Title
Aberrant Modulation of Brain Oscillatory Activity and Attentional Impairment in Attention-Deficit/Hyperactivity Disorder.

Permalink
https://escholarship.org/uc/item/9v26k93r

Journal
Biological psychiatry. Cognitive neuroscience and neuroimaging, 3(1)

ISSN
2451-9022

Authors
Lenartowicz, Agatha
Mazaheri, Ali
Jensen, Ole
et al.

Publication Date
2018

DOI
10.1016/j.bpsc.2017.09.009

Copyright Information
This work is made available under the terms of a Creative Commons Attribution License, available at https://creativecommons.org/licenses/by/4.0/

Peer reviewed
Aberrant Modulation of Brain Oscillatory Activity and Attentional Impairment in Attention-Deficit/Hyperactivity Disorder

Agatha Lenartowicz, Ali Mazaheri, Ole Jensen, and Sandra K. Loo

ABSTRACT
Electroencephalography and magnetoencephalography are noninvasive neuroimaging techniques that have been used extensively to study various resting-state and cognitive processes in the brain. The purpose of this review is to highlight a number of recent studies that have investigated the alpha band (8–12 Hz) oscillatory activity present in magnetoencephalography and electroencephalography, to provide new insights into the maladaptive network activity underlying attentional impairments in attention-deficit/hyperactivity disorder (ADHD). Studies reviewed demonstrate that event-related decrease in alpha is attenuated during visual selective attention, primarily in ADHD inattentive type, and is often significantly associated with accuracy and reaction time during task performance. Furthermore, aberrant modulation of alpha activity has been reported across development and may have abnormal or atypical lateralization patterns in ADHD. Modulations in the alpha band thus represent a robust, relatively unexplored putative biomarker of attentional impairment and a strong prospect for future studies aimed at examining underlying neural mechanisms and treatment response among individuals with ADHD. Potential limitations of its use as a diagnostic biomarker and directions for future research are discussed.

Keywords: Alpha, Biomarker, EEG, MEG, Neurophysiology, Spectral power

Over the last decade, cognitive neuroscience has made many gains in understanding the engagement and interactions of multiple brain networks that underlie cognitive processes (1–3). Electroencephalography (EEG) and magnetoencephalography (MEG) are extensively used techniques that capture, on millisecond time scales, brain oscillatory activity present in electrophysiological signals; this allows for the study of cognitive processes via quantification of brain network interactions as they occur, ostensibly in real time (4–7). The object of this review is to highlight recent studies that have used task-related modulations of alpha-band (8–12 Hz) oscillatory activity to offer new insights into maladaptive network activity underlying attentional impairments in attention-deficit/hyperactivity disorder (ADHD). ADHD is one of the most prevalent disorders in childhood, affecting an estimated 5% to 11% of children (8), with longitudinal studies indicating that 30% to 70% of these individuals continue to meet diagnostic criteria into adulthood (9). In addition to highly variable rates of diagnostic persistence and treatment response, the need to further understand the neural mechanisms underlying ADHD is underscored by extremely poor outcomes in adulthood such as frequent psychiatric comorbidity, substance abuse, incarceration, divorce, poor health, and high societal cost [$143–$266 billion annually (10)]. In this review, we suggest that studies of oscillatory activity may address this need. We begin with a historical overview of oscillatory studies in ADHD, then focus on task-related modulations of alpha-band activity, which have emerged more recently as promising indicators of the neurophysiological underpinnings of the cognitive deficits present in ADHD. Finally, we discuss oscillatory power as a potential biomarker in ADHD and consider possible directions, and challenges, for future research.
low accuracy [range: 38% to 63% (22)]. Furthermore, the significant heterogeneity among study results suggests that the grand mean effect size of 0.62 of the TBR in ADHD is misleading and potentially an overestimation of the true effect size (23). While a sufficient number of individuals with ADHD (20% to 30%) have an elevated TBR that drives a significant group effect, the TBR is not a valid discriminator of ADHD diagnosis.

Findings for alpha-band spectral power at rest in ADHD have been mixed and may depend on developmental level, ADHD subtype, and psychiatric comorbidities. Overall, higher levels (21,24–26), no significant differences (27–31), and lower levels (30,32–39) of alpha spectral power between samples with and without ADHD have been reported; however, no clear pattern has emerged according to age or ADHD subtype, the latter of which is not often reported. Recent studies suggest significant heterogeneity in resting-state EEG spectral power characteristics within ADHD (36,40) and at the population level (41) (see Figure 1A). Furthermore, while spectral power is the predominant metric used to reflect alpha-band activity, there are other measures that have been reported such as power density, mean frequency, peak frequency, coherence, and laterality (see Table 1 for summary and definitions). While the plurality of results may reflect poor control over what participants are actually doing during resting state, this also suggests that there may not be a resting-state electrophysiological profile that accurately discriminates between those individuals with and those without ADHD. The purpose of the present review is to suggest that other EEG/MEG signals, and in particular task-related suppression of alpha-band activity, may provide a more fruitful avenue for future research. These effects are more closely tied to specific neural systems and cognitive functions, such as attention and working memory.

**TASK-RELATED MODULATION OF ALPHA POWER**

The observation of a coupling between the power of oscillations in electrophysiological signals and cognitive processing was first reported by Hans Berger (42). He noted 8- to 12-Hz oscillations (alpha) in patients, resting with eyes closed, that disappeared when the eyes were opened, a phenomenon later referred to as alpha blocking. In 1934, Adrian and Matthews (43) reported that while alpha generation is most strongly modulated by visual inputs (and was abolished by blindness), it is also linked with cognitive processing of visual inputs, or attention. For instance, they noted that alpha increased in the presence of light when the participant was not expecting to see a stimulus, and conversely, it is attenuated when the eyes were closed but the subject was mentally searching for something. Based on these findings, alpha oscillations were thought to represent the brain in an idling state (44), a view that has now been replaced by the consensus that alpha oscillations functionally inhibit specific regions, which serves to route information by blocking task-irrelevant pathways (2,45–47). This has been demonstrated in a variety of experiments of attention and working memory, and using a spectrum of methods including MEG, spike-field animal data, concurrent EEG-functional magnetic resonance imaging (fMRI), and neuromodulation. For instance, anticipation of visual targets decreases visual cortex alpha activity, whereas anticipation of visual distractors increases it (48–50). Similarly, alpha-band activity increases with attention and working-memory load to selectively suppress external inputs and task-irrelevant information (51–55). In sum, the picture emerging is that alpha oscillations are associated with top-down executive control in attention and working-memory tasks by selectively inhibiting (when alpha increases) or disinhibiting (when alpha decreases) specific brain regions [i.e., serving a gating function in the visual cortex (46,53,56,57)]. Given that children with ADHD have problems in these domains, it is natural to examine if they also have reduced abilities to modulate their alpha oscillations.

Across several types of attention and working memory tasks (Figure 2A, B), differences between children with and without ADHD have been observed in modulation of alpha-band oscillatory power. For example, within a spatial working memory (SWM) delayed match-to-sample task (Figure 2A), robust ADHD (54) diagnostic group effects were observed.
## Table 1. Alpha-Band Power Findings in ADHD

<table>
<thead>
<tr>
<th>First Author</th>
<th>Year</th>
<th>n (ADHD, Control Groups)</th>
<th>Age Group</th>
<th>Task</th>
<th>Frequency Band (Hz)</th>
<th>Measure</th>
<th>Region</th>
<th>Alpha in ADHD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Resting State</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poil (21)</td>
<td>2014</td>
<td>48, 68</td>
<td>CH, AD</td>
<td>EC</td>
<td>8–13</td>
<td>S(^{a}), MF</td>
<td>F, F/P</td>
<td>CH: higher power; AD: lower MF(^{2})</td>
</tr>
<tr>
<td>Koehler (26)</td>
<td>2009</td>
<td>34, 34</td>
<td>AD</td>
<td>EC</td>
<td>7.5–12.5 Power density</td>
<td>C, P</td>
<td>Higher power density</td>
<td></td>
</tr>
<tr>
<td>Bresnahan (24)</td>
<td>2002</td>
<td>50, 100</td>
<td>AD</td>
<td>EO</td>
<td>8–12</td>
<td>S</td>
<td>P</td>
<td>Higher power</td>
</tr>
<tr>
<td>Chabot (25)</td>
<td>1996</td>
<td>407, 310</td>
<td>CH</td>
<td>EC</td>
<td>8–12</td>
<td>S, coherence(^{c}) MF</td>
<td>F, C</td>
<td>Higher power with 1) normal MF (46%) and 2) lower MF (30%)</td>
</tr>
<tr>
<td>van Dongen-Boomsma (31)</td>
<td>2010</td>
<td>24, 24</td>
<td>AD, EO</td>
<td>EC</td>
<td>8–12</td>
<td>S, PF(^{d})</td>
<td>P</td>
<td>ND in power or PF; greater decrease from EC to EO</td>
</tr>
<tr>
<td>Bresnahan (28)</td>
<td>2006</td>
<td>50, 50</td>
<td>AD</td>
<td>EO</td>
<td>8–12</td>
<td>S</td>
<td>—</td>
<td>ND</td>
</tr>
<tr>
<td>Hermens (29)</td>
<td>2004</td>
<td>36, 36</td>
<td>AD</td>
<td>EC</td>
<td>8–12</td>
<td>S</td>
<td>—</td>
<td>ND</td>
</tr>
<tr>
<td>Bresnahan (27)</td>
<td>1999</td>
<td>75, 75</td>
<td>CH, AD</td>
<td>EO</td>
<td>8–12</td>
<td>S</td>
<td>—</td>
<td>ND</td>
</tr>
<tr>
<td>Pomeron (39)</td>
<td>2014</td>
<td>96, 376</td>
<td>AD, EO</td>
<td>EC</td>
<td>8–12</td>
<td>S, F, C</td>
<td>Lower power</td>
<td></td>
</tr>
<tr>
<td>Wottering (38)</td>
<td>2012</td>
<td>18, 17</td>
<td>AD</td>
<td>EO</td>
<td>8–12</td>
<td>S, F, C, P</td>
<td>Lower power</td>
<td></td>
</tr>
<tr>
<td>Barry (32)</td>
<td>2009</td>
<td>30, 30</td>
<td>CH</td>
<td>EC</td>
<td>8–12</td>
<td>S</td>
<td>—</td>
<td>Global Lower power</td>
</tr>
<tr>
<td>Magee (36)</td>
<td>2005</td>
<td>253, 67</td>
<td>CH</td>
<td>EC</td>
<td>8–12</td>
<td>S, F, P</td>
<td>Lower power</td>
<td></td>
</tr>
<tr>
<td>Clarke (33)</td>
<td>2001</td>
<td>160, 80</td>
<td>CH</td>
<td>EC</td>
<td>8–12</td>
<td>S, P</td>
<td>—</td>
<td>Lower power in boys and older CH, ND in girls and younger CH</td>
</tr>
<tr>
<td>Nazari (37)</td>
<td>2011</td>
<td>16, 16</td>
<td>CH</td>
<td>EO</td>
<td>8–12</td>
<td>S</td>
<td>—</td>
<td>Global Lower power resting, higher power in CPT</td>
</tr>
<tr>
<td>Loo (30)</td>
<td>2010</td>
<td>384, 147</td>
<td>CH, AD</td>
<td>EO, CPT</td>
<td>8–12</td>
<td>S, P</td>
<td>—</td>
<td>Lower power in ADHD-C adults vs. ADHD-I adults and control subjects; ND if CH</td>
</tr>
<tr>
<td>El Sayed (34)</td>
<td>2002</td>
<td>36, 63</td>
<td>AD</td>
<td>EO, CPT</td>
<td>8–12</td>
<td>S</td>
<td>—</td>
<td>Global Lower power all conditions</td>
</tr>
<tr>
<td>Hale (69)</td>
<td>2009</td>
<td>29, 62</td>
<td>AD</td>
<td>EC, CPT</td>
<td>8–10, 10–12</td>
<td>Laterality(^{e})</td>
<td>P</td>
<td>Greater R laterality all conditions</td>
</tr>
<tr>
<td>Baving (149)</td>
<td>1999</td>
<td>47, 70</td>
<td>CH</td>
<td>EO</td>
<td>8–10</td>
<td>Laterality</td>
<td>F</td>
<td>Greater R laterality in boys, L laterality in girls</td>
</tr>
<tr>
<td><strong>Task</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lenartowicz (121)</td>
<td>2016</td>
<td>8, 13</td>
<td>CH</td>
<td>SWM</td>
<td>8–12</td>
<td>ERD/ERI</td>
<td>P</td>
<td>Less ERD</td>
</tr>
<tr>
<td>Hasler (65)</td>
<td>2016</td>
<td>21, 20</td>
<td>AD</td>
<td>Flanker</td>
<td>8–13</td>
<td>ERD/ERI</td>
<td>P</td>
<td>Less ERD to cue/target</td>
</tr>
<tr>
<td>Lenartowicz (54)</td>
<td>2014</td>
<td>52, 47</td>
<td>CH</td>
<td>SWM</td>
<td>8–12</td>
<td>ERD/ERI</td>
<td>P</td>
<td>Less ERD for LL, not for HL</td>
</tr>
<tr>
<td>Mazaheri (59)</td>
<td>2014</td>
<td>34, 23</td>
<td>CH</td>
<td>Cued flanker</td>
<td>8–12</td>
<td>ERD/ERI, CP</td>
<td>P</td>
<td>Less ERD in ADHD-I; weak CP with frontal theta</td>
</tr>
<tr>
<td>Missionnier (66)</td>
<td>2013</td>
<td>15, 15</td>
<td>AD</td>
<td>n-back</td>
<td>9–15</td>
<td>ERD/ERI</td>
<td>F</td>
<td>Less ERD then higher ERI, especially LL vs. HL</td>
</tr>
<tr>
<td>Yordanova (62)</td>
<td>2013</td>
<td>14, 14</td>
<td>CH</td>
<td>EC, auditory selective attention</td>
<td>8–12</td>
<td>ERD/ERI, S, MC</td>
<td>Greater ERD in left MC to nontarget; Resting: ND</td>
<td></td>
</tr>
<tr>
<td>Mazaheri (58)</td>
<td>2010</td>
<td>14, 11</td>
<td>CH</td>
<td>Cued visual attention</td>
<td>8–12</td>
<td>ERD/ERI, CP</td>
<td>P</td>
<td>Less ERD in ADHD; no FP CP</td>
</tr>
<tr>
<td>Gomarou (64)</td>
<td>2009</td>
<td>15, 15, 15, PDD CH</td>
<td>Visual selective memory</td>
<td>8–12</td>
<td>ERD/ERI</td>
<td>P</td>
<td>ND in ERD; ADHD hyperactive-impulsive type only</td>
<td></td>
</tr>
<tr>
<td>Heinrich (63)</td>
<td>2014</td>
<td>24, 19</td>
<td>CH</td>
<td>Flanker</td>
<td>7.5–12.5</td>
<td>S</td>
<td>Greater power on no-cue trials</td>
<td></td>
</tr>
<tr>
<td>Ter Huurne (68)</td>
<td>2017</td>
<td>17, 18</td>
<td>AD</td>
<td>VS attention</td>
<td>8–12</td>
<td>Laterality</td>
<td>MC</td>
<td>MEG; no typical lateralization</td>
</tr>
<tr>
<td>Vollenbregt (61)</td>
<td>2016</td>
<td>30, 30</td>
<td>CH</td>
<td>VS attention</td>
<td>8–12</td>
<td>Laterality</td>
<td>P</td>
<td>MEG; no typical lateralization</td>
</tr>
<tr>
<td>Ter Huurne (67)</td>
<td>2013</td>
<td>17, 18</td>
<td>AD</td>
<td>VS attention</td>
<td>9–12</td>
<td>Laterality</td>
<td>P</td>
<td>MEG; initial laterality not sustained</td>
</tr>
</tbody>
</table>

---

All studies involved electroencephalography results unless noted otherwise.

AD, adult; ADHD, attention-deficit/hyperactivity disorder; ADHD-C, combined-type attention-deficit/hyperactivity disorder; ADHD-I, inattentive-type attention-deficit/hyperactivity disorder; C, central; CH, child; CP, coupling; CPT, continuous performance test; EC, eyes closed; EO, eyes open; ERD, event-related decrease; ERI, event-related increase; F, frontal; FP, frontal-parietal; HL, high load; L, left; LL, low load; MC, motor cortex; MEG, magnetoencephalography; MF, mean frequency; ND, no difference; P, posterior; PDD, pervasive developmental disorder; PF, peak frequency; R, right; S, spectral power; SWM, spatial working memory; VS, visual-spatial.

\(^{a}\)Mean power averaged across the frequency band interval.

\(^{b}\)Frequency at which half the alpha band power lies above and below.

\(^{c}\)Correspondence of alpha phase or magnitude between two channels or regions.

\(^{d}\)Frequency between 8 and 12 Hz with the highest power.

\(^{e}\)Power difference between hemispheres.
during the encoding phase of the task when compared with typically developing control children (Figure 2C). During this encoding phase, control children showed an event-related decrease (ERD) in alpha-band power, consistent with increased attention to and processing of the visual inputs. In children with ADHD, however, the alpha ERD during encoding was attenuated (Cohen’s $d > 0.79$), which occurred primarily at low load rather than at high load, was more prominent among younger children with ADHD (7–10 years of age) versus older children with ADHD (11–14 years of age), and was predictive of task performance. This finding is broadly consistent with reports by Mazaheri et al. (58,59), who, using cross-modal attention and flanker tasks, also found attenuated alpha ERD in ADHD (Figure 2B). The alpha ERD finding was significant after an informative (response preparation) cue but not after a null cue (suggesting a tight coupling to attentional processes) and was associated with reaction time benefit among typically developing children but not among those children with ADHD (59). In visuospatial attention paradigms (60) (Figure 2B), alpha ERD arises as a lateralization effect, in which alpha power decreases over the hemisphere contralateral to the attended visual hemifield relative to alpha power increases over the ipsilateral hemisphere. Using this paradigm, Vollebregt et al. (61) observed that boys with ADHD were unable to modulate lateralized alpha in posterior regions when compared with their typically developing peers (Figure 2D); however, alpha lateralization was not associated to performance in either group. In a study of lateralized activity in the motor cortex, Yordanova et al. (62) reported exaggerated suppression of alpha activity over the sensorimotor cortex (i.e., mu wave) in response to nonattended (distractor) stimuli, potentially an indicator of enhanced processing of distractors and deficient inhibition of motor cortical networks in ADHD. Attenuated lateralization of alpha may be indicative of inappropriate allocation of attention between attended and ignored streams of inputs. Finally, Heinrich et al. (63) reported higher alpha power (which likely represents attenuated alpha ERD) during attention–network task segments without stimulus processing or overt behavior among children with ADHD compared with control children, consistent with poor attentional allocation during the task.

We note that alpha ERD group differences seem to be associated primarily with ADHD inattentive symptoms. Lenartowicz et al. (54) reported a correlation between alpha

Figure 2. Alpha event-related decrease (ERD) is attenuated in attention-deficit/hyperactivity disorder (ADHD) during visual attention. (A) In the spatial working-memory task participants encode the spatial locations of 1 or 3 (low load) or 5 or 7 (high load) dots. Following a maintenance interval, they indicate if the probe dot occurs in the same or different location than any of the stimuli in the encoding stimulus. Reproduced with permission from Lenartowicz (54). (B) Attention of alpha ERD in ADHD was apparent during the 2-s encoding period (relative to prestimulus baseline). This effect was most pronounced at low load among children with ADHD (top left). Alpha ERD plots are calculated from the time-courses of a single occipitally distributed (inset) independent component. Reproduced with permission from Mazaheri et al. (59) in a cued spatial attention task. Attenuation of alpha ERD at electrode Oz in response to cues (cue duration is 1 s) was more pronounced in inattentive-type ADHD than in combined-type ADHD relative to typically developing (TD) control subjects. Reproduced with permission from Mazaheri et al. (59). (C) In the prototypical cued spatial attention task, a cue indicates the most likely location of the upcoming target stimulus (e.g., < indicates left). Following a preparation interval, the target appears on either right or left of the fixation cross (+), requiring participants to indicate on which side the target appeared. In this paradigm, alpha ERD is lateralized, greater in the hemisphere contralateral to the hemifield indicated by the cue (attended, e.g., right) than in the hemisphere ipsilateral to the hemifield indicated by the cue (ignored, e.g., left). The normalized difference can be quantified as a modulation index ($MI$), the difference in alpha power for left minus right attention cues. The expected topography of the MI during the preparation interval is evident in panel (E) for TD boys, a relative decrease in alpha power for contralateral cues (attended) and an increase for ipsilateral cues (ignored). This effect was significantly attenuated in boys with ADHD. Panels (D) and (E) reproduced with permission from Vollebregt et al. (61). ITI, intertrial interval.
Aberrant Brain Oscillations in ADHD

ERD and inattentive symptoms (p = .008), but less so for hyperactive symptoms (p = .08). In the Mazaheri et al. (59) study, alpha ERD was attenuated among adolescents with inattentive-type ADHD but not with combined-type ADHD (see Figure 2E). Similarly, alpha ERD deficits were not observed by Gomaras et al. (64) during a visual selective-memory task in which the ADHD sample was characterized primarily by hyperactive-impulsive behaviors. Overall, alpha ERD is attenuated primarily in inattentive-type ADHD, consistent with ineffective selective attention to visual inputs, and is often associated with poorer task performance (accuracy, reaction time, or reaction time variability).

Aberrant alpha modulation has also been consistently observed in studies examining adults with ADHD during attentional tasks. While performing a flanker task, posterior alpha ERD was significantly attenuated among adults with ADHD during visuospatial orienting (65). During stimulus processing in an n-back working-memory task, adults with ADHD exhibited reduced alpha ERD in frontal channels relative to control adults. Attenuated alpha ERD was particularly pronounced during the low-load condition versus the high-load condition (66), an interaction that was also present in the SWM study with children (cf. Figure 2C) (54). This suggests that aberrant alpha modulation may interact with sluggish recruitment of attention or maintenance of vigilance, which is more difficult in easier task conditions. Finally, MEG studies have found that adults with ADHD also have difficulty sustaining posterior hemispheric alpha lateralization during visuospatial attention (cf. Figure 2B) in the period between the cue and target, particularly when attending to the left visual hemifield (67). A follow-up study revealed a similar deficit in alpha power observed over sensorimotor cortex (i.e., mu wave) (68). Coupled with behavioral performance results, the authors suggested that adults with ADHD have an attention bias to the right visual field, which has been linked to not only ADHD severity but also other ADHD risk factors such as gender, handedness, and genetic factors (69). Collectively, adult ADHD studies are consistent with effects observed in children and support the notion of continued deficits in the ability to modulate alpha power across development, with a potential rightward bias in alpha power.

NEURAL MECHANISMS UNDERLYING ALPHA OSCILLATORY ACTIVITY

A mechanistic understanding of alpha oscillations has clear implications for the neural circuitry underlying deficient attention control in ADHD. Seminal in vivo (70,71) and in vitro (72–74) experiments of thalamic alpha, and studies of occipital alpha (75–77) in the dog, have identified a circuit between excitatory thalamocortical cells and inhibitory reticular neurons that generates alpha oscillations in thalamocortical neurons via a feedback loop between excitation and inhibition (78,79). These studies were initially interpreted as supporting the hypothesis that alpha oscillations were indicative of the brain in an idling state (80). This is because the thalamic generator of alpha is dependent on decreasing arousal (79,81,82), whereby ascending cholinergic projections “deinactivate” (i.e., inactivation gate reopens and activation gate closes) low-threshold Ca\(^{2+}\) channels, which reduces the reactivity of cortex to inputs (83–85). And while alpha oscillations are typically strongest over the occipital cortex, they are also detectable in the sensorimotor (the mu wave) and temporal (the tau wave) cortices (86–89), supporting a general mechanism by which sensory processing is gated by the thalamus. Hence, core thalamocortical interactions may play an important role in the aberrant alpha patterns observed in ADHD at rest. It is noteworthy that the dependence of thalamic generators of alpha on decreasing arousal is reminiscent of and consistent with energetic (low-arousal) models of ADHD etiology (90). However, given a lack of consistency in group differences in alpha during rest, further research is warranted to establish if links exist among alpha-generating thalamocortical interactions, alpha at rest, and ADHD diagnosis.

In addition to the thalamocortical mechanisms, the modulation of alpha during task is thought to represent frontoparietal interactions biasing activity in occipital cortex in line with attentional goals. This idea is supported by 1) recordings in (primarily) the primate occipital cortex of alpha generators in deep layers (which receive inputs from cortical regions other than thalamus) (91–93); 2) intracranial and MEG recordings, and Granger causality modeling showing that alpha-range (and beta-range) oscillations carry feedback information from higher-order association areas (in contrast to >30-Hz gamma oscillations, most prominent in superficial layers and carrying feedforward information) (94–99); and 3) disruption of frontal/parietal activities by transcranial magnetic stimulation that compromises performance and alpha modulation during visual attention (83,100–102). Attenuated alpha ERD in ADHD is therefore a likely indicator of weakened attention control and, given prior association of frontoparietal circuitry with alpha power (103–106), it predicts weakened interactions between the frontoparietal network and occipital cortex during tasks. Consistent with this prediction, alpha ERD impairments do not appear to indicate an impairment with basic sensory processing, as alpha ERD is independent of perceptual processing (53); it can occur before (101,107,108) or after (109) the stimulus, and can be absent during a stimulus when no postperceptual processing is required (110).

It is an outstanding question whether thalamus (111) or frontoparietal interactions via either the thalamus and/or the superior longitudinal fasciculus (112) (Figure 3A) are critical in generating the aberrant alpha patterns in ADHD. A thalamic impairment can certainly account for ineffective frontoparietal activities (e.g., contributing to poor alpha ERD) because the thalamus (in particular the pulvinar nuclei) displays attentional modulation signals and has been shown to drive alpha synchrony in the primate occipital cortex during attentional selection (113,114). Thus, it may be a mediating structure for frontoparietal top-down control. In turn, the relationship between thalamic generators of alpha and ascending cholinergic projections (79,81,82) implies that faulty arousal regulation could impact both thalamic and frontoparietal activities. It is noteworthy that these alternatives are analogous with (i.e., capture the same circuits as) existing multipathway models of ADHD [e.g., (115)]. Further research into the mechanisms of alpha generation versus modulation will be imperative in distinguishing the critical pathways behind both alpha (and related behavioral) deficits in ADHD, and thereby informing
existing models. Increasingly promising are multimodal approaches such as concurrent EEG-fMRI, which has been fruitful in noninvasively confirming the associations between alpha power and thalamic, occipital, and frontoparietal activities (103–106,116–122). Extensions of such approaches to map the functional connectivity of alpha in ADHD (121,123) may prove particularly revealing. Indeed, a recent study used concurrent EEG-fMRI recordings during SWM (Figure 2A) in a small sample of adolescent boys with and without ADHD (n = 30, 15 with ADHD [121]). Overall, alpha ERD during SWM encoding was associated with occipital activation and fronto-parieto-occipital functional connectivity (Figure 3B), with the latter predicting ADHD symptoms and response variability. The degree to which these two substrates were recruited differed by diagnosis, with greater occipital activation in control subjects and greater fronto-parietal-occipital connectivity in participants with ADHD. The finding is consistent with the pattern of results in the larger EEG-only sample (54), namely that ADHD participants had to work harder (through recruitment of executive function frontoparietal mechanisms) to compensate for a poor visual attention response.

OSCILLATIONS AS BIOMARKERS OF ADHD

Can measures of alpha oscillations serve as a biomarker of ADHD? Given the large effect sizes of group differences in alpha modulation, and clearly defined mechanistic targets, it seems the answer ought to be yes. However, large effect sizes are not sufficient to define a biomarker, which additionally needs to show reliability as well as both sensitivity (ability to detect the disorder) and specificity (ability to discriminate between disorders). Less commonly reported alpha measures such as lateralization, coherence, and mean/peak frequency have not been well studied with respect to reliability; however, several previous studies indicate high within-subject reliability of alpha ERD. Neuper et al. (124) (n = 29, 18–45 years of age) reported a Cronbach’s α > .85 and r27 > 0.7 test-retest reliability of alpha ERD (up to 107 days apart) during numerical
processing. Similar results were reported for resting-state alpha power by Tenke et al. (125) (n = 39 adults, 18–65 years of age), test–retest reliability was 0.84, recorded 5 to 16 days apart; and in McEvoy et al. (126) (n = 20 adults, 18–29 years of age), test–retest correlation was >0.8 in a psychomotor vigilance task and >0.9 in a Sternberg working-memory task, recorded 7 days apart. Impressively, Næpflin et al. evaluated both resting-state alpha (127) and alpha ERD in a modified Sternberg working-memory task (128) in test–retest sessions 12 to 40 months apart (n = 55, 19–79 years of age). They were able to predict whether the oscillatory metrics came from within the same subject or from different subjects, with a sensitivity over 87% and a specificity over 99%. Thus, we cautiously conclude that alpha ERD is a reliable signature within individuals, an important property for a biomarker, though it is notable that all of these studies were performed in adults and may not generalize to children.

However, the sensitivity and specificity of alpha ERD are questionable, and we suggest that alpha ERD, like its TBR predecessor, is not likely to provide a reliable biomarker of ADHD diagnosis. The reason for this conclusion lies in the clinical (129), mechanistic (130,131), and etiologic (132) heterogeneity of the disorder, which likely degrades the reliability of putative biomarkers of ADHD. For example, the ADHD-200 Global Competition, which challenged scientists to develop diagnostic group classifiers for ADHD based on over 700 MRI datasets, had accuracy rates ranging from 43% to 62% (mean 56%), with the highest prediction accuracy of 62.5% coming from a prediction model that did not include any imaging data at all (133).

Several EEG/event-related potential studies have had more success using multivariate EEG profiles (~90%, e.g., (134–136)), but the high-accuracy results require further validation because of potential statistical model overfitting. This is because of either small sample size precluding the ability to split the data into independent training and testing sets (n < 22 per group) (134,135,137,138), or the common practice of selecting classification features from the same dataset that is subsequently used for the classification (i.e., artificially inflating diagnostic classification accuracy) (139). For instance, in two large-sample EEG studies, Mueller et al. (140) reported diagnostic classification accuracy of 92% (n = 150), and Tenev et al. (141) reported an accuracy of 82% (n = 112), but in both cases the features used for the classification were those that were most discriminant in the sample, thus creating circularity in the analysis [critique also applies to the findings of Hammer et al. (142), who cited 92.5% classification based on fMRI data]. Notably, in an independent validation sample of 17 adults, Mueller et al. (136) reported an impressive accuracy of 94%, yet because the validation sample contained only individuals with ADHD, it is impossible to assess whether the classifier was inaccurately labeling all new data as ADHD (i.e., specificity). Moreover, across the studies, there is a lack of consistency in the features that are most effective in diagnostic classification [i.e., in EEG studies: TBR, absolute or relative power within various frequency bands, fractal measures, and event-related potential components (22)]. We may therefore conclude that past classification efforts, including those using TBR, have not yielded reliable diagnostic classification results, a finding that is not surprising if we consider the distribution overlap in EEG features across groups (e.g., Figure 1B for alpha ERD).

It may be a more useful exercise to consider the prognostic utility of alpha oscillatory effects as a biomarker of a cognitive process (and associated neural circuits), developmental outcomes, or treatment response rather than diagnosis. As noted previously, attenuated alpha ERD was associated with inattentive symptoms (54) and subtype of ADHD (58,143) and much less so with the combined-type ADHD (64,143). Moreover, stronger alpha ERD is predictive of better task performance both in studies of ADHD (54,143) and otherwise, with alpha power predicting success of visual discrimination (108), errors on no-go trials (144), and successful inhibition of distractor items during working memory (145). Alpha oscillations may therefore be considered a putative predictor of visual attention processes and related behavioral outcomes. In the context of ADHD, this may translate into prediction of inattentive symptoms and how they may change with development or in response to treatment. The practical significance lies in the strong relationship between attention processes and real-life outcomes. We know that working-memory deficits can have significant effects on academic achievement, educational attainment (repeating a grade, special education classes, learning disabilities) and IQ (146), which contribute significantly to occupational, academic, and social functioning in adulthood. Furthermore, the demonstrated population-level heterogeneity in alpha-band activity (40,41) may be framed as a potential advantage of EEG-based measures if it reveals neurophysiologically distinct clusters. If so, alpha suppression may potentially be used as not only a measure of treatment response but also a predictor of which treatment may be effective for a given individual.

**CONCLUSIONS, CHALLENGES, AND FUTURE DIRECTIONS**

EEG and MEG oscillatory activity have long been used to quantify neural mechanisms and network interactions underlying cognitive processes such as attention. Alpha ERD appears to be a robust, yet relatively unexplored putative biomarker of attentional impairment in ADHD that subsequently impacts performance on working memory and other executive function tasks. Despite its potential utility, there remain a number of challenges in the interpretation of alpha that need to be addressed. First, the group differences in alpha ERD that we have described require replication in larger samples, under identical task conditions. For instance, while attenuation of alpha suppression during SWM encoding and attenuation of alpha lateralization in ADHD are hypothesized to stem from similar mechanisms, a study comparing the paradigms (and alpha measures) within the same population would be instructive. Similarly, while most group differences have been reported over occipital electrodes and/or the occipital cortex (Table 1), some group effects have also been reported over frontal electrodes and/or over the sensorimotor cortex. It is not currently known if these alpha measures in various regions represent different or overlapping mechanisms. Moreover, effects of prestimulus alpha on group differences in alpha modulation have not been systematically considered and likely introduce another source of variability [e.g., prestimulus alpha differences were present in Heinrich et al. (63) but not Lenartowicz et al. (54)]. Finally, it is not clear if alpha
suppression deficit reflects a fundamental dysfunction in associated circuitry or if this is a downstream effect (e.g., a problem with arousal).

In addition, more work is needed to address clinical correlates associated with alpha ERD. In terms of inattention symptoms, it would be important to understand whether alpha ERD indexes specific types of inattention, such as distractibility, a lack of vigilance, or daydreaming. More specificity with respect to which inattention symptoms are represented by alpha ERD may support its use as a biomarker of treatment response or developmental outcomes. Such specificity would also be instructive in interpreting deficits in alpha modulation in other disorders [e.g., alpha suppression impairment occurs during working memory in patients with schizophrenia (147) and in a visual attention task among patients with autism (148)]. Finally, further research is critical to ascertain whether alpha ERD is indeed predictive of clinical features typically associated with working-memory deficits. If so, the association could potentially reveal shared neural mechanisms underlying inattention and academic achievement or identify risk for highly comorbid diagnoses such as learning disability among children with ADHD. Remaining challenges notwithstanding, the promising research findings described herein suggest that alpha ERD is a strong prospect for future studies aimed at examining underlying neural mechanisms and putative biomarkers of ADHD.

ACKNOWLEDGMENTS AND DISCLOSURES
This work was supported by National Institutes of Health Grant Nos. MH101282 and NS071484 (to SKL) and the James S. McDonnell Foundation Understanding Human Cognition Collaborative Award Grant No. 2200200448 (to OJ).

The authors report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION
From the Semel Institute for Neuroscience and Human Behavior (AL, SKL), David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, California; and the Center for Human Brain Health (AM, OJ), University of Birmingham, Birmingham, United Kingdom.

Address correspondence to Sandra K. Loo, Ph.D., UCLA Department of Psychiatry & Biobehavioral Sciences, 760 Westwood Plaza, A7–456, Los Angeles, CA 90095; E-mail: sloo@mednet.ucla.edu.

Received Jun 24, 2017; revised Sep 13, 2017; accepted Sep 14, 2017.

REFERENCES
Aberrant Brain Oscillations in ADHD


61. Hasler R, Perroud N, Meziane HB, Herrmann F, Prada P, Giannakopoulos P, Deiber MP (2016): Attention-related EEG markers in adult ADHD. Neuropsychologia 87:120–133.


67. Hasler R, Perroud N, Meziane HB, Herrmann F, Prada P, Giannakopoulos P, Deiber MP (2016): Attention-related EEG markers in adult ADHD. Neuropsychologia 87:120–133.


Aberrant Brain Oscillations in ADHD


