

UC Davis

UC Davis Previously Published Works

Title

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

Permalink

<https://escholarship.org/uc/item/6qp7r2qb>

Journal

Biological Psychiatry, 76(5)

ISSN

0006-3223

Authors

Mazaheri, Ali
Fassbender, Catherine
Coffey-Corina, Sharon
et al.

Publication Date

2014-09-01

DOI

10.1016/j.biopsych.2013.08.023

Peer reviewed

Published in final edited form as:

Biol Psychiatry. 2014 September 1; 76(5): 422–429. doi:10.1016/j.biopsych.2013.08.023.

Differential Oscillatory EEG between Attention Deficit Hyperactivity Disorder Subtypes and Typically Developing Adolescents

Ali Mazaheri^{a,*}, Catherine Fassbender^{b,c,d,e}, Sharon Coffey-Corina^e, Tadeus A. Hartanto^b, Julie B. Schweitzer^{b,c}, and George R. Mangun^{e,f,g}

^aAcademic Medical Center, Department of Psychiatry, University of Amsterdam, The Netherlands

^bM.I.N.D. Institute, University of California, Davis, CA, USA ^cDepartment of Psychiatry and Behavioral Sciences, University of California, Davis, CA, USA ^dImaging Research Center, University of California, Davis, CA, USA ^eCenter for Mind and Brain, University of California, Davis, CA, USA ^fDepartment of Psychology, University of California, Davis, CA, USA

^gDepartment of Neurology, University of California, Davis, CA, USA

Abstract

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 (associated with symptoms of inattention, as well as impulsivity/hyperactivity; CB) subtypes of ADHD.

Methods—EEG was recorded from 57 rigorously screened adolescents (aged 12 to 17 years; 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 following 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 post-cue 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

© 2013 Society of Biological Psychiatry. Published by Elsevier Inc. All rights reserved.

*Correspondence should be addressed to: Ali Mazaheri, Academic Medical Center, Department of Psychiatry, University of Amsterdam, The Netherlands, ali.mazah@gmail.com.

Financial Disclosures

All the authors reported no biomedical financial interests or potential conflicts of interest.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

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.

Keywords

Attention deficit hyperactivity disorder; Cue-processing; EEG oscillations; Connectivity; Top-down control; Response preparation

INTRODUCTION

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 hyper-activity and impulsivity.

The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (1) distinguished between three subtypes of ADHD: (i) the predominantly inattentive (IA), (ii) the predominantly impulsive/hyperactive (not involved in this study) (iii) 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 may represent distinct clinical disorders while others suggest that they, at the very least, manifest distinct neurobiological and behavioral impairment profiles (2, 3). DSM 5 uses the term “presentations,” rather than subtypes to acknowledge differences between symptom presentation. Previous research has successfully distinguished among ADHD subtypes based on inattention symptoms, demographics, 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 utilizing 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 EEG during a cued flanker task to obtain specific neurobiological signatures of the two most common subtypes of ADHD (IA & 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 in order for the participants to properly utilize 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.

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 TD children and adults suggest that the interaction between frontal theta and posterior alpha to be indicative of top-down attentional control (43–45). Finally, we used suppression of beta activity (22–25 Hz), at electrode locations contra-lateral 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, aged 12 to 17 years with typical development (TD, N=23), ADHD, combined type (CB; manifesting both inattention and hyperactivity/impulsivity, N=17) or primarily inattentive type (IA, N=17) were enrolled following 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. ADHD was diagnosed and categorized according to DSM-IV-TR criteria (see supplemental material 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 prior to 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. As 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 supplemental information for full paradigm description.

EEG Recording

Electroencephalograms were recorded from 32 electrodes, using an electro-cap (Electro-cap International), 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 using a bandpass of DC to 100 Hz, using an analog-to-digital sampling rate of 1000 samples per second. 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 the supplemental material.

Cross-frequency coupling between frontal-theta and posterior alpha

Traditionally, examining connectivity between brain regions using 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 using Fischer’s r-to-z transform in order to obtain a normally distributed variable (43, 44, 52).

Statistical Analysis

The statistical analysis of these correlations was assessed within groups using a one-sample t-test of the correlations and between groups using a one-way ANOVA. Repeated-measures

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

RESULTS

Behavior

The Response Preparation (RP) cue significantly improved performance in all three groups (Table 1). Accuracy (percent correct) was higher ($F(2,54) = 19.673, p < 0.0001$), and reaction times on correct trials were faster ($F(2,54) = 122.414, p < 0.0001$) in the RP cued versus Null cued conditions. These patterns of improved behavior indicate that all 3 groups were utilizing the information in the cues. There was also a significant effect of *Group* on reaction times ($F(2,54) = 8.115, p = 0.001$). The TD group displayed the greatest number of correct responses and the fastest RTs, while the CB group had the lowest number of correct responses and slowest RTs. Post-hoc analyses (Tukey HSD) revealed that both TD and IA groups had significantly faster reaction times than the CB group ($p < 0.0001$ and $p = 0.03$ respectively). However there was no significant Group X Cue interaction with respect to correct RT ($p > 0.4$).

Electrophysiology

Alpha activity—Overall, collapsed across all groups, the RP cues resulted in a suppression of alpha activity, which was maximal over occipital electrodes (Fig. 2A). In the corresponding TFR plot, this suppression of alpha activity can be seen to start around 150 ms after cue onset, extending 1250 to 1500 ms post cue (Fig. 2B). There was a significant main effect of *Time*, with alpha suppression being greatest 0 to 500 ms, directly after the cue ($F(2,108) = 7.5, p < 0.001$).

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 post-cue occipital alpha power for the three groups can be seen in Figure 2C. A significant interaction was found between the time and group (*Time X Group*: $F(4,108) = 3.34, p < .014$). The TD adolescents had the largest amount of alpha suppression 0 to 500 ms after the cue, whereas the IA adolescents had the least, ($-5.4 \mu V^2$ vs. $-0.39 \mu V^2, p < 0.02$). An effect size analysis (53) revealed the differences in alpha suppression between the TD and IA adolescents to be a very large effect ($d = 0.9$).

IA and CB adolescents did not significantly differ in the degree of alpha suppression ($-0.39 \mu\text{V}^2$ vs. $-2.18 \mu\text{V}^2$, $p < 1$). 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 ($-5.4 \mu\text{V}^2$ vs. $-2.18 \mu\text{V}^2$, $p < 0.28$). The effect size analysis here suggested that a sample size of over 118 participants would be needed to detect statistical difference (Cohen's $d = 0.5$) 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 ($F(4, 108) = 1.13$, $p = 0.297$). Moreover, alpha suppression was significantly less after Null cues than after RP cues, across all time points post cue ($-0.04 \mu\text{V}^2$ vs. $-2.5 \mu\text{V}^2$, $p < 0.001$), 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 wash out period, commonly employed in many ADHD studies (e.g., (54–56)) to reduce any potential effects of medication on brain responses and behavioural 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 non-medicated IA adolescents. We found no significant difference between the two sub-groups ($-0.738 \mu\text{V}^2$ vs. $0.01 \mu\text{V}^2$, $t(15) = -0.39$, $p < 0.7$). 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 0.19, 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 cue's behavioral benefit, we correlated the immediate alpha suppression after cue onset (0–500 ms) with the mean RT difference between RP and Null cues on the incongruent trials (see Fig. 3). Analysis was restricted to trials with correct responses only. The TD group contained an outlier whose alpha suppression was 2 standard deviations 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 (Fig. 3A; Outlier included: $r = -0.47$, $p < 0.02$, Without outlier: $r = -0.69$, $p < 0.001$). This correlation was not significant in either the CB (Fig. 3B; $r = 0.01$, $p < 0.9$) or IA (Fig. 3C; $r = 0.1$, $p < 0.86$) 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 ($r=0.06$, $p>0.7$)

Cross-frequency coupling between Frontal Theta and Posterior Alpha in TD

Group—The grand-averaged TFRs over electrodes and subjects can be seen in Figure 4A (left). The RP cues elicited an increase in theta activity at 50 to 300 ms post-cue which was largest over frontal-midline electrodes (Fig. 4A, right). We found that the theta increase was largest at an interval 0 to 500 ms after cue onset ($F(2,53) = 14.63$, $p < .0001$). However, there were no differences in the theta increase between the three groups (*Time X Group*: ($F(4,53) = 2.09$, $p < 0.091$). 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 (Fig. 4B). A one-way ANOVA of the normalized correlations revealed a significant main effect of *Group* ($F(2,54) = 3.4$, $p < 0.03$). This resulted from a significant trial-by-trial anti-correlation between occipital alpha and theta power after the RP cue for TD adolescents ($r = -0.24$, $t(22) = -2.324$, $p < 0.05$, one-sample t-test), but not for the other groups. This correlation was both positive and non-significant in both IA ($r = 0.19$, $t(16) = 0.9$, $p < 0.34$) and CB ($r = 0.28$, $t(16) = 1.5$, $p < 0.13$) groups. Finally, we compared the medicated versus non-medicated 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. $r = 0.57$, $t(15) = -1.91$, $p = 0.075$). Subsequently, our effect size analysis found this to be a very large effect ($d = .93$) which could have a power of 0.8 with a sample size of 40 or more.

Beta activity

Beta Activity Suppression is diminished in the CB Group—RP cues resulted in a suppression of beta activity, maximally at electrodes C3/4. (Fig. 5A). In Figure 5B the time course of post-cue beta power over the electrode contra-lateral to the cued hand is shown separately for the three groups. A significant interaction was found between group and time (*Group X 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 to 1300 ms after the RP cue, whereas the CB showed the least ($-1.010 \mu V^2$ vs. $-.075 \mu V^2$, $p < 0.03$). The difference in beta suppression between the TD and IA groups was not significant ($p < 0.4$). Although the IA group demonstrated greater beta suppression ($-0.42 \mu V^2$) than the CB adolescents, this difference did not reach significance ($p > 0.09$).

Beta Activity is Correlated with Behavior in the TD Group—Finally, we investigated the relationship between the post-cue beta power and RT to the targets. This was done by correlating the power of contra-lateral 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, post-cue beta power was correlated with RTs ($r = 0.46$, $t(22) = 2.08$, $p < 0.05$). Neither IA ($r = 0.16$, $t(16) = 0.6$, $p < 0.55$) nor CB ($r = -0.02$, $t(16) = -0.12$, $p < 0.9$) adolescents demonstrated a significant relationship between post-cue beta activity and RTs.

DISCUSSION

In the current study we investigated the neurophysiological differences between typically developing (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) which 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 post-cue alpha suppression was correlated with a behavioral index of attentional benefit (i.e. shorter reaction time) 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 following cue presentation in the CB group, as their diagnostic 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 pre-flanker interval 500 ms 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 fMRI 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 to IA groups; significantly more CB than IA adolescents were being prescribed ADHD medication (see Supplementary Information). However, all participants had to refrain from medication at least 24 hours prior to 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 ADHD), did not show large sustained changes in the brain areas involved in the control of attention. With regards 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 may slightly reduce our capacity to detect a significant difference in beta suppression between the CB and IA group is the cut-off we employed (3 or fewer) 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 characterise resting state activity (e.g. (66)) could be a particularly fruitful venture given that it allows for separation of spectrally specific patterns which 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 (eg (69–74)). It would be interesting to use tasks which 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, using techniques such as rTMS (75, 76) or tACS (77, 78, 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 (80)).

Conclusion

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).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by VENI grant from the Netherlands Organisation for Scientific Research (NWO) to A.M., NIMH/NIH grant to G.R.M. R01MH055714, Klingenstein Third Generation Foundation ADHD Fellowship to C.F., MIND Institute pilot grant to C.F and J.B.S. and NIMH grant MH066310 to J.B.S.. The authors would like to thank all the volunteers and their families who participated in this study. We would like to thank Cameron Carter for helpful suggestions regarding data analysis, Stephen Whitmarsh and Mike X Cohen for editing an earlier version of this manuscript. Authors are also grateful to Faye Dixon, Danielle Miziuri, Kyle Rutledge, Lauren Boyle, Joan Gunther and Dorothy Yip for their assistance in the study.

References

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Washington, D.C: American Psychiatric Association; 1994.
2. Barkley RA, DuPaul GJ, McMurray MB. Comprehensive evaluation of attention deficit disorder with and without hyperactivity as defined by research criteria. *J Consult Clin Psychol.* 1990; 58:775–789. [PubMed: 2292627]
3. Milich R, Balentine AC, Lynam DR. ADHD combined type and ADHD predominantly inattentive type are distinct and unrelated disorders. *Clinical Psychology: Science and Practice.* 2001; 8:463–488.
4. McLoughlin G, Ronald A, Kuntsi J, Asherson P, Plomin R. Genetic support for the dual nature of attention deficit hyperactivity disorder: substantial genetic overlap between the inattentive and hyperactive-impulsive components. *J Abnorm Child Psychol.* 2007; 35:999–1008. [PubMed: 17690977]
5. Waldman ID, Rowe DC, Abramowitz A, Kozel ST, Mohr JH, Sherman SL, et al. Association and linkage of the dopamine transporter gene and attention-deficit hyperactivity disorder in children: heterogeneity owing to diagnostic subtype and severity. *Am J Hum Genet.* 1998; 63:1767–1776. [PubMed: 9837830]
6. Rasmussen ER, Neuman RJ, Heath AC, Levy F, Hay DA, Todd RD. Familial clustering of latent class and DSM-IV defined attention-deficit/hyperactivity disorder (ADHD) subtypes. *J Child Psychol Psychiatry.* 2004; 45:589–598. [PubMed: 15055377]
7. Larsson H, Lichtenstein P, Larsson JO. Genetic contributions to the development of ADHD subtypes from childhood to adolescence. *J Am Acad Child Adolesc Psychiatry.* 2006; 45:973–981. [PubMed: 16865040]
8. Barkley RA. The inattentive type of ADHD as a distinct disorder: What remains to be done. *Clinical Psychology: Science and Practice.* 2001; 8:489–493.
9. Barkley RA, DuPaul GJ, McMurray MB. Attention deficit disorder with and without hyperactivity: clinical response to three dose levels of methylphenidate. *Pediatrics.* 1991; 87:519–531. [PubMed: 2011430]

10. Weiss M, Worling D, Wasdell M. A chart review study of the inattentive and combined types of ADHD. *J Atten Disord.* 2003; 7:1–9. [PubMed: 14738177]
11. Stein MA, Sarampote CS, Waldman ID, Robb AS, Conlon C, Pearl PL, et al. A dose-response study of OROS methylphenidate in children with attention-deficit/hyperactivity disorder. *Pediatrics.* 2003; 112:e404. [PubMed: 14595084]
12. Pfiffner LJ, Yee Mikami A, Huang-Pollock C, Easterlin B, Zalecki C, McBurnett K. A randomized, controlled trial of integrated home-school behavioral treatment for ADHD, predominantly inattentive type. *J Am Acad Child Adolesc Psychiatry.* 2007; 46:1041–1050. [PubMed: 17667482]
13. Adams ZW, Derefinko KJ, Milich R, Fillmore MT. Inhibitory functioning across ADHD subtypes: recent findings, clinical implications, and future directions. *Dev Disabil Res Rev.* 2008; 14:268–275. [PubMed: 19072751]
14. Klorman R, Hazel-Fernandez LA, Shaywitz SE, Fletcher JM, Marchione KE, Holahan JM, et al. Executive functioning deficits in attention-deficit/hyperactivity disorder are independent of oppositional defiant or reading disorder. *J Am Acad Child Adolesc Psychiatry.* 1999; 38:1148–1155. [PubMed: 10504814]
15. Lockwood KA, Marcotte AC, Stern C. Differentiation of attention-deficit/hyperactivity disorder subtypes: application of a neuropsychological model of attention. *J Clin Exp Neuropsychol.* 2001; 23:317–330. [PubMed: 11404810]
16. Nigg JT, Blaskey LG, Huang-Pollock CL, Rappley MD. Neuropsychological executive functions and DSM-IV ADHD subtypes. *J Am Acad Child Adolesc Psychiatry.* 2002; 41:59–66. [PubMed: 11800208]
17. Iaboni F, Douglas VI, Baker AG. Effects of reward and response costs on inhibition in ADHD children. *J Abnorm Psychol.* 1995; 104:232–240. [PubMed: 7897047]
18. Oosterlaan J, Sergeant JA. Response inhibition and response re-engagement in attention-deficit/hyperactivity disorder, disruptive, anxious and normal children. *Behav Brain Res.* 1998; 94:33–43. [PubMed: 9708837]
19. Casey BJ, Castellanos FX, Giedd JN, Marsh WL, Hamburger SD, Schubert AB, et al. Implication of right frontostriatal circuitry in response inhibition and attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry.* 1997; 36:374–383. [PubMed: 9055518]
20. Casey BJ, Durston S, Fossella JA. Evidence for a mechanistic model of cognitive control. *Clinical Neuroscience Research.* 2001; 1:267–282.
21. Broyd SJ, Johnstone SJ, Barry RJ, Clarke AR, McCarthy R, Selikowitz M, et al. The effect of methylphenidate on response inhibition and the event-related potential of children with Attention Deficit/Hyperactivity Disorder. *Int J Psychophysiol.* 2005
22. Borger N, van der Meere J. Motor control and state regulation in children with ADHD: a cardiac response study. *Biol Psychol.* 2000; 51:247–267. [PubMed: 10686368]
23. Leth-Steensen C, King Elbaz Z, Douglas VI. Mean response times, variability and skew in the responding of ADHD children: a response time distributional approach. *Acta Psychologica.* 2000:167–190.
24. van der Meere J, van Baal M, Sergeant J. The additive factor method: a differential diagnostic tool in hyperactivity and learning disability. *J Abnorm Child Psychol.* 1989; 17:409–422. [PubMed: 2794254]
25. Huang-Pollock CL, Mikami AY, Pfiffner L, McBurnett K. ADHD subtype differences in motivational responsivity but not inhibitory control: evidence from a reward-based variation of the stop signal paradigm. *J Clin Child Adolesc Psychol.* 2007; 36:127–136. [PubMed: 17484686]
26. Derefinko KJ, Adams ZW, Milich R, Fillmore MT, Lorch EP, Lynam DR. Response style differences in the inattentive and combined subtypes of attention-deficit/hyperactivity disorder. *J Abnorm Child Psychol.* 2008; 36:745–758. [PubMed: 18175214]
27. Booth JE, Carlson CL, Tucker DM. Performance on a neurocognitive measure of alerting differentiates ADHD combined and inattentive subtypes: a preliminary report. *Arch Clin Neuropsychol.* 2007; 22:423–432. [PubMed: 17339094]

28. Patino LR, Adler CM, Mills NP, Strakowski SM, Fleck DE, Welge JA, et al. Conflict monitoring and adaptation in individuals at familial risk for developing bipolar disorder. *Bipolar Disord.* 2013; 15:264–271. [PubMed: 23528067]
29. Westerhausen R, Kompus K, Hugdahl K. Unaffected control of distractor interference in schizophrenia: a meta-analysis of incompatibility slowing in flanker tasks. *J Psychiatr Res.* 2013; 47:246–251. [PubMed: 23140904]
30. Loman MM, Johnson AE, Westerlund A, Pollak SD, Nelson CA, Gunnar MR. The effect of early deprivation on executive attention in middle childhood. *J Child Psychol Psychiatry.* 2013; 54:37–45. [PubMed: 22924462]
31. Geburek AJ, Rist F, Gediga G, Stroux D, Pedersen A. Electrophysiological indices of error monitoring in juvenile and adult attention deficit hyperactivity disorder (ADHD)--a meta-analytic appraisal. *Int J Psychophysiol.* 2013; 87:349–362. [PubMed: 22902313]
32. Yordanova J, Kolev V, Albrecht B, Uebel H, Banaschewski T, Rothenberger A. May posterror performance be a critical factor for behavioral deficits in attention-deficit/hyperactivity disorder? *Biol Psychiatry.* 2011; 70:246–254. [PubMed: 21531386]
33. McLoughlin G, Albrecht B, Banaschewski T, Rothenberger A, Brandeis D, Asherson P, et al. Performance monitoring is altered in adult ADHD: A familial event-related potential investigation. *Neuropsychologia.* 2009; 47:3134–3142. [PubMed: 19643116]
34. Foxe JJ, Simpson GV, Ahlfors SP. Parieto-occipital approximately 10 Hz activity reflects anticipatory state of visual attention mechanisms. *Neuroreport.* 1998; 9:3929–3933. [PubMed: 9875731]
35. Jensen O, Mazaheri A. Shaping functional architecture by oscillatory alpha activity: gating by inhibition. *Front Hum Neurosci.* 2010; 4:186. [PubMed: 21119777]
36. Klimesch W, Sauseng P, Hanslmayr S. EEG alpha oscillations: the inhibition-timing hypothesis. *Brain Res Rev.* 2007; 53:63–88. [PubMed: 16887192]
37. Pfurtscheller G. Functional brain imaging based on ERD/ERS. *Vision Res.* 2001; 41:1257–1260. [PubMed: 11322970]
38. Pfurtscheller G, Neuper C, Mohl W. Event-related desynchronization (ERD) during visual processing. *Int J Psychophysiol.* 1994; 16:147–153. [PubMed: 8089033]
39. Schurmann M, Basar E. Functional aspects of alpha oscillations in the EEG. *Int J Psychophysiol.* 2001; 39:151–158. [PubMed: 11163894]
40. Mazaheri A, Picton TW. EEG spectral dynamics during discrimination of auditory and visual targets. *Brain Res Cogn Brain Res.* 2005; 24:81–96. [PubMed: 15922161]
41. Gevins A, Smith ME, McEvoy L, Yu D. High-resolution EEG mapping of cortical activation related to working memory: effects of task difficulty, type of processing, and practice. *Cereb Cortex.* 1997; 7:374–385. [PubMed: 9177767]
42. Ishii R, Shinosaki K, Ukai S, Inouye T, Ishihara T, Yoshimine T, et al. Medial prefrontal cortex generates frontal midline theta rhythm. *Neuroreport.* 1999; 10:675–679. [PubMed: 10208529]
43. Mazaheri A, Coffey-Corina S, Mangun GR, Bekker EM, Berry AS, Corbett BA. Functional disconnection of frontal cortex and visual cortex in attention-deficit/hyperactivity disorder. *Biol Psychiatry.* 2010; 67:617–623. [PubMed: 20060100]
44. Mazaheri A, Nieuwenhuis IL, van Dijk H, Jensen O. Prestimulus alpha and mu activity predicts failure to inhibit motor responses. *Hum Brain Mapp.* 2009; 30:1791–1800. [PubMed: 19308934]
45. van Driel J, Ridderinkhof KR, Cohen MX. Not all errors are alike: theta and alpha EEG dynamics relate to differences in error-processing dynamics. *J Neurosci.* 2012; 32:16795–16806. [PubMed: 23175833]
46. Pfurtscheller G, Berghold A. Patterns of cortical activation during planning of voluntary movement. *Electroencephalogr Clin Neurophysiol.* 1989; 72:250–258. [PubMed: 2465128]
47. Tzagarakis C, Ince NF, Leuthold AC, Pellizzer G. Beta-band activity during motor planning reflects response uncertainty. *J Neurosci.* 2010; 30:11270–11277. [PubMed: 20739547]
48. Eriksen BA, Eriksen CW. Effects of noise letters upon the identification of a target letter in a nonsearch task. *Perception and Psychophysics.* 1974; 16:143–149.
49. Nunez PL, Srinivasan R, Westdorp AF, Wijesinghe RS, Tucker DM, Silberstein RB, et al. EEG coherency. I: Statistics, reference electrode, volume conduction, Laplacians, cortical imaging, and

- interpretation at multiple scales. *Electroencephalogr Clin Neurophysiol*. 1997; 103:499–515. [PubMed: 9402881]
50. Kamphuisen A, Bauer M, van Ee R. No evidence for widespread synchronized networks in binocular rivalry: MEG frequency tagging entrains primarily early visual cortex. *J Vis*. 2008; 8(4): 1–8. [PubMed: 18842075]
 51. Bengson JJ, Mangun GR, Mazaheri A. The neural markers of an imminent failure of response inhibition. *Neuroimage*. 2012; 59:1534–1539. [PubMed: 21889992]
 52. de Lange FP, Jensen O, Bauer M, Toni I. Interactions between posterior gamma and frontal alpha/beta oscillations during imagined actions. *Front Hum Neurosci*. 2008; 2:7. [PubMed: 18958208]
 53. Cohen J. A power primer. *Psychol Bull*. 1992; 112:155–159. [PubMed: 19565683]
 54. Valera EM, Faraone SV, Biederman J, Poldrack RA, Seidman LJ. Functional neuroanatomy of working memory in adults with attention-deficit/hyperactivity disorder. *Biol Psychiatry*. 2005; 57:439–447. [PubMed: 15737657]
 55. Valera EM, Brown A, Biederman J, Faraone SV, Makris N, Monuteaux MC, et al. Sex differences in the functional neuroanatomy of working memory in adults with ADHD. *Am J Psychiatry*. 2010; 167:86–94. [PubMed: 19884224]
 56. Carr L, Henderson J, Nigg JT. Cognitive control and attentional selection in adolescents with ADHD versus ADD. *J Clin Child Adolesc Psychol*. 2010; 39:726–740. [PubMed: 21058121]
 57. Weiler MD, Bernstein JH, Bellinger D, Waber DP. Information processing deficits in children with attention-deficit/hyperactivity disorder, inattentive type, and children with reading disability. *J Learn Disabil*. 2002; 35:448–461. [PubMed: 15490541]
 58. Ter Huurne N, Onnink M, Kan C, Franke B, Buitelaar J, Jensen O. Behavioral Consequences of Aberrant Alpha Lateralization in Attention-Deficit/Hyperactivity Disorder. *Biol Psychiatry*. 2013
 59. Cohen MX, Bour L, Mantione M, Figeet M, Vink M, Tijssen MA, et al. Top-down-directed synchrony from medial frontal cortex to nucleus accumbens during reward anticipation. *Hum Brain Mapp*. 2012; 33:246–252. [PubMed: 21547982]
 60. Cohen MX. Error-related medial frontal theta activity predicts cingulate-related structural connectivity. *Neuroimage*. 2011; 55:1373–1383. [PubMed: 21195774]
 61. Fassbender C, Zhang H, Buzy WM, Cortes CR, Mizuiri D, Beckett L, et al. A lack of default network suppression is linked to increased distractibility in ADHD. *Brain Res*. 2009; 1273:114–128. [PubMed: 19281801]
 62. Mostofsky SH, Rimrod SL, Schafer JG, Boyce A, Goldberg MC, Pekar JJ, et al. Atypical motor and sensory cortex activation in attention-deficit/hyperactivity disorder: a functional magnetic resonance imaging study of simple sequential finger tapping. *Biol Psychiatry*. 2006; 59:48–56. [PubMed: 16139806]
 63. Mostofsky SH, Newschaffer CJ, Denckla MB. Overflow movements predict impaired response inhibition in children with ADHD. *Percept Mot Skills*. 2003; 97:1315–1331. [PubMed: 15002876]
 64. Konrad K, Neufang S, Fink GR, Herpertz-Dahlmann B. Long-term effects of methylphenidate on neural networks associated with executive attention in children with ADHD: results from a longitudinal functional MRI study. *J Am Acad Child Adolesc Psychiatry*. 2007; 46:1633–1641. [PubMed: 18030085]
 65. Volk HE, Todorov AA, Hay DA, Todd RD. Simple identification of complex ADHD subtypes using current symptom counts. *J Am Acad Child Adolesc Psychiatry*. 2009; 48:441–450. [PubMed: 19318883]
 66. Brookes MJ, Woolrich M, Luckhoo H, Price D, Hale JR, Stephenson MC, et al. Investigating the electrophysiological basis of resting state networks using magnetoencephalography. *Proc Natl Acad Sci USA*. 2011; 108:16783–16788. [PubMed: 21930901]
 67. Muthukumaraswamy SD, Edden RA, Jones DK, Swettenham JB, Singh KD. Resting GABA concentration predicts peak gamma frequency and fMRI amplitude in response to visual stimulation in humans. *Proc Natl Acad Sci U S A*. 2009; 106:8356–8361. [PubMed: 19416820]
 68. Bauer M, Kluge C, Bach D, Bradbury D, Heinze HJ, Dolan RJ, et al. Cholinergic enhancement of visual attention and neural oscillations in the human brain. *Curr Biol*. 2012; 22:397–402. [PubMed: 22305751]

69. Fries P, Reynolds JH, Rorie AE, Desimone R. Modulation of oscillatory neuronal synchronization by selective visual attention. *Science*. 2001; 291:1560–1563. [PubMed: 11222864]
70. Bauer M, Oostenveld R, Peeters M, Fries P. Tactile spatial attention enhances gamma-band activity in somatosensory cortex and reduces low-frequency activity in parieto-occipital areas. *J Neurosci*. 2006; 26:490–501. [PubMed: 16407546]
71. Jensen O, Kaiser J, Lachaux JP. Human gamma-frequency oscillations associated with attention and memory. *Trends Neurosci*. 2007; 30:317–324. [PubMed: 17499860]
72. Vidal JR, Chaumon M, O'Regan JK, Tallon-Baudry C. Visual grouping and the focusing of attention induce gamma-band oscillations at different frequencies in human magnetoencephalogram signals. *J Cogn Neurosci*. 2006; 18:1850–1862. [PubMed: 17069476]
73. Vidal JR, Ossandon T, Jerbi K, Dalal SS, Minotti L, Ryvlin P, et al. Category-Specific Visual Responses: An Intracranial Study Comparing Gamma, Beta, Alpha, and ERP Response Selectivity. *Front Hum Neurosci*. 2010; 4:195. [PubMed: 21267419]
74. Vidal JR, Freyermuth S, Jerbi K, Hamame CM, Ossandon T, Bertrand O, et al. Long-distance amplitude correlations in the high gamma band reveal segregation and integration within the reading network. *J Neurosci*. 2012; 32:6421–6434. [PubMed: 22573665]
75. Romei V, Thut G, Mok RM, Schyns PG, Driver J. Causal implication by rhythmic transcranial magnetic stimulation of alpha frequency in feature-based local vs. global attention. *Eur J Neurosci*. 2012; 35:968–974. [PubMed: 22394014]
76. Thut G, Veniero D, Romei V, Miniussi C, Schyns P, Gross J. Rhythmic TMS causes local entrainment of natural oscillatory signatures. *Curr Biol*. 2011; 21:1176–1185. [PubMed: 21723129]
77. Zaehle T, Rach S, Herrmann CS. Transcranial alternating current stimulation enhances individual alpha activity in human EEG. *PLoS One*. 2010; 5:e13766. [PubMed: 21072168]
78. Herrmann CS, Rach S, Neuling T, Struber D. Transcranial alternating current stimulation: a review of the underlying mechanisms and modulation of cognitive processes. *Front Hum Neurosci*. 2013; 7:279. [PubMed: 23785325]
79. Neuling T, Rach S, Herrmann CS. Orchestrating neuronal networks: sustained after-effects of transcranial alternating current stimulation depend upon brain states. *Front Hum Neurosci*. 2013; 7:161. [PubMed: 23641206]
80. Thut G, Pascual-Leone A. A review of combined TMS-EEG studies to characterize lasting effects of repetitive TMS and assess their usefulness in cognitive and clinical neuroscience. *Brain Topogr*. 2010; 22:219–232. [PubMed: 19862614]
81. Roberts W, Milich R. Examining the Changes to ADHD in the DSM-5: One Step Forward and Two Steps Back. *The ADHD Report*. 2013; 21:6.

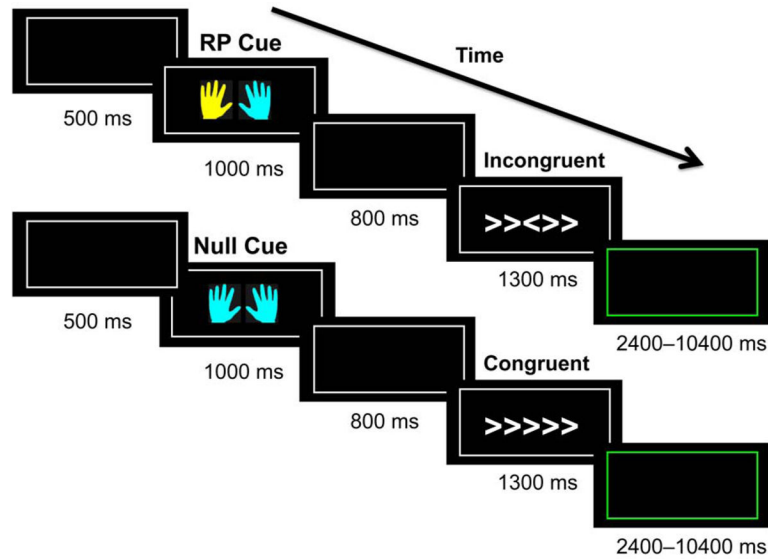


Figure 1.

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 which consisted of two colored cartoon hands. The figure shows the Null cue, which provided no information about the subsequent stimulus and the 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 inter-trial interval (ITI; 2,400–10,400 ms). This was indicated by a color change of the surrounding border from white to green. Participants were instructed to relax their eyes during this ITI.

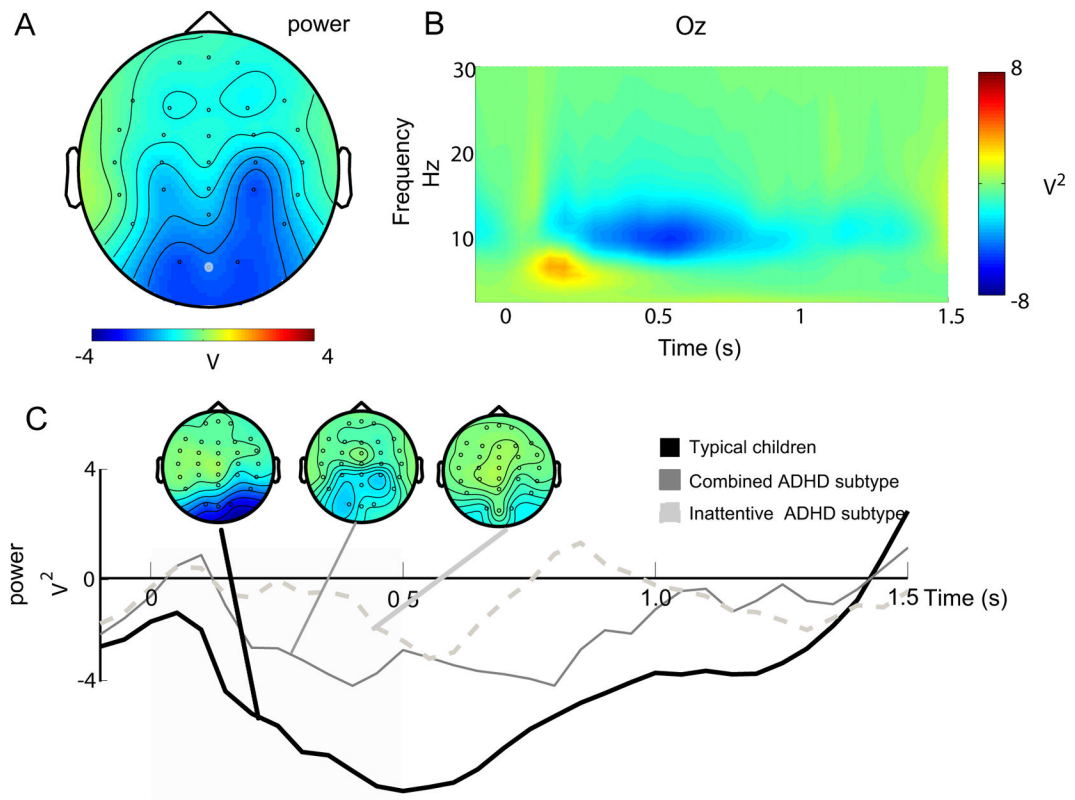


Figure 2.

Alpha suppression after the response preparation (RP) cues. A) The topography of the post-cue 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 TD adolescents showed the greatest amount of alpha suppression 0–500 ms after the cue, whereas the IA had the least amount of alpha suppression.

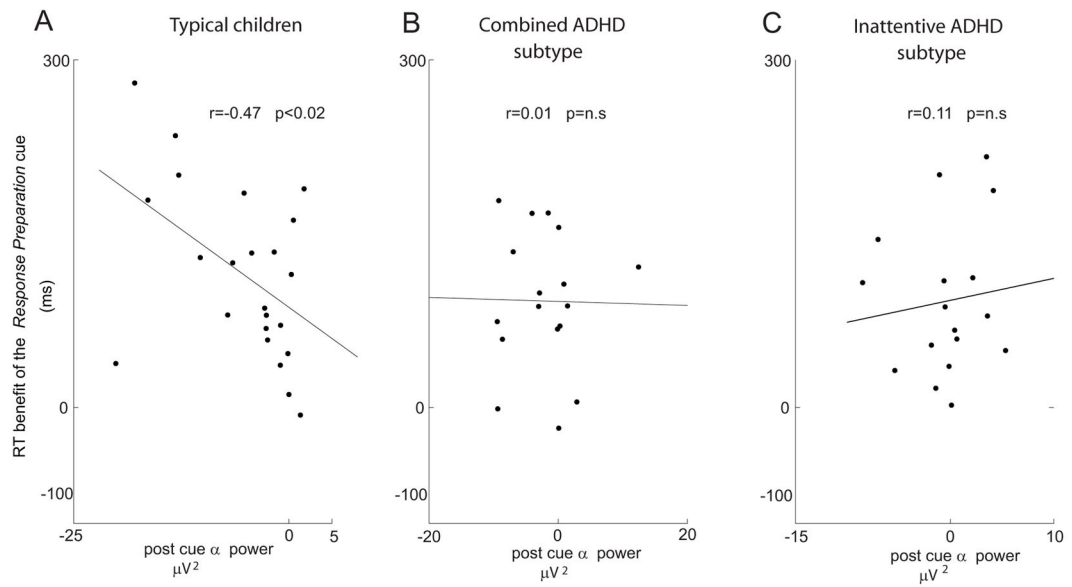
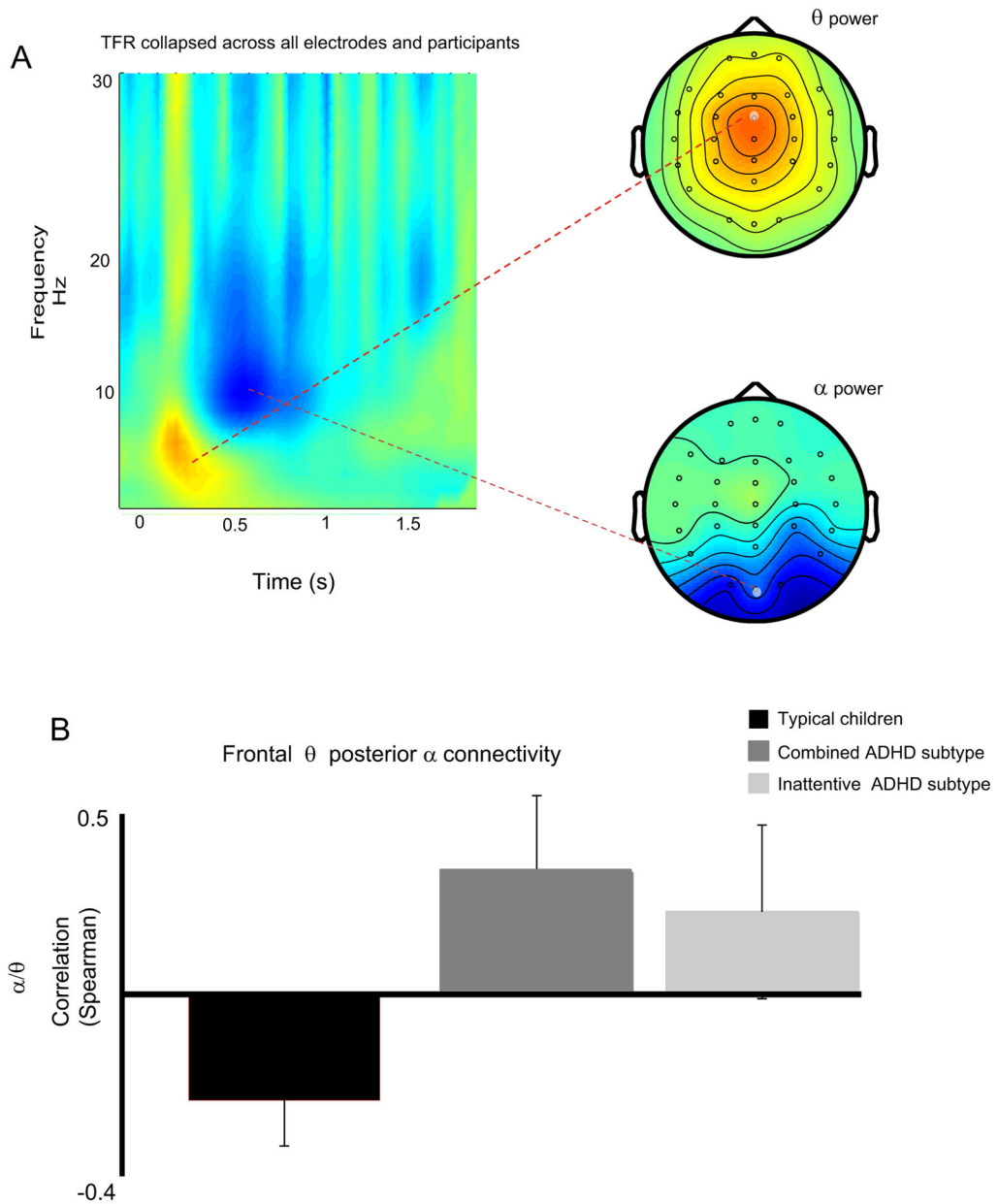


Figure 3.

Attentional benefit of the RP cue and alpha suppression. In the TD adolescents, the amount of alpha suppression was significantly correlated with the behavioral benefit (i.e. 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 sub-types of 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 RP cue collapsed across groups and electrodes. B) The increase in theta activity at 50–300 ms post-cue was greatest over frontal-midline electrodes. The subsequent alpha suppression that followed occurred over occipital electrodes. C) For TD 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 ADHD subtypes.

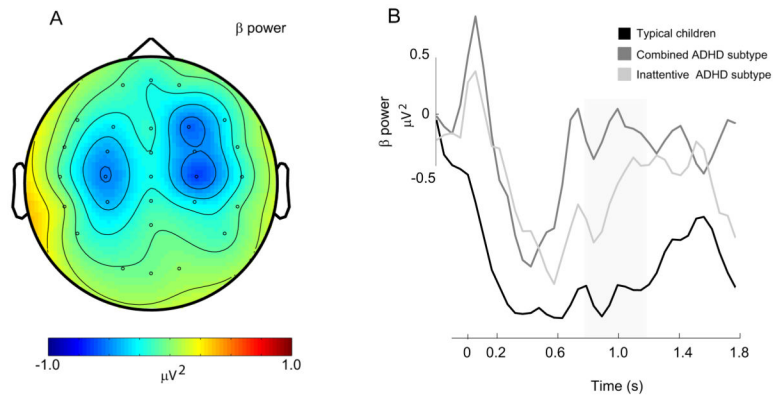


Figure 5.

The suppression of beta activity is diminished in the CB group. A) The topography of the post-cue beta activity, collapsed across the three groups. The RP cues resulted in a suppression of beta activity centered on electrodes over the motor cortex. B) The time course of post-cue beta power over the electrode contra-lateral to the cued hand in the three groups of adolescents (smoothed using a 5 point moving average method). From 800–1300 ms after cue onset, TD 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.

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)

Note: means are displayed with standard deviation in parentheses.

Percent errors represent commission errors.