Abstract

This study investigated the stability and state-related characteristics of electroencephalographic (EEG) deviances in attention-deficit/hyperactivity disorder (ADHD). Three minutes resting EEG with eyes closed and eyes open were compared between 21 children with ADHD and 29 typically developing children. Across resting conditions, children with ADHD exhibited divergent topographic distribution for theta, alpha and beta power compared to typically developing children. In addition, less alpha and theta suppression to eye opening was found in children with ADHD, but only in those without comorbid ODD/CD. Findings of the present study refer to a consistent divergence in topographic distribution in ADHD across resting state conditions, yet demonstrate that state-related factors and comorbidity may also contribute to resting EEG deviances in ADHD. The state-related findings are in accord with several theoretical accounts emphasizing the role of contextual and state factors defining deficits in ADHD.

Keywords

EEG reactivity, eye opening, alpha, theta, arousal, state, ADHD, ODD, CD

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder, affecting an estimated 5 to 7 % of the worldwide population (Willcutt, 2012), and is characterized by varying age-inappropriate levels of inattention and/or hyperactivity/impulsivity, leading to impairment in multiple life domains (American Psychiatric Association, 2013). Although the mechanisms are not fully understood, it has often been claimed that ADHD is associated with a dysfunction in the central nervous system (CNS), which has frequently been investigated by means of electroencephalography (EEG).

Resting EEG studies with either eyes closed or open typically have reported increased theta power or an elevated proportion of slow to fast frequency power, theta/beta ratio (TBR), in children with ADHD compared to typically developing children (e.g., Barry, Clarke, & Johnstone, 2003; Dupuy, Clarke, Barry, McCarthy, & Selikowitz, 2011; González-Castro, Rodríguez, López, Cueli, & Álvarez, 2013; Lansbergen, Arns, van Dongen-Boomsma, Spronk, & Buitelaar, 2011; Loo et al., 2010; Shi et al., 2012; Snyder et al., 2008). However, lately the robustness of these EEG deviances characterizing the whole ADHD population has become the focus of a debate, as a number of studies, mainly addressing eyes open resting EEG, could not invariably distinguish children with ADHD from a typically developing group based on theta power or TBR (Coolidge, Starkey, & Cahill, 2007; Liechti et al., 2013; Loo et al., 2013; Nazari, Wallois, Aarabi, & Berquin, 2011; Ogrim, Kropotov, & Hestad, 2012; Swartwood, Swartwood, Lubar, & Timmermann, 2003). This also appears to find support by a meta-analysis, revealing less discrepancy in eyes open TBR between children with and without ADHD in recent compared to earlier studies (Arns, Conners, & Kraemer, 2013). In addition, in a recent study, eyes closed theta activity was observed to be enhanced in 60%, yet reduced in 40% of children

with ADHD (Clarke et al., 2011). EEG findings regarding brain wave activity in the faster frequency bands appear to be even more mixed. That is, although some studies have documented decreased beta (Clarke, Barry, McCarthy, & Selikowitz, 1998, 2002a; Clarke et al., 2003; Dupuy et al., 2011; Shi et al., 2012), others have reported increased beta power in a subgroup of children with ADHD (Chabot & Serfontein, 1996; Clarke et al., 1998; Clarke, Barry, McCarthy, & Selikowitz, 2001a) or failed to find group differences in beta power (Liechti et al., 2013; Loo et al., 2010). Likewise, alpha power has often been reported to be reduced in children with ADHD (Barry, Clarke, Johnstone, McCarthy, & Selikowitz, 2009; Clarke et al., 1998, 2001a, 2002, 2003; Dupuy et al., 2011), but has also been found to be enhanced (Chabot & Serfontein, 1996; Clarke et al., 2011), or equivalent to that of typically developing children (Loo et al., 2010; Shi et al., 2012). Various factors may have contributed to the apparent discrepant findings between studies, including sample characteristics and resting state condition in which EEG was recorded (i.e., eyes open or closed). ADHD presents a heterogeneous clinical expression with different subtypes, often comorbid with other conditions such as oppositional defiant disorder (ODD) or conduct disorder (CD). These sample characteristics may vary across studies and although not often taken into account, available research indicates that these may mediate EEG deviances in ADHD (e.g., Buyck & Wiersema, 2014; Clarke et al., 2002; Loo et al., 2013). Studies also differ in the resting state condition in which EEG was recorded. Crucially, in order to consider EEG deviances as a trait-like hallmark of ADHD, there should be stability in these abnormalities across different states. Although several studies have demonstrated intra-individual stability of EEG in typically developing children over time (e.g., Fein, Galin, Yingling, Johnstone, & Nelson, 1984; Gasser, Bacher, & Steinberg, 1985), brain oscillations have also been found to be affected by contextual and state factors, such as opening

of the eyes (e.g., Barry, Clarke, Johnstone, Magee, & Rushby, 2007; Karhu, Könönen, Herrgard, & Partanen, 1996; Ristanovic, Martinovic, & Jovanovic, 1999; Samson-Dollfus, & Goldberg, 1979). Opening of the eyes has been related to an increase in arousal (Barry et al., 2007; Hüfner et al., 2009). Interestingly, although some recent studies challenge this account (Barry et al., 2009; Clarke et al., 2013), one of the dominant theories interpreting the most consistent EEG deviances in ADHD (i.e., aberrant theta and TBR) has been that the abnormalities represent hypoarousal of the CNS (for reviews, see Barry et al., 2003; Barry & Clarke, 2009). This raises the question whether changes in arousal state with eye opening is an important factor that should be taken into account in characterizing EEG deviances in ADHD.

So far, most EEG studies on ADHD have focused on evaluating EEG in either an eyes closed or an eyes opened resting condition, with only a few addressing both resting conditions (Fonseca, Tedrus, Bianchini, & Silva, 2013; Lansbergen et al., 2011; Liechti et al., 2013; Loo et al., 2009, 2010, 2013; van Dongen-Boomsma et al., 2010; Woltering, Jung, Liu, & Tannock, 2012). Interestingly, some of these latter studies reported that deviances in TBR in children (Lansbergen et al., 2011) or adults (Loo et al., 2013) with ADHD were detected in the eyes closed but not in the eyes open condition. Hence, these findings suggest that, whether or not the EEG profile in ADHD is aberrant, it may depend on arousal state. The notion that state factors may play a role when investigating resting EEG in ADHD is further supported by findings of group differences in EEG reactivity to opening or closing the eyes. That is, studies have demonstrated reduced frontal and/or posterior alpha suppression to opening the eyes in children as well as adults with ADHD (Fonseca et al., 2013; Loo et al., 2010; Woltering et al., 2012, but see Loo et al., 2009, van Dongen-Boomsma et al., 2010). Also, a greater theta power increase to closing the eyes has been observed in children with ADHD (Liechti et al., 2013). Although

studies that investigated resting EEG in ADHD during different arousal states are scarce, the findings seem to highlight a state-related factor in EEG deviances in ADHD. Interestingly, these results are in line with several theoretical frameworks that emphasize the role of contextual and state factors instead of fixed factors in defining deficits in ADHD, such as the state regulation deficit model (Sergeant, 2005; van der Meere, 2005) and the delay aversion model (Sonuga-Barke, Taylor, Sembi, & Smith, 1992), which emphasize respectively dynamic underlying failures of energetic state or motivational factors in ADHD (Sonuga-Barke, Wiersema, van der Meere, & Roeyers, 2010).

To gain further insight into the role of state-related factors (i.e., arousal) in determining EEG deviances in ADHD, in the current study, EEG activity in an eyes closed and eyes open resting condition will be compared between children with ADHD and typically developing children. Although most studies on ADHD address sagittal topographical differences in EEG reactivity following eye opening, to our knowledge EEG differences between groups on the lateral plane (i.e., left hemisphere, midline and right hemisphere) have hardly been investigated. Yet, this may be important, since a few studies documented hemispherical divergence in EEG activity in ADHD (Hale et al., 2009, 2010a, 2010b; Keune et al., 2011). Therefore, in the present study, sagittal as well as lateral scalp regions were included, enabling a thorough investigation of possible topographical differences between groups and conditions. Furthermore, as only a few studies on EEG reactivity in ADHD have systematically addressed a wide range of EEG frequencies and TBR, brain wave activity from theta to beta frequency bands and TBR related to eye opening will be evaluated.

If elevated theta power and TBR are trait-like markers of ADHD, then increased theta power and TBR are expected in both resting state conditions. An interaction effect between

group and resting state condition would indicate that state factors are associated with EEG abnormalities in ADHD. In line with literature findings, the largest group differences are expected in the eyes closed condition. In addition, based on previous reactivity studies, children with ADHD are hypothesized to show less alpha suppression when opening the eyes.

2. Materials and methods

2.1. Participants

Participants were 22 children with ADHD and 29 typically developing children between 7 and 14 years old with an estimated full scale IQ of 80 or higher (Table 1), which were recruited through advertisements, schools, and staff members. Children with ADHD were furthermore referred by child neurologists. Participants with ADHD were previously diagnosed with ADHD in a clinical setting according to criteria as specified in DSM-IV. ADHD-diagnosis was confirmed by administering the parent version of the behavioral module of the Diagnostic Interview Schedule for Children IV (DISC-IV) (Schaffer et al., 2000). Disruptive Behavior Disorder Rating Scale (DBD-RS) (Pelham, Gnagy, Greenslade, & Milich, 1992) and Child Behavior Checklist (Achenbach & Rescorla, 2001) were used to evaluate respectively ADHD symptoms and possible presence of psychiatric problems in both groups. Intelligence functioning was assessed by an abbreviated Wechsler Intelligence Scale for Children-III (Grégoire, 2000; Wechsler, 1991). Exclusion criteria for participation consisted of a history of brain related illness, neurological disorder, serious medical condition, learning disorder, and autism spectrum disorder. Children from the control group were required to reach scores below clinical cut off on DBD-RS and Child Behavior Checklist (CBCL) (Achenbach & Rescorla, 2001). One child with ADHD had to be excluded from the analyses as it received a diagnosis of

autism spectrum disorder during the study. This resulted in an ADHD group comprising 9 children of the predominantly inattentive type, 1 child of the predominantly hyperactive/impulsive type and 11 children of the combined type. 4 children with ADHD also met criteria for ODD and 1 child met criteria for both ODD and CD, as determined by the DISC-IV. Children with ADHD using stimulant medication for ADHD symptoms (i.e., 11 children) were asked to refrain from medication for at least 48 hours before participation in the experiment.

The participants in the present study largely overlap with the children that have been incorporated in the study of Buyck and Wiersema (2014).

Table 1. Sample characteristics

	CONTROL (*n* = 29)	ADHD (*n* = 21)
Male/female	14/15	13/8
Age in years	*M* 10.46 (*SD* 1.75)	*M* 10.20 (*SD* 1.73)
Estimated FSIQ	*M* 108.10 (*SD* 11.55)	*M* 103.10 (*SD* 12.43)
DBD-RS inattention	*M* 3.31 (*SD* 4.06)	*M* 16.76 (*SD* 4.28)
DBD-RS hyperactivity impulsivity	*M* 3.21 (*SD* 3.41)	*M* 12.81 (*SD* 5.18)
Number of segments EC	*M* 112.72 (*SD* 35.33)	*M* 107.95 (*SD* 33.99)
Number of segments EO	*M* 126.59 (*SD* 33.13)	*M* 105.14 (*SD* 39.75)

Note: M: mean, *SD*: standard deviation, FSIQ: Full Scale Intelligence Quotient, DBD-RS: Disruptive Behavior Disorder Rating Scale, EC: eyes closed, EO: eyes open.

2.2. Procedure

Written informed consent was obtained from parents before their child participated in the experiment, in line with a research protocol approved by the ethic committee of the Faculty of Psychology and Educational Sciences at Ghent University.

Participants first completed the questionnaires, after which the DISC was administered to parents and intelligence of the children was assessed. Electrophysiological registration was planned in another session that comprised neuropsychological testing (not discussed in the current paper) and recording of resting state EEG. For the purpose of the current study, resting EEG from the eyes open and eyes closed condition (3 minutes each) recorded after neuropsychological testing was evaluated. During eyes open resting conditions, participants were instructed to fixate on a white cross that was presented on a black background in the middle of a computer screen. Resting state EEG conditions were counterbalanced across participants. The total session (i.e., the time that was needed for placement of the EEG cap and the execution of the experiment) took about 1.5 hour.

2.3. Electrophysiological measures

Participants were fitted with a 128 electrode cap with 10 mm Ag/AgCl electrodes (EasyCap Active, EasyCap GmbH) placed according to the 10/5 International System (Oostenveld & Praamstra, 2001). Data were collected with a sample rate of 500 Hz and average referenced with the ground electrode mounted within the cap at Fpz. Electro-oculogram was registered through electrodes enclosed in the cap near the eyes. A QuickAmp amplifier (Brain Products, Gilching, Germany) was employed to amplify signals with an open pass-band from direct current to 100 Hz. Brain Vision Analyzer software (version 2.0.1) was used to filter (0.5

Hz to 50 Hz band-pass, notch filter of 50 Hz) and segment (2 s epochs with 1 s overlap) data offline. Ocular artefact correction was conducted according to the Gratton and Coles algorithm (Gratton, Coles & Donchin, 1983). Segments with amplitudes exceeding ±100 μV were removed from further analyses. The remaining number of segments for analyses did not differ between conditions (F (1, 48) = 1.79, p = .19) and groups (F (1, 48) = 2.00, p = .16) (Table 1). Spectral power was calculated using Fast Fourier Transform with a 20% Hanning window. For comparison purposes (Barry et al., 2009), absolute power estimates were derived for the theta (3.5-7.5 Hz), alpha (7.5-12.5 Hz) and beta (12.5-25 Hz) band and divided in nine regions: left frontal (AF3, F3, F7), midline frontal (Fz, FCz), right frontal (AF4, F4, F8), left central (T7, C3), midline central (Cz), right central (T8, C4), left posterior (P7, P3, O1), midline posterior (Pz, Oz) and right posterior (P8, P4, O2). Theta/beta power ratio was obtained by dividing the power of the theta band by the power of the beta band. A natural logarithmic transform, ln(x), was applied to approach normal spreading of the data.

2.4. Statistical analyses

Eyes closed and eyes open EEG activity in children with and without ADHD were compared by running separate analyses of variance with repeated measures for each EEG measure with condition (eyes closed, eyes open), sagittal region (frontal, central, posterior) and lateral region (left, midline, right) as within-subject factors and group (ADHD, controls) as between-subject factor. When the assumption of sphericity was violated, degrees of freedom were corrected using Greenhouse-Geisser (when $\varepsilon < .75$) or Huynh-Feldt (when $\varepsilon > .75$) estimates of sphericity. Effect sizes were determined by partial eta squared (η^2_p) and are interpreted as small (< 0.06), medium (0.06 - 0.14), or large (> 0.14) (Cohen, 1988).

Since comorbid ODD/CD has been documented to possibly play a mediating role in detecting EEG deviances in ADHD (Clarke et al., 2002b; Loo et al., 2013), a supplementary analysis was performed excluding children with comorbid ODD/CD (i.e., 5/21) (see also Liechti et al., 2013). As age and gender have been demonstrated to affect EEG (e.g., Clarke Barry, McCarthy, Selikowitz, 2001b; Dupuy, Barry, Clarke, McCarthy, & Selikowitz, 2013), separate additional analyses were run with these factors as covariates.

In view of the scope of the present study, only effects involving diagnostic status are discussed. Because of the relative paucity of studies on this topic, not only significant effects but also effects on a subtreshold level of significance (i.e., $.05 < p < .10$) are reported to encourage future research (see also Barry et al., 2004).

3. Results

3.1. Group characteristics

The Disruptive Behavior Disorder Rating Scale confirmed that children with ADHD experienced more problems with inattention (F (1, 48) = 127.76, $p < .001$) as well as hyperactivity/impulsivity (F (1, 48) = 62.54, $p < .001$) than typically developing children. The groups did not significantly differ in terms of age (F (1, 48) = 0.26, $p = .62$) and estimated full scale IQ (F (1, 48) = 2.15, $p = .15$) (Table 1).

3.2. EEG analyses

The topographic power distributions for eyes closed and eyes open resting conditions and the differences in power distribution between conditions in each frequency band and TBR are presented in Figure 1.

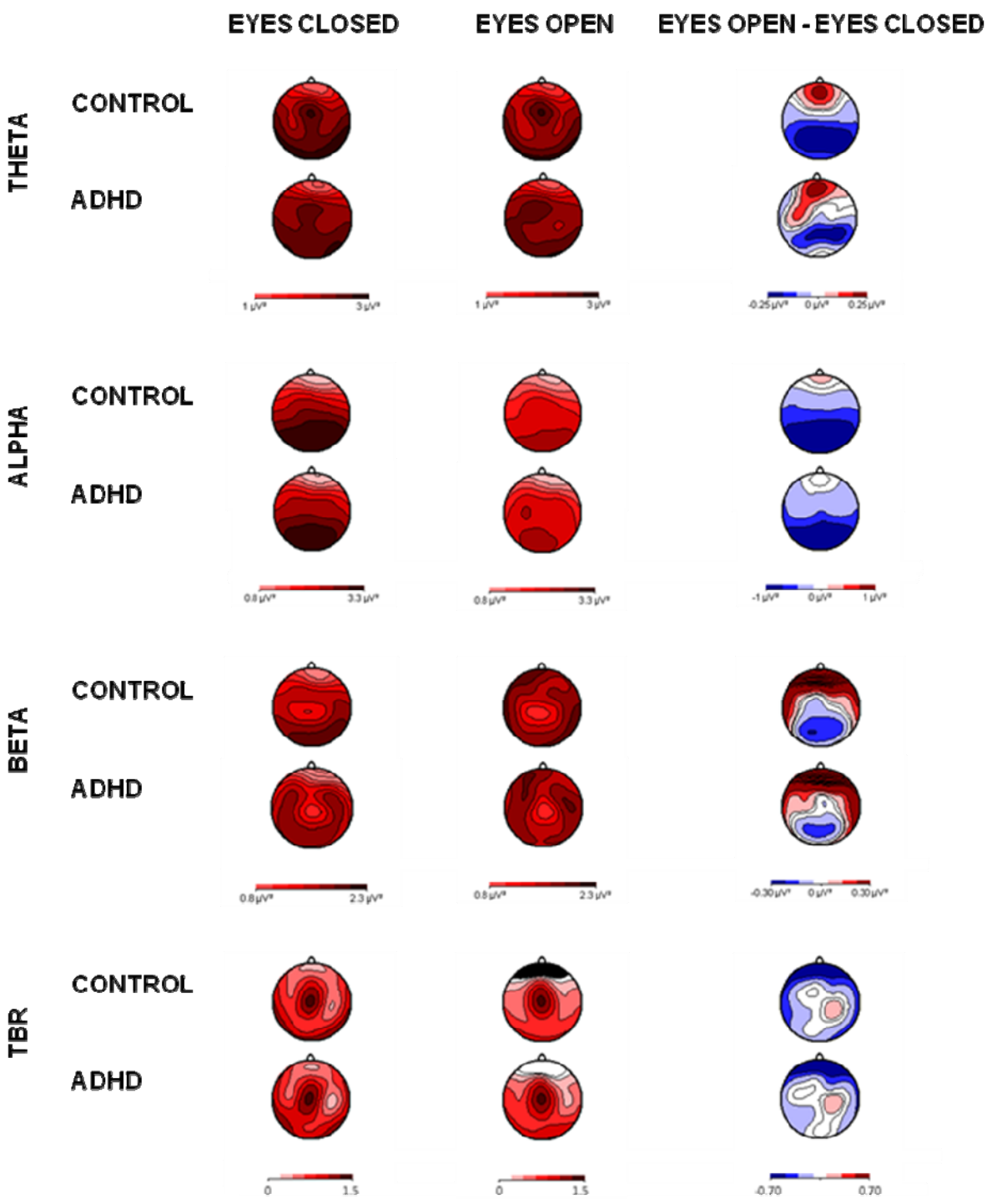

Figure 1. Spectral analysis for eyes closed and eyes open conditions. Absolute power for theta, alpha and beta frequency bands (lnμV²) and TBR (theta/beta ratio) (ln). Differences between eyes open and eyes closed conditions.

Theta power. As for theta power, a group-by-lateral region interaction was found (F (2, 96) = 4.40, p = .02, η^2_p = .084), indicating theta power across resting state conditions was higher for controls than for ADHD at midline than at lateral electrode sites. Yet, group differences did not reach significance at either midline or lateral region.

Alpha power. Likewise, a significant interaction between group and lateral region was detected for alpha power (F (2, 96) = 3.77, p = .03, η^2_p = .073). Although groups did not significantly differ in either region, higher alpha power at midline than at lateral sites was detected in the control group but not in the ADHD group.

Beta power. Beta power also differed between groups on the lateral plane (F (2, 96) = 3.52, p = .03, η^2_p = .068). Further testing revealed a greater reduction in power at midline compared to lateral sites in children with ADHD than in typically developing children (F (1, 48) = 7.26, p = .01, η^2_p = .131). Yet, again, no significant differences between groups were detected at either midline or lateral region.

TBR. No significant interaction effects involving group were detected for TBR.

Supplementary analyses with age and sex as a covariate did not change the group related effects for all frequency bands and TBR.

Supplementary analyses excluding children with comorbid ODD/CD. Regarding topographic differences between groups, the p-levels in alpha and beta power slightly reduced but the effect sizes remained in the same range (respectively p = .06, η^2_p = .073 and p = .08, η^2_p = .068). Since the interpretations of the effect sizes between the analyses with and without children with comorbid ODD/CD were comparable, the slight decreases in p-levels probably resulted from the reduction in power following the exclusion of 5 children from the analyses.

The significant effect in theta power remained when only children without comorbid ODD/CD were included in the analyses.

Further, excluding children with comorbid ODD/CD from the analyses revealed that topographic distribution on the sagittal plane for alpha power differed between groups (F (2, 86) = 4.87, p = .01, η^2_p = .102), indicating a steeper increase from anterior to posterior sites in typically developing children than in children with ADHD (F (2, 86) = 8.98, p < .01, η^2_p = .173). In addition, a group-by-condition effect was detected (F (1, 43) = 5.12, p = .03, η^2_p = .106) in alpha power, denoting alpha suppression with eye opening was lower in the ADHD group than in the control group. Yet, group differences did not reach significance in either condition. Also, a marginally significant group x condition x sagittal region effect appeared (F (1.74, 74.83) = 2.75, p = .08, η^2_p = .060), meaning that the smaller alpha attenuation with eye opening in ADHD was most apparent in central (F (1, 43) = 8.05, p < .01, η^2_p = .158) and posterior (F (1, 43) = 4.56, p = .04, η^2_p = .098) region (Figure 2).

Furthermore, EEG response to eye opening tended to differ between groups in theta power (F (1, 43) = 3.43, p = .07, η^2_p = .074), resulting from a slight theta decrease in the control group (F (1, 28) = 2.97, p < .10, η^2_p = .096) which was not apparent in the ADHD group. No group differences in theta power were detected in either condition. Further testing regarding the marginally significant group x condition x sagittal region effect in theta power (F (1.66, 71.25) = 2.88, p = .07, η^2_p = .063), revealed that the group difference in EEG reactivity to eye opening was significant in posterior region (F (1, 43) = 4.59, p = .04, η^2_p = .096) (Figure 2) and marginally significant in central region (F (1, 43) = 3.57, p = .07, η^2_p = .077).

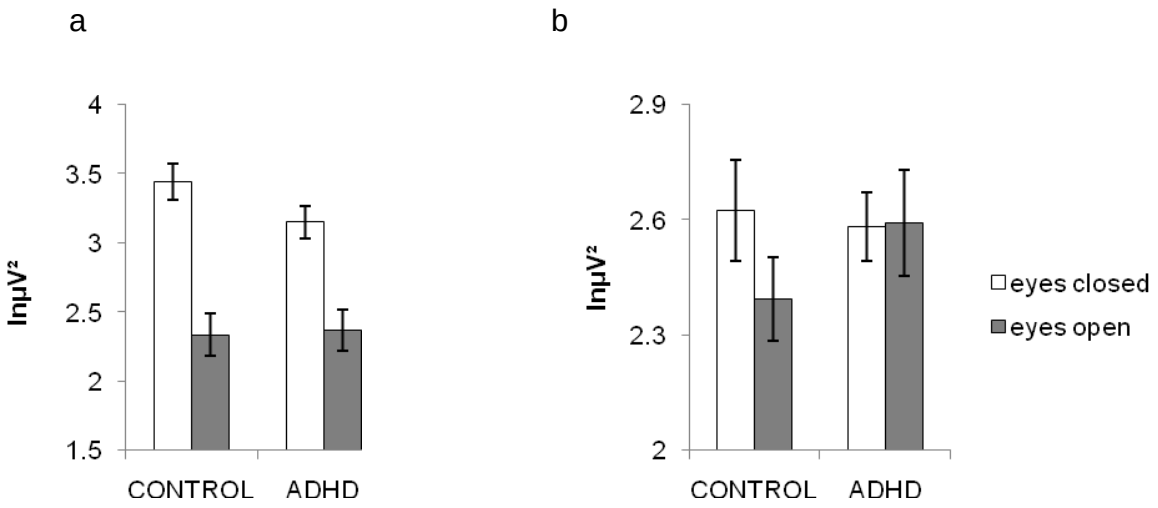

Figure 2. Mean (a) alpha and (b) theta power for posterior sites in eyes closed and eyes open conditions for children with ADHD without comorbid ODD/CD and control children. Error bars represent the standard error of the mean.

4. Discussion

In the present study, the stability and state-related characteristics of EEG deviances in ADHD were investigated. While no aberrant theta power and TBR were found in children with ADHD, a divergence in topographic distribution between midline and lateral sites was observed between groups in theta, alpha and beta power across resting conditions. Further, children with ADHD without comorbid ODD/CD exhibited less suppression of central and posterior alpha and theta power with eye opening than typically developing children.

In the current study, more derivations were used to investigate EEG compared to most existing studies, which enabled us to reveal group differences in lateral distribution of EEG activity. The observed midline distribution for theta power in typically developing children highly corresponds with other studies (for a review, see Barry & Clarke, 2009). Findings regarding beta and alpha power are less in line with other studies, in which a midline distribution

for beta power and a more equivalent distribution for alpha power across the lateral plane has been documented in control groups (for a review, see Barry & Clarke, 2009). Although other studies did not report the more equivalent distribution of EEG activity in ADHD that we observed in the present study, they also point to more deviance between groups at midline than lateral regions (e.g., Clarke et al., 1998; Clarke et al., 2001), which underlines the importance of investigating widespread cortical activity in ADHD. Therefore, it is recommended that future studies investigating EEG deviances in ADHD incorporate a sufficient number of electrodes. The paucity in the literature concerning power distribution across a lateral dimension including the midline, impedes drawing firm conclusions regarding the brain mechanisms underlying the deviances between children with ADHD and typically developing children. Nevertheless, during resting state, preservation of a physiological and functional balance in the brain relies on different local cortical neural activities and long-range corticocortical/cortico-subcortical neural activities that coexist and may interact with each other (Woltering et al., 2012). Variations in topographical distribution in ADHD may therefore reflect deficient neural communication or dysfunction in distributed network organization (for a review, see Konrad & Eickhoff, 2010), which may be related to ADHD symptomatology. Before drawing further conclusions on this, the robustness of the current findings should be replicated in future research.

Still, our findings regarding comparable theta and TBR between groups are in contrast with other studies (Barry et al., 2003; Clarke et al., 2007, 2011; Dupuy et al., 2011; González-Castro et al., 2013; Lansbergen et al., 2011; Loo et al., 2010; Shi et al., 2012; Snyder et al., 2008), but correspond with some recent studies that also failed to replicate increased theta or TBR in ADHD (Coolidge et al., 2007; Liechti et al., 2013; Loo et al., 2013; Nazari et al., 2011; Ogrim et al., 2012; Swartwood et al., 2003). As for alpha and beta power, our results are not

unexpected since deviances in those frequency ranges in ADHD have not been consistently observed across studies (see Section 1).

Among others, it is plausible that differences in sample characteristics for both children with and without ADHD may have contributed to divergent findings across studies (Arns et al., 2013; Liechti et al., 2013). Regarding sex, it has been suggested that boys have different EEG abnormalities than girls with ADHD (for a review, see Dupuy et al., 2013). In the current study, more girls were included in the control group than in the ADHD group. Furthermore, the proportion of boys to girls in our ADHD sample was somewhat lower than in most studies (e.g., Shi et al., 2012). However, higher theta or TBR in ADHD has been detected in samples with even a smaller boy to girl ratio than in the current study (e.g., Clarke et al., 2001; Loo et al., 2010). Moreover, controlling for sex in our analyses did not change the results. Therefore, we cautiously conclude that sex did not act as a confounding factor. Our study included children with ADHD with different subtypes and it may be that enhanced theta or TBR is only related to one of these subtypes. However not much research has been done on EEG differences between ADHD subtypes and so far disparate findings have been reported, with some studies documenting comparability in EEG activity between ADHD subtypes, and others observing more pronounced quantitative EEG differences in one subtype relative to the other and/or the control group (Buyck & Wiersema, 2014; Clarke et al., 1998, 2001b; Loo et al., 2010; Dupuy et al., 2011). Unfortunately, the size of our sample impedes reliable investigation of divergence according to ADHD subtypes, yet this could be further explored in future work. Furthermore, in the current study, 11 children with ADHD were on stimulant medication in daily life. Studies addressing the impact of stimulant medication on brain wave activity have indicated a power decrease in the theta band (Loo, Teale, & Reite, 1999; Clarke et al., 2003; Clarke, Barry,

McCarthy, Selikowitz, & Johnstone, 2007) and a reduction in TBR (Clarke, Barry, Bond, McCarthy, & Selikowitz, 2002) following medication. Although we are not aware of studies investigating the specific duration of medication effects on EEG activity, a medication wash-out period of 48 hours was respected, which is even more restrictive than regular research procedures across EEG studies (e.g., Loo et al., 2010) in ADHD. Consequently, we do not regard daily medication use in a part of our ADHD sample as a confounding factor for our results, yet further research may be warranted investigating (long-term) effects of daily life use of stimulants on EEG in ADHD.

Another source of heterogeneity in ADHD samples across studies refers to the presence of comorbid disorders. It is well established that a large proportion of children with ADHD has at least one comorbid psychiatric diagnosis, with ODD occurring the most frequently (Biederman, 2005). Yet, often studies have not controlled for comorbid ODD/CD and research on how this comorbidity influences EEG in ADHD is scarce. One study has documented that comorbidity with ODD/CD possibly enlarges TBR deviance in children with ADHD (Loo et al., 2013), while another study did not detect this effect and instead reported that focal theta abnormalities were more pronounced in an ADHD only group than in an ADHD group with ODD/CD comorbidity (Clarke et al., 2002). However, both studies focussed on an eyes closed resting condition only and were therefore not able to address the influence of comorbid ODD/CD on EEG response to eye opening. In the present study, although no divergence was found in the separate resting state conditions, group differences in alpha and theta reactivity on eye opening emerged when excluding children with comorbid ODD/CD, alluding more deviance in children with pure ADHD (i.e., not suffering from comorbid disruptive behaviour disorder). Currently, the debate is still ongoing whether comorbid oppositional symptoms in ADHD should be

considered as a component of ADHD or whether ADHD+ODD/CD represents a distinct pathological entity (Connor, Steeber, & McBurnett, 2010), as also defined in the International Classification of Diseases and Related Health Problems classification system (ICD-10, World Health Organisation, 2008). Our results appear to be more in line with the latter interpretation, although this conclusion is putative since it is not derived from a direct comparison between ADHD groups with and without comorbidity, as the sample size of the comorbid ADHD group (i.e., $n = 5$) was not sufficient to perform these analyses. Future studies incorporating more children with ADHD with comorbid disruptive behavior disorder are warranted to shed more light on the possible mediating effects of comorbid disorders in EEG deviances in ADHD.

As for less alpha attenuation on eye opening in ADHD, this has previously been observed in another study focussing on EEG response to eye opening in children with ADHD (Fonseca et al., 2013) and has been confirmed in two studies in adults with ADHD (Loo et al., 2010; Woltering et al., 2012). The finding of less theta attenuation in ADHD following eye opening has to the best of our knowledge not been reported before. Modulation of EEG activity between eyes closed and eyes open conditions has been proposed to be an indicator of function of thalamocortical networks (Boord et al., 2008) resulting from cortical processing of visual input (Barry et al., 2007). This suggests that in the ADHD group, neuronal networks are impaired to adjust to the changes in input between eyes closed and eyes open states. Furthermore, recent studies indicate that alpha power can be regarded as a marker of arousal, since an inverse relationship has repeatedly been established between alpha power and skin conductance level (SCL) (Barry et al., 2004; Barry, Clarke, Johnstone, McCarthy, & Selikowitz, 2009; Clarke et al., 2013), which is considered to be a reliable measure of autonomic arousal (for a review, see Critchley, 2002). For a long time, deviances in the theta frequency band have also been

associated with the concept of arousal, yet recent studies failed to find an association between theta power and SCL (Barry et al., 2004, 2009). Consequently, in specific, less alpha suppression in children with ADHD may possibly be regarded as reflecting an arousal dysfunction in ADHD. Important to note is that the ADHD group exhibited no aberrant alpha power in the conditions separately, yet expressed a difference in modulation of EEG activity between conditions. This may imply that deviances in ADHD are not characterized by a simple arousal impairment in one condition relative to the other, but rather reflect a deficiency in arousal *regulation*. Despite the lack of a well established autonomic measure of arousal (i.e., SCL) in our study design to strengthen this hypothesis, interpretations regarding deficient arousal modulation are in line with theoretical accounts of ADHD. According to the optimal stimulation theory, ADHD is related to difficulty with arousal regulation with the symptomatology reflecting a behavioural strategy to compensate for a state of underarousal (Zentall & Zentall, 1983). In support of this theory, research documented that in low stimulation environments, children with ADHD showed increased stimulation seeking activity whereas in high stimulation environments, behavioural responses in children with ADHD did not differentiate from typically developing children (Antrop, Buysse, Roeyers, & Van Oost, 2005; for a review, see Zentall & Zentall, 1983). Also the state regulation account (Sergeant, 2005; van der Meere, 2005), an influential explanatory account of ADHD, which is derived from the cognitive-energetic model (Sanders, 1983), states that individuals with ADHD have difficulties in maintaining and regulating an optimal energetic arousal/activation state. Research in this respect revealed convincing behavioural and psychophysiological support for disrupted energetic state regulation in ADHD during task execution (Börger & van der Meere, 2000; for a meta-analysis, see Metin, Roeyers,

Wiersema, van der Meere, & Sonuga-Barke, 2012; Sergeant, 2005; Sonuga-Barke et al., 2010; Wiersema, van der Meere, Roeyers, Van Coster, & Baeyens, 2006).

5. Conclusions

In conclusion, although no aberrant theta and TBR were found in children with ADHD in the present study, the findings refer to a consistent variation in topographic distribution in ADHD across resting state conditions compared to typically developing children, indicating the usefulness of inclusion of electrodes beyond the midline. The finding of less central alpha and theta attenuation with eye opening in children with ADHD who do not suffer from comorbid ODD/CD, suggest that EEG deviances in ADHD may reflect arousal regulation difficulties and stress the importance to take into account comorbidity with ODD/CD. Furthermore, the findings indicate that it is unlikely that stable, univariate EEG abnormalities are implicated in all children with ADHD and that it is important to take into account state-dependent characteristics when evaluating EEG in ADHD. From a clinical perspective, this implies that cautiousness is warranted in using simple EEG measures as a supplementary diagnostic tool, as has been proposed by some researchers (Monastra, Lubar, & Linden, 2001; Snyder et al., 2008).

References

Achenbach, T.M., & Rescorla, L.A. (2001). Manual for the ASEBA School-Age Forms and Profiles. Burlington, Vermont: University of Vermont, Research Center for Children, Youth, and Families.

American Psychiatric Association (2013). Diagnostic and statistical manual of mental disorders (5th ed.). Arlington, VA: American Psychiatric Publishing.

Antrop, I., Buysse, A., Roeyers, H., & Van Oost, P. (2005). Activity in children with ADHD during waiting situations in the classroom: A pilot study. *British Journal of Educational Psychology, 75*, 51-69.

Arns, M., Conners, C.K., & Kraemer, H.C. (2013). A decade of EEG theta/beta ratio research in ADHD: a meta-analysis. *Journal of Attention Disorders, 17*, 374-383.

Barry, R.J., Clarke, A.R. (2009). Spontaneous EEG oscillations in children, adolescents, and adults: Typical development, and pathological aspects in relation to AD/HD. *Journal of Psychophysiology, 23*(4), 157-173.

Barry, R.J., Clarke, A.R., & Johnstone, S.J. (2003). A review of electrophysiology in attention-deficit/hyperactivity disorder. I. Qualitative and quantitative electroencephalography. *Clinical Neurophysiology, 114,* 171-183.

Barry, R.J., Clarke, A.R., Johnstone, S.J., Magee, C.A., & Rushby, J.A. (2007). EEG differences between eyes-closed and eyes-open resting conditions. *Clinical Neurophysiology, 118,* 2765-2773.

Barry, R.J., Clarke, A.R., Johnstone, S.J., McCarthy, R., & Selikowitz, M. (2009). Electroencephalogram theta/beta ratio and arousal in attention-deficit/hyperactivity disorder: evidence of independent processes. *Biological Psychiatry, 66,* 398-401.

Barry, R.J., Clarke, A.R., McCarthy, R., Selikowitz, M., Rushby, J.A., & Ploskova, E. (2004). EEG differences in children as a function of resting-state arousal level. *Clinical Neurophysiology, 115,* 402-408.

Biederman (2005). Attention-deficit/hyperactivity disorder: a selective overview. *Biological Psychiatry, 57*(11), 1215-1220.

Boord, P., Siddall, P.J., Tran, Y., Herbert, D., Middleton, J., & Craig, A. (2008). Electroencephalographic slowing and reduced reactivity in neuropathic pain following spinal cord injury. *Spinal Cord, 46*, 118-123.

Börger, N.A., & van der Meere, J.J. (2000). Motor control and state regulation in children with ADHD: a cardiac response study. *Biological Psychology, 51*, 247-267.

Buyck, I., & Wiersema, J.R. (2014). Resting electroencephalogram in attention deficit hyperactivity disorder: developmental course and diagnostic value. *Psychiatry Research, 216*(3), 391-397.

Chabot, R.J., & Serfontein, G. (1996). Quantitative electroencephalographic profiles of children with attention deficit disorder. *Biological Psychiatry, 40*, 951-963.

Clarke, A., Barry, R., McCarthy, R., & Selikowitz, M. (1998). EEG analysis in attention-deficit/hyperactivity disorder: a comparative study of two subtypes. *Psychiatry Research, 81*, 19-29.

Clarke, A., Barry, R., McCarthy, R., & Selikowitz, M. (2001b). Age and sex effects in the EEG: differences in two subtypes of attention-deficit/hyperactivity disorder. *Clinical Neurophysiology, 112*, 806-814.

Clarke, A., Barry, R., McCarthy, R., & Selikowitz, M. (2002a). EEG analysis of children with attention-deficit/hyperactivity disorder and comorbid reading disabilities. *Journal of Learning Disabilities, 35*, 276-285.

Clarke, A.R., Barry, R.J., Bond, D., McCarthy, R., & Selikowitz, M. (2002). Effects of stimulant medications on the EEG of children with attention-deficit/hyperactivity disorder. *Psychopharmacology, 164*(3), 277-284.

Clarke, A.R., Barry, R.J., Dupuy, F.E., Heckel, L.D., McCarthy, R., Selikowitz, M., & Johnstone, S.J. (2011). Behavioural differences between EEG-defined subgroups of children with Attention-Deficit/Hyperactivity Disorder. *Clinical Neurophysiology, 122*, 1333-1341.

Clarke, A.R., Barry, R.J., Dupuy, F.E., McCarthy, R., Selikowitz, M., & Johnstone, S.J. (2013). Excess beta activity in the EEG of children with attention-deficit/hyperactivity disorder: A disorder of arousal? *International Journal of Psychophysiology, 89*, 314-319.

Clarke, A.R., Barry, R.J., McCarthy, R., & Selikowitz, M. (2001a). Excess beta in children with attention-deficit/hyperactivity disorder: An atypical electrophysiological group. *Psychiatry Research, 103*, 205-218.

Clarke, A.R., Barry, R.J., McCarthy, R., & Selikowitz, M. (2002b). Children with attention-deficit/hyperactivity disorder and comorbid oppositional defiant disorder: an EEG analysis. *Psychiatry Research, 111*(2-3), 181-190.

Clarke, A.R., Barry, R.J., McCarthy, R., Selikowitz, M., Clarke, D., & Croft, R. (2003). EEG in girls with attention-deficit/hyperactivity disorder. *Clinical Neurophysiology, 114*, 319-328.

Clarke, A.R., Barry, R.J., McCarthy, R., Selikowitz, M., & Johnstone, S.J. (2007). Effects of stimulant medications on the EEG of girls with Attention-Deficit/Hyperactivity. *Clinical Neurophysiology, 118*(12), 2700-2708.

Cohen, J. (1988). Statistical Power Analysis for the Behavioral Sciences (2nd ed.). Laurence Erlbaum, Hillsdale, N.J.

Connor, D.F., Steeber, J., & McBurnett, K. (2010). A review of attention-deficit/hyperactivity disorder complicated by symptoms of oppositional defiant disorder or conduct disorder. *Journal of Developmental and Behavioral Pediatrics, 31*(5), 427-440.

Coolidge, F.L., Starkey, M.T., & Cahill, B.S. (2007). Comparison of a Parent-Rated DSM-IV Measure of Attention-Deficit/Hyperactivity Disorder and Quantitative EEG Parameters in an Outpatient Sample of Children. *Journal of Clinical Neurophysiology, 24*(4), 348-351.

Critchley, H.D. (2002). Book Review: Electrodermal Responses: What Happens in the Brain. *The Neuroscientist, 8,* 132-142.

Dupuy, F.E., Clarke, A.R., Barry, R.J., McCarthy, R., & Selikowitz, M. (2011). Girls with attention-deficit/hyperactivity disorder: EEG differences between DSM-IV types. *Clinical EEG and Neuroscience, 42*(1), 1-5.

Dupuy, F.E., Barry, R.J., Clarke, A.R., McCarthy, R., & Selikowitz, M. (2013). Sex differences between the combined and inattentive types of attention-deficit/hyperactivity disorder: An EEG perspective. *International Journal of Psychophysiology, 89*(3), 320-327.

Fein, G., Galin, D., Yingling, C.D., Johnstone, J., & Nelson, M.A. (1984). EEG spectra in 9-13-year-old boys are stable over 1-3 years. *Electroencephalography and Clinical Neurophysiology, 58*(6), 517-518.

Fonseca, L.C., Tedrus, G.M.A.S., Bianchini, M.C., & Silva, T.F. (2013). Electroencephalographic alpha reactivity on opening the eyes in children with attention-deficit hyperactivity disorder. *Clinical EEG and Neuroscience*, *44*(1), 53-57.

Gasser, T., Bacher, P., & Steinberg, H. (1985). Test-retest reliability of spectral parameters of the EEG. *Electroencephalography and Clinical Neurophysiology, 60*(4), 312-319.

González-Castro, P., Rodríguez, C., López, A., Cueli, M., & Álvarez, L. (2013). Attention Deficit Hyperactivity Disorder, differential diagnosis with blood oxygenation, beta/theta ratio, and attention measures. *International Journal of Clinical and Health Psychology, 13*(2), 101-109.

Gratton, G., Coles, M.G.H., & Donchin, E. (1983). A new method for off-line removal of ocular artifact. *Electroencephalography and Clinical Neurophysiology, 55,* 468-484.

Grégoire, J. (2000). L'évaluation clinique de l'intelligence de l'enfant. Liège: Mardaga.

Hale, T.S., Smalley, S.L., Dang, J., Hanada, G., Macion, J., McCracken, J.T., McGough, J.J., & Loo, S.K. (2010a). ADHD familial loading and abnormal EEG alpha asymmetry in children with ADHD. *Journal of Psychiatric Research*, *44*(9), 605-615.

Hale, T.S., Smalley, S.L., Hanada, G., Macion, J., McCracken, J.T., McGough, J.J., & Loo, S.K. (2009). Atypical alpha asymmetry in adults with ADHD. *Neuropsychologia, 47*(10), 2082-2088.

Hale, T.S., Smalley, S.L., Walshaw, P.D., Hanada, G., Macion, J., McCracken, J.T., McGough, J.J., Loo, S.K. (2010b). Atypical EEG beta asymmetry in adults with ADHD. *Neuropsychologia, 48*(12), 3532-3539.

Hüfner, K., Stephan, T., Flanagin, V.L., Deutschlander, A., Stein, A., Kalla, R., Dera, T., Fesl, G., Jahn, K., Strupp, M., & Brandt, T. (2009). Differential effects of eyes open or closed in darkness on brain activation patterns in blind subjects. *Neuroscience Letters*, *466*, 30-34.

Karhu, J., Könönen, M., Herrgård, E., & Partanen, J. (1996). Spectra and reactivity of EEG in visual, sensori-motor and auditory areas in children. *Electroencephalography and Clinical Neurophysiology, 99*(4), 300-301.

Keune, P.M., Schoenenberg, M., Wyckoff, S., Mayer, K., Riemann, S., Hautzinger, M., & Strehl, U. (2011). Frontal alpha-asymmetry in adults with attention deficit hyperactivity disorder: Replication and specification. *Biological Psychology, 87*(2), 306-310.

Konrad, K., & Eickhoff, S.B. (2010). Is the ADHD Brain Wired Differently? A Review on Structural and Functional Connectivity in Attention Deficit Hyperactivity Disorder. *Human Brain Mapping, 31*(6), 904-916.

Lansbergen, M., Arns, M., van Dongen-Boomsma, M., Spronk, D., & Buitelaar, J. (2011). The increase in theta/beta ratio on resting state EEG in boys with attention-deficit/hyperactivity disorder is mediated by slow alpha peak frequency. *Progress in Neuropsychopharmacology & Biological Psychiatry. 35*(1), 47-52.

Liechti, M.D., Valko, L., Müller, U.C., Döhnert, M., Drechsler, R., Steinhausen, H.C., & Brandeis, D. (2013). Diagnostic value of resting electroencephalogram in attention-deficit/hyperactivity disorder across the lifespan. *Brain Topography, 26*(1), 135-151.

Loo, S.K., Cho, A., Hale, T.S., McGough, J., McCracken, J., & Smalley, S.L. (2013). Characterization of the Theta to Beta Ratio in ADHD: Identifying Potential Sources of Heterogeneity. *Journal of Attention Disorders, 17*(5), 384-392.

Loo, S.K., Hale, T.S., Hanada, G., Macion, J., Shrestha, A., McGough, J.J., McCracken, J.T., Nelson, S., & Smalley, S.L. (2010). Familial clustering and DRD4 effects on electroencephalogram measures in multiplex families with attention deficit/hyperactivity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry, 49*(4), 368-377.

Loo, S.K., Hale, T.S., Macion, J., Hanada, G., McGough, J.J., McCracken, J.T., & Smalley, S.L. (2009). Cortical activity patterns in ADHD during arousal, activation and sustained attention. *Neuropsychologia, 47*, 2114-2119.

Loo, S.K., Teale, P.D., & Reite, M.L. (1999). EEG correlates of methylphenidate response among children with ADHD: A preliminary report. *Biological Psychiatry, 45*(12), 1657-1660.

Metin, B., Roeyers, H., Wiersema, J.R., van der Meere, J., & Sonuga-Barke, E. (2012). A Meta-Analytic Study of Event Rate Effects on Go/No-Go Performance in Attention-Deficit/Hyperactivity Disorder. *Biological Psychiatry, 72,* 990-996.

Monastra, V.J., Lubar, J.F., & Linden, M. (2001). The development of a quantitative electroencephalographic scanning process for attention deficit-hyperactivity disorder: reliability and validity studies. *Neuropsychology, 15,* 136-144.

Nazari, M.A., Wallois, F., Aarabi, A., & Berquin, P. (2011). Dynamic changes in quantitative electroencephalogram during continuous performance test in children with attention-deficit/hyperactivity disorder. *International Journal of Psychophysiology, 81*(3), 230-236.

Ogrim, G., Kropotov, J., & Hestad, K. (2012). The QEEG TBR in ADHD and normal controls: Sensitivity, specificity and behavioral correlates. *Psychiatry Research, 198*(3), 482-488.

Oostenveld, R., & Praamstra, P. (2001). The five percent electrode system for high resolution EEG and ERP measurements. *Clinical Neurophysiology, 112,* 713-719.

Pelham, W., Gnagy, E.M., Greenslade, K.E., & Milich, R. (1992). Teacher ratings of DSM-III-R symptoms for the disruptive behavior disorders. *Journal of the American Academy of Child and Adolescent Psychiatry, 31,* 210-218.

Ristanovic, D., Martinovic, Z.J., & Jovanovic, V. (1999). Topography of visual EEG reactivity in school-age children. *Brain and Development, 21,* 236-243.

Samson-Dollfus, D., & Goldberg, P. (1979). Electroencephalographic quantification by time domain analysis in normal 7-15-Year-Old Children. *Electroencephalography and Clinical Neurophysiology, 46,* 147-154.

Sanders, A.F. (1983). Towards a model of stress and human performance. *Acta Psychologica, 53,* 61-97.

Schaffer, D., Fisher, P., Lusac, C.P., Dulcan, M.K., & Schwab-Stone, M.E. (2000). NIMH Diagnostic Interview Schedule for Children version IV (NIMH DISC-IV): Description, differences from previous versions and reliability of some common diagnoses. *Journal of the American Academy of Child and Adolescent Psychiatry, 39,* 28-38.

Sergeant, J. (2005). Modeling attention-deficit/hyperactivity disorder: a critical appraisal of the cognitive-energetic model. *Biological Psychiatry, 57,* 1248-1255.

Shi, T., Li, X., Song, J., Zhao, N., Sun, C., Xia, W., Wu, L., & Tomoda, A. (2012). EEG characteristics and visual cognitive function of children with attention deficit hyperactivity disorder (ADHD). *Brain and Development, 34*(10), 806-811.

Snyder, S.M., Quintana, H., Sexson, S.B., Knott, P., Haque, A.F., & Reynolds, D.A. (2008). Blinded, multi-center validation of EEG and rating scales in identifying ADHD within a clinical sample. *Psychiatry Research, 159*(3), 346-358.

Sonuga-Barke, E., Wiersema, J.R., van der Meere J., & Roeyers, H. (2010). Context-dependent Dynamic Processes in Attention Deficit/Hyperactivity Disorder: Differentiating Common and Unique Effects of State Regulation Deficits and Delay Aversion. *Neuropsychological Review, 20,* 86-102.

Sonuga-Barke, E.J.S., Taylor, E., Sembi, S., & Smith, J. (1992). Hyperactivity and delay aversion: I. The effect of delay on choice. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 33*(2), 387-398.

Swartwood, J.N., Swartwood, M.O., Lubar, J.F., & Timmermann, D.L. (2003). EEG differences in ADHD-combined type during baseline and cognitive tasks. *Pediatric Neurology, 28*(3), 199-204.

van der Meere, J.J. (2005). State regulation and ADHD. In D. Gozal & D. L. Molfese (Eds.), Attention deficit hyperactivity disorder: From genes to animal models to patients (pp. 413-433). Totowa, NJ: Humana.

van Dongen-Boomsma, M., Lansbergen, M.M., Bekker, E.M., Kooij, J.J.S., van der Molen, M., Kenemans, J.L., & Buitelaar, J.K. (2010). Relation between resting EEG to cognitive performance and clinical symptoms in adults with attention-deficit/hyperactivity disorder. *Neuroscience Letters, 469*, 102-106.

Wechsler, D. (1991). The Wechsler intelligence scale for children-third edition. San Antonio, TX: The Psychological Corporation.

Wiersema, J.R., van der Meere, J.J., Roeyers, H., Van Coster, R., Baeyens, D. (2006). Event rate and event-related potentials in ADHD. *Journal of Child Psychology and Psychiatry, 47*, 560-567.

Willcutt, E.G. (2012). The prevalence of DSM-IV attention-deficit/hyperactivity disorder: a meta-analytic review. *Neurotherapeutics, 9*(3), 490-499.

Woltering, S., Jung, J., Liu, Z., & Tannock, R. (2012). Resting state EEG oscillatory power differences in ADHD college students and their peers. *Behavioral and Brain Functions, 8,* 60.

World Health Organization (2008). ICD-10: International statistical classification of diseases and related health problems (10th Rev. ed.). New York, NY: World Health Organization.

Zentall, S.S., & Zentall, T.R. (1983). Optimal stimulation: a model of disordered activity and performance in normal and deviant children. *Psychological Bulletin, 94*(3), 446-447.