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

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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 to17 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.

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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-sec cue-to-target interval after the RP cue onset. See Supplement 1 for full paradigm description.

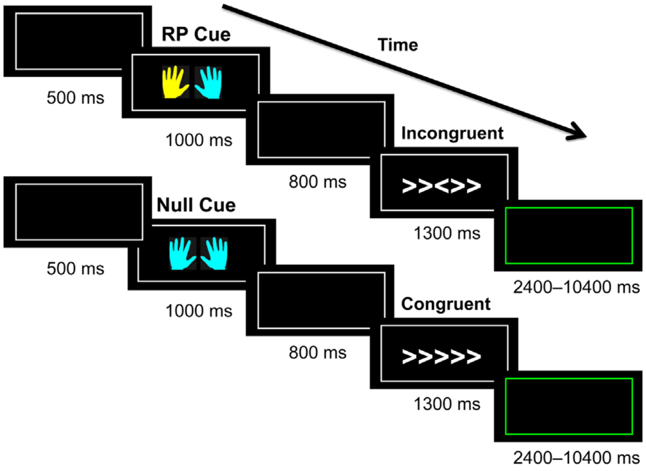

Figure 1. Task figure. Participants were required to respond by button press to the centrally presented arrow in a horizontal array of five arrows, while ignoring the surrounding or “flanking” arrows. Participants pressed with the right hand to a rightward facing arrow and the left hand to a leftward 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