

## ARCHIVAL REPORT

# Differential Oscillatory Electroencephalogram Between Attention-Deficit/Hyperactivity Disorder Subtypes and Typically Developing Adolescents

Ali Mazaheri, Catherine Fassbender, Sharon Coffey-Corina, Tadeus A. Hartanto, Julie B. Schweitzer, and George R. Mangun

**Background:** A neurobiological-based classification of attention-deficit/hyperactivity disorder (ADHD) subtypes has thus far remained elusive. The aim of this study was to use oscillatory changes in the electroencephalogram (EEG) related to informative cue processing, motor preparation, and top-down control to investigate neurophysiological differences between typically developing (TD) adolescents, and those diagnosed with predominantly inattentive (IA) or combined (CB) (associated with symptoms of inattention as well as impulsivity/hyperactivity) subtypes of ADHD.

**Methods:** The EEG was recorded from 57 rigorously screened adolescents (12 to 17 years of age; 23 TD, 17 IA, and 17 CB), while they performed a cued flanker task. We examined the oscillatory changes in theta (3–5 Hz), alpha (8–12 Hz), and beta (22–25 Hz) EEG bands after cues that informed participants with which hand they would subsequently be required to respond.

**Results:** Relative to TD adolescents, the IA group showed significantly less postcue alpha suppression, suggesting diminished processing of the cue in the visual cortex, whereas the CB group showed significantly less beta suppression at the electrode contralateral to the cued response hand, suggesting poor motor planning. Finally, both ADHD subtypes showed weak functional connectivity between frontal theta and posterior alpha, suggesting common top-down control impairment.

**Conclusions:** We found both distinct and common task-related neurophysiological impairments in ADHD subtypes. Our results suggest that task-induced changes in EEG oscillations provide an objective measure, which in conjunction with other sources of information might help distinguish between ADHD subtypes and therefore aid in diagnoses and evaluation of treatment.

**Key Words:** Attention-deficit/hyperactivity disorder, connectivity, cue-processing, EEG oscillations, response preparation, top-down control

Attention can be described as the focusing of cognitive resources on relevant information while filtering or ignoring extraneous information. Attention-deficit/hyperactivity disorder (ADHD) is a neurobehavioral disorder of attention, affecting individuals across their lifespan, and characterized by a persistent pattern of age-inappropriate levels of inattention and/or hyperactivity and impulsivity.

The DSM-IV (1) distinguished between three subtypes of ADHD: 1) the predominantly inattentive (IA); 2) the predominantly impulsive/hyperactive (not involved in this study); 3) and the combined subtype (CB), which is associated with symptoms of inattention as well as impulsivity/hyperactivity. However, there is much controversy about the validity of the subtypes of ADHD; some argue that these subtypes might represent distinct clinical disorders, whereas others suggest that they, at the very least, manifest distinct neurobiological and behavioral impairment profiles (2,3). The DSM-V uses the term “presentations” rather

than subtypes to acknowledge differences between symptom presentations. Previous research has successfully distinguished among ADHD subtypes on the basis of inattention symptoms, demographic data, genetic profile (4–7), and differential response to medication (3,8–11) and cognitive treatment (12).

The debate about the presence of subtypes in ADHD is partially due to a potential contamination of results by inclusion of individuals with sub-threshold CB type in the IA group (13). Researchers (3) have recommended that studies of ADHD subtypes should delineate the IA subtype by excluding individuals with larger numbers of hyperactive/impulsive symptoms (usually four or more). Impairments associated with the CB subtype include planning (14–16), response inhibition (17–21), and response execution (22–25). In contrast, the IA group displays difficulty using environmental cues to prepare behavior (15,26) and altered arousal effects (27).

The aim of the current study was to use the top-down modulation of oscillatory activity of the electroencephalogram (EEG) during a cued flanker task to obtain specific neurobiological signatures of the two most common subtypes of ADHD (IA and CB). The Eriksen Flanker task has been widely used in ADHD and other disorders to evaluate various aspects of cognitive control, including cognitive flexibility, selective attention, response conflict, and performance monitoring [some recent examples: (28–33)].

We focused our investigation on the oscillatory changes induced by response preparation cue, which predicted the most likely hand needed to respond correctly. We reasoned that, for the participants to properly use these cues, several steps are required. First, the visual stimulus must be perceived, next the control regions of the brain should interact with sensory regions to make a decision about a potential action, and finally the decision should be transformed into a motor operation.

From the Academic Medical Center (AM), Department of Psychiatry, University of Amsterdam, The Netherlands; M.I.N.D. Institute (CF, TAH, JBS); Department of Psychiatry and Behavioral Sciences (CF, JBS); Imaging Research Center (CF); Center for Mind and Brain (CF, SC-C, GRM); Department of Psychology (GRM); and the Department of Neurology (GRM), University of California, Davis, California.

Address correspondence to Ali Mazaheri, Ph.D., Academic Medical Center, Department of Psychiatry, University of Amsterdam, 1070AW Amsterdam, the Netherlands; E-mail: [ali.mazaher@gmail.com](mailto:ali.mazaher@gmail.com).

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We focused on the suppression of occipital alpha activity (8–12 Hz) as an index of cue processing. Oscillatory activity in the EEG alpha range is proposed to play a pivotal mechanistic role in attention, by gating information flow to relevant sensory regions (34–36). A number of studies have found that the amount of alpha suppression after a visual stimulus is related to the degree of feature extraction and cognitive processing afforded to the stimulus (37–40). As such, the suppression of alpha activity in response to an external cue can be considered an index of the depth of processing. We investigated the cross-frequency coupling between frontal theta (3–5 Hz) and occipital alpha as a measure of top-down control. Increased frontal theta activity has been associated with higher cognitive function, such as focused attention (41,42). Recent studies in both typically developing (TD) children and adults suggest that the interaction between frontal theta and posterior alpha is indicative of top-down attentional control (43–45). Finally, we used suppression of beta activity (22–25 Hz), at electrode locations contralateral to the response hand, to gauge motor planning. The beta rhythm is an oscillation predominantly localized over the somatosensory areas. Voluntary movement and motor preparation are preceded by an attenuation of beta activity over contralateral sensorimotor areas (46,47).

## Methods and Materials

### Participants

Fifty-seven adolescents, 12 to 17 years of age, with typical development (TD) ( $n = 23$ ), ADHD, CB (manifesting both inattention and hyperactivity/impulsivity,  $n = 17$ ) or primarily IA type ( $n = 17$ ) were enrolled after both informed written parental consent and written assent by all participants, approved by the Institutional Review Board of University of California, Davis. Data from 2 additional participants (1 CB, 1 IA) were excluded from analysis, due to excessive artifact.

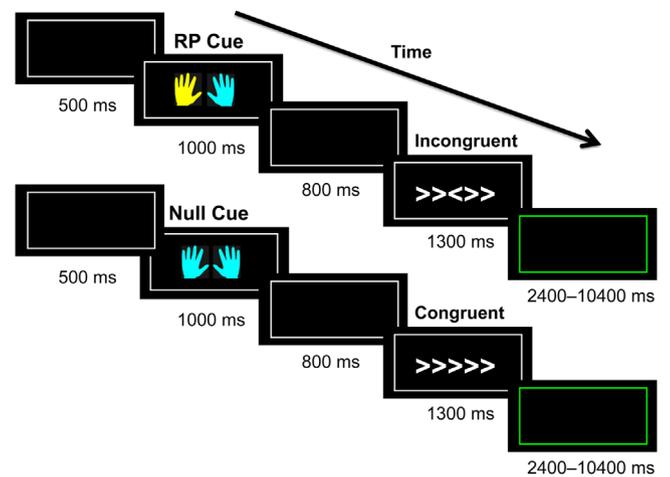
Licensed psychologists evaluated participants. The ADHD was diagnosed and categorized according to DSM-IV-TR criteria (see Supplement 1 for more details). Participants were excluded for academic learning disabilities, as defined by a discrepancy between IQ and achievement testing paired with achievement standard scores below 80. Stimulant medication was withheld 24 hours before EEG measurements.

### Flanker Task

A cued variant of the classic Eriksen flanker paradigm (48) (Figure 1), probed cognitive control processes.

Each target/flanker stimulus array was preceded by one of three cue types, which consisted of pairs of colored (blue and yellow) cartoon hands: 1) response preparation (RP) cue, which predicted (84%) the most likely hand of response to the target stimulus on that trial (subjects were instructed that one color, for example, blue, signaled which hand was likely to be the correct response for the upcoming target: which color signaled this was counterbalanced across subjects); 2) Null cue, which provided no information about the following flanker (both hands in the same, for example, blue color); or 3) Warning cue, which informed participants that the following trial would be an incongruent trial (both hands in the same, for example, yellow color).

The instructions to the participants emphasized both speed and accuracy. Because response preparation was our critical process of interest, we focused our EEG analyses on the 2-second cue-to-target interval after the RP cue onset. See Supplement 1 for full paradigm description.



**Figure 1.** Task figure. Participants were required to respond by button press to the centrally presented arrow in a horizontal array of five arrows, while ignoring the surrounding or “flanking” arrows. Participants pressed with the right hand to a rightward facing arrow and the left hand to a leftward facing arrow. All stimuli were surrounded by a white border. Participants were instructed to restrict their gaze within the confines of the white border. The central arrow could be facing in either the same (congruent) or opposite (incongruent) direction to the flanking arrows. Neutral trials consisted of a centrally presented arrow surrounded by flanking plus signs. Each stimulus was preceded by a cue that consisted of two colored cartoon hands. The figure shows the Null cue, which provided no information about the subsequent stimulus, and the response preparation (RP) cue, which informed the participants with 84% certainty as to the motor response (left or right hand button press) that would be required for the subsequent stimulus. Trials were separated by a variable intertrial interval (2400–10,400 msec). This was indicated by a color change of the surrounding border from white to green. Participants were instructed to relax their eyes during this intertrial interval.

### EEG Recording

Electroencephalograms were recorded from 32 electrodes, with an electro-cap (Electro-cap International, Eaton, Ohio), located at the sites of the International 10–20 system. Horizontal eye movements were recorded with two bipolar electrodes, placed at the outer canthi of both eyes. Vertical eye movements were recorded with one electrode placed below the left eye. All electrode impedances were maintained below 10 kOhms. The signals were recorded with a bandpass of direct current to 100 Hz, with an analog-to-digital sampling rate of 1000 samples/sec. The recording was down-sampled offline to 250 Hz. The left mastoid served as the reference electrode both during recording and for the analyses presented here. For the EEG processing and time frequency analyses please refer to Supplement 1.

### Cross-Frequency Coupling Between Frontal Theta and Posterior Alpha

Traditionally, examining connectivity between brain regions with EEG has been difficult, due to the problem of volume conduction, in that nearby electrodes pick up activity from the same sources (49,50). One recent approach that circumvents volume conduction is to examine the trial-by-trial negative correlations between different oscillatory activities across distinct regions of the brain (43,44,51). This method, known as “cross-frequency power correlations,” avoids the volume conduction problem because it is less likely to have a common source generate an increase in amplitude of one frequency at one region of the brain and a simultaneous decrease of amplitude of another frequency at a distant region. In the current study, the trial-by-trial

alpha power from occipital alpha was anti-correlated with the frontal theta power. For each participant the correlation coefficients were converted to *z* values with Fischer's *r*-to-*z* transform to obtain a normally distributed variable (43,44,52).

### Statistical Analysis

The statistical analysis of these correlations was assessed within groups with a one-sample *t* test of the correlations and between groups with a one-way analysis of variance (ANOVA). Repeated-measures ANOVAs were used to analyze alpha and beta suppression after the Null and RP cues. *F*-ratios were tested with degrees of freedom adjusted with the Greenhouse–Geisser procedure. Post hoc pairwise comparisons between means were conducted with Tukey's test, and a Bonferroni correction was applied to account for multiple-comparisons. Significant interactions were further analyzed with simple effects analyses. For the changes in theta and alpha power, the factors used were Group (TD, IA, CB) and Time (0–500, 500–1000, and 1000–1500 msec after cue). We did not perform analyses 1500 msec after cue onset to avoid spectral leakage from target processing (the targets arrived 1800 msec after the cue). For the beta power we used the time intervals of 800–1300 msec and 1300–1800 msec after cue onset, to exclude overlap from alpha activity and movement artifact from subject response.

## Results

### Behavior

The RP cue significantly improved performance in all three groups (Table 1). Accuracy (percentage correct) was higher ( $F_{2,54} = 19.673, p < .0001$ ), and reaction times (RTs) on correct trials were faster ( $F_{2,54} = 122.414, p < .0001$ ) in the RP cued versus Null cued conditions. These patterns of improved behavior indicate that all three groups were using the information in the cues. There was also a significant effect of Group on RTs ( $F_{2,54} = 8.115, p = .001$ ). The TD group displayed the greatest number of correct responses and the fastest RTs, whereas the CB group had the lowest number of correct responses and slowest RTs. Post hoc analyses (Tukey honestly

**Table 1.** Behavioral Results

Group	TD (n = 23)	IA (n = 17)	CB (n = 17)
Null Cue % Corr	92.82 (5.56)	90.08 (7.05)	88.97 (9.19)
RP Cue % Corr	95.72 (4.75)	94.96 (6.06)	91.84 (6.77)
Null Cue % Error	6.49 (5.61)	7.19 (6.08)	5.46 (5.69)
RP Cue % Error	2.00 (2.46)	1.26 (1.90)	3.22 (4.98)
Null Cue Corr RT	572.92 (88.38)	620.35 (116.93)	705.19 (126.38)
RP Cue Corr RT	461.60 (100.67)	528.91 (137.28)	614.25 (129.52)

Means are displayed with SD in parentheses. Percentage errors represent commission errors.

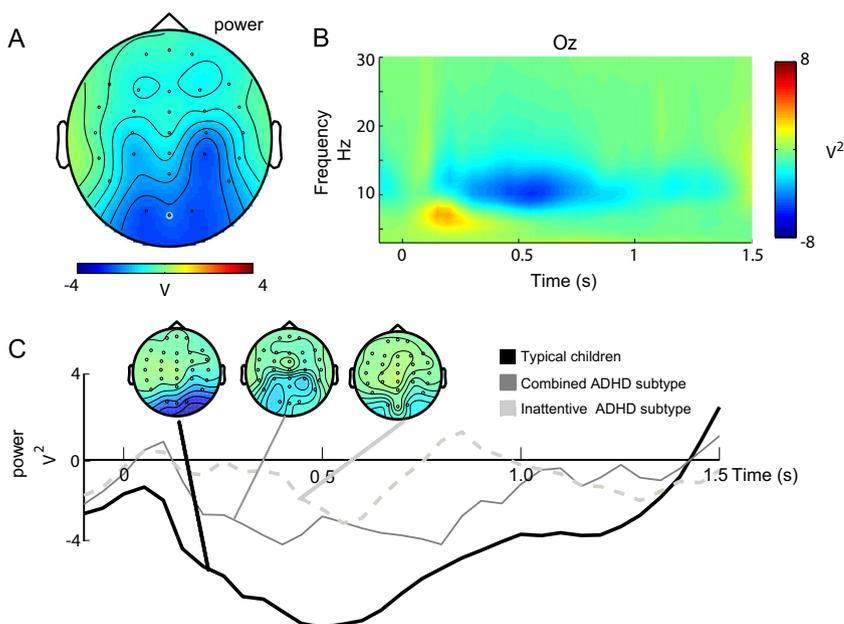
CB, combined subtype; Corr, correct; IA, predominantly inattentive; RP, response preparation; RT, reaction time; TD, typically developing.

significant difference) revealed that both TD and IA groups had significantly faster RTs than the CB group ( $p < .0001$ , and  $p = .03$ , respectively). However there was no significant Group  $\times$  Cue interaction with respect to correct RT ( $p > .4$ ).

### Electrophysiology

**Alpha Activity.** Overall, collapsed across all groups, the RP cues resulted in a suppression of alpha activity, which was maximal over occipital electrodes (Figure 2A). In the corresponding time–frequency representation plot, this suppression of alpha activity can be seen to start approximately 150 msec after cue onset, extending 1250–1500 msec postcue (Figure 2B). There was a significant main effect of Time, with alpha suppression being greatest 0–500 msec, directly after the cue ( $F_{2,108} = 7.5, p < .001$ ).

**IA Group Produces Diminished Alpha Suppression to RP Cues.** The magnitude and time course of alpha suppression to the RP cues differed between groups. The time course of the postcue occipital alpha power for the three groups can be seen in Figure 2C. A significant interaction was found between the time and group (Time  $\times$  Group:  $F_{4,108} = 3.34, p < .014$ ). The TD adolescents had the largest amount of alpha suppression 0–500 msec after the cue, whereas the IA adolescents had the least, ( $-5.4 \mu V^2$  vs.  $-.39 \mu V^2, p < .02$ ). An effect size analysis (53) revealed the differences in alpha suppression between the TD and IA adolescents to be a very large effect ( $d = .9$ ).



**Figure 2.** Alpha suppression after the response preparation cues. (A) The topography of the postcue alpha power reduction collapsed across the three groups. (B) The time-frequency spectra locked to cue-onset, at the occipital electrode Oz, collapsed across the three groups. (C) The time-course of alpha activity in the three groups of adolescents. The typically developing adolescents showed the greatest amount of alpha suppression 0–500 msec after the cue, whereas the predominantly inattentive had the least amount of alpha suppression. ADHD, attention-deficit/hyperactivity disorder.

The IA and CB adolescents did not significantly differ in the degree of alpha suppression ( $-.39 \mu V^2$  vs.  $-2.18 \mu V^2$ ,  $p < .1$ ). Subsequently, an effect size analysis suggested a sample size of over 350 participants would be needed to have 80% chance of detecting a statistical difference (Cohen's  $d = .35$ ) between the IA and CB adolescents. Finally, TD and CB adolescents did not significantly differ in the degree of alpha suppression ( $-5.4 \mu V^2$  vs.  $-2.18 \mu V^2$ ,  $p < .28$ ). The effect size analysis here suggested that a sample size of over 118 participants would be needed to detect statistical difference (Cohen's  $d = .5$ ) between the TD and CB adolescents.

**Groups Do Not Differentiate in Alpha Suppression in Response to Null Cues.** No differences in alpha suppression were found between groups in Null cues ( $F_{4,108} = 1.13$ ,  $p = .297$ ). Moreover, alpha suppression was significantly less after Null cues than after RP cues, across all time points postcue ( $-.04 \mu V^2$  vs.  $-2.5 \mu V^2$ ,  $p < .001$ ), suggesting the Null cues were not processed to the same extent in the visual cortex. This pattern indicates that group differences in cue processing were evident only in the presence of the informative RP cue. We therefore focused our subsequent analyses on the RP cues.

### Effect of Medication on Alpha Suppression

In our study, 9 of 17 participants diagnosed as an IA subtype had a history of taking medication, whereas all 17 in the CB group had a history of taking medication. All participants underwent at least a 24-hour medication washout period, commonly employed in many ADHD studies [e.g., (54–56)] to reduce any potential effects of medication on brain responses and behavioral measures. Nonetheless, the long-term effect of ADHD medication on brain activity is currently unknown (see Discussion). We set out to examine whether medication had an influence on alpha suppression or alpha-theta coupling.

We first compared the alpha suppression between the medicated and nonmedicated IA adolescents. We found no significant difference between the two sub-groups ( $-.738 \mu V^2$  vs.  $.01 \mu V^2$ ,  $t_{15} = -.39$ ,  $p < .7$ ). To reduce the likelihood that this null result might be due to the relatively small number of subjects analyzed, we computed an effect size analysis (53). We found that the Cohen's  $d$  for this comparison was quite small .19 and that over 850 subjects would be needed to detect a significant difference if one existed. This suggests that medication differences were unlikely to account for our alpha suppression findings.

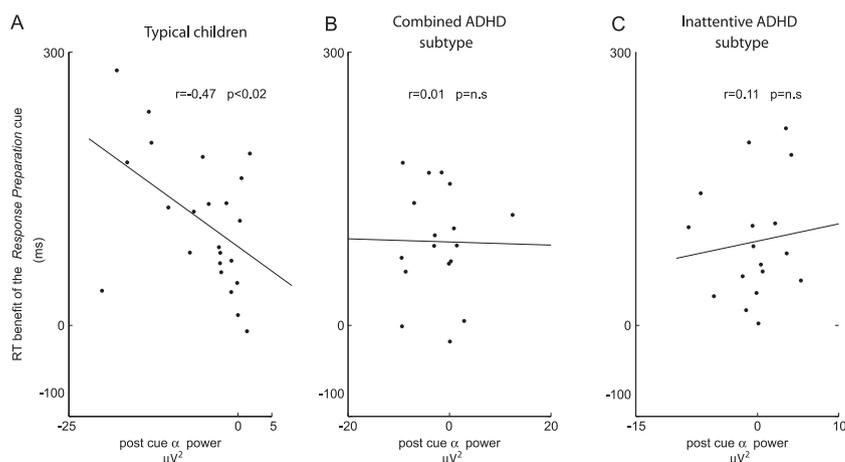
**Behavioral Benefit of RP Cue Is Related to Alpha Suppression in the TD Group.** To determine whether there was a relationship between the alpha suppression after the RP cue and

the behavioral benefit of the cue, we correlated the immediate alpha suppression after cue onset (0–500 msec) with the mean RT difference between RP and Null cues on the incongruent trials (Figure 3). Analysis was restricted to trials with correct responses only. The TD group contained an outlier whose alpha suppression was 2 SDs bigger than the rest of the participants in the group. The amount of alpha suppression was significantly correlated with the behavioral benefit of the cue in the TD group with and without the inclusion of the outlier (Figure 3A) (Outlier included:  $r = -.47$ ,  $p < .02$ , Without outlier:  $r = -.69$ ,  $p < .001$ ). This correlation was not significant in either the CB (Figure 3B) ( $r = .01$ ,  $p < .9$ ) or IA (Figure 3C) ( $r = .11$ ,  $p < .86$ ) groups. Alpha suppression after the Null cues was not correlated with the behavioral benefit of the RP cues in either the typical or ADHD adolescents ( $r = .06$ ,  $p > .7$ ).

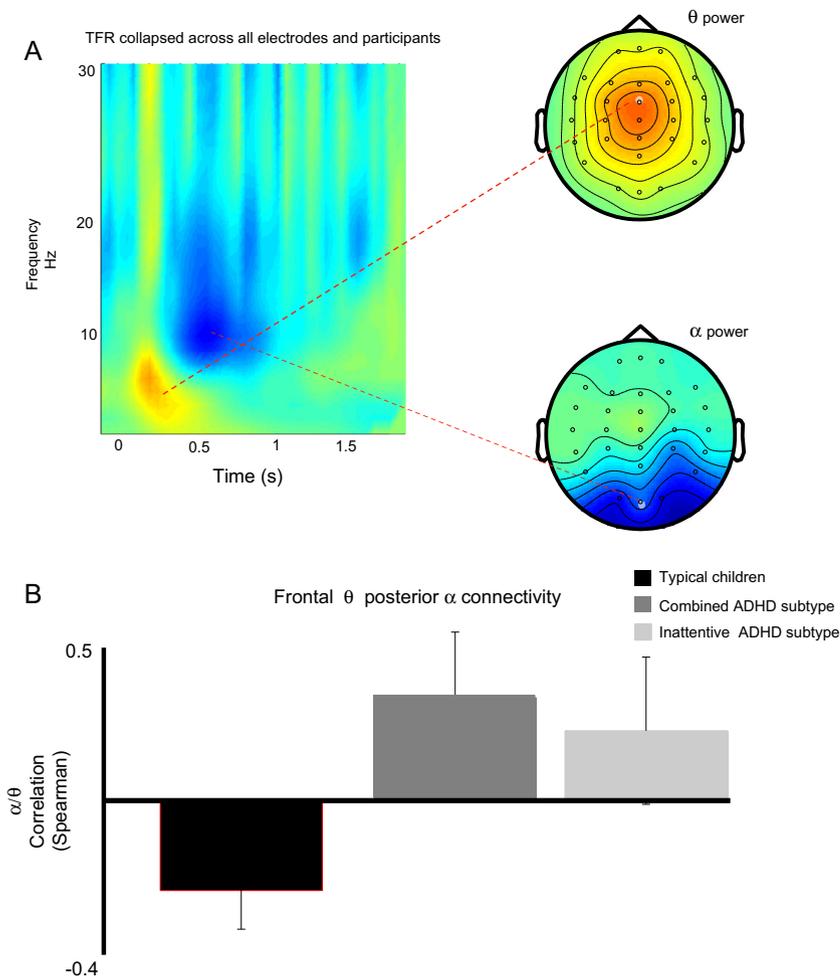
**Cross-Frequency Coupling Between Frontal Theta and Posterior Alpha in TD Group.** The grand-averaged time-frequency representations over electrodes and subjects can be seen in Figure 4A (left). The RP cues elicited an increase in theta activity at 50–300 msec postcue, which was largest over frontal-midline electrodes (Figure 4A, right). We found that the theta increase was largest at an interval 0–500 msec after cue onset ( $F_{2,53} = 14.63$ ,  $p < .0001$ ). However, there were no differences in the theta increase between the three groups (Time  $\times$  Group:  $F_{4,53} = 2.09$ ,  $p < .091$ ). We correlated the power of the frontal theta activity at electrode site FCz with occipital alpha power at Oz on a trial-by-trial basis and found significant differences between the groups (Figure 4B). A one-way ANOVA of the normalized correlations revealed a significant main effect of Group ( $F_{2,54} = 3.4$ ,  $p < .03$ ). This resulted from a significant trial-by-trial anti-correlation between occipital alpha and theta power after the RP cue for TD adolescents ( $r = -.24$ ,  $t_{22} = -2.324$ ,  $p < .05$ , one-sample  $t$  test) but not for the other groups. This correlation was both positive and nonsignificant in both IA ( $r = .19$ ,  $t_{16} = .9$ ,  $p < .34$ ) and CB ( $r = .28$ ,  $t_{16} = 1.5$ ,  $p < .13$ ) groups. Finally, we compared the medicated versus nonmedicated IA adolescents with regard to the trial-by-trial theta-alpha coupling. We found that there was a trend for medicated participants to have a greater negative coupling ( $r = -.14$  vs.  $r = .57$ ,  $t_{15} = -1.91$ ,  $p = .075$ ). Subsequently, our effect size analysis found this to be a very large effect ( $d = .93$ ), which could have a power of .8 with a sample size of 40 or more.

### Beta Activity

**Beta Activity Suppression Is Diminished in the CB Group.** The RP cues resulted in a suppression of beta activity, maximally at electrodes C3/4 (Figure 5A). In Figure 5B the time course of



**Figure 3.** Attentional benefit of the response preparation (RP) cue and alpha suppression. In the typically developing adolescents, the amount of alpha suppression was significantly correlated with the behavioral benefit (i.e., reaction time [RT] differences between null cued and RP cued correct targets) of the RP cue. Alpha suppression was not correlated with behavioral benefits of the cue in either subtypes of attention-deficit/hyperactivity disorder (ADHD).



**Figure 4.** Trial-by-trial correlations between the frontal theta increase and the posterior alpha decrease. **(A)** The grand-average time-frequency spectra of response preparation cue collapsed across groups and electrodes. **(B)** The increase in theta activity at 50–300 msec postcue was greatest over frontal-midline electrodes. The subsequent alpha suppression that followed occurred over occipital electrodes. **(C)** For typically developing adolescents, there was a strong anti-correlation between midline fronto-central theta power and occipital alpha. This correlation was not significant in either of the attention-deficit/hyperactivity disorder (ADHD) subtypes. TFR, time–frequency representation.

postcue beta power over the electrode contralateral to the cued hand is shown separately for the three groups. A significant interaction was found between group and time (Group  $\times$  Time:  $F_{2,53} = 4.47$ ,  $p < .017$ ). A post hoc comparison of the means showed that the TD group displayed the largest amount of beta suppression 800–1300 msec after the RP cue, whereas the CB showed the least ( $-1.010 \mu V^2$  vs.  $-.075 \mu V^2$ ,  $p < .03$ ). The difference in beta suppression between the TD and IA groups was not significant ( $p < .4$ ). Although the IA group demonstrated greater beta suppression ( $-.42 \mu V^2$ ) than the CB adolescents, this difference did not reach significance ( $p > .09$ ).

#### Beta Activity Is Correlated with Behavior in the TD Group.

Finally, we investigated the relationship between the postcue beta power and RT to the targets. This was done by correlating the power of contralateral beta activity for each trial with the RT to the target. These correlations were then subjected to a one-sample  $t$  test. We found that, only in the TD group, postcue beta power was correlated with RTs ( $r = .46$ ,  $t_{22} = 2.08$ ,  $p < .05$ ). Neither IA ( $r = .16$ ,  $t_{16} = .6$ ,  $p < .55$ ) nor CB ( $r = -.02$ ,  $t_{16} = -.12$ ,  $p < .9$ ) adolescents demonstrated a significant relationship between postcue beta activity and RTs.

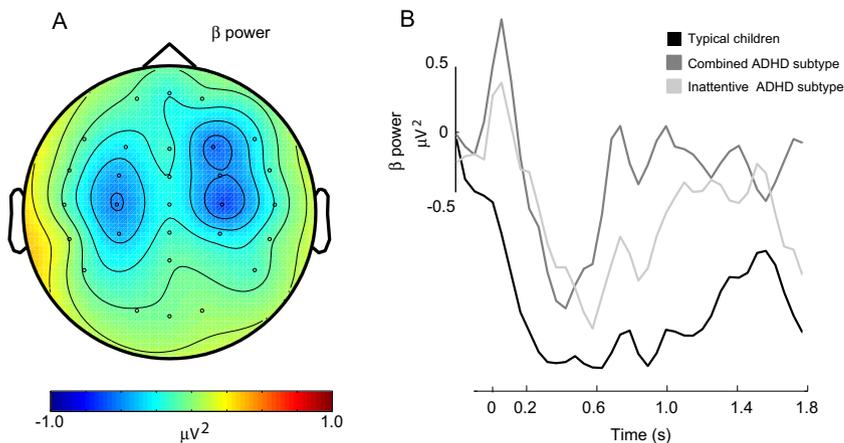
## Discussion

In the current study we investigated the neurophysiological differences between TD adolescents and those diagnosed with

predominantly inattentive (IA) and combined (CB) subtypes of ADHD. We focused on the oscillatory changes in the EEG induced by cues (RP) that predicted the most likely hand needed to respond correctly in a Flanker task. We found both distinct and common neurophysiological impairments in the ADHD subtypes. The IA subtype had less posterior alpha suppression after the cues than the TD adolescents, whereas the CB subtype exhibited less beta suppression at the electrode contralateral to the hand cued. Neither ADHD subtype showed any significant frontal-theta/posterior alpha coupling in contrast to the TD adolescents.

#### Diminished Alpha Suppression After the RP Cues in the IA Subtypes

We found that, across the TD adolescents, the postcue alpha suppression was correlated with a behavioral index of attentional benefit (i.e., shorter RT) provided by the RP cue. A number of studies have found that the amount of suppression of alpha activity after a visual stimulus is related to the degree of feature extraction and cognitive processing afforded to the stimulus (37–40). As such, our findings point to a diminished ability in IA adolescents to adequately process the information provided by cues. This interpretation is consistent with behavioral studies reporting visual processing problems for IA subtypes (56,57). It is perhaps not surprising that we find some evidence (to a lesser degree than IA) of inefficiency in suppressing alpha after cue presentation in the CB group, because their diagnostic



**Figure 5.** The suppression of beta activity is diminished in the combined subtype (CB) group. **(A)** The topography of the postcue beta activity, collapsed across the three groups. The response preparation cues resulted in a suppression of beta activity centered on electrodes over the motor cortex. **(B)** The time course of postcue beta power over the electrode contralateral to the cued hand in the three groups of adolescents (smoothed with a 5-point moving average method). From 800–1300 msec after cue onset, typically developing adolescents had the largest amount of beta suppression, whereas CB adolescents showed the least. On a trial-by-trial basis, the beta activity after the cue was found to be significantly correlated with reaction times to targets.

categorization also defines them as displaying significant attentional impairments (the CB diagnosis requires the presence of at least six inattentive as well as six hyperactive/impulsive symptoms).

A recent MEG study examining changes in posterior alpha activity of adults with ADHD during a spatial attention task found impairment in modulation of anticipatory lateralized visual alpha (58). When we examined the preflanker interval 500 msec before stimulus onset, we did not find any differences in alpha activity between groups ( $F_{2,56} = .7, p < .84$ ). It is likely that our task, which presented stimuli centrally, did not allow us to detect potential between-group differences in anticipatory alpha activity.

#### Frontal Theta/Posterior Alpha Coupling Absent in Both ADHD Subtypes

A number of studies have reported a coupling (power-to-power, and phase-locking) of the posterior alpha activity and frontal theta during the engagement of cognitive control (43–45,59,60). The absence of this coupling in both ADHD subtypes suggests that a lack of top-down control over the alpha activity represents a common impairment for both subtypes. It is conceivable that lack of top-down control of alpha activity in ADHD subtypes could translate to a reduced gating or filtering of external information, which could account for some of their shared symptoms of distractibility (61). Our results suggest that, although both the IA and CB exhibit frontal-sensory disconnection in terms of the cross-frequency coupling, medication might potentially restore the functional connectivity in IA subtype but not in the CB group. However, this conjecture is made with great caution, and we suggest that a future study with a much larger sample could examine the differential effects of ADHD medication on task-related changes in ADHD subtypes.

#### Diminished Beta Suppression After the RP Cues in the CB Subtype

We found that on a trial-by-trial basis the beta power was correlated with RT to the targets in all subjects. A number of previous studies have reported that voluntary movement and motor preparation are preceded by an attenuation of beta activity over contralateral sensorimotor areas (46,47). Thus, the lack of the beta suppression in the CB type suggests they had difficulties in the formation of the appropriate motor operation. This is in line with previous functional magnetic resonance imaging studies showing anomalies in the motor functioning and the motor system of individuals with ADHD (62,63).

#### Caveats

A potential limitation of our study was a differential rate of medication treatment in the CB compared with IA groups; significantly more CB than IA adolescents were being prescribed ADHD medication (Supplement 1). However, all participants had to refrain from medication at least 24 hours before EEG recording, which very likely reduced this confound. Nevertheless, very few studies have examined the long-term effects of methylphenidate on brain structure and function. One study by Konrad *et al.* (64) suggested that methylphenidate treatment (the first-choice pharmacological intervention for the treatment of ADHD) did not show large sustained changes in the brain areas involved in the control of attention. With regard to sample size, a larger sample size would have permitted further investigation into the differentiation between the subtypes of ADHD participants. A potential factor that might slightly reduce our capacity to detect a significant difference in beta suppression between the CB and IA group is the cutoff we employed (3 or fewer hyperactive/impulsive symptoms) for inclusion in our IA group. However, some researchers have argued for the use of two or less hyperactive/impulsive symptoms as a conservative inclusion factor for these “pure” IA individuals (56,65).

#### Future Directions

In the current study we used an established cognitive paradigm to identify specific processes involved in the pathology of ADHD. The use of EEG and MEG to characterize resting state activity [e.g., Brookes *et al.* (66)] could be a particularly fruitful venture, given that it allows for separation of spectrally specific patterns that have been shown to relate to biologically relevant features (67,68). In our study we chose to focus on the theta, alpha, and beta activity. Higher-frequency oscillations in the gamma range ( $>30$  Hz) have also been intimately related to selective attentional processes [e.g., (69–74)]. It would be interesting to use tasks that reliably elicit gamma oscillations as a tool to study neural information processing deficits in the ADHD population.

Task-related changes in the oscillatory activity of the EEG provide an objective biological measure of ADHD symptoms. A number of recent studies have shown that it is possible to modulate the oscillatory activity, particularly in the alpha band, with techniques such as repetitive transcranial magnetic stimulation (75,76) or transcranial alternating current stimulation (77–79). These techniques combined with novel testing paradigms will likely present an exciting new avenue of research into treatment

aiming to normalize brain activity (for a review of this topic, see Thut and Pascual-Leone [80]).

## Conclusions

Our EEG results represent an important first step in pinpointing task-related discrete neurophysiological deficits in the ADHD subtypes. Future research will need to establish whether or not those with the ADHD inattentive presentation, restrictive type, are actually best considered a distinct and unrelated disorder to the ADHD, combined type (81).

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