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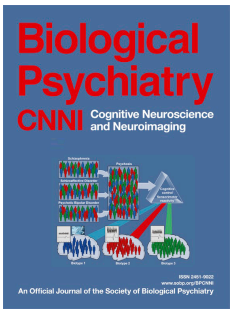

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ABERRANT MODULATION OF BRAIN OSCILLATORY ACTIVITY AND ATTENTIONAL IMPAIRMENT IN ADHD

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Abstract

Electroencephalography (EEG) and magnetoencephalography (MEG) are non-invasive 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 MEG and EEG, 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. Modulations in the alpha band thus represent a robust, relatively unexplored putative biomarker of attentional impairment in ADHD, 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.

Over the last decade, cognitive neuroscience has made much gain 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 5-11% of children (8), with longitudinal studies indicating that 30-70% of 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 co-morbidity, substance abuse, incarceration, divorce, poor health, and high societal cost ($143-$266B 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 modulation 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.

Resting State EEG and ADHD. There is a long history of EEG studies in ADHD, with the first study of resting state brain oscillations in children with behavioral problems consistent with ADHD reported in 1938 by Jasper et al (11). The earliest observations were described as frontocentral "slowing" in the EEG of affected children (11), which means an increase in the power expressed within slower frequency oscillations (theta band, 4-7 Hertz [Hz]) over frontal and central scalp (12, 13). This led to a sustained (40-years and counting!) focus of research on elevated theta power ("slowing" of brain activity) and diminished power in "faster" frequencies (i.e., beta band, 13-25 Hz), as well as the corresponding ratio of theta- to beta-band power, also known as the theta to beta ratio

(TBR) (14). Efforts to validate the TBR as a biomarker of ADHD diagnosis seemed promising until fairly recently (pre-2010). Previous research studies and meta-analysis of the TBR reported high accuracy (89%; 15, 16) and large effect size (ES=3.1; 13) for ADHD diagnosis. However, recent independent replication studies and meta-analysis (17-21) reported low accuracy (range: 38 to 63%; 22) and significant heterogeneity among study results, suggesting that even though the overall ES of 0.62 is significant for ADHD diagnosis, it is misleading and potentially an overestimation of the true ES (23). While a sufficient number of individuals with ADHD (20-30%) have elevated TBR, which 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 Fig. 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 with and without ADHD. The purpose of the present paper 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 to cognitive functions, such as attention and working memory.

Insert Figure 1 & Table 1 here

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 8-12 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 & 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-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 type tasks (Fig. 2ab), differences between children with ADHD and controls have been observed in modulation of alpha band oscillatory power. For example, within a spatial working memory (SWM) delayed match-to-sample task (Fig. 2a), robust ADHD (54) diagnostic group effects were observed during the encoding phase of the task when compared to typically developing (TD) controls (Fig. 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 high load, was more prominent among younger children (7-10 years) versus older children (11-

14 years) with ADHD, 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 (Fig 2e). 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 TD children but not those with ADHD (59). In visuospatial attention paradigms (60) (Fig. 2b), alpha ERD arises as a lateralization effect, where 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 to typically developing peers (Fig. 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 sensorimotor cortex (i.e., mu wave) in response to non-attended (distractor) stimuli, potentially an indicator of enhanced processing of distractors and deficient inhibition of motor cortical networks. Attenuated lateralization of alpha may be indicative of inappropriate allocation of attention between attended and ignored streams of inputs. Finally, Heinrich (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 to controls, 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 ERD and inattentive symptoms ($p=0.008$), but less so for hyperactive symptoms ($p=0.08$). In the Mazaheri et al (59) study, alpha ERD was attenuated among adolescents with Inattentive Type but not with Combined Type ADHD (see Fig. 2e). Similarly, alpha ERD deficits were not observed by Gomarus et al (64) during a visual selective memory task where the ADHD sample was characterized primarily by hyperactive-impulsive behaviors. Overall, alpha ERD is attenuated primarily in ADHD inattentive type, consistent with ineffective selective attention to visual inputs, and is often associated with poorer task performance (accuracy, reaction time or reaction time variability).

Insert Figure 2 here

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 a N-back working memory task, adults with ADHD exhibited reduced alpha ERD in frontal channels relative to controls. Attenuated alpha ERD was particularly pronounced during the low versus high load condition (66), an interaction that was also present in the SWM study with children (c.f., Fig. 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 (c.f., Fig 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 not only to 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 occipital cortex, they are also detectable in sensorimotor (the "mu" wave) and temporal cortices (the "tau" wave) (86-89), supporting a general mechanism by which sensory processing is gated by the thalamus. Hence, core thalamo-cortical 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 between alpha-generating thalamo-cortical interactions, alpha at rest and ADHD diagnosis.

In addition to the thalamo-cortical mechanisms, the modulation of alpha during task is thought to represent fronto-parietal interactions biasing activity in occipital cortex in line with attentional goals. This idea is supported by: (a) recordings in (primarily) primate occipital cortex of alpha generators in deep layers (which receive inputs from cortical regions other than thalamus) (91-93); (b) intracranial and MEG recordings, and Granger causality modeling showing that alpha (and beta) range oscillations carry feedback information from higher-order association areas (in contrast to >30Hz gamma oscillations, most prominent in superficial layers and carrying feedforward information) (94-99); and (c) 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 fronto-parietal circuitry with alpha power (103-106), it predicts weakened interactions between the fronto-parietal 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 post-perceptual processing is required (110).

Insert Figure 3 here

It is an outstanding question whether thalamus (111) or fronto-parietal interactions via either

the thalamus and/or the superior longitudinal fasciculus (112) (Fig. 3a), are critical in generating the aberrant alpha patterns in ADHD. A thalamic impairment can certainly account for ineffective fronto-parietal 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 primate occipital cortex during attentional selection (113, 114). It may thus be a mediating structure for fronto-parietal 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 fronto-parietal activities. It is noteworthy that these alternatives are analogous with (i.e., capture the same circuits as) existing multi-pathway 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 non-invasively confirming the associations between alpha power and thalamic, occipital and fronto-parietal activities (103-106, 116-122). Extensions of such approaches to map the functional connectivity of alpha in ADHD (123, 124) may prove particularly revealing. Indeed, a recent study used concurrent EEG-fMRI recordings during SWM (Fig. 2a) in a small sample of adolescent boys with and without ADHD (N=30, 15 ADHD; 121). Overall, alpha ERD during SWM encoding was associated with occipital activation and fronto-parieto-occipital functional connectivity (Fig. 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 controls and greater fronto-parieto-occipital connectivity in 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 fronto-parietal 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 (125) (n=29, 18-45 years) reported a *Cronbach's alpha*>0.85 and $r(27)>0.7$ test-retest reliability of alpha ERD (up to 107 days apart) during numerical processing (125). Similar results were reported for resting state alpha power by Tenke et al (126), in 39 adults (18-65 years), test-retest reliability of 0.84 recorded 5-16 days apart, and by McEvoy et al (127) (n=20, 18-29 years), test-retest correlation >0.8 in psychomotor vigilance task and >0.9 in a Sternberg working memory task, recorded 7 days apart. Impressively, Näpflin, Wildi and Sarnthein evaluated both resting state alpha (128) and alpha ERD in a modified Sternberg working-memory task (129) in test-retest sessions 12-40 months apart (n=55, 19-79 years). They were able to predict if the oscillatory metrics came from within the same subject or from different subjects with a sensitivity over 87% and specificity over 99%. Thus, we cautiously conclude that alpha ERD is a reliable signature within individual, 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 theta-beta ratio predecessor, is not likely to provide a reliable biomarker of ADHD diagnosis. The reason for this conclusion lies in the clinical (130), mechanistic (131, 132), and etiologic (133) heterogeneity of the disorder, which likely degrades the reliability of putative biomarkers of ADHD. For example, the ADHD 200 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 (134).

Several EEG/ERP studies have had more success using multivariate EEG profiles, (~90%, e.g., 135, 136, 137) but the high accuracy results require further validation because of potential statistical model overfitting. This is because of either small sample size precluding ability to split the data into independent training and testing sets (N < 22 per group; 135, 136, 138, 139), 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) (140). For instance, in two large-sample EEG studies, Mueller et al (141) reported diagnostic classification accuracy of 92% (n=150), and Tenev et al (142) 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 (143) who cited 92.5% classification based on fMRI data). Notably, in an independent validation sample of 17 adults, Mueller et al (137) reported an impressive accuracy of 94%, yet because the validation sample was comprised of 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 theta-beta ratio, 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., Fig. 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, 144) and much less so with the ADHD combined subtype (64, 144). Moreover, stronger alpha ERD is predictive of better task performance both in studies of ADHD (54, 144) and otherwise, with alpha power predicting success of visual discrimination (108), errors on no-go trials (145) and successful inhibition of distractor items during working memory (146). 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 (147), 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 not only as 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 (in ADHD) putative biomarker of attentional impairment that subsequently impacts performance on WM 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/cortex (Table 1), some group effects have also been reported over frontal electrodes and/or over sensorimotor cortex. It is not currently known if these alpha measures in various regions represent different or overlapping mechanisms. Moreover, effects of pre-stimulus alpha on group differences in alpha modulation have not been systematically considered and likely introduce another source of variability (e.g., pre-stimulus alpha differences were present in (63) but not (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 during working memory in patients with schizophrenia (148) and, in a visual attention task among those with autism (149). 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 co-morbid 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.

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Table 1. Alpha band power findings in ADHD

First Author	Year	N (ADHD, Con)	Age Grp	Task	Frequency band (Hz)	Measure	Region	Alpha in ADHD
Resting State								
Poil (20)	2014	48, 68	CH, AD	EC	8-13	S, MF	F, F/P	CH: higher pow; AD: lower MF
Koehler (25)	2009	34, 34	AD	EC	7.5-12.5	PD	C, P	Higher PD
Bresnahan (23)	2002	50, 100	AD	EO	8-12	S	P	Higher pow
Chabot (24)	1996	407, 310	CH	EC	8-12	S, Coh, MF	F, C	Higher pow w/ 1. normal MF (46%), 2. lower MF (30%)
van Dongen-Boomsma (30)	2010	24, 24	AD	EO, EC	8-12	S, PF	P	ND in pow or PF. Greater decrease from EC to EO.
Bresnahan (27)	2006	50, 50	AD	EO	8-12	S	--	ND
Hermens (28)	2004	36, 36	AD	EC	8-12	S	--	ND
Bresnahan (26)	1999	75, 75	CH, AD	EO	8-12	S	--	ND
Pomoerov (38)	2014	96, 376	AD	EO, EC	8-12	S	F, C	Lower pow
Woltering (37)	2012	18, 17	AD	EO, EC	8-12	S	F, C, P	Lower pow
Barry (31)	2009	30, 30	CH	EC	8-12	S	G	Lower pow
Magee (35)	2005	253, 67	CH	EC	8-12	S	F, P	Lower pow
Clarke (32)	2001	160, 80	CH	EC	8-12	S	P	Low pow in boys and older CH, ND is girls and younger CH
Nazari (36)	2011	16, 16	CH	EO, CPT	8-12	S	G	Lower pow resting, higher pow CPT
Loo (29)	2010	384, 147	CH, AD	EO, EC, CPT	8-12	S	P	Lower pow in adults ADHD-C vs ADHD-I & Cons. CH: ND
Loo (34)	2009	38, 42	AD	EO,EC, CPT	8-12	S	F,P	Lower pow all conditions
El Sayed (33)	2002	36, 63	CH	EO, CPT	8-12.5	S	G	Lower pow all conditions
Hale (68)	2009	29, 62	AD	EC, CPT	8-10, 10-12	Lat	P	Greater R lat all conditions
Baving (150)	1999	47, 70	CH	EO	8-10	Lat	F	Greater R lat-boys, L lat-girls
Task								
Lenartowicz (53)	2016	8, 13	CH	SWM	8-12	ERD/ERI	P	Less ERD
Hasler (64)	2016	21, 20	AD	Flanker	8-13	ERD/ERI	P	Less ERD to cue/target
Lenartowicz (120)	2014	52, 47	CH	SWM	8-12	ERD/ERI	P	Less ERD for LL, not HL
Mazaheri (58)	2014	34, 23	CH	Cued flanker	8-12	ERD/ERI, CP	P	Less ERD in ADHD-I; weak CP with frontal TH
Missonnier (65)	2013	15, 15	AD	N-back	9-15	ERD/ERI	F	Less ERD then higher ERI, esp LL vs HL
Yordanova (61)	2013	14, 14	CH	EC, aud sel attn	8-12	ERD/ERI, S	MC	Greater ERD in left MC to non-target; Resting: ND
Mazaheri (57)	2010	14, 11	CH	Cued vis attn	8-12	ERD/ERI, CP	P	Less ERD in ADHD; no FP CP
Gomarus (63)	2009	15, 15, 15 PDD	CH	Vis sel mem	8-12	ERD/ERI	P	ND in ERD; ADHD is Hyp/Imp type
Heinrich (62)	2014	24, 19	CH	Flanker	7.5-12.5	S	P	Higher pow on no cue

								trials
ter Huurne (67)	2017	17, 18	AD	VS attn	8-12	Lat	MC	MEG. No typical lateralization
Vollebregt (60)	2016	30, 30	CH	VS attn	8-12	Lat	P	MEG. No typical lateralization
ter Huurne (66)	2013	17, 18	AD	VS atten	9-12	Lat	P	MEG. Initial lat not sustained

Note. All studies are EEG results unless noted. ADHD=Attention-deficit hyperactivity disorder; ADHD-I=Inattentive; ADHD-C=Combined; Hyp/Imp=Hyperactive/ Impulsive; Con=control; Grp=group; Hz=hertz; CH=child; AD=adult; EC=eyes closed; EO=eyes open; CPT=continuous performance test; SWM=spatial working memory; Aud=auditory; Vis=visual; VS=visual-spatial; sel=selective; attn=attention; S=spectrum (power); MF=mean frequency i.e., frequency above and below which half the alpha band power lies); PD=power density; Coh=coherence (i.e., correspondence of alpha phase or magnitude between two channels or regions); PF=peak frequency (i.e., frequency between 8-12 Hz with the highest power); Lat=laterality (i.e., power difference between hemispheres); ERD=event related decrease; ERI=event related increase; CP=coupling; F=Frontal; C=Central; P=Posterior; MC=motor cortex; G=Global; Pow=power; ND=No difference; R=right; L=left; LL=low load; HL=high load, TH=theta; MEG=Magnetoencephalography

Figure legends

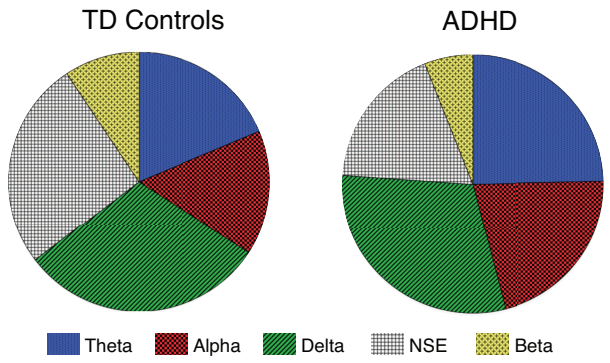
Figure 1. Heterogeneity within and between groups limits potential of existing EEG metrics as biomarkers of ADHD. (A) Population-level EEG heterogeneity is evident in the presence of five clusters within both ADHD and typically developing (TD) control groups. Each cluster is defined by elevations in oscillatory power within a frequency band (delta 1-3 Hertz [Hz] theta, 4-7 Hz, alpha 8-12 Hz, beta 13-20 Hz) and no spectral elevation [NSE]). There is no cluster or spectral power profile characteristic of either ADHD or TD group, suggesting resting EEG spectral power measures are insufficient to serve as a biomarker of ADHD. Figure reproduced with permission from (41). (B) The distribution of alpha ERD during the encoding interval in Fig. 2c. The image illustrates that ADHD and TD controls, despite a significant difference in group mean, have largely overlapping distributions of alpha ERD. These data, argue for the unsuitability of a single EEG metric as a diagnostic biomarker of ADHD.

Figure 2. Alpha ERD is attenuated in ADHD during visual attention. In the spatial working memory task (A) participants encode the spatial location 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. Attenuation of alpha event-related decrease (ERD) in ADHD was apparent during the 2-sec encoding period (C) (relative to pre-stimulus 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. Figure reproduced with permission from (54). (E) A similar result was reported by 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 ADHD Inattentive Type than ADHD Combined Type (left panel), relative to TD controls. Figure reproduced with permission from (59). In the prototypical cued spatial attention task (B), a cue indicates the most likely location of the upcoming target stimulus (e.g., left). Following a preparation interval, the target appears either on

right or left, 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 (D) for typically developing (TD) boys, a relative decrease in alpha power for contralateral cues (attended) and increase for ipsilateral cues (ignored). This effect was significantly attenuated in boys with ADHD. Figure reproduced with permission from (61). In both (A) and (B), ITI is intertrial interval.

Figure 3. Candidate neural mechanisms of alpha modulation include thalamo-occipital and fronto-parietal interactions. (A) Modulation of alpha in occipital cortex is likely the result of one of three pathways: bidirectional interactions between occipital cortex and thalamus (Direct Thalamic Pathways), or fronto-parietal interactions exerting top-down influence over occipital activities either via thalamus (Thalamus-Mediated Pathway) or directly (Direct Prefrontal Pathway) via the superior longitudinal fasiculus. (B) Results from a small (n=21) concurrent EEG-fMRI study (121) indicates that alpha ERD in the encoding phase of a spatial working memory trial (c.f., Fig. 2ac) is correlated with both increases in occipital cortex activation and strengthening of functional connectivity between occipital cortex and fronto-parietal regions that include frontal pole, inferior frontal gyrus, post-central sulcus, and, in posterior cortex, intraparietal sulcus and lateral/superior occipital regions. The connectivity also included thalamus (not shown). The data thus support the thalamus-mediated and direct frontal models. Overlays in this image are regression parameters, with threshold at $z>2.0$, $p<0.05$ (whole-brain corrected for multiple comparisons using Gaussian random field theory) and mapped to the PALS atlas of human cortex, PFC=prefrontal cortex, PPC=posterior parietal cortex, Th=thalamus, Occ=occipital cortex, iPS=intraparietal sulcus, iFG=inferior frontal gyrus, FP=frontal pole, FEF=frontal eye fields, SLF=superior longitudinal fasiculus.

A)



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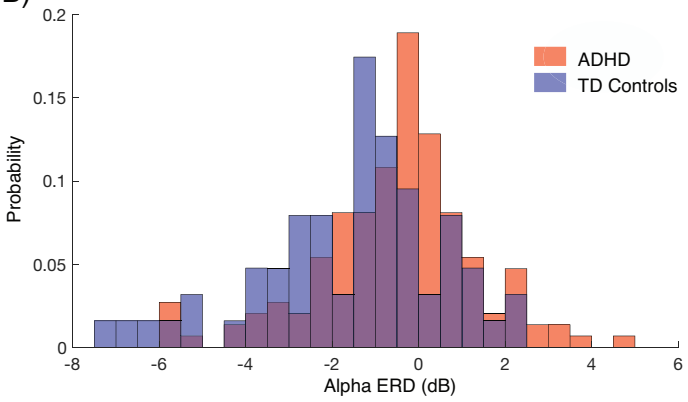
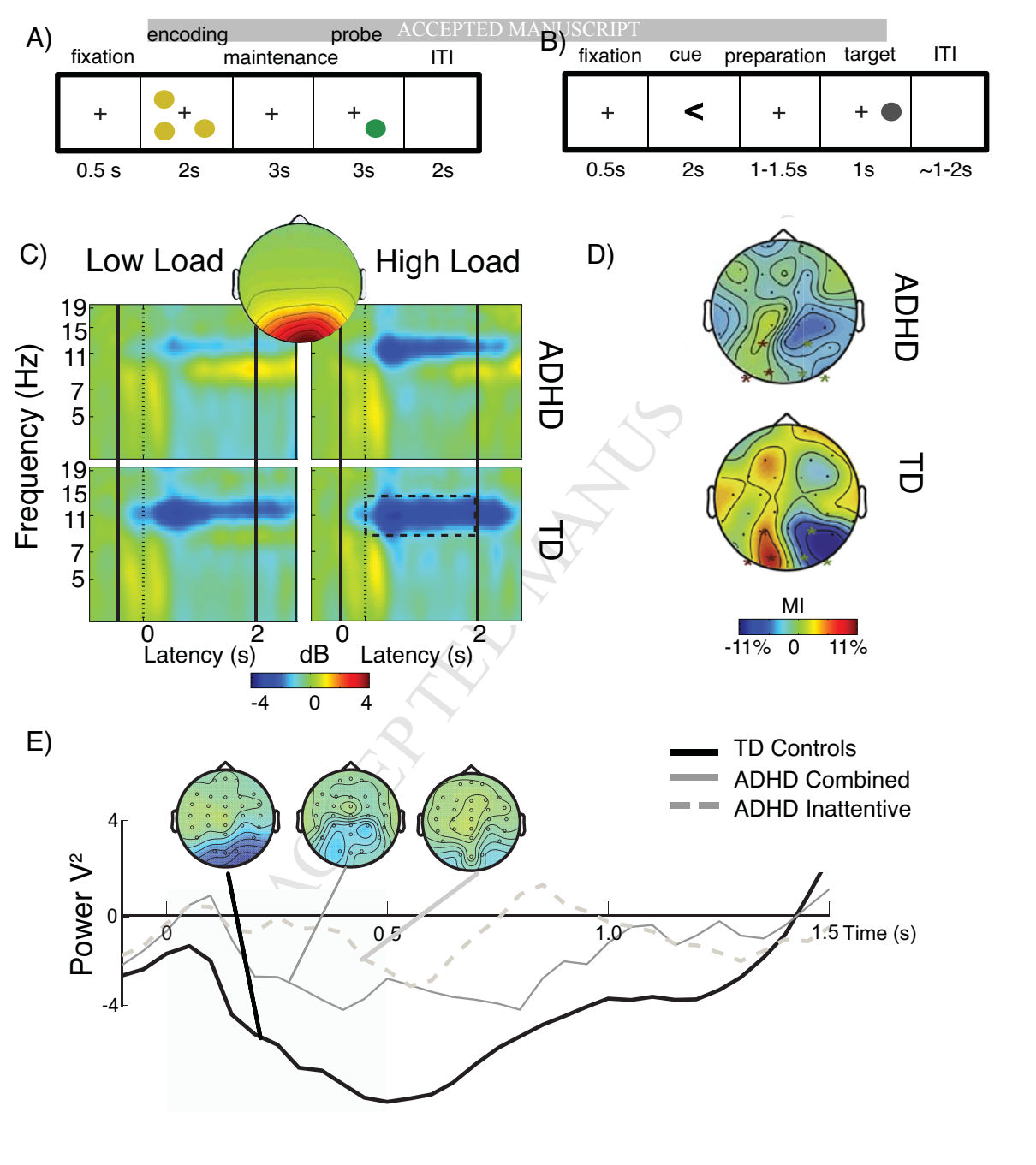
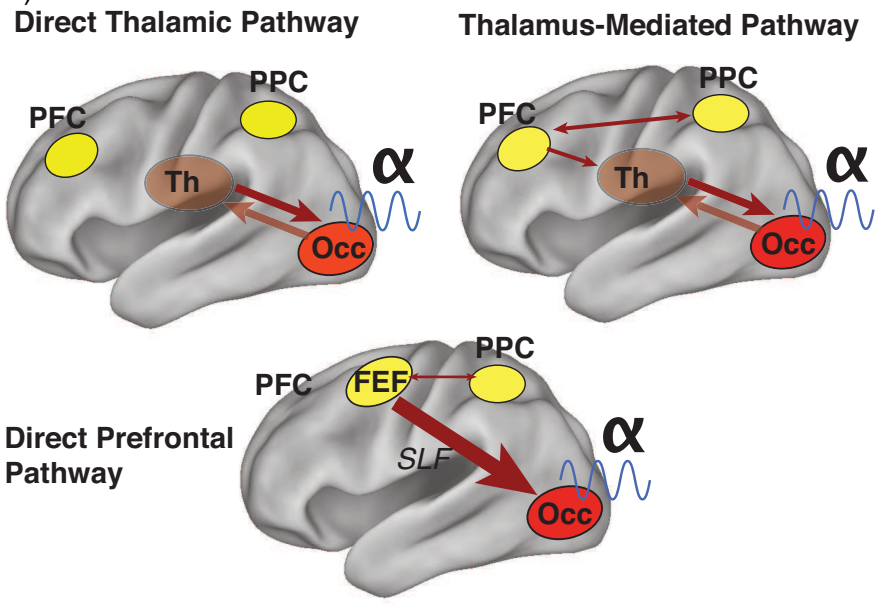




Models of Alpha Modulation

A)



B) Neural Correlates of Alpha ERD