Posterior Alpha Oscillations as an Index for the Attentional Bias in Children with Attentional Deficit Hyperactivity Disorder

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Until now, event-related potential studies in children with ADHD showed an altered process of selecting stimuli in the environment that are relevant to current behavior while ignoring those that are not. Although a deviant neural oscillatory pattern during rest was often measured in this group, very few studies included data on oscillations during task performance. The alpha frequency band (8-12 Hz) is thought to play an inhibitory role in the cortex by selectively decreasing or increasing power when that region is task relevant or irrelevant respectively. Support for this hypothesis comes from studies addressing alpha modulation and lateralization during task performance in healthy adults. The present study was designed to investigate similar measures in 7-10 year old children with (N=5) and without (N=9) ADHD. A covert visuospatial attentional cueing paradigm was used while recording electrophysiology and eye movements. Cues directed attention with a 75% congruency with respect to the upcoming target. The average cue-locked response over all children confirmed that even in this age range it is possible to elicit alpha modulation and lateralization in occipital channels. Unlike in healthy adults, the maintenance of the alpha lateralization did not sustain until target presentation, possibly explaining the observed lack of behavioral benefit of the cue. Strikingly, we found that in the ADHD group the maintenance of alpha lateralization as a response to the left cue, was correlated to the ADHD symptom-rating. In addition, the time course of the averaged alpha power over all trials showed a stronger decrease followed by a stronger increase in children with than without ADHD. Children of both groups showed a behavioral rightward bias in bisecting lines but no such significant bias in alpha lateralization. In conclusion, these findings demonstrate that the different pattern of alpha lateralization can potentially be used as a biomarker of ADHD.

Children with Attention-Deficit/Hyperactivity Disorder (ADHD) display a persistent pattern of inattentive and/or hyperactive-impulsive behavior, which leads to a clinically significant impairment in social, academic, or occupational functioning (American Psychiatric Association, 2000). The worldwide prevalence of the disorder is 5.3% (Polanczyk & Rohde, 2007). Currently, the diagnosis of ADHD is based on the presence or absence of clinical symptoms as described in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) (American Psychiatric Association, 2000).

According to the DSM, inattention and distractibility are part of the clinical symptoms of ADHD. The related process of selecting stimuli in the environment that are relevant to current behavior while ignoring those that are not is referred to as selective attention (Halperin, 1991). Selective attention has not consistently shown to be affected in ADHD when studied with classical measures such as the Stroop and Eriksen Flanker task (Brodeur & Pond, 2001; Sergeant et al., 2003; Huang-Pollock & Nigg, 2003; Huang-Pollock et al., 2005). Nevertheless, studies looking at event-related potentials (ERPs) of neural activity during these tasks clearly indicated an early selection deficit in the visual modality (van der Stelt et al., 2001; Jonkman et al., 2004). Based on these ERP-studies it was suggested that children with ADHD might have a deficit in an early stage of attention-modulated processing. Another ERP-study, however, suggested that ADHD is not clearly linked with an abnormal or deficient initial focus of attention but rather with an abnormal late differential distribution of attentional resources (Lopez et al., 2006). Apparently, although not clear exactly how, ERPs are able to detect differential activity between children with and without ADHD during attentional tasks, in a way that classical paradigms could not.

In addition to ERP-analyses, electro physiological research in children with ADHD has been conducted on resting state neural oscillatory data. In oscillatory research, five frequency bands are usually distinguished: delta (0.5 to 3.5 Hz), theta (4 to 7 Hz), alpha (8 to 12 Hz), beta (13 to 30 Hz) and gamma (> 30 Hz). These frequency bands are hypothesized to reflect different physiological roles and relate to specific perceptual, sensorimotor and cognitive operations, although these are still debated and require further support. Most studies that explore frequency bands in ADHD have suggested that the activity pattern often seen in ADHD is a reflection of cortical under-arousal. The majority of resting state electroencephalography (EEG) in these children is characterized by increased slow-wave activity and decreased fast-wave activity, primarily theta and beta, respectively. These slow and fast waves are often coupled, resulting in elevated theta/alpha and theta/beta ratios (see Barry et al. (2003) for a review). Note that increased theta and decreased beta activity can only be found when using similar frequency bands for all subjects, not when individualizing these frequency bands. Low alpha peak frequencies are therefore suggested to mediate the previously found heightened theta/beta ratio (Lansbergen et al., 2011).

Although resting state EEG abnormalities are an interesting and valuable phenomenon, it has been known for a long time that EEG during cognitive tasks can reveal different cortical dysfunction than EEG during rest (Gevins et al., 1979; Petsche et al., 1986). A study that addressed the differentiating oscillatory activation between cognitive performance and rest in children with ADHD (age 10.51 ± 2.6 years) indeed showed that the decrease in the absolute and relative alpha frequency bands was more apparent during attentional load in a vigilance task than during resting state (El-Sayed et al., 2002). Although ERP-studies were typically performed during task performance, very few studies have investigated neural oscillatory activity during task performance in children with ADHD. Yet, the relation between frequency bands and cognitive performance may inform us about the content and representation of different frequency bands both in the healthy population and in disorders such as ADHD. In the current study, we focused on one of the frequency bands only; the alpha band.

Alpha waves were initially known for its appearance when closing the eyes (H. Berger, 1929). Ever since, a lot of discussion has arisen about what alpha might reflect (for an overview see: Palva & Palva (2007)), including the long assumed reflection of 'idling'; an alert-but-still brain state. Based on the more recent 'inhibition-timing hypothesis' alpha is actively involved in task performance (Klimesch et al., 2007). According to this hypothesis alpha plays an inhibitory role in the cortex by selectively increasing in power when that region is task irrelevant, while inhibition is released where reduced alpha power is measured. Recently, strong evidence has been obtained for the inhibition-timing hypothesis, when addressing the differences in attention to a visual hemifield per hemisphere with the alpha modulation index and addressing the differences between hemispheres with attention to one visual hemifield with the alpha lateralization index. By using a covert visuospatial attention task in which a cue directed attention to the left or right visual hemifield, it was shown that higher occipital alpha power was measured contralateral to the unattended side than contralateral to the attended side during a covert attentional cueing task (Worden et al., 2000; Yamagishi et al., 2003; Sauseng et al., 2005; Kelly et al., 2006; Händel et al., 2011). In favor of the inhibition- timing hypothesis, the amount of difference in power correlated with participants´ task performance. Alpha modulation in 8-12 year old typically developing children likewise showed a decrease in alpha as response to a cue, suggesting release of inhibition (Mazaheri et al., 2010). In contrast, in similarly aged children with ADHD, a cue did not elicit any significant posterior alpha modulations, indicating a possible deficit in the inhibition process. Like adults, typically developing children showed a negative correlation between occipital alpha activity and behavioral benefits of a cue, while no such a relationship was present in children with ADHD (Mazaheri et al., 2010).

Mazaheri et al. (2010) did not compare visual hemifields or hemispheres because they used an attentional modality switching task rather than a covert visuospatial attention task. The comparison between hemispheres, however, can be of particular interest since both adults and children with ADHD have a faster response to the right visual hemifield than to the left visual hemifield (Voeller & Heilman, 1988; Sheppard et al., 1999; Geeraerts et al., 2008). Eight to 14 year old children with ADHD displayed a higher distractibility when distracters were presented in the right visual field, while typically developing children showed higher distractibility when distractors were presented in the left visual hemifield (Chan et al., 2009). Indeed, the rightward bias seen in ADHD contradicts the pseudoneglect phenomenon which is the leftward bias seen in healthy adults (Bowers & Heilman, 1980). In healthy development, a shift seems to occur over time; if asked to use their right hand on a so called line bisection task (LBT) in which horizontal lines should be bisected through the middle, 10-12 year old children bisected these lines with a rightward bias, while older children bisected these with a leftward bias (Hausmann et al., 2003).

Resting state electro-physiological data in children with ADHD point in a similar direction as behavioral measures. Excess right hemisphere power in theta and alpha band was eight times more likely to occur than excess left hemisphere power (Chabot & Serfontein, 1996). Complementary, in ERP-research, it is known that some ERP-components, reflecting activation rather than inhibition, are biased away from the right hemisphere (DeFrance et al., 1996). Looking at oscillatory data, a study that correlated resting-state EEG with the LBT in healthy adults showed that greater alpha power correlated with diminished pseudoneglect (Çiçek et al., 2003).

Combining these lines of research, ter Huurne et al. (2012) recently studied the modulation of alpha power in adults with ADHD addressing the alpha modulation index and the alpha lateralization index, again using a covert visuospatial attention cueing paradigm including cues of 80% predictability, although attention was directed towards the cued side in unaffected adults, only the right cue was effective in adults with ADHD, resulting in a significant difference between left and right cue conditions in behavioral performance. Also, the lateralization of alpha power for the left visual hemifield was significantly smaller in the ADHD group than in the control group. A combination of these measures showed that a correlation between the behavioral benefit of the cue and the lateralization of alpha power was seen in controls but absent in the ADHD group. Note that ter Huurne et al. (2012) studied adults with ADHD. However, the diagnostic criteria for ADHD have been developed for children and have never been validated in adults (Faraone et al., 2006). Conceptually, there is a difference between children with ADHD and adults with ADHD because the disease will not persist until adulthood in all children with ADHD, while the disease per definition had an onset in childhood in adults with ADHD (Faraone & Biederman, 2005). This is why findings in adults with ADHD cannot readily be generalized to children with ADHD. The disease is not the only aspect that undergoes an age related difference; alpha activity also changes with development (Yordanova & Kolev, 1997). When comparing healthy 6-11 year old children with healthy adults, a higher amplitude, weaker phase locking, and the maximal responses located more parietal were found in the alpha band of children (Yordanova & Kolev, 1997). Cognitive features, such as reaction time and accuracy on an attentional task have been shown to be in full development in healthy 6 to 9 year old (Rueda et al., 2004). Given these age related differences in the disease conceptualization, alpha activity, attentional task performance, and the earlier mentioned shift towards pseudoneglect, the findings of ter Huurne et al. (2012) do not necessarily apply to children.

The present study was designed to investigate how alpha modulation and alpha lateralization are reflected in development both in children with and without ADHD by using a covert visuospatial attentional cueing paradigm. After innovatively showing that it is possible to elicit alpha lateralization in children in a similar way as in adults, results were compared between children with and without ADHD. Alpha-responses were related to behavioral aspects such as the cueing effect of response times (RTs) and hit rate, the attentional bias measured with a line bisection task, and ADHD severity rated by parents. Using these measurements, we further explored the role of alpha in active inhibition and the attentional bias in ADHD. The current study thus gave more insight in both healthy brain development and brain development with the common disorder ADHD.

Methods

Participants

15 right-handed children were included in this study. One participant decided not to continue after inclusion leading to 14 children that were enrolled (6 with ADHD and 9 controls; age range 7-10 years). Children with ADHD were recruited through Karakter, University Centre for Child and Adolescent Psychiatry, Nijmegen. Children without ADHD were recruited through primary schools in the area of Nijmegen. All measurements were performed at the Donders Institute for Brain, Cognition and Behavior, Nijmegen. The study was approved by the Dutch Central Medical Ethics Committee (www.ccmo.nl) and was conducted in accordance with the declaration of Helsinki. All parents gave their written informed consent before participation. Parents received reimbursement while children received a present.

One child in the ADHD group (male, age 7.3) was not able to perform above chance level and was therefore excluded, leaving the ADHD group with 5 children (2 males, mean age = 9.0 ± 1 year). Of these, three children were diagnosed with the combined type, one child with the attentional type, and one child with the hyperactive type. One child in the ADHD group had never been exposed to ADHD-related medication; all others used methylphenidate varying from 2 to 20 mg a day. The 4 children who were taking ADHD-related medication underwent a wash-out period of at least 12 hours prior to the EEG-measurement. One child was clinically diagnosed with oppositional deviant disorder in the past and one child was diagnosed with dyslexia. However, none of the included children with ADHD had scores in the clinical range on The Child Behavior Checklist (CBCL; Verhulst et al. (1996)), a broadband scale for behavior problems completed by parents, or had any neurological, cardiovascular, serious motor- or perceptual disorders/handicaps.

All 9 children in the typically developing group (4 males, mean age = 8.5 ± 1 year) were undiagnosed with ADHD or any other psychiatric, neurological, cardiovascular, serious motor- or perceptual disorders/handicap assessed with CBCL.

If intelligence had not been measured during the last 2 years, average performance on two subtests of the Wechsler Intelligence Scale for Children (WISC-III; Wechsler & Corporation (1991); Dutch version: Kort et al. (2002)) Vocabulary and Block Design, was determined for all children. In three children these tasks were already assessed within 2 years prior to inclusion. In one child a full version of the WISC was measured within 2 years prior to inclusion.

Study procedure

All children and their parents visited the institute twice. First, if necessary, two subtests of the WISC-III were administered to estimate intelligence. Following, children performed the Line Bisection Test (LBT; Schenkenberg et al. (1980). After these behavioral tasks the covert attention task was explained and practiced. This practice session was conducted while tracking the eyes, but without EEG measurement. On the second visit the covert attention task was performed while tracking the eyes and recording EEG. If children used medication during the first visit in the ADHD-group, they were asked to perform the LBT without medication during the second visit instead. Also two resting state EEGs were recorded during the second visit.

Measurements

ADHD rating The ADHD rating scale, according to the DSM-IV, was filled out by parents to rate the current severity of ADHD symptoms. All nine attentional items, six hyperactive items and three impulsive items were rated. This was done using a 4-point Likert scale in which every item is scored as 0 (does never occur), 1 (occurs sometimes), 2 (occurs often) or 3 (occurs very often). For those children that used medication, symptoms were rated when based on time they were withdrawn from medication. The ADHD rating was filled out for both children with and without ADHD, only reaching the diagnostic cut off point in the first group.

Line Bisection Task The line-bisection task comprised 17 horizontal black lines of 2-mm width on an off-white sheet of paper (21 x 30 cm). The distance between the lines was 6 mm, except for the distance between the 11^{th} and 12^{th} line, which was 31 mm. The length of the lines ranged from 72 mm to 149 mm, with an average length of 112 mm. They were pseudo randomly positioned so that 5 lines appeared 50 mm from the left margin, 5 lines appeared 50 mm from the right margin and the other 7 lines appeared in the middle of the sheet. The left lateralized lines had lengths of 72, 101, 117, 141, 149 mm, with an average of 114 mm. The right lateralized lines had lengths of 88, 101, 119, 132, 147 mm with an average of 117 mm. The centered lines had lengths of 112, 134, 90, 103, 119, 72, 111 mm with an average of 106 mm. The sheet was laid in front of the child's midline. In a random half of the participants, the sheet was presented upside down, flipping left and right and creating the big distance between the 6^{th} and 7^{th} line. Next, the child was instructed to bisect the line in what he or she thought to be two parts of equal length. This was done with a ballpoint pen. Only one line was presented at a time, the others were covered with two blank off-white sheets of paper. All children performed the task with their right, preferred, hand without any time restrictions.

Covert attention task The covert attention task has its origins in Posner's cuing paradigm for spatial orienting of attention (Posner, 1980). Analogous to the 'feed the fish' game used in an earlier study (A. Berger et al., 2000), the task was presented as a 'save the fish' game. Before start, a shark recapped the most important instructions in an introduction video of approximately 1 minute.

Sharks were presented at the left and the right side of the screen (figure 1). This neutral pre-cue period (500 ms + time it takes to fixate on the fish in the middle of the screen) was followed by an attentional cue in which the fish in the middle looked at the left or the right shark for 200 ms. Then a neutral cue-target interval (1000-1500 ms) similar to the pre-cue period followed, proceeding the target presentation (100 ms). During this period, the child would prepare for the upcoming target. The target followed, consisting of both mouths of the sharks opening. The one opening widest was the target. Responses were given with the right index finger for a left target and the right middle finger for a right target. The maximum response time (RT) was set at 1400 ms after target presentation. Both types of cues occurred with equal probability and predict the target location in 75% of the trials. During the practice session on the first visit, this probability was set to 80% in order to encourage the child to use the cue information. If the child correctly responded within response interval, the target disappeared and a positive feedback was given. If the child responded incorrectly or did not respond within response interval, negative feedback was given. Feedback was displayed for 500 ms. Regardless of the performance, a video returned every 37 trials containing a shark that motivated the child to save more fish. During the first visit, 100 trials of the task (40 trials per congruent condition and 10 per incongruent condition per hemifield) were practiced.

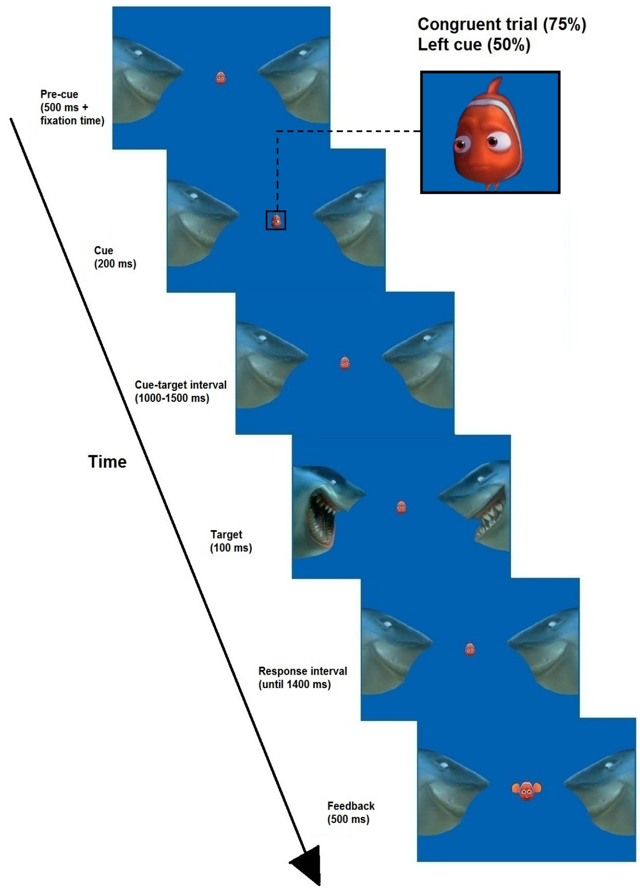

Figure 1. Schematic overview of the experimental paradigm. After a pre-cue period the trial started as soon as both starting criteria were fulfilled (1. A minimum of 500 ms pre-cue time, 2. Fixating in the middle). First, the cue consisting of a fish in the middle looking to the left or right side of the screen, was projected for 200 ms. This cue congruently predicted the side of the target in 75% of the trials. In 25% of the trials, the target appeared on the other side than the cue predicted. The cue was followed by a cue-target interval of 1000-1500 ms (jittered) in which the child would prepare for the upcoming target. If the child looked away from the fish during this period, a cartoon shark instructed the child to fixate. The target consisted of both mouths of the sharks opening and was presented for 100 ms. The one opening widest was the target. The child had to respond correctly within 1400 ms in order to receive positive feedback. If the child responded incorrectly or not within the response interval, negative feedback was given. This feedback was displayed for 500 ms.

The task during the second visit consisted of 368 trials: 276 trials of the congruent condition (138 left congruent, 138 right congruent) and 92 trials of the incongruent condition (46 left incongruent, 46 right incongruent).

Eye tracking After face-to-face task instructions, eyes were calibrated using a 5 point calibration procedure enabling fixation measurement during task execution. A corneal reflection eye tracker recorded both eyes (Tobii 1750, Tobii Technology Sweden) and ClearView software was used for calibration. When all 5 points were calibrated validly, the eye tracker was regarded ready for use. Information of the eye tracker was used during the pre-cue period and during the cue-target interval. During the pre-cue period the eye tracker did not allow the cue to begin until the child fixated on the middle of the screen. During the cue-target interval, if the average deviation from fixation was bigger than a 10^{th} of the screen width during the cue-target interval, a video in which a cartoon shark instructed the child to stay fixated on the middle was presented. Depending on the deviation (small, middle, large), one of the three different videos was presented, respectively instructing to stay fixated on the eyes, stay fixated on the fish, or not to look at the sharks. The maximum amount of these videos was set at 20.

EEG recordings Electroencephalography was recorded from 32 scalp electrodes from an Acticap box. The reference was placed on top of the head and electrode impedance was kept below 20 kOhm. EEG data were filtered with a band-pass filter of 2-30 Hz. The sampling rate was set to 256 Hz. First, EEG was assessed during a 2-min eyes open and 2-min eyes closed resting-state condition. Children were instructed to sit quietly during measurement. The covert attention task was then performed while recording EEG.

Analyses

Data were processed and analyzed using MATLAB 7.5.0 (The MathWorks, Inc., Natrick, MA) and the FieldTrip software package (http://fieldtrip.fcdonders.nl, a MATLAB-based toolbox for the analysis of electro physiological data). In all analyses unless when explicitly stated different, the significance level was set at $p = 0.05$.

ADHD rating For both groups the ADHD severity, meaning the amount of occurrences per item of the ADHD-criteria, was determined by summing the scores of all items resulting in a score which we called $ADHD_{total}$. The $ADHD_{total}$ could vary between 0 (no symptoms at all) and 54 (all 18 items occur very often) with the threshold for having one of the subtypes of ADHD (attentional or hyperactive type) lying at 18. The $ADHD_{total}$ scores were compared to this threshold by performing a one sample t-test per group. The two groups were then compared conducting a two sample t-test.

Line Bisection Task To behaviorally measure if there was a bias to one of the visual fields, a line bisection task was used. Analysis was done in a similar way as previous studies (Scarisbrick et al., 1987; Shuren et al., 1994; Hausmann et al., 2003). The left end of the line until bisection point was measured with 1 mm accuracy. Taking into account individual line length, the percentage of deviation from the midline was computed as follows:

$$\text{Line deviation}_{\text{mean}} = \frac{(\text{indicated left half}) - (\text{true half})}{\text{true half}} * 100$$

in which a negative value indicates a leftward bias. First, to determine whether Line $deviation_{mean}$ deviated from 0 a one sample t-test was conducted per group. Using a Spearman Brown correlation, the correlation between age and Line $deviation_{mean}$ was determined for the children of both groups. An analysis of variance (ANOVA) with Line $deviation_{mean}$ as dependent variable and group (ADHD vs. non-ADHD) as between subject variable was conducted. Followed by a similar analysis of covariance (ANCOVA) with age as covariate.

Behavioral part of the covert attention task First, the hit rates over all conditions were computed using a two sample t-test to test whether both groups were able to perform the test equally well. Next, to test if there was a difference between the congruent and incongruent trials or a so-called cueing effect, for both groups separately, hitrate was compared between conditions (congruent vs. incongruent), again using a two sample t-test. Following, we conducted a two tailed repeated measures analysis of variance (ANOVA) with hit rate as dependent variable, condition (congruent vs. incongruent) and visual hemifield (left vs. right) as within subject variables and group (ADHD vs. non-ADHD) as between subject variable. All these analyses were then repeated replacing hit rate with RT.

EEG part of the covert attention task Artifacts such as vertical and horizontal EOG artifacts, muscle potentials, amplifier or electrode noise, were removed when restricted to trials but spread over channels or were repaired by taking the mean over neighbor channels when spread over trials but restricted to one channel. This was done using a semiautomatic routine within FieldTrip. Only those trials in which participants' gaze was pointed near the fixation point were used for further analyses. Time frequency representations of power (2-30 Hz) were calculated using a Fast Fourier Transform (FFT) and a Hanning window. The entire interval was -0.5-1.5s, cue-locked. The window contained 5 cycles and was computed every 50ms shifted.

The alpha band (8-12 Hz) was the frequency of interest and the cue-target interval was the time of interest. Based on results of ter Huurne et al. (2012), the maintenance of lateralization until target was expected to show a difference between ADHD and the control group, reflected by the ADHD-group not being able to maintain lateralization. Therefore the time course of the modulation was possibly thought to hold interesting information. Analyses were conducted for the entire cue-target interval and for an early interval of 0-0.7s after cue-onset and a late interval of 0.7-1.35s after cue-onset.

The cue-locked time course of alpha power averaged over all trials and averaged over children of both groups was used to select the time points with the lowest values while using an absolute baseline. For these time points alpha power was topographically plotted. The channels showing most cue-related alpha decrease over trials were then chosen for further analysis. Based on results of Yordanova & Kolev (1997), maximal responses in the alpha-band were expected over the parietal channels. To be able to show that modulation of the alpha-band was specific to occipital channels, parietal channels were chosen as a control measure. For the occipital channels, the difference in alpha power between groups was tested with a two-sample t-test. The alpha modulation index (ΔAMI) was computed over the 0.8-1s after cue-onset time points per channel and per subject without baseline correction for both occipital channels and parietal channels separately in the following way:

$$\mathtt{AMI}_{\mathtt{left\ or\ right}} = \frac{(\alpha_{\mathtt{power\ left\ cue\ trials}}) - (\alpha_{\mathtt{power\ right\ cue\ trials}})}{(\alpha_{\mathtt{power\ left\ cue\ trials}}) + (\alpha_{\mathtt{power\ right\ cue\ trials}})}$$

in which AMI_{left} represents the average over left channels and AMI_{right} represents the average over right channels. AMI_{right} was then subtracted from AMI_{left} and averaged over all subjects resulting in the ΔAMI. This measure was used to check if there was modulation of the alpha band and whether this was specific to occipital channels.

The alpha lateralization index (ΔALI) was calculated over time per cue direction and per subject, using an absolute baseline for the selected occipital and parietal channels separately in the following way:

$$\mathtt{ALI}_{\mathtt{left\ or\ right}} = \frac{(\alpha_{\mathtt{power\ left\ channels}}) - (\alpha_{\mathtt{power\ right\ channels}})}{(\alpha_{\mathtt{power\ left\ channels}}) + (\alpha_{\mathtt{power\ right\ channels}})}$$

in which ALI_{left} represents the average over left cue trials and ALI_{right} represents the average over right cue trials. ALI_{right} was subtracted from ALI_{left} and averaged over all subjects resulting in the ΔALI. For all time points, we determined whether this point was significantly different from the pre-cue period. Since this was done for the entire time interval, significance levels were Bonferonni corrected to avoid the multiple comparison problem. Next, similar analyses were conducted per group. Also per group, for all time points of the ALI_{left} and ALI_{right}, we determined whether there was a positive and negative shift compared to the pre-cue period respectively. The significant time points were chosen to compare either the ALI_{left}, ALI_{right}, or ΔALI between groups. Since the maintenance of lateralization until target was expected to show a difference between ADHD and no ADHD, we conducted a two-tailed repeated-measures analysis of variance (ANOVA) studying the alpha power with visual hemifield (left vs. right cue) and time point within the cue-target interval (early vs. late time point) as within-subjects factor and group (ADHD vs. non-ADHD) as between-subjects factor.

Combining the analyses To determine if there was a negative correlation between the ΔALI and the behavioral benefits of the cue, the ΔALI at the selected time points was correlated with the cueing effect, defined by the difference between congruent and incongruent trials in RT or in hitrate. This was done using Spearman Brown correlations. To determine whether the severity of ADHD-symptoms (ADHD_{total}) was negatively correlated with the ΔALI, these two variables were correlated as well. Finally, a possible behavioral bias as measured with the Line $\mathrm{deviation}_{mean}$, was correlated with ΔALI.

Results

No further children were excluded leaving 5 children in the ADHD group and 9 children in the control group.

Behavioral results

IQ estimation The mean estimated IQ for the ADHD-group was 98.75 (sd = 3.86, range = 96-103) and 123.56 (sd = 18.20, range = 103-145) for the typically developing children. This difference was significant (p = 0.012).

ADHD rating The ADHD_{total} in the ADHD group was 32 (± 5.96, ranging 26-40) and 6 (± 5,78, ranging 0-18) in the control group. In the control group, this score was significantly lower than the ADHD-threshold ($p < 0.0001$). In the ADHD group, this score was significantly higher than the ADHD-threshold ($p = 0.0063$). The ADHD_{total} was significantly different between groups (p = 0.0016).

Line Bisection Task The Line $\mathrm{deviation}_{mean}$ was significantly different from zero in both groups (controls: mean = 3.30 ± 2.35, $p = 0.0205$; ADHD: mean 3.27 ± 2.10, $p = 0.0253$). These positive means indicate that both groups showed a significant rightward bias. A significant correlation between age and Line $\mathrm{deviation}_{mean}$ was not found ($r = -0.1243$, $p = 0.6720$). There was no significant difference between the two groups without controlling age (p = 0.962) nor when controlling age (p = 0.765).

Behavioral measures in the covert attention task On average, both groups were able to perform the task equally well as reflected in the mean percentage hits over all trials (controls: mean = 78.9 ± 25.28; ADHD: mean = 83.34 ± 23.12; $p = 0.7519$). When comparing congruent and incongruent trials, there was a trend towards a higher hitrate in the congruent condition in the control group (congruent: mean = 94.15 ± 4.80; incongruent: mean = 63.66 ± 46.61; $p = 0.0652$), but not in the ADHD group (congruent: mean = 91.05 ± 8.02; incongruent: mean = 75.63 ± 38.26; $p = 0.3187$). In other words the control group showed a trend towards a benefit of the cue while the ADHD group did not. A closer look at the results of the control group, revealed that three children were unable to respond correctly to the

Table 1
This table shows both congruent and incongruent trials separately for the left, right, and entire visual field for the two different groups; children with ADHD and children without ADHD. The control group of children without ADHD was split into two groups; children that were able to respond correctly on incongruent trials (controls1) and children that were not able to respond correctly on incongruent trials (controls2). For all conditions, the mean percentage hits, errors, misses, and RTs on correct trials and its standard deviation are shown. Note that for the latter control group RTs could not be calculated for the low percentage hits on incongruent trials.

Group	Visual field	Trial	Hit	Error	Miss	Response time
ADHD (N=5)	**Left**	**Congruent**	92.68±7.73	2.23±1.32	5.11±8.33	509.47±158.93
		Incongruent	75.15±38.63	21.19±30.30	3.83±8.39	510.56±165.26
	Right	**Congruent**	89.52±8.53	4.36±2.07	6.14±8.01	530.55±113.93
		Incongruent	76.19±38.10	19.34±31.39	4.65±6.93	473.19±179.00
	Both	**Congruent**	91.05±8.02	3.28±1.47	5.68±6.04	515.60±166.66
		Incongruent	75.63±38.26	20.26±30.69	4.15±7.60	526.38±107.53
Controls (N=9)	**Left**	**Congruent**	93.87±4.88	3.18±3.25	2.97±4.14	472.50±164.64
		Incongruent	63.44±47.04	33.21±43.61	3.56±4.46	-
	Right	**Congruent**	94.42±4.93	2.41±2.28	3.20±3.98	472.00±164.94
		Incongruent	63.85±46.93	35.15±44.78	1.16±3.24	-
	Both	**Congruent**	94.15±4.18	2.78±2.58	3.07±4.01	480.16±171.08
		Incongruent	94.67±5.22	4.29±4.23	1.26±1.89	-
Controls1 (N=6)	**Left**	**Congruent**	96.32±2.04	3.02±2.37	0.68±0.88	578.84±48.99
		Incongruent	94.67±5.22	4.29±4.23	1.26±1.89	551.28±64.34
	Right	**Congruent**	97.13±1.80	2.10±1.74	0.79±0.93	577.97±52.10
		Incongruent	94.63±5.04	5.45±5.03	0.08±0.02	556.13±67.38
	Both	**Congruent**	96.74±1.48	2.54±1.59	0.72±0.77	588.94±62.03
		Incongruent	94.47±3.44	4.78±3.46	0.59±0.88	551.28±64.34
Controls2 (N=3)	**Left**	**Congruent**	88.97±5.54	3.50±5.29	7.54±4.41	259.82±25.53
		Incongruent	0.97±1.50	91.06±5.61	8.14±4.79	-
	Right	**Congruent**	88.98±4.76	3.02±3.51	8.02±3.00	260.07±31.37
		Incongruent	2.30±3.87	94.53±4.99	3.33±5.61	-
	Both	**Congruent**	88.97±5.13	3.27±4.43	7.76±3.62	262.61±31.14
		Incongruent	1.63±1.79	92.80±5.22	5.61±4.40	-

incongruent trials each having less than 7% correct on the incongruent trials (see table 1; controls 2). When splitting the control group into a group that was able to perform correctly on incongruent trials and a group that was not, the significant difference between conditions was present in the latter group (congruent: mean = 88.97 ± 5.13; incongruent: mean = 1.63 ± 1.79; p = 0.0020), but not in the first group (congruent: mean = 96.74 ± 1.48; incongruent: mean = 94.67 ± 3.44; p = 0.1239). Conducting an ANOVA with hit rate as dependent variable, condition (congruent vs. incongruent) and visual hemifield (left vs. right) as within subject variables and group (ADHD vs. non-ADHD) as between variable, no interaction effects were found. Since we could not compare RTs between conditions in the group that was unable to perform correctly on the incongruent trials, RT analyses were only performed in the group that was able to perform correctly in both conditions. In the ADHD group all children performed comparable on both conditions and were therefore not split in two groups. Based on RT, again both groups were able to perform the task equally well as reflected in the mean RT over all trials (controls1: mean = 577.29 ± 57.04; ADHD: mean = 521.00 ± 133.55; p = 0.3706). When comparing congruent and incongruent trials, there was no significant difference between conditions in the control group (congruent: mean = 588.94 ± 62.03; incongruent: mean = 565.64 ± 53.67; p = 0.5024) nor in the ADHD group (congruent: mean = 515.60 ± 166.66; incongruent: mean = 526.66 ± 107.53; p = 0.9063). Results of an ANOVA between children with and without ADHD having condition (congruent vs. incongruent) and visual hemifield (left vs. right) as within variables, revealed no interactions at all. Neither when comparing controls with ADHD on their hit rates, nor when comparing all controls1 with ADHD on their RT.

Electro-physiological results

ΔAMI during the covert attention task The time frequency representations (TFRs) of the average power over all children and trials showed clear modulation of the alpha band (figure 2A). The lowest post-cue alpha band values were between 0.35-0.45s after cue-onset. For this time interval, the topoplot of alpha power showed occipital

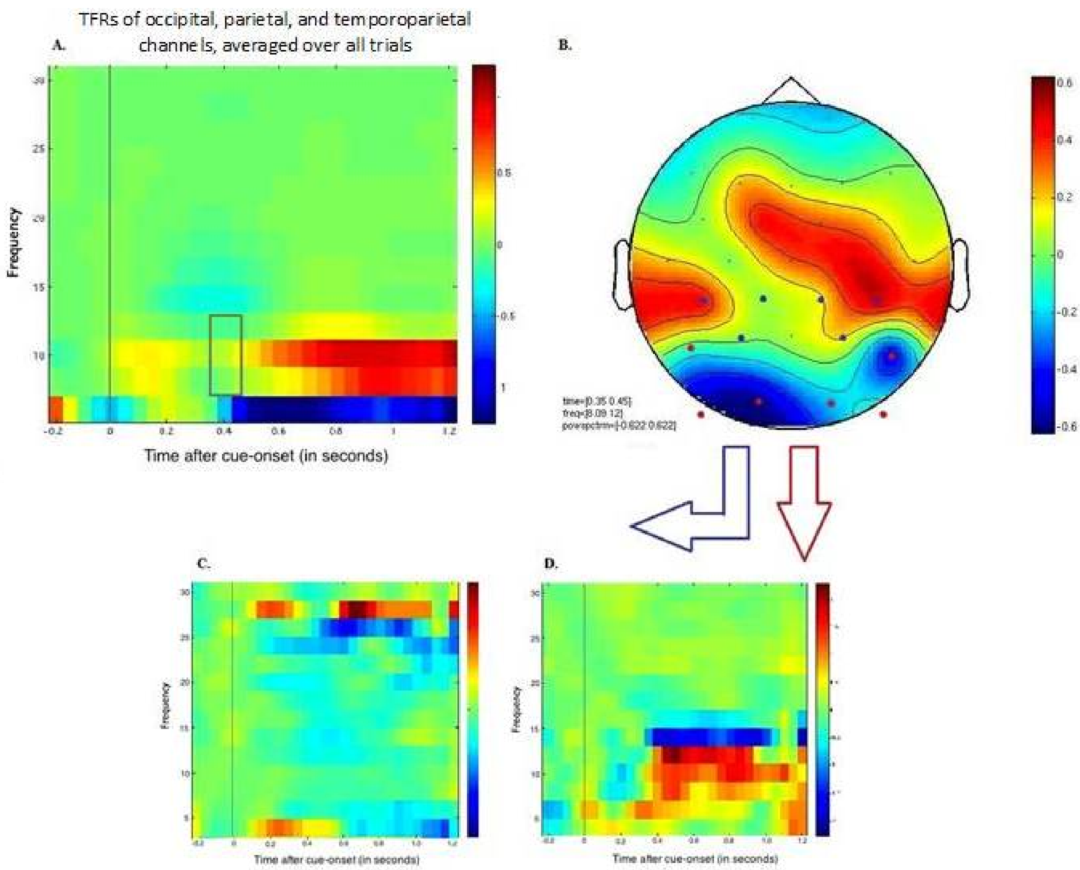

Figure 2. (A) Time frequency representations (TFRs) for 6-30 Hz are displayed for the average over trials of the occipital, parietal and temporoparietal channels. The gray line denotes the time of cue-onset. 1.2s denotes the first option of the target to occur. The gray square indicates the frequency range (8-12 Hz) and time points (0.35-0.45s) that were used for the channel selection. (B) Topoplot of the alpha power averaged over trials for 0.35-0.45 s after cue-onset. The blue dots denote the parietal channel selection, the red dots denote the occipital channel selection. (C) The TFRs for the ΔAMI of 2-30 Hz for parietal channels. (D) The TFRs for the ΔAMI of 2-30 Hz for parietal channels.

decrease (figure 2B). When comparing groups over the entire cue-target interval, no significant difference in alpha power was found (p = 0.9751). When splitting the cue-target interval in an early and a late part, the ADHD-group showed significantly more decrease than controls in the early time window (p = 0.0340) and significantly more increase in the late time window (p = 0.0345). The TFRs of ΔAMI averaged over all children showed clear alpha modulation in the occipital electrodes (figure 2D), but not in the parietal electrodes (figure 2C).

ΔALI during the covert attention task In the occipital channels, the ΔALI averaged over all children showed significant deviation from the pre-cue period during the first 50 ms of the cue presentation and 0.40-0.95s after cue-onset when not corrected for the multiple comparisons problem (figure 3A). When Bonferonni-corrected for 100 ms sampling, ΔALI was significantly different from pre-cue time points at 0.75-0.85s after cue-onset (figure 3A). When looking at ΔALI per group, the time points at 0.45-0.90s after cue-onset were significantly different from the pre-cue period in the control group. In the ADHD group, this was the case during cue presentation (0.00-0.20s) and at 1.15-1.20s after cue-onset, right before the first possibility of the target to appear (figure 3A). Although these latter values were only significant when a liberal p-criterion was used, these values were regarded the best approach to a lateralized response to use in further analyses.

First, all time points of the ALI_{left} and ALI_{right} were compared to the pre-cue period per group. For these analyses, in the control group only the ALI_{left} showed a significant positive shift compared to the pre-cue period at 0.5-0.6s after cue-onset. Although in the expected negative direction, there were no time points in the ALI_{right} that

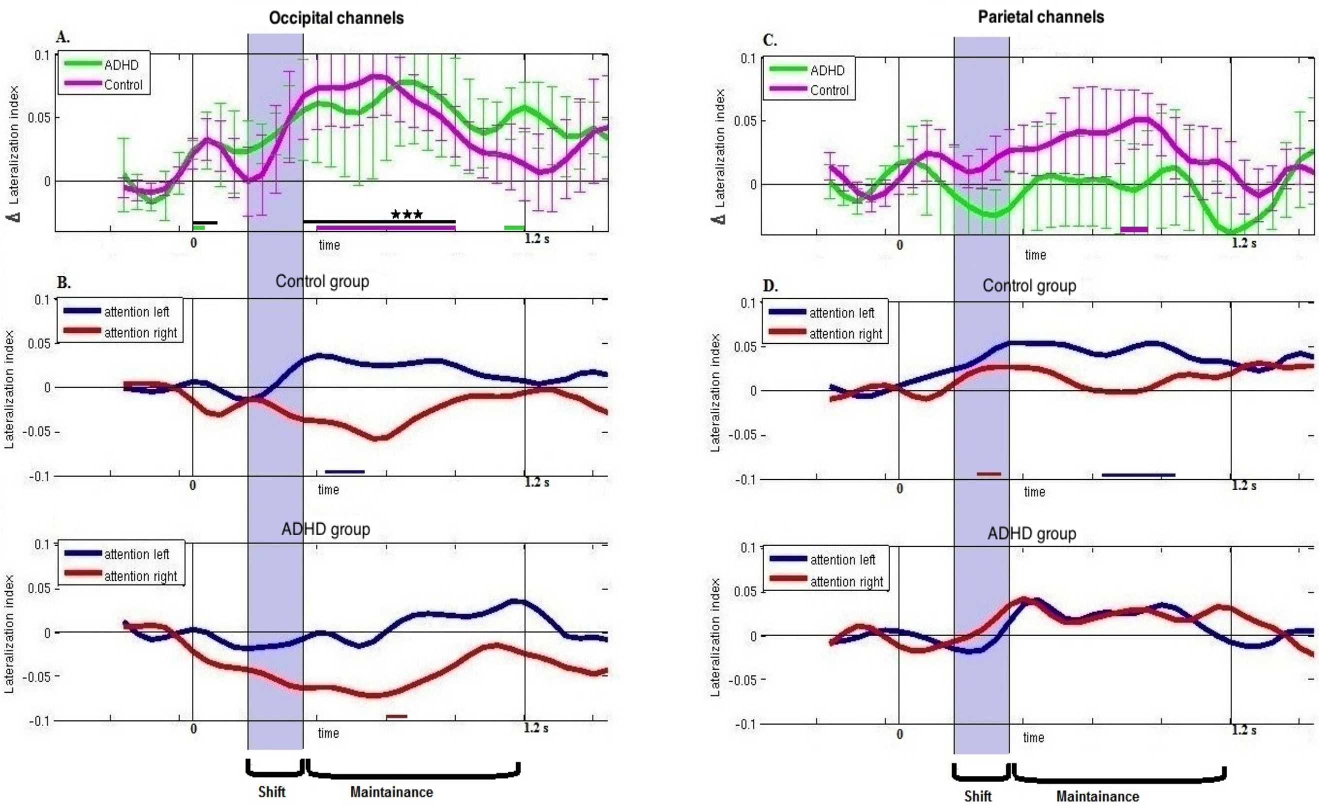

Figure 3. (A) Mean cue-locked ΔALI for occipital channels over time. Both groups show a shift in lateralization. The black line denotes the uncorrected significant deviations from pre-cue period for a total of both groups. The black stars denote the time points that remained significant after a 100 ms sampling rate Bonferroni correction. The lines colored matching the legend denote the uncorrected significant deviations from pre-cue period per group. (B) Mean occipital ALI_{left} and mean ALI_{right} plotted against time for control group and ADHD group separately. Higher ALI_{left} or ALI_{right} denotes a leftward shift while lower ALI_{left} or ALI_{right} denotes a rightward shift. The lines colored matching the legend shows the uncorrected significant deviation from pre-cue period (C) Mean cue-locked ΔALI for parietal channels over time. A shift in lateralization is seen in the control group, but not in the ADHD group. The lines colored matching the legend shows the uncorrected significant deviation from pre-cue period (D) Mean parietal ALI_{left} and mean ALI_{right} plotted against time for control group and ADHD group separately. Higher ALI_{left} or ALI_{right} denotes a leftward shift while lower ALI_{left} or ALI_{right} denotes a rightward shift.

significantly deviated from the pre-cue interval (figure 3B). In the ADHD group, ALI_{right} showed a significant negative shift compared to the pre-cue period at 0.2-0.25s after cue-onset (figure 3B). No time points in the ALI_{left} were significantly deviating from the pre-cue interval (figure 3B). The maintenance of ΔALI was addressed by choosing an early and a late time point. The liberally significant time points of the ADHD group were clearly later than of the control group. Therefore, we chose the first earliest liberally significant time points those of the control group ΔALI and the latest liberally significant time points of the ADHD ΔALI as early and late timepoint on which to perform a two tailed repeated-measures analysis of variance (ANOVA). A main effect of visual hemifield (left vs. right) was found ($p = 0.0028$). No main effects were found on time points (early vs. late), or on group (ADHD vs. no ADHD), neither were there any interactions. Although confirming the expected direction, no statistical evidence for our hypotheses was found. In the parietal channels, ΔALI averaged over children of both groups showed no significant deviation from the pre-cue period at any time points (figure 3C). When looking at ΔALI per group using a liberal significance level, the time points at 0.80-0.90s after cue-onset were significantly different from the pre-cue period in the control group. Also in the control group, parietal ALI_{left} showed a significant positive shift at 0.75-1s after cue onset and ALI_{right} showed a significant positive shift at 0.3-0.4s after cue-onset (figure 3D). Note that the latter positive shift contradicts the negative shift in the occipital channels. No significant shift for any cue-target interval time points were found in the ADHD group (figure 3D).

Electro-physiological and behavioral results combined

Correlation task performance and alpha activity Although there were no robust cueing effects, the amount of benefits of the cue could still possibly be correlated to the ΔALI. However this was not the case for the hit rate cueing effect and ΔALI (controls: r = -0.0336, p = 0.9316; ADHD: r = -0.0430, p = 0.9453) nor between the RT cueing effect and ΔALI (controls1: r = 0.5646, p = 0.2431; ADHD: r = 0.0269, p = 0.9657). When addressing the left and right visual hemifield separately there were no significant correlations found either. When the cue-target interval was split into an early and a late interval, still no correlations were found for any of the measures.

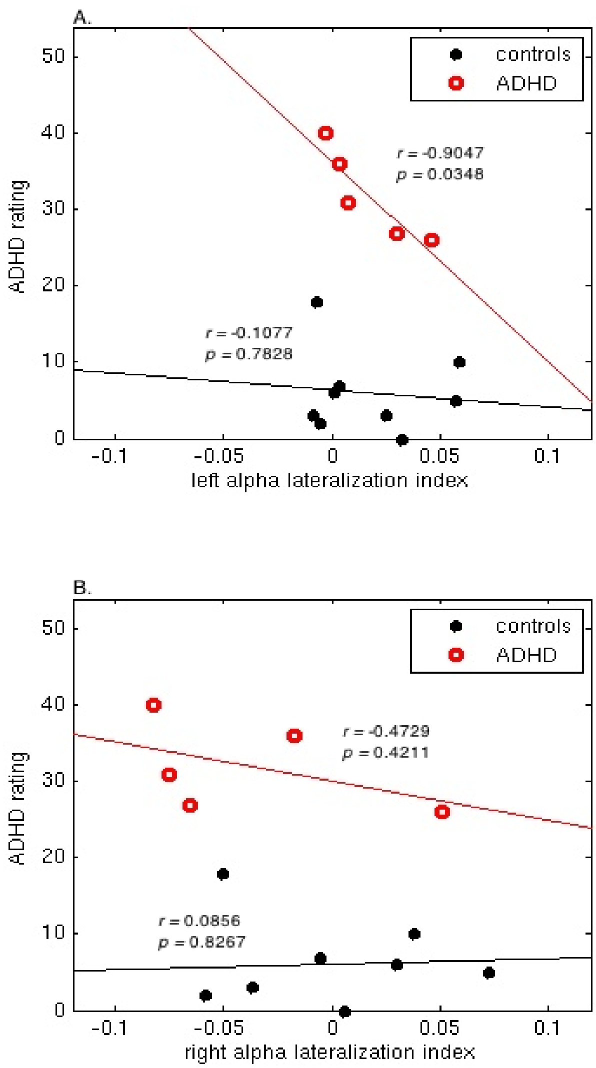

Figure 4. (A) Correlation between the ALI_{left} and the $ADHD_{total}$ for all individuals separately plotted for the control group and ADHD group. (B) Correlation between the ALI_{right} and the $ADHD_{total}$ for all individuals separately plotted for the control group and ADHD group.

Correlation ADHD rating and alpha activity Over all trials, there were no significant correlations between the $ADHD_{total}$ and ΔALI in either group (controls: r = -0.1773, p = 0.6482; ADHD: r = 0.0514, p = 0,9345). When studying the left and right cued directions separately, still no significant correlations were found. However, when the cue-target interval was split into an early and a later interval, a significant negative correlation was found between the mean ALI_{left} over the late time points (0.7-1.2s after cue-onset) and the $ADHD_{total}$ in the ADHD group (r = -0.9047, p = 0.0348), being a striking relationship showing that longer maintenance of ALI_{left} was related to a lower $ADHD_{total}$ in the ADHD group (Figure 4). This was not the case for the right visual hemifield (r = -0.4729, p = 0.4211) nor for either visual hemifield in the control group (left: r = -0.1077, p = 0.7828; right: r = 0.0856, p = 0.7123) (Figure 4).

Correlation LBT and alpha activity When relating the Line $deviation_{mean}$ to the ΔALI no significant correlations were found for either group. When addressing the left and right visual hemifield and early and late time points separately there were still no significant correlations found.

Discussion

The first issue that was addressed in the current study was the question if it is possible to elicit alpha modulation and alpha lateralization in children in a similar way as previous studies showed in adults in a cued visual spatial attention task (Worden et al., 2000; Yamagishi et al., 2003; Sauseng et al., 2005; Kelly et al., 2006; Händel et al., 2011; ter Huurne et al., 2012). Analyses affirmatively showed a response to the cue in the oscillatory activity averaged over all children, which was restricted to the alpha band. A decrease of occipital alpha was seen for the early time window and a increase of this alpha, that was stronger for the left visual hemifield than for the right visual hemifield, was seen in the late time window. Even when Bonferonni corrected, the difference in alpha lateralization between visual hemifields was at some time points during the cue-target interval significantly larger than the pre-cue period. These analyses were done for both occipital and parietal channels to be able to show specificity of occipital involvement in the alpha modulation. Indeed, there was no significant modulation visible in the parietal channels. These results are in line with previous research in adults.

Behaviorally however, barring a trend towards a higher hitrate in the congruent condition in the control group, driven by three children that were unable to respond correctly on the incongruent trials, none of the results confirmed a significant benefit of the cue or a difference between visual hemifields in either group. Neither was there a difference between groups. Behavioral results also did not correlate with any of the measured brain responses, independent of children having ADHD or not. The absence of a correlation between alpha lateralization and behavior, which ter Huurne et al. (2012) found in the ADHD group only, was explained by an inability to sustain the alpha lateralization during the entire cue-target interval. When looking at the average over all children in the current study, even when using a liberal significance criterion alpha lateralization did not significantly differ from pre-cue period from 0.95s after cue-onset on, even though the first possible option of the target to come on was at 1.2s. A similar explanation that could apply to adults with ADHD could, due to developmental issues, possibly apply to all children, independent of having ADHD or not. Mazaheri et al. (2010) however, did find a behavioral cueing effect both in children with and without ADHD. Children that were tested in this study ranged 8-12 years rather than 7-10 years, therefore developmental issues could still possibly play a role in the lack of cueing effect that was found in the present study. Also a difference in paradigm (cross-modal attention task vs covert spatial attention task) might partially explain the difference in findings. In line with this option, ter Huurne et al. (2012), whose paradigm was much more similar to ours, did not find a cueing effect in the ADHD group where Mazaheri et al. (2010) did. Note that a lack of cueing effect in behavior if alpha lateralization is not sustained until target onset is in line with the inhibition timing hypothesis. Hence, if there is no inhibition of the uncued side at target onset, then no difference in behavioral response is expected. Although a lack of ΔALI maintenance could possibly explain the lack of cueing effect, development does not necessarily have to be the explanation. In the paradigm of ter Huurne et al. (2012), the first possibility of a target to appear was at 0.85s compared to 1.2s in our paradigm. In our results, the ΔALI averaged over all children sustained above zero until 0.95s. The question if it is possible to elicit occipital alpha modulation and alpha lateralization in children in a similar way as was previously done in adults, was confirmed. Either due to development or difference in paradigm, the maintenance of this occipital alpha lateralization differed from adults and possibly led to a lack of cueing effect in this study.

The second issue that was addressed in the current study was the question whether there was a difference between children with and without ADHD. When studying the time course of alpha power over all trials, in the early time window of the cue-target interval, children with ADHD showed more decrease than controls and in the late time window children with ADHD showed more increase than controls. These results contradict the findings of Mazaheri et al. (2010), which showed that without comparing hemispheres or hemifields, children with ADHD showed less alpha modulation overall. Again, a difference in age and a difference in paradigm could possibly have resulted in such a difference. In contrast to the alpha modulation, the alpha lateralization index for the difference between visual hemifields did not show a significant difference between groups. More specifically, we wanted to see whether the rightward bias previously found in behavioral measures (Voeller & Heilman, 1988; Sheppard et al., 1999; Geeraerts et al., 2008; Chan et al., 2009) and resting state oscillatory activity (Chabot & Serfontein, 1996; DeFrance et al., 1996) in children with ADHD, could be replicated when integrating these measures in a similar way that ter Huurne et al. (2012) did in adults with ADHD. When comparing time points from the cue-target interval to the pre-cue period addressing the alpha lateralization of left cue trials and right cue trials separately, only some time points in the left cue trials showed a significant deviation in typically developing children while only some points of the right cue trials showed a significant deviation in children with ADHD. This was the case when using a liberal significance criterion only. Although liberally significant, these results fragilely point in the direction of children with ADHD having a rightward bias while children without ADHD have a leftward bias. It was expected, however, that the typically developing group with a mean age of 8.46 years old would, although to a lesser extent than the ADHD group, also show a rightward bias since they were younger than the child group in which a previously shown leftward bias occurred (Hausmann et al., 2003). Indeed, in line with previous research, results of the line bisection task did show a rightward bias in both groups. Not surprisingly, neither a significant correlation was found between the alpha lateralization and the attentional bias as measured with the line bisection task, nor was there a difference on line bisection task performance between groups. Since ter Huurne et al. (2012) found that sustaining the alpha lateralization differed between groups, the cue-target interval was split up in an early and a late period. When doing this, a striking correlation was found between the amount of alpha lateralization in the late time window as a response to a left cue and the total score on the ADHD rating. According to the direction of this correlation it can be said that in children with ADHD, the less severe the ADHD was rated by their parents, the longer the alpha lateralization as a response to the left cue was sustained. The question whether there is a difference between children with and without ADHD was confirmed. Children with ADHD showed a stronger decrease and increase in the early and late time window of the cue-target interval respectively than children without ADHD. The question whether a rightward bias in children with ADHD could be replicated integrating behavior and oscillatory measurements, cannot strongly be confirmed. Although all behavioral and oscillatory results were in the expected direction, overall no strong rightward bias was detected in either behavior or alpha lateralization. The lack of sustaining alpha lateralization when cued to the left however, was strongly correlated to the severity of their ADHD. Therefore, in line with what ter Huurne et al. (2012) found, especially sustaining maintenance of alpha lateralization seems to be a crucial aspect in its behavioral consequences.

An issue that should not go unmentioned is that three children were unable to perform above chance level on the incongruent trials. The children were kept in the analyses because they individually showed a clear alpha lateralization. One might argue that these children were not following task instructions. In order to receive positive feedback they were not allowed to press the button before target onset, meaning that they always had to wait for the mouths of the sharks to open before they could press the button and were not able to just pay attention to the cue. One could still argue that these children prepared to press the button on the side of the cue and did so as soon as something in the cued visual field changed. Taking a perspective that would be in line with the inhibition timing hypothesis is that these children might have been so good in inhibiting the unattended side that they were actually unable to detect an incongruent trial before the motor signal was sent through.

Research in adults consistently showed alpha-band activity over the occipital channels (Worden et al., 2000; Yamagishi et al., 2003; Sauseng et al., 2005; Kelly et al., 2006; Händel et al., 2011; ter Huurne et al., 2012). Research in children, however, showed maximal alpha amplitudes and phase-locking over the parietal side (Yordanova & Kolev, 1997). To examine the possibility of alpha lateralization occurring over parietal channels in children, we performed similar analyses on both occipital and parietal channels. A shift in lateralization was observed in the occipital channels only. Over the parietal channels, some time points during the cue-target interval were significantly higher than the pre-cue period. This was only the case for children without ADHD. A lateralization in the beta band is expected due to motor preparation of the right hand for the button response. However, the shift we found in the alpha band was in the opposite direction (Figure 3C and 3D). Future research should disentangle the contribution of different areas.

Even though we have been able to show some interesting findings which should direct future research, the current study has some major limitations. The sample size was very small and in addition to that, there was a difference in sample size between groups (5 children in the ADHD group, 9 in the control group). The small sample size could have resulted in higher Type II errors, hence falsely rejecting significant time points in the ALI. The proportion of actual positives correctly identified for occipital areas is only 37%. Meaning that 63% of the variance of resting state EEG asymmetry is thought to be due the particular situation or to person-situation interaction (Hagemann et al., 2005). The influence of this variance would become smaller with a bigger sample size, therefore lowering the chance of making a Type II error. A second limitation is that there was a significant difference in IQ between groups which was not controlled for in any of the analyses. Defending this latter limitation, it has been suggested that IQ should not be used as a covariate because of its genetic overlap with ADHD as well as its neurobiological consequences in ADHD (de Zeeuw et al., 2012). In this case however, the significant difference is mainly caused by a higher than average IQ in the control group rather than a lower than average IQ in the ADHD group that de Zeeuw et al. (2012) discussed. A third limitation is that channel selection was based on the entire sample and that a fixed alpha frequency band of 8-12 Hz was used. Although we chose to use these methods to avoid double dipping, we might have missed out on information as a result. Since there is a developmental shift in peak frequency and a shift in the localization of this peak (Yordanova & Kolev, 1997), children with ADHD which are thought to show developmentally inappropriate behavior (American Psychiatric Association, 2000), might show different peak frequencies and peak localization in the ADHD-group than in the control-group.

In summary, we have shown that it is possible to elicit alpha modulation and alpha lateralization in children which is specific to occipital channels. The alpha modulation over all trials was stronger in the ADHD group than in the control group. The maintenance of occipital alpha lateralization averaged over all children did not last until target presentation, possibly explaining the lack of significant differences between cued and uncued direction responses. All children were shown to have a behavioral rightward bias in bisecting lines. Although there were no significant differences between children with and without ADHD in alpha lateralization, the maintenance of the alpha lateralization as a response to the left cue was correlated to the ADHD-rating in the ADHD group only. Future research should investigate whether the currently non-significant direction of a stronger rightward bias in ADHD than in controls was non-significant due to the sample-size or due to other reasons.

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