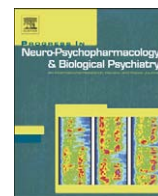




Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

The increase in theta/beta ratio on resting-state EEG in boys with attention-deficit/hyperactivity disorder is mediated by slow alpha peak frequency

Marieke M. Lansbergen^{a,*}, Martijn Arns^{b,c}, Martine van Dongen-Boomsma^{a,d},
Desirée Spronk^{a,b}, Jan K. Buitelaar^{d,e}

^a Department of Psychiatry, Radboud University Nijmegen Medical Centre, Donders Institute for Brain, Cognition and Behaviour, Nijmegen, The Netherlands

^b Research Institute Brainclinics, Nijmegen, The Netherlands

^c Department of Experimental Psychology, Utrecht University, Utrecht, The Netherlands

^d Karakter Child and Adolescent Psychiatry University Centre, Nijmegen, The Netherlands

^e Department of Cognitive Neuroscience, Radboud University Nijmegen Medical Centre, Donders Institute for Brain, Cognition and Behaviour, Nijmegen, The Netherlands

ARTICLE INFO

Article history:

Received 1 June 2010

Received in revised form 21 July 2010

Accepted 5 August 2010

Available online xxxx

Keywords:

Alpha peak frequency

Attention-deficit/hyperactivity disorder (ADHD)

Electroencephalography (EEG)

IntegNeuro

Theta/beta ratio

ABSTRACT

Attention-deficit/hyperactivity disorder (ADHD) was found to be characterized by a deviant pattern of electrocortical activity during resting state, particularly increased theta and decreased beta activity. The first objective of the present study is to confirm whether individuals with slow alpha peak frequency contribute to the finding of increased theta activity in ADHD. The second objective is to explore the relation between resting-state brain oscillations and specific cognitive functions. From 49 boys with ADHD and 49 healthy control boys, resting-state EEG during eyes open and eyes closed was recorded, and a variety of cognitive tasks were administered. Theta and beta power and theta/beta ratio were calculated using both fixed frequency bands and individualized frequency bands. As expected, theta/beta ratio, calculated using fixed frequency bands, was significantly higher in ADHD children than control children. However, this group effect was not significant when theta/beta ratio was assessed using individualized frequency bands. No consistent relation was found between resting-state brain oscillations and cognition. The present results suggest that previous findings of increased theta/beta ratio in ADHD may reflect individuals with slow alpha peak frequencies in addition to individuals with true increased theta activity. Therefore, the often reported theta/beta ratio in ADHD can be considered a non-specific measure combining several distinct neurophysiological subgroups such as frontal theta and slowed alpha peak frequencies. Future research should elucidate the functional role of resting-state brain oscillations by investigating neurophysiological subgroups, which may have a clearer relation to cognitive functions than single frequency bands.

Crown Copyright © 2010 Published by Elsevier Inc. All rights reserved.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is the most common psychiatric disorder in childhood, affecting 5–10% of all children worldwide (Faraone et al. 2003). In 40–60% of all cases ADHD persists in adolescence and adulthood (Faraone et al. 2006). Electrophysiological studies have revealed consistent evidence for abnormal brain oscillations during resting state in individuals with ADHD (Barry et al. 2003). The EEG of the majority of children with

ADHD is characterized by a deviant pattern of baseline cortical activity, specifically increased slow-wave activity, primarily in the theta band, and decreased fast-wave activity, primarily in the beta band, often coupled (i.e., increased theta/beta ratio; Barry et al. 2003). A meta-analysis of EEG and ADHD including 9 studies (1498 participants) reported significant effect sizes for theta and beta power, and theta/beta ratio (effect size = 1.31, –0.51, 3.08, respectively; Snyder and Hall 2006). However, recently, it has been suggested that at least two different EEG subtypes in ADHD, a subgroup with true frontal slow EEG (i.e., enhanced theta activity) and a subgroup with slow alpha peak frequency, might lead to the finding of increased 'theta' power (Arns et al., 2008), and thus increased theta/beta ratio, in ADHD. Moreover, these two EEG subtypes differed in their response to stimulant medication (Arns et al. 2008). So, the robust finding of increased theta and theta/beta ratio in ADHD may largely depend on a subgroup of children with ADHD who have a slow alpha peak frequency. In earlier studies, based on visual inspection of EEG data, it has already been reported that

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; BRID, Brain Resource International Database; CPRS, Conners' Parent Rating Scale; CPT, continuous performance test; EEG, electroencephalography; IAF, individual alpha peak frequency; SPHERE-12, Somatic and Psychological Health Report questionnaire.

* Corresponding author.

E-mail addresses: M.Lansbergen@psy.umcn.nl (M.M. Lansbergen), martijn@brainclinics.com (M. Arns), M.vanDongen-Boomsma@psy.umcn.nl (M. van Dongen-Boomsma), desiree@brainclinics.com (D. Spronk), J.Buitelaar@psy.umcn.nl (J.K. Buitelaar).

slow alpha peak frequency was correlated to hyperactive behavior, whereas the frontal EEG abnormalities such as frontal slow EEG showed no relation to the ADHD symptomatology (Stevens et al. 1968). When EEG power is calculated from individual adjusted frequency bands (based on the individual alpha peak frequency) rather than from fixed frequency bands (Klimesch 1999), the finding of increased theta power in one group relative to another group is not contaminated by participants with slow alpha peaks. Especially in children it is known that the alpha peak frequency matures starting at 4–6 Hz at age 2–12 months to 10 Hz at 10 years of age (Niedermeyer and Da Silva 2004), and hence the use of individual adjusted frequency bands is especially important. So far, all studies comparing resting-state EEG between children with and without ADHD used fixed frequency bands to estimate EEG power. The first objective of the present study is to address the question whether the robust findings of increased theta activity in ADHD are still present when controlling for children who exhibit slower alpha peak frequencies.

Few studies have addressed the functional role of resting-state brain oscillations. Do specific resting-state brain oscillations relate to specific cognitive functions?

Decades of research have established well-replicated findings of several cognitive deficits in attention-deficit/hyperactivity disorder (ADHD) such as attention deficits, working memory problems and deficient inhibitory control (Nigg 2005). However, the question remains whether cognitive impairments may relate to abnormal brain oscillations.

It has been argued that alpha activity reflects arousal (i.e., “the current energetic level of the organism”) and theta and beta activity reflect task- or situation-specific activation changes resulting from stimulus processing (Barry et al. 2007). Based on findings from animal and human research, it has been suggested that task-induced increases in theta power and the phase relationship between theta and gamma oscillations are important for memory processes, particularly episodic long-term memory and working memory (Knyazev 2007; Sauseng et al. 2010). Recently, it has also been postulated that theta oscillations reflect a “more general brain integrative mechanism” rather than an integrative mechanism specific for memory processes (Sauseng et al. 2010). Event-related increases in alpha power have been associated with top-down inhibitory control processes of visual information (Jensen et al. 2002).

Klimesch (1999) argued that low levels of theta activity and high levels of alpha activity during resting state predict increased theta power and decreased alpha power during task performance, that subsequently lead to improved cognitive performance. However, few studies investigated directly the relation between brain oscillations in a resting human (not during task performance) and subsequent cognitive performance. Consistent with the hypothesis of Klimesch (1999), increased theta power and increased alpha power at rest have been related to impaired cognitive performance in children with ADHD as well as in control children (Hermens et al., 2005; Loo and Smalley 2008; Sumich et al. 2009). However, discrepant findings have also been reported (Swartwood et al. 1998; Wienbruch et al. 2005). So, the functional role of EEG oscillations during resting state is still unclear. One possible explanation for the inconsistent findings is the wide variety of behavioral paradigms that have been used, which all tap different cognitive functions. The second goal is to explore the relation between resting-state brain oscillations (calculated using individualized frequency bands) and task performance on a variety of cognitive tasks. By setting this goal, the present study may reveal baseline EEG markers of specific neurocognitive dysfunctions in ADHD, and give more insight into the functional role of resting-state EEG.

Based on previous independent findings of increased slow-wave and decreased fast-wave activity as well as impaired cognitive performance in ADHD, we expect that increased theta power, decreased beta power, and increased theta/beta ratios will be

associated with decreased cognitive performance in ADHD patients. Based on the assumption of Klimesch (1999) that increased alpha activity at rest predicts decreased event-related alpha activity which reflects increased cognitive performance, we hypothesized that alpha power at rest correlates positively with cognitive performance.

2. Method

2.1. Participants

Forty-nine boys diagnosed with ADHD ($M = 12.2$ years; $SD = 3.0$; range 6–18) were matched on age, gender, and education with 49 healthy control boys ($M = 12.5$ years; $SD = 2.8$; range 7–18). Performance on the Spot the Real Word Test, which is a good indicator of premorbid IQ (Paul et al. 2005), did not differ significantly between the groups (36.8 and 37.4 for the ADHD and control group, respectively; $F_{(1,91)} < 1$). The data from the participants in the present study were acquired as part of the Brain Resource International Database (BRID; <http://www.brainresource.com>) and have already partially been published (Arns et al. 2008). Data acquisition for the BRID is performed in a standardized manner with identical hardware, software, paradigms, and experimental procedures (Gordon et al. 2005).

All children were recruited from the Sydney metropolitan region. Two pediatricians evaluated the children with ADHD using a semi-structured interview based on DSM-IV criteria for ADHD (Williams et al., 2010) and Conners' Parent Rating Scale (CPRS; Conners et al. 1998) (T-scores 1 SD above the norm for either inattentive or hyperactive/impulsive subscores). Twenty-one participants met criteria for ADHD combined subtype, 22 met the criteria for ADHD predominantly inattentive type, and 2 boys met the criteria for ADHD predominantly hyperactive/impulsive subtype. The classification of ADHD subtype was missing for 3 participants. The average number of inattentive and hyperactive/impulsivity DSM-IV symptoms for the ADHD group was 8.0 ($SD = 1.3$) and 5.2 ($SD = 2.9$), respectively. The average scores on the cognitive problems/inattentive, hyperactive, and impulsive subscales of the CPRS were 70.3 ($SD = 7.4$), 73.5 ($SD = 14.9$), and 73.0 ($SD = 9.8$), respectively.

Exclusion criteria for ADHD and healthy control children included a personal history of physical brain injury, neurological disorder, genetic disorder, or other serious medical condition and a personal history of substance abuse or dependency. Additionally, ADHD children were excluded if they had an Axis I psychiatric disorder (other than ADHD), assessed by two pediatricians in a semi-structured interview. Children in the control group were excluded if the Somatic and Psychological Health Report questionnaire (SPHERE-12; Hickie et al. 2001) revealed an Axis I disorder. All children were medication free for at least 48 h before testing. Moreover, for at least 2 h prior to testing participants were required to refrain from caffeine-intake and smoking.

All subjects and their caretakers provided written informed consent to participate in the study. In the informed consent, permission is asked to add the participant's de-linked data to the brain database, and to use their de-linked data for the specified and other scientific investigations. The study was approved by the Western Sydney Area Health Service Human Research Ethics Committee.

2.2. Intelligence

2.2.1. Spot the Real Word Test

This test is a computerized adaptation of the Spot the Word Test (Baddeley et al. 1993). The estimated IQ derived from this test correlates highly with full scale IQ, as assessed by the WAIS-III ($r = 0.76$; Paul et al. 2005). On each of the 60 trials, a real word is presented simultaneously with a nonsense word. Participants were required to select the real word. The estimated IQ is derived from the total correct score.

2.3. Neuropsychological tests

The cognitive tests were part of the IntegNeuro battery, a fully computerized and standardized neuropsychological battery that is presented on a touch-screen computer. The IntegNeuro battery consists of 12 tests that tap five domains of cognitive functions: sensori-motor functions, attention and working memory, executive function, learning and memory, and language skills (for more details, see Clark et al. 2006; Paul et al. 2005; Williams et al. 2005). Test–retest reliability and convergent and divergent validity of the IntegNeuro battery have been reported (Paul et al. 2005; Williams et al. 2005). Moreover, it has recently been demonstrated that the IntegNeuro battery could distinguish patients with ADHD from control participants with relatively high sensitivity and specificity (Williams et al., 2010).

Standardized visual and auditory task instructions were presented. Each test was preceded by a practice trial. The test trials were presented only if participants passed the practice trial accurately. The present paper presents and discusses EEG data and the results of 6 cognitive tests covering the sensori-motor, attention/memory, and language domains. Since details of the neuropsychological tasks of the IntegNeuro battery have been extensively described previously (Clark et al. 2006; Paul et al. 2005), here only the most important details are reported.

Sensori-motor functions were assessed by the Choice Reaction Time test. Dependent variable is the mean reaction time across trials (i.e., mean choice reaction time [Choice RT]).

The digit span task (forward and backward version) and span of visual memory task (forward and backward version) were used to tap verbal and visuo-spatial short-term memory (forward version) and verbal and visuo-spatial working memory (backward version), respectively. Dependent variables are the maximum number of digits and maximum number of squares correctly recalled.

The continuous performance test (CPT) and a Go/No-Go paradigm were used to tap attention, as reflected in mean reaction time to correct target/go-stimuli.

Finally, language skills (verbal fluency) were assessed by the word generation task in which the total number of correct words generated across three letters was the variable of interest.

2.4. Electrophysiological recordings

EEG and EOG activity were recorded using a Quickcap (NuAmps) with 26 electrodes according to the 10–20 electrode international system. Data were referenced to averaged mastoids with the ground electrode placed at Fpz. Horizontal electrooculogram (HEOG) was recorded from electrodes placed lateral to the outer canthi of both eyes and vertical electrooculogram (VEOG) from electrodes attached above and below the left eye. Electrode impedance was kept below 5 k Ω . The sampling rate was 500 Hz and the data were filtered online with a 100 Hz low-pass filter (40 dB attenuation).

2.5. Procedure

Participants were placed in a sound-attenuated testing room and asked to sit quietly for 4 min, 2 min with their eyes open and 2 min with their eyes closed during which baseline EEG was recorded. Afterwards, participants completed the IntegNeuro battery in front of the touch-screen computer in approximately 50 min. Details of the procedure have been published (Gordon et al. 2005; Paul et al. 2005).

2.6. EEG analyses

Since EEG data from one boy with ADHD were not recorded at all electrode sites of interest (i.e., Fz, F3, F4, Cz, C3, C4, Pz, P3, and P4), he was excluded from the EEG analyses. EEG data during the eyes

open and eyes closed resting condition were processed and analyzed separately using BrainVision Analyzer software (www.brainproducts.com). EEG data were filtered using a band-pass filter of 0.5–100 Hz and a notch filter of 50 Hz. The sampling rate was changed to 256 Hz. The continuous EEG data were segmented into 2-s epochs, separately for the eyes open and eyes closed condition. Epochs were rejected from further analyses if data exceeded 100 μ V and ocular artifact correction was conducted according to the Gratton et al. (1983) algorithm. The average number of EEG epochs used for the FFT analyses was 57.3 (SD = 9.6) for the eyes open and 57.6 (SD = 9.0) for the eyes closed condition in the ADHD group and 57.8 (SD = 5.9) for the eyes open and 56.3 (SD = 6.8) for the eyes closed condition in the control group. EEG data were Fourier transformed (Hanning window length of 20%) and subsequently ln-transformed (Gasser et al., 1982).

First, mean theta and beta power were calculated using fixed frequency bands (4–7.5 Hz for theta and 12.5–25 Hz for beta). Additionally, since alpha peak frequency and consequently also EEG frequency bands vary as a function of age (Klimesch 1999; Niedermeyer and Da Silva 2004) and may differ between individuals (Arns et al. 2008), separately for each participant, the average power values of the different frequency bands were also calculated using individual alpha peak frequency as anchor point (Doppelmayr et al. 1998). First, the frequency was assessed at which alpha power was maximum within 5–15 Hz at the parietal and occipital electrodes (Pz, P3, P4, Oz, O1, and O2) in the eyes closed condition. Second, EEG data in the eyes open resting condition were subtracted from the EEG data in the eyes closed resting condition to find the frequency (within 5–15 Hz) at which alpha power was most attenuated by opening of the eyes (Posthuma et al. 2001). When peak frequencies derived from the two methods and different electrode sites did not differ more than 0.5 Hz, the mean peak frequency at which alpha power was most attenuated by opening of the eyes across the parietal and occipital electrodes was used as individual alpha peak frequency (IAF). For peak frequencies occurring at the boundaries of the search window and for peak frequencies which differed between electrode sites and the two methods, visual inspection of the EEG data was conducted to determine the true individual alpha peak frequency.

Three boys with ADHD did not show clear alpha peak frequencies and were excluded from the analysis of the individual frequency bands. For 2 boys with ADHD and 1 control boy, who did not show alpha attenuation after opening the eyes, but did show a clear alpha peak, individual alpha peak frequencies were assessed using the EEG data in the eyes closed resting condition. Further, for 2 ADHD boys and 2 control boys, who showed only alpha attenuation at occipital electrode sites and not at parietal sites, mean individual alpha peak frequencies were calculated from the difference power spectrum (eyes closed minus eyes open) across occipital electrode sites. The bandwidth for the theta, alpha, and beta bands were defined using IAF as anchor point: $0.4 \cdot \text{IAF} - 0.6 \cdot \text{IAF}$, $0.6 \cdot \text{IAF} - 0.8 \cdot \text{IAF}$, $0.8 \cdot \text{IAF} - \text{IAF}$, $\text{IAF} - 1.2 \cdot \text{IAF}$, and $1.2 \cdot \text{IAF} - 25 \text{ Hz}$ for theta, lower-1-alpha, lower-2-alpha, upper alpha, and beta, respectively (Doppelmayr et al. 1998).

For both fixed frequency and individualized frequency bands, average power spectra were calculated at frontal (Fz, F3, and F4), central (Cz, C3, and C4) and parietal (Pz, P3, and P4) sites. Separately for each electrode, theta/beta power ratio was calculated by dividing the power of the slower frequency band by the power of the faster frequency band.

2.7. Statistical analyses

Since the behavioral data were not normally distributed, Mann–Whitney U tests were conducted for each dependent variable with group as between-subjects factor (ADHD vs. matched controls) to examine differences between boys with and without ADHD on cognitive performance in several domains.

Group differences with regard to mean IAF were tested by a one-way analysis of covariance (ANCOVA) with group as between-subjects factor and age as covariate. Separately for theta and beta power and theta/beta ratio, ln-transformed EEG data were analyzed with repeated-measures ANCOVAs with resting-state condition (eyes open vs. eyes closed), area (frontal [Fz, F3, and F4] vs. central [Cz, C3, and C4] vs. parietal [Pz, P3, and P4]), and laterality (left vs. midline vs. right) as within-subjects factors, group (ADHD vs. controls) as between-subjects factor, and age as covariate. The alpha-level of significance was set at 0.05 two-tailed. Only significant (interaction with) group effects were reported.

Furthermore, partial correlation coefficients were calculated between behavioral variables and ln-transformed EEG data (mean power across electrodes for frontal, central, and parietal areas) with age as covariate, to explore the relation between resting-state brain oscillations and cognitive performance. To correct for the large number of statistical tests, the alpha-level of significance was set at 0.01 two-tailed. Bonferroni corrections were not conducted, because the test statistics were assumed to be highly dependent. Note that the Bonferroni adjusted alpha-level of significance would be 0.00020.

3. Results

3.1. Behavioral data

Table 1 presents performance data for the ADHD and the control group. Boys with ADHD recalled significantly less number of squares in the span of visual memory task as compared to healthy control children, $Z = -2.58$, $p = 0.010$ (3.6 ± 2.0 and 4.6 ± 1.7 , respectively). No significant differences between boys with and without ADHD were found for number of digits recalled in the digit span task, number of correct words generated in the word generation task or for mean reaction time in the choice reaction time task, CPT, and Go/No-Go task.

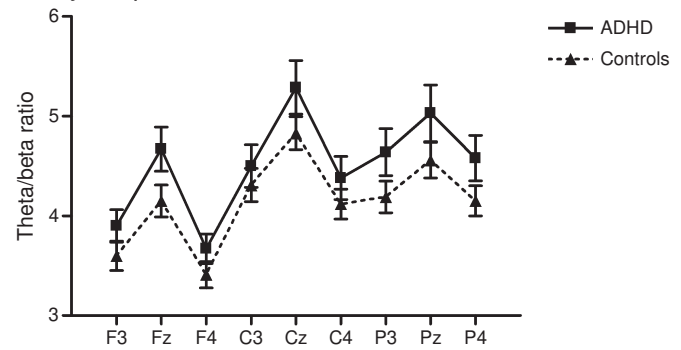
3.2. Ln-transformed electrophysiological (EEG) data

Mean individual alpha peak frequency did not differ significantly between the ADHD and control group (IAF = 9.42 ± 0.8 and IAF = 9.47 ± 0.8 for the ADHD and control group, respectively).

Repeated-measures ANCOVAs for theta and beta power, and theta/beta power ratio, as assessed with fixed frequency bands, revealed no significant main effects of group. A significant area \times laterality \times condition \times group effect was found for theta/beta ratio, $F_{(4,376)} = 2.56$, $p = 0.038$. As illustrated in Fig. 1, boys with ADHD had higher theta/beta ratios power than control boys in both resting conditions and at all electrode sites. Post-hoc ANCOVAs per condition and electrode site, with group as between-subjects factor and age as covariate, revealed significant group effects in the eyes closed resting condition at Fz, F3, Cz, Pz, and P4 (p -values of 0.030, 0.057, 0.041, 0.055, and 0.035; not corrected for multiple comparisons).

Using the individualized frequency bands based on the IAF, repeated-measures ANCOVAs for theta (3.8 ± 0.3 – 5.7 ± 0.5 Hz) and beta power (11.4 ± 0.9 – 25 Hz), and theta/beta power ratio, revealed no significant main effects of group or interaction effects with group (see the data for theta/beta ratio in Fig. 2).

A. Eyes open



B. Eyes closed

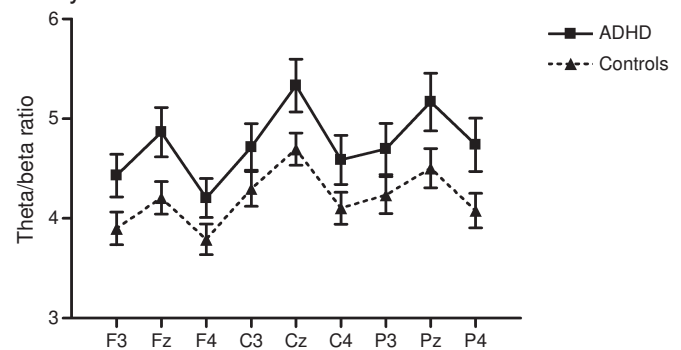


Fig. 1. Theta/beta ratio, derived from fixed frequency band analyses for the ADHD and control group at each electrode, separately for the eyes open (A) and eyes closed (B) conditions.

3.3. Relation between behavioral and ln-transformed EEG data

Partial correlation coefficients between behavioral performance and EEG power (based on individual frequency bands) for the whole sample were relatively small and after controlling for age, only 2 correlations were found to be significant at the alpha-level of 0.01 (see Supplementary Table 1). Impaired performance on the Go/No-Go task was significantly correlated with increased lower-1-alpha power (5.7 ± 0.5 Hz– 7.5 ± 0.6 Hz) in the eyes closed resting condition at central sites, $r = 0.294$, $p = 0.005$, and parietal sites, $r = 0.306$, $p = 0.003$.

4. Discussion

The first goal of the present study was to test the hypothesis that at least two different EEG subtypes in ADHD, a subgroup with true frontal slow EEG (i.e., enhanced theta activity) and a subgroup with slow alpha peak frequency contribute to increased 'theta' power, and thus increased theta/beta power ratio, in ADHD (Arns et al., 2008). In other words, it was investigated whether the robust finding of increased theta activity and increased theta/beta ratio in children with ADHD relative to control children could be replicated, even after

Table 1
Behavioral data for the ADHD and control group.

	Digit span F	Digit span B	Span of VM	Verbal fluency	Choice RT	Go/No-Go RT	CPT RT
ADHD group	4.5 (2.1)	3.0 (1.9)	3.7 (2.1)	8.4 (3.6)	918.3 (393.8)	308.7 (75.6)	614.9 (164.7)
Control group	5.2 (1.2)	3.1 (1.9)	4.6 (1.7)	9.5 (3.8)	885.3 (293.5)	294.4 (43.6)	573.5 (138.1)

Note. Standard deviation (SD) is provided in parentheses. Digit span F = digit span forward; digit span B = digit span backward; VM = visuo-spatial memory; RT = reaction time; CPT = continuous performance test.

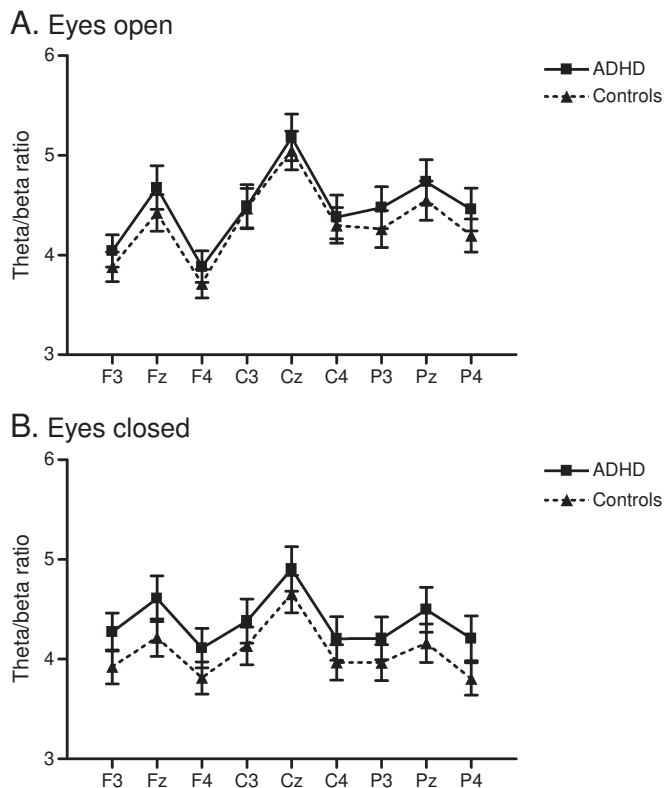


Fig. 2. Theta/beta ratio, derived from individual frequency band analyses for the ADHD and control group at each electrode, separately for the eyes open (A) and eyes closed (B) conditions.

controlling for individuals with slow alpha peak frequencies. Consistent with our hypothesis, we replicated increased theta/beta ratio in boys with ADHD using fixed frequency bands to calculate EEG power, but this group effect attenuated when theta and beta power were calculated based on individual frequency bands. This result suggests that previous findings of increased theta power and increased theta/beta ratio in ADHD may be partially due to a subgroup of patients showing slow alpha peak frequencies instead of enhanced theta activity. Without correcting for individual alpha peak frequency, it is not possible to disentangle these neurophysiologically different EEG subtypes. Since only boys were included in the present study, the results cannot be generalized to girls. Although differences in theta power between ADHD and control participants appear to be smaller in females than males (Clarke et al., 2001; Hermens et al., 2005), there are no indications for a higher prevalence of slow alpha peak frequency in females or males. Therefore, the present results may also be expected in a group of girls.

Although the ADHD children in the present study showed increased theta activity, decreased beta activity, and increased theta/beta ratio relative to control participants (based on fixed frequency bands), group differences were only significant regarding theta/beta ratio. Increased theta/beta ratio has already been demonstrated to be the most robust finding in ADHD (effect size of 3.08; Snyder and Hall 2006). Possible explanations for the small differences in the present study may be the great heterogeneity of ADHD (i.e., different DSM-IV subtypes) and/or the heterogeneity of age within the sample (6–18 years). These factors may have increased interindividual variability and canceled out between-group differences. It is important to note that recent findings question whether the ADHD subtypes are really distinct and unrelated disorders (Baeyens et al., 2006; Todd et al., 2008). A second explanation for the small differences may be the length of EEG recording. Whereas a majority of studies recorded approximately 20 min (Clarke, personal communi-

cation), the present study only recorded 2 min of EEG. The differences between ADHD and control children in EEG activity during rest may increase with resting time. Several distinct stages of brain activity (i.e., vigilance stages) occur over time and it has been demonstrated that children with ADHD fluctuate more between stages (Sander et al., 2010). Therefore, longer EEG recordings may distinguish better between ADHD and control participants. Finally, note that not all studies have found clear differences with regard to increased theta and increased theta/beta ratio between ADHD and control groups (Loo et al. 2009; Swartwood et al. 2003).

The second objective of the present study was to yield more insight into the functional role of EEG oscillations during a resting state. The relationship was examined between brain oscillations (corrected for individual alpha peak frequency) at rest and cognitive performance. Correlation coefficients were small and after controlling for age, most correlation coefficients were not significant. Only increased power in the lower-1-alpha frequency band (at central and parietal sites in eyes closed condition) correlated with impaired attention in the Go/No-Go task. These findings are not in line with the hypothesis of Klimesch (1999) that increased alpha power at rest predicts decreased event-related power which is related to better performance. Assuming alpha activity at rest reflects a state of arousal (Barry et al. 2007), it may be speculated that increased arousal (i.e., low levels of alpha power) at rest is associated with better performance. However, note that the association was only significant for the eyes closed resting condition at central and parietal sites and not present for attention, as assessed by the CPT. Moreover, when applying Bonferroni corrections for multiple tests the associations were not significant anymore. In sum, so far, no straightforward and consistent relations have been found between EEG activity in a resting human and cognitive performance on a variety of tasks. The inconsistent findings with regard to the relation between single frequency bands and cognitive functions dispute the view that the level of cortical activity at rest predicts or is strongly related to specific cognitive processes. So, the presence or absence of specific single frequency bands by itself cannot be regarded as an indication of impaired or improved cognitive function, but it should rather be investigated in relation to the task at hand (Sauseng et al. 2010). It has already been suggested that the phase of the oscillation is also important. For example, neuronal oscillations tend to entrain (phase-lock) to the rhythm of an attended stimulus sequence (Lakatos et al. 2008). So, the question remains whether EEG activity at rest is related or even predicts task-induced changes in EEG activity. More research is needed to unravel the relation between resting-state neuronal oscillations, task-induced neuronal oscillations, and cognitive task performance.

One possible explanation for the inconsistent findings with regard to the relation between EEG activity and cognitive performance is the idea that not specific brain oscillations, but rather the profile of the whole power spectrum of an individual is related to cognition. Recently, Arns et al. (2008) demonstrated that the EEG subtypes, as defined by Johnstone et al. (2005), are present in ADHD patients, but also within the normal population. Moreover, different EEG subtypes responded different to medication (Arns et al. 2008). Thus, the relation between EEG subtypes and cognition may be more evident than the relation between specific brain oscillations and cognition, as was investigated in the present study.

5. Conclusions

The deviant pattern of increased theta activity and increased theta/beta ratio in ADHD appears to largely depend on a subgroup of children with ADHD who have slow alpha peak frequencies rather than increased theta activity. Therefore, the often reported theta/beta ratio in ADHD can be considered a non-specific measure combining several distinct neurophysiological subgroups, which also respond differentially to medication (Arns et al., 2008). Further studies should

replicate this finding in larger samples and investigate whether these two subgroups also differ clinically and neuropsychologically. Furthermore, the present results suggest that EEG activity in a resting human does not have a clear association with cognitive processes. Future research might address the relation between resting-state and task-induced neuronal oscillations, and subsequent behavioral performance, also in larger samples. Furthermore, looking at different EEG subtypes rather than specific frequency bands may elucidate a clearer relationship between brain oscillations and cognitive deficits.

Acknowledgments

The authors gratefully acknowledge the support of the BrainGain Smart Mix Programme of the Netherlands Ministry of Economic Affairs and the Netherlands Ministry of Education, Culture and Science. Further, we acknowledge the support of the Brain Resource International Database (under the auspices of Brain Resource – www.brainresource.com) for use of normative and clinical data. We also thank the individuals who gave their time to participate in the database. Access to the database for scientific purposes is administered independently via the scientific network (BRAINnet; www.brainnet.net), which is coordinated independently of the commercial operations of Brain Resource.

Supplementary materials related to this article can be found online at [doi:10.1016/j.pnpbp.2010.08.004](https://doi.org/10.1016/j.pnpbp.2010.08.004).

References

- Arns M, Gunkelman J, Breteler M, Spronk D. EEG phenotypes predict treatment outcome to stimulants in children with ADHD. *J Integr Neurosci* 2008;7:421–38.
- Baddeley A, Emslie H, Nimmo-Smith I. The Spot-the-Word test: a robust estimate of verbal intelligence based on lexical decision. *Br J Clin Psychol* 1993;32(Pt 1):55–65.
- Baeyens D, Roeyers H, Walle JV. Subtypes of attention-deficit/hyperactivity disorder (ADHD): distinct or related disorders across measurement levels? *Child Psychiatry Hum Dev* 2006;36:403–17.
- Barry RJ, Clarke AR, Johnstone SJ. A review of electrophysiology in attention-deficit/hyperactivity disorder: I. Qualitative and quantitative electroencephalography. *Clin Neurophysiol* 2003;114:171–83.
- Barry RJ, Clarke AR, Johnstone SJ, Magee CA, Rushby JA. EEG differences between eyes-closed and eyes-open resting conditions. *Clin Neurophysiol* 2007;118:2765–73.
- Clark CR, Paul RH, Williams LM, Arns M, Fallahpour K, Handmer C, et al. Standardized assessment of cognitive functioning during development and aging using an automated touchscreen battery. *Arch Clin Neuropsychol* 2006;21:449–67.
- Clarke AR, Barry RJ, McCarthy R, Selikowitz M. Age and sex effects in the EEG: differences in two subtypes of attention-deficit/hyperactivity disorder. *Clin Neurophysiol* 2001;112:815–26.
- Conners CK, Sitarenios G, Parker JD, Epstein JN. The revised Conners' Parent Rating Scale (CPRS-R): factor structure, reliability, and criterion validity. *J Abnorm Child Psychol* 1998;26:257–68.
- Doppelmayr M, Klimesch W, Pachinger T, Ripper B. Individual differences in brain dynamics: important implications for the calculation of event-related band power. *Biol Cybern* 1998;79:49–57.
- Faraone SV, Sergeant J, Gillberg C, Biederman J. The worldwide prevalence of ADHD: is it an American condition? *World Psychiatry* 2003;2:104–13.
- Faraone SV, Biederman J, Mick E. The age-dependent decline of attention deficit hyperactivity disorder: a meta-analysis of follow-up studies. *Psychol Med* 2006;36:159–65.
- Gasser T, Bächer P, Möcks J. Transformations towards the normal distribution of broad band spectral parameters of the EEG. *Electroencephalogr Clin Neurophysiol* 1982;53:119–24.
- Gordon E, Cooper N, Rennie C, Hermens D, Williams LM. Integrative neuroscience: the role of a standardized database. *Clin EEG Neurosci* 2005;36:64–75.
- Gratton G, Coles MG, Donchin E. A new method for off-line removal of ocular artifact. *Electroencephalogr Clin Neurophysiol* 1983;55:468–84.
- Hermens DF, Kohn MR, Clarke SD, Gordon E, Williams LM. Sex differences in adolescent ADHD: findings from concurrent EEG and EDA. *Clin Neurophysiol* 2005a;116:1455–63.
- Hermens DF, Soei EX, Clarke SD, Kohn MR, Gordon E, Williams LM. Resting EEG theta activity predicts cognitive performance in attention-deficit hyperactivity disorder. *Pediatr Neurol* 2005b;32:248–56.
- Hickie IB, Davenport TA, Naismith SL, Scott EM. SPHERE: a national depression project. *SPHERE National Secretariat. Med J Aust* 2001;175(Suppl):S4–5.
- Jensen O, Gelfand J, Kounios J, Lisman JE. Oscillations in the alpha band (9–12 Hz) increase with memory load during retention in a short-term memory task. *Cereb Cortex* 2002;12:877–82.
- Johnstone J, Gunkelman J, Lunt J. Clinical database development: characterization of EEG phenotypes. *Clin EEG Neurosci* 2005;36:99–107.
- Klimesch W. EEG alpha and theta oscillations reflect cognitive and memory performance: a review and analysis. *Brain Res Brain Res Rev* 1999;29:169–95.
- Knyazev GG. Motivation, emotion, and their inhibitory control mirrored in brain oscillations. *Neurosci Biobehav Rev* 2007;31:377–95.
- Lakatos P, Karmos G, Mehta AD, Ulbert I, Schroeder CE. Entrainment of neuronal oscillations as a mechanism of attentional selection. *Science* 2008;320:110–3.
- Loo S, Smalley S. Preliminary report of familial clustering of EEG measures in ADHD. *Am J Med Genet B (Neuropsychiatr Genet)* 2008;147:107–9.
- Loo SK, Hale TS, Macion J, Hanada G, McGough JJ, McCracken JT, et al. Cortical activity patterns in ADHD during arousal, activation and sustained attention. *Neuropsychologia* 2009;47:2114–9.
- Niedermeyer E, Da Silva FHL. *Electroencephalography: basic principles, clinical applications, and related fields*; 2004.
- Nigg JT. Neuropsychologic theory and findings in attention-deficit/hyperactivity disorder: the state of the field and salient challenges for the coming decade. *Biol Psychiatry* 2005;57:1424–35.
- Paul RH, Lawrence J, Williams LM, Richard CC, Cooper N, Gordon E. Preliminary validity of “integneuro”: a new computerized battery of neurocognitive tests. *Int J Neurosci* 2005;115:1549–67.
- Posthuma D, Neale MC, Boomsma DI, de Geus EJ. Are smarter brains running faster? Heritability of alpha peak frequency, IQ, and their interrelation. *Behav Genet* 2001;31:567–79.
- Sander C, Arns M, Olbrich S, Hegerl U. EEG-vigilance and response to stimulants in paediatric patients with attention deficit/hyperactivity disorder. *Clin Neurophysiol* 2010;121(9):1511–8.
- Sauseng P, Griesmayr B, Freunberger R, Klimesch W. Control mechanisms in working memory: a possible function of EEG theta oscillations. *Neurosci Biobehav Rev* 2010;34:1015–22.
- Snyder SM, Hall JR. A meta-analysis of quantitative EEG power associated with attention-deficit hyperactivity disorder. *J Clin Neurophysiol* 2006;23:440–55.
- Stevens JR, Sachdev K, Milstein V. Behavior disorders of childhood and the electroencephalogram. *Arch Neurol* 1968;18:160–77.
- Sumich A, Matsudaira T, Gow RV, Ibrahimovic A, Ghebremeskel K, Crawford M, et al. Resting state electroencephalographic correlates with red cell long-chain fatty acids, memory performance and age in adolescent boys with attention deficit hyperactivity disorder. *Neuropharmacology* 2009;57:708–14.
- Swartwood MO, Swartwood JN, Lubar JF, Timmermann DL, Zimmerman AW, Muenchen RA. Methylphenidate effects on EEG, behavior, and performance in boys with ADHD. *Pediatr Neurol* 1998;18:244–50.
- Swartwood JN, Swartwood MO, Lubar JF, Timmermann DL. EEG differences in ADHD-combined type during baseline and cognitive tasks. *Pediatr Neurol* 2003;28:199–204.
- Todd RD, Huang H, Todorov AA, Neuman RJ, Reiersen AM, Henderson CA, et al. Predictors of stability of attention-deficit/hyperactivity disorder subtypes from childhood to young adulthood. *J Am Acad Child Adolesc Psychiatry* 2008;47:76–85.
- Wienbruch C, Paul I, Bauer S, Kivelitz H. The influence of methylphenidate on the power spectrum of ADHD children – an MEG study. *BMC Psychiatry* 2005;5:29.
- Williams LM, Simms E, Clark CR, Paul RH, Rowe D, Gordon E. The test–retest reliability of a standardized neurocognitive and neuropsychological test battery: “neuromarker”. *Int J Neurosci* 2005;115:1605–30.
- Williams LM, Hermens DF, Thein T, Clark CR, Cooper NJ, Clarke SD, et al. Using brain-based cognitive measures to support clinical decisions in ADHD. *Pediatr Neurol* 2010;42(2):118–26.