 Hz wave activity during CPT and this increase in wave activity was related to a decline in false positive responses on the same task.

The results are interpreted as dysfunction in global coordination of cortical inhibition. This interpretation is consistent with models of ADHD dysfunction, particularly those emphasizing deficits in executive function and behavioral inhibition.

4.1. Event-related delta-band wave activity and the P3 in normative samples

The peak frequency of global power associated with the auditory Oddball P3 increases during development. This effect can be seen clearly by comparing the results for two age groups: the control group of 6–18-year-olds in the present study and the 25–50 years olds in Alexander et al. (2006c). There is a low frequency peak at ~1.2 Hz for Fig. 2d, middle panel, and the analogous peak is at ~2.5 Hz in adult subjects (Alexander et al., 2006c, Fig. 6, bottom right panel). Closely tracking this developmental increase in frequency of the P3-related peak in global power is the P3-related peak in wave activity. This can be seen by comparing the low frequency peak in Fig. 2a, middle panel, to the analogous peak in Alexander et al. (2006c, Fig. 6, bottom left panel). The increase in frequency of P3-related wave activity changes smoothly with age over the age range of 6–30 years from 1 to 2.8 Hz (Alexander et al., 2006d). The measures of peak global power and wave activity are therefore consistent with previous analyses showing that the P3 ERP is largely comprised of delta-band activity (Basar-Eroglu et al., 1992; Demiralp et al., 1999). The ~1 Hz wave activity differences between ADHD subjects and controls in the present results are therefore clearly in the delta-band, for the present study population with a mean age of ~12 years. To our knowledge, this is the first time an age-related frequency shift has been reported for the delta band, analogous to that seen for alpha peak frequency (Klimesch, 1999; Clark et al., 2004).

Normal developmental changes in the P3 include a decline in P3 latency from 6 to 23 years (Courchesne, 1977). In the present population the latency of the P3-related grand-average peak in wave activity was 470 ms, which compares to 375 ms for an adult population (Alexander et al., 2006c). In addition to an overall decrease in P3 latency during development, there is a qualitative shift in the pattern of P3-related latencies across the scalp with age. The present results and those of Johnstone et al. (2003), Fig. 2, show that ERPs averaged from delta-band filtered EEG are associated with a posterior to anterior latency gradient in subject populations of late childhood/early adolescence. The present results show the grand-average wave map at the peak in P3-related wave activity is dominated by posterior to anterior waves for late childhood/early adolescence populations. In adults, the pattern of P3 latencies across the scalp is anterior to posterior (Anderer et al., 1996). In adults, the grand-average wave map at the peak in P3-related wave activity is dominated by anterior to posterior waves ( Alexander et al., 2006c).

Alexander et al. (2006c), in an adult sample, have demonstrated correspondences for the P3 ERP component between the timing, spectral characteristics and the pattern of ERP latencies across the scalp and the equivalent properties at the P3-related peak in wave activity. These same correspondences between properties of the P3 ERP and P3-related peak in wave activity also apply to the present control sample with mean age 12 years, even though the timing, spectral characteristics and patterns of ERP latencies across the scalp all differ from the adult sample. In other words, the development trajectory of these three properties appears to run in parallel across the two different types of measures.

Lower mean ERP amplitudes can reflect a lack of trial to trial phase locking, rather than low single trial amplitudes, per se (Sayers et al., 1974; Makeig et al., 2004; Gruber et al., 2005; see Fig. 3, this study). The measure of wave activity in the present study analyzes the extent of smoothly changing wave patterns across the scalp within a single time sample of EEG activity. The present results therefore suggest that previous findings of diminished P3 amplitudes in ADHD (Johnstone and Barry, 1996; Kemner et al., 1998; Lazzaro et al., 2001) and more specifically, smaller ERP amplitudes derived from low frequency components of the EEG (Johnstone et al., 2003), arise at least in part because of a decrease in smoothly propagating wave activity at the individual trial level. This was demonstrated in the present research by the moderate correlation between ~1 Hz global wave activity and P3 amplitudes at Pz in the control subjects. Additionally, the phase-only 0.5–1.5 Hz ERP amplitude at Pz showed a similar pattern of correlations with the wave activity measure. This means that, in the ~1 Hz band, the measure of within trial, smoothly propagating wave activity across the scalp explained up to 16% of the variance of the measure phase jitter across trials at site Pz.

4.2. Delta-band wave activity and its relationship to the P3 in ADHD

The main result of the present study was lower ~1 Hz wave activity in ADHD subjects. This lower wave activity
during auditory Oddball targets was shown to be related to lower P3 ERP amplitudes in the control population. The lower wave activity can therefore be related to previous finding of reduced P3 ERPs during auditory Oddball (Johnstone and Barry, 1996; Kemner et al., 1998; Lazzaro et al., 2001).

We hypothesize that there is a disorganization of wave activity in the delta band in ADHD subjects at the time of the P3 ERP, resulting in less trial to trial phase locking at individual sites and in turn to lower P3 ERP amplitudes in trial-averaged data. The amount of variance explained by the correlations between P3 amplitudes and wave activity indicates that the hypothesized effect is not the only source of interpersonal differences in P3 ERP amplitudes. By contrast, however, there were no differences in event-related delta or theta band global power in the two groups, nor significant correlations between global power at P3-related times/frequencies and P3 amplitude at Pz.

A problem confronting application of traditional ERP analysis to clinical disorders is an often-time lack of specificity. For example, auditory Oddball P3 ERP amplitudes are diminished in a range of disorders, including the adolescent disorders of ADHD, FEP and learning disorder (Frank et al., 1994; Jeon and Polich, 2003). Of interest here is a previous finding that the decrease in delta-band wave activity may be specific to ADHD (Alexander et al., 2006b). When other clinical groups were compared to their own matched controls (FEP, post-traumatic stress disorder and elderly subjects with subjective memory complaints) for auditory Oddball target condition, only the ADHD group showed decreased wave activity in the (age-adjusted) delta band. This suggests that a diminishment of delta-band wave activity is sensitive to the P3-related changes specific to ADHD (Alexander et al., 2006b). For example, while studies of FEP subjects have revealed a diminished P3 in this clinical population (Ford et al., 1992; Bramon et al., 2004), wave activity at the P3-related peak shows a trend-level increase in FEP. Instead, a difference in the organization of anterior–posterior component of the P3-related wave activity appears to account for the diminished P3 in FEP (Alexander et al., 2006d). While diminished P3 amplitudes at Pz are not apparent for children with autism and dyslexia (Kemner et al., 1998), it will be informative to make comparisons to more clinical groups in the adolescent age-range on the measure of delta-band wave activity.

### 4.3. Event-related delta-band wave activity as a marker for ADHD

In a previous study, the wave activity of ADHD subjects was compared to matched controls on a variety of tasks, including Go-Nogo, auditory habituation and a passive letter viewing task (Alexander et al., 2006b). The same deficit in ~1 Hz activity was shown for each of these tasks, but the exact timing of the maximal difference between groups varied from task to task: 150 ms for Go-Nogo, Nogo condition, 300 ms for auditory habituation and 500 ms for letter viewing. For these latter two tasks, while the subjects were instructed to attend to the stimuli, no overt behavioral response was required during entire task. Since the decrease in low frequency wave activity was not dependent on a behavioral response, it is likely related to cognitive processing rather than behavioral output per se. The range of tasks for which the diminished ~1 Hz wave activity is seen reflects a diverse range of cognitive loads.

Barry et al. (2003b) have reviewed the ERP components applicable to the study of ADHD. These ERP components are specific from task to task and across sensory modalities, resulting in a complex set of relationships between different ERP components and brain function. The diversity in ERP components across tasks is matched in the present results by times and frequencies of event-related peaks in wave activity for different tasks (compare Fig. 2a, middle panel, with Fig. 2b, middle panel). Despite these many combinations of ERP components, diminished ~1 Hz wave activity in ADHD is a consistent finding across at least five tasks (Alexander et al., 2006b). The wave activity measure may therefore provide a cutting edge for the Gordian Knot of task by ERP component combinations that are potentially applicable to the study of ADHD. The generality of the present results suggests a brain-functional disturbance associated with ADHD, common across a variety of cognitive domains, including tasks that do not elicit a P3 ERP.

While the basic effect of diminished ~1 Hz wave activity is apparent for a range of tasks, CPT showed the most consistent results across a range of relationships to other measures. The correlations of CPT wave activity with the Hyperactivity/Impulsivity scale revealed a peak correlation at a similar time and frequency to the maximal group difference between the ADHD and control groups. Similarly, the maximal correlation with false positive responses during CPT peaked in this same region of the time by frequency plot. For the auditory Oddball 1 Hz mean wave activity, only correlations with false positive responses proved significant. The hypothesis relating delta-band wave activity to Hyperactive/Impulsive symptoms is therefore supported most strongly by the data from CPT non-targets. The CPT wave activity profile of ADHD subjects in response to stimulant medication was markedly similar to the wave activity profile of the matched controls (compare Fig. 2b, middle panel, to Fig. 2c, middle panel). The correlation between the medication response on the measure of wave activity and the medication response to the number of false positives for the CPT also revealed a substantial effect in the ~1 Hz band. Across these various comparisons for the CPT there were also some inconsistent effects in the alpha and theta band, during pre-stimulus, immediately post-stimulus and late post-stimulus periods.

CPT is the most commonly used objective measure in discriminating ADHD (Corkum and Siegel, 1993), assessing an individual’s ability to sustain attention. The present study provides confirmation of the utility of CPT in assessment of ADHD, since the ~1 Hz wave activity during CPT
non-targets was most reliably related to clinical and behavioral measures and medication effects, in comparison to auditory Oddball and a number of other tasks (Alexander et al., 2006b). Interestingly, the clinical and behavioral measures that showed consistent relationships were the Impulsivity/ Hyperactivity score and related behavioral measure of false positive responses. These findings suggest that the wave activity measure and CPT used in combination have utility in assessing the Hyperactive/ Impulsive features of ADHD, particularly when the non-target condition is assessed. An alternative explanation for the consistency of results during CPT may be the high cognitive load of CPT compared to other tasks.

4.4. Relevance to models of ADHD

Some models of ADHD emphasize fronto-parietal network dysfunction (Pliszka et al., 1996; Silberstein et al., 1998; Levy and Farrow, 2001; Shaw et al., 2006). The CPT is reliant on these networks (Clark et al., 1998; Weber et al., 2005) and stimulant medication has been shown to selectively decrease cerebral blood flow within frontal and parietal regions (Mehta et al., 2000). Models of fronto-parietal network dysfunction tend to emphasize the attentional aspects of ADHD during working memory tasks.

A second class of models of ADHD emphasizes deficits in executive function and failure of behavioral inhibition (Barkley, 1997; Quay, 1997; Williams, 2006). In short, the failure of behavioral inhibition by anterior cingulate arises from difficulties in processing context dependent salience in the lateral pre-frontal cortex. Increased activity in rostral anterior cingulate and left lateral frontal cortices have been associated with false positive responses in normals (Kiehl et al., 2000), and there is evidence for an abnormality in the recruitment of these areas in ADHD (Bush et al., 1999; Hermens et al., 2005a,b). An fMRI study suggests that the response of ADHD subjects to stimulant medication is different to controls and is characterized by atypical frontal–striatal functioning (Vaidya et al., 1998).

These two models of dysfunction in ADHD are generally consistent with the present findings, since they both involve coordination of large-scale cortical networks. Cortical wave activity comprises an excellent candidate mechanism for the general process of global cortical coordination (Alexander et al., 2006c). Since the present findings concern delta range activity, it is likely that the observed effects involve control of cortical activity via gross suppression of unwanted cortical modes. Delta-band activity is associated with cortical inactivation, selectively suppressing non-relevant brain activity during performance of mental tasks (Harmony et al., 1996) or detection of near-threshold stimuli (Basar, 2000). Consistent with this view, P3-related delta activity arising during event-related experimental tasks is involved in internal decision-making processes (Basar-Eroglu et al., 1992) and context updating (Donchin and Coles, 1988). We speculate that delta-band wave activity is suppressing superfluous cognitive activity during cognitive closure on a particular decision. The relationships of the present results to Hyperactive/Impulsive symptom scales, the related behavioral measure of false positive responses, and the relationship to the P3 ERP as ‘context update’ suggest the present results are more related to dysfunction in the coordination of context and behavior in ADHD. A dysfunction of cortical inhibitory processes has been linked to the overt behavioral symptoms of ADHD (Barry et al., 2003b; Williams, 2006).

The underlying dysregulation in fronto-striatal networks is thought to arise from disturbance of the neuromodulation in the cortex, affecting the balance of excitatory versus inhibitory activity (Levy and Farrow, 2001; Williams, 2006). During task activity, this imbalance may manifest as a deficit in global inhibitory (delta-band) coordination mechanisms, without differences in global, event-related delta-band power. Stimulant medication, acting via the catecholamines dopamine and noradrenaline (Zametkin and Rapoport, 1986; Helman et al., 1991; Volkow et al., 2001), appears to re-instate event-related delta-band wave activity to normal levels, and improve at least one behavioral measure of impulsivity in direct relation to improvement in wave activity levels. The results are therefore consistent with stimulants as anti-hyperactivity/impulsivity medications (Seeman and Madras, 2002, 1998).

In conclusion, decreased ~1 Hz wave activity is a promising new marker for ADHD, particularly for subjects with Hyperactive/Impulsive symptomatology. The new marker can be related directly to existing findings of reduced P3 ERPs in ADHD, although it appears to be more general (across tasks) and more specific (across disorders) than the phenomenon of lower auditory Oddball P3 amplitudes in ADHD. Diminished ~1 Hz wave activity also has important functional implications that can be applied to the study of ADHD. The measured effect implies a specific mechanism for the observed deficits in the coordination of attention and behavior, via a hypothesized dysfunction in global inhibitory coordination. Further exploration of this phenomenon will have empirical utility in distinguishing and refining existing models of ADHD dysfunction, especially those models that posit a breakdown of functional interactions between widespread regions of cortex.

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References


