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

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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.

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.

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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.