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Is the Theta/Beta EEG Marker for ADHD Inherently Flawed?

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Abstract

Objective: Despite advances in our understanding of ADHD as a neurodevelopmental disorder, robust biomarkers are yet to be established in clinical practice. More than 40 years of electroencephalography (EEG)-based research has culminated in the recent Food and Drug Administration (FDA) approval of the theta/beta (EEG power) ratio (TBR) as a diagnostic marker of ADHD. **Method:** This review article focuses on resting-state EEG power research in ADHD. **Results:** Inconsistent findings in the literature and suggestions of reduced specificity threaten the utility of TBR as a biomarker of ADHD. The use of fixed EEG bands may be a significant limitation, particularly in youth, and alternative approaches are needed. **Conclusion:** We propose that a personalized theta-to-alpha cut point or "transition frequency" is a better frame of reference for the measurement of TBR. Such an approach is better placed to test maturational lag and cortical hypoarousal models of ADHD and may in turn have greater utility in supporting diagnosis. *(J. of Att. Dis. XXXX; XX(X) XX-XX)*

Keywords

ADHD, FDA approval, theta/beta ratio, EEG power, cortical hypoarousal

Introduction

ADHD, a neurodevelopmental condition across the life span, is categorized by deficits in attention, hyperactivity, impulsivity, and diminished executive function. Although prevalence rates are reported in up to 10% of the child and adolescent population (Loo et al., 2009), a lack of known causality, coupled with the absence of robust objective diagnostic measures, has contributed to stigma and controversy toward the condition (Thome et al., 2012). In terms of standardized assessments for ADHD, symptom ratings such as the widely used Connors Rating Scales, completed by the individual, parent/s, teacher, and/or "observer" (for adults), are commonly used to support the clinical diagnosis (Conners, Sitarenios, Parker, & Epstein, 1998). Objective cognitive assessments such as continuous performance tasks (CPTs) are utilized to assist the diagnosis of ADHD, which evaluate speed and accuracy within the context of sustained attention.

Neurobiological studies of ADHD children/adolescents have reported (a) fronto-subcortical disturbances (Barkley, Grodzinsky, & DuPaul, 1992; Bradley & Golden, 2001; Purper-Ouakil, Ramoz, Lepagnol-Bestel, Gorwood, & Simonneau, 2011), (b) maturational delay in the temporal cortex (Shaw et al., 2007), (c) delayed cortical thinning (Biederman & Faraone, 2005; Bledsoe, Semrud-Clikeman, & Pliszka, 2009; Bradley & Golden, 2001; Faraone & Biederman, 1998; Makris et al., 2013; Niedermeyer & Naidu, 1997; Shaw et al., 2007), (d) decreased caudate volume (Semrud-Clikeman, Pliszka, Lancaster, & Liotti, 2006), and (e) changes in the thalamo-cortical loops (Romanos et al., 2010). In addition (and most recently), research (Makris et al., 2013) has implicated structural changes in the anterior cingulate, orbitofrontal, and cerebellar cortices of ADHD adults supporting theories of persistent cortical and functional brain abnormalities. Further validation of such neuroimaging-based research has significant implications for the earlier psychophysiological-based models of ADHD, such as maturational lag (Kinsbourne, 1973), developmental deviation (John, Prichep, & Easton, 1987), and cortical hypoarousal (Satterfield, Cantwell, & Satterfield, 1974). Such models are underpinned by neurotransmitter systems, particularly those of the catecholamines, noradrenaline (NA) and dopamine (DA), whereby

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the former regulates cortical arousal and serves a "tuning" function with respect to the brain's ability to extract the "signal from the noise," and the latter is specialized for activation, particularly with respect to frontal redundancy modulation and serves to mediate "switching" between inputs and outputs of specific brain regions (Levy & Swanson, 2001; Oades, 1985; Solanto, 1998; Tucker & Williamson, 1984). In comparison with EEG-based studies conducted over four to five decades, neuroimaging studies of ADHD are still in their infancy, and despite the promise of neuroimaging markers, their clinical utility across the ADHD population remains limited (Cortese & Castellanos, 2012).

EEG measures are useful, non-invasive indices of central nervous system (CNS) function used to assess both the baseline (tonic) and dynamic (phasic) features underlying the neurobiology of ADHD. Hitherto, the most robust and reproducible psychophysiological finding in ADHD has been increased theta band power (typically 4-7 Hz) and, in particular, increased theta relative to beta band power (typically 13-30 Hz) otherwise expressed as the "theta-to-beta" ratio (TBR). In July 2013, the U.S. Food and Drug Administration (FDA) approved the use of the Neuropsychiatric EEG-Based Assessment Aid Health (FDA, 2013), a system marketed as a "brain wave diagnostic tool" for the assessment of ADHD, based on the use of the TBR to inform diagnosis. However, the clinical utility of TBR remains inconclusive based on research findings to date (Arns, Conners, & Kraemer, 2013; Klimesch, 1999; Loo & Makeig, 2012), and validation of research supporting the clinical efficacy of the TBR in ADHD is warranted.

This article examines the evidence to support the use of an individually determined TBR as a diagnostic marker of ADHD by adopting the methodology proposed by Klimesch (1999). Rather than replicating the studies focused on the generic, fixed frequency bands used to produce TBR, we propose that the transition frequency (TF) may offer a personalized solution. The TF is the point at which resting and event-related EEG spectra intersect, and according to Klimesch (1999), it may provide the true, individually determined, cut point between theta and alpha EEG power—Such a paradigm shift would have significant implications for the TBR. Before this methodology and approach is detailed further, it is important to consider the evolution of ADHD in the literature from a psychophysiological viewpoint. In the following sections, first, we summarize three key psychophysiological models of ADHD and then describe, in more detail, the EEG-based findings in various ADHD samples.

Psychophysiological Models in ADHD

The Maturational Lag Model

More than 40 years ago, Kinsbourne (1973) brought a focus to the etiology of ADHD referred to as minimal brain dysfunction (MBD) at the time, by proposing a neurodevelopmental or maturational lag model. MBD was believed to result from a relative delay in neurobiological maturation processes. As a consequence, there is a slowed evolution of cerebral control of the ascending reticular activation system (ARAS) emanating from the brain stem, which is more representative of the normal state in younger children. Kinsbourne (1973) added that this lag affected various aspects of the CNS, and, accordingly, symptoms vary in magnitude. This notion is supported by more recent claims that these lagged trajectories may eventually "catch up" to their normal peers with increasing age (El-Sayed, Larsson, Persson, Santosh, & Rydelius, 2003; Murias, Swanson, & Srinivasan, 2007).

In more detail, Kinsbourne (1973) reasoned that individuals with MBD achieve cortical control over subcortical attentional switching at a delayed rate. In normal healthy brains, the reticular formation (RF; within the ARAS) incorporates a rigid pattern of attentional shifting, but this pattern gradually comes under cortical (i.e., executive) control. Kinsbourne (1973) noted that cortical stimulants enhance control over attention, while cortical depressants reduce it. Providing support for this model, Satterfield, Cantwell, Saul, Lesser, and Podosin (1973) demonstrated (using a visual clinical analysis of raw EEG) that there is excessive slow-wave EEG activity in ADHD children consistent with a brain maturational delay and an associated immaturity in behavior. The literature continued to build on this model. Matsuura et al. (1993) concluded that evidence of increased frontal slow-wave EEG was a biological link to brain immaturity in hyperactive males. More specifically, increased EEG theta in ADHD children, adolescents, and adults (albeit in separate samples) is consistent with the notion of delayed cortical maturation (Hermens, Kohn, Clarke, Gordon, & Williams, 2005). Importantly, more recent research utilizing structural and functional magnetic resonance imaging (MRI) methods suggests that ADHD individuals demonstrate a developmental lag of up to 5 years for frontal cortical thickness with particular delays in the maturation of ventral fronto-subcortical circuitry (Durston et al., 2003; Liechti et al., 2013; Shaw et al., 2007). Importantly, the approach proposed in this article (see below) would be useful to such ADHD research due to the inherent confounds of a potential maturational effect. That is, if traditional fixed bands are used for an ADHD sample, then (for example) what is being considered as theta band EEG may in fact be slow alpha. Maturational models of ADHD can only be fully examined when this approach is adopted, and the subsequent analysis determines that the same physiologically relevant EEG oscillations are being quantified and then compared.

The Developmental Deviation Model

The developmental deviation model of ADHD is an alternative to the maturational lag model. It describes ADHD as a

CNS dysfunction, with a profile unlike that of normal healthy profiles at any age. The developmental deviation model stems from the work of John et al. (1987) regarding functional deviation in EEG profiles. Using this approach, Chabot and Serfontein (1996) demonstrated, in a sample of more than 400 ADHD children (aged 6-17 years), a frontal EEG dysfunction that could not be a reflection (they argue) of immature CNS activity. They considered this to be a deviation from normal development and that the ADHD phenotype stems from this. This notion was supported by the structural MRI findings that parallel (i.e., compared with controls) developmental trajectories in ADHD are fixed and non-progressive (Castellanos & Tannock, 2002). It has been suggested that such a deviation is the result of early (genetic and/or environmental) influences on brain development in ADHD (Castellanos & Tannock, 2002).

More specifically, Chabot and Serfontein (1996) reported two distinct neurophysiological subgroups: One subgroup showed increased fronto-central theta/alpha and normal alpha mean frequency (accounting for 46% of ADHD patients), and the other subgroup showed increased theta/alpha across the scalp, with decreased alpha mean frequency (accounting for 30% of ADHD patients). The former group was considered representative of increased cortical arousal, whereas the latter was considered decreased cortical arousal. Thus, EEG-defined cortical arousal, across a large age range of ADHD individuals, was abnormally high or low and yet consistent with previous findings (Frank, 1993). Thus, in a large sample of patients, Chabot and Serfontein (1996) provided evidence of an ADHD-related EEG continuum, with frontal slowing at one end and increased beta activity (a third subgroup) at the other; the authors argued that increased beta was indicative of increased cortical arousal and was associated with anxiety. It is important to note that although the developmental deviation model incorporated both low and high cortical arousal subgroups, it was preceded by a model that specifically addressed the former, on the basis that this best represented the majority of ADHD patients.

The Cortical Hypoarousal Model

Based on studies of "Hyperactive Child Syndrome" (the contemporary equivalent of ADHD), Satterfield et al. (1974) argued that the general phenomenon of cortical hypoarousal (or low CNS arousal) was reflected by both an increase in slow-wave EEG activity and a decrease in tonic electrodermal activity (EDA), a putative index of the autonomic nervous system (ANS). It is important to highlight that the cortical hypoarousal model is an "alternative" model to the aforementioned maturational lag and developmental deviation models in terms of having specificity with regard to the brain state of an individual with ADHD; it can be cross-sectional or longitudinal, whereas the other two models both depend (probably) on a longitudinal viewpoint. Thus, the cortical hypoarousal model may not necessarily contradict the maturational lag (or a component of the developmental deviation; see above) models. Indeed "cortical hypoarousal" may be a more apt description in terms of the functional aspects of the underlying pathology, and it may have better clinical utility (i.e., a clearer treatment target). To highlight this, Satterfield et al. (1974) found that lower levels of CNS arousal corresponded with greater deficits in motor control (hyperactivity), attention, and impulsivity, and that these symptoms were ameliorated by stimulant medications. Because stimulants are known to increase arousal, this feature supported the model. The cortical hypoarousal model gained support from later EEG studies and with the incorporation of decreased EEG beta activity as well as further observations of increased theta and alpha (Barry, Clarke, & Johnstone, 2003; Lubar, 1991). Despite the robustness of the theta findings, DeFrance, Smith, Schweitzer, Ginsberg, and Sands (1996) called for a refinement of the dominant maturational lag hypothesis, given that elevated theta could also be accounted for by a disturbance in arousal regulation. The concept of cortical hypoarousal is appealing to ADHD models because it can help explain a range of physiological/behavioral observations (Nigg, 2005).

More specifically, posterior attentional deficiencies (due to an underlying noradrenergic disturbance) and concomitant reductions in ANS measures support the notion of a centrally driven (albeit from the ARAS/locus coeruleus) deficit in arousal (Hermens et al., 2004). Stimulation of the ARAS leads to observable EEG changes, such as alpha desynchronization or increases in beta activity, regarded as markers of general arousal (John, 2002). An "inverse-U" shaped relationship between arousal and performance suggests that optimal arousal is typically mediated by moderate levels of general arousal (Boucsein, 1992). A CNS arousal deficit, due to decreased reticular arousal in ADHD, can explain the decreased levels of performance seen across a range of cognitive tasks.

EEG-Based Research of ADHD

With its high temporal resolution, EEG measured at the scalp reflects CNS activity, and changes in its frequency distribution are thought to correspond with changes in cortical activation and arousal (Lim et al., 1996; McCormick, 1989; Schomer & da Silva, 2012). Baseline or "tonic" CNS arousal level, as indexed by EEG, has been suggested to reflect the activity of the fundamental reticulo-thalamo-cortical network with functional links between these subnetworks being mediated by concomitant cerebral and autonomic arousal (Lim et al., 1996). More specifically, brain stem, limbic, thalamic, and cortical processes, all involving large neuronal populations, mediate EEG

regulation and utilize all the major neurotransmitters (John, 2002), yet despite the underlying complexities, EEG regulation reflects a homeostatic system and is relatively predictable (John, 2002). EEG activity, representing the combined electrical fluctuations in membrane potentials generated from the interactions of the primary inhibitory and excitatory neurons (Gordon, 2000; Nunez, 1995), reflects the number of neurons that discharge synchronously (Klimesch, 1999). The EEG spectrum can be divided into two overarching aspects, each comprising two classic bands: Delta (1.5-3.5 Hz) and theta (4-7.5 Hz) constitute the regular high voltage slow-wave activity (HVSA), while alpha (8-13 Hz) and beta (14.5-30 Hz) constitute the low voltage fast wave activity (LVFA) of the EEG. In general, increased HVSA is considered to be an index of decreased arousal or increased drowsiness (Moruzzi & Magoun, 1949; Schomer & da Silva, 2012), whereas increases in LVFA reflect "more activation," associated with increased cortical arousal (Balatoni & Detari, 2003; Castro-Alamancos, 2002; Moruzzi & Magoun, 1949; Munk, Roelfsema, Konig, Engel, & Singer, 1996; Steriade & McCarley, 1990).

Two types of EEG analysis have been used in ADHD research: clinical and quantitative. Clinical EEG is the practice of observing and scoring the ongoing traces of EEG output. Quantitative EEG (QEEG) involves a spectral analysis and quantification into frequency band bins. QEEG has been found to be a sensitive indicator of cortical dysfunction in psychiatric disorders, providing objective, physiologically based data to supplement clinical assessment (Mann, Lubar, Zimmerman, Miller, & Muenchen, 1992). The traditional and most common approach of QEEG research has been to determine the absolute (and relative) power derived from fixed frequency bands during resting-state (eyes-closed [EC] or eyes-open [EO]) conditions (Klimesch, 1999). By comparison, there is a paucity of studies (especially in ADHD research) that have examined QEEG under active (i.e., event-related) conditions; this "domain" is typically indexed by event-related potentials (which represent phasic aspects of brain activity). An advantage of calculating relative EEG (e.g., alpha relative to total EEG) compared with absolute EEG is that it helps to control for individual differences (e.g., in scalp resistance and thickness; Demos, 2005). Specifically in ADHD research, it has been suggested that relative theta power has greater reliability in determining deviation within the test group (Boutros, Fraenkel, & Feingold, 2005). The majority of studies reported here involve QEEG; for simplistic purposes, the term *EEG* is used throughout this article.

The last 40 to 50 years have witnessed numerous attempts at establishing neurophysiological markers of ADHD. From such work, there has been a strong emphasis on fronto-central theta band EEG power and its ratio to beta band EEG power; thus, increased TBR in ADHD populations compared with non-ADHD "healthy control" groups has been one of the most consistent neurophysiological markers (Loo & Makeig, 2012). Typically measured under resting conditions, the TBR has been utilized as a source of critical information about the baseline state of the brain (in terms of maturation and/or arousal; see above) as well as a pertinent prelude to any subsequent brain activity that may be associated with increased cognitive demand (Barry, Clarke, & Johnstone, 2003). EEG research in ADHD evolved following Satterfield et al.'s (1973) observations of children with ADHD and their (clinical) EEG patterns with regard to stimulant medication response. The indexation of cerebral dysfunction in ADHD can be captured through the utilization of EEG, and the reporting of objective physiological data may provide a clear advantage in assisting diagnostic accuracy (Chabot & Serfontein, 1996), that is, in addition to subjective rating scales and sustained attention tasks (Mann et al., 1992). Furthermore, EEG has contributed significantly to elucidating the neurobiological mechanisms of ADHD and has shown a high degree of sensitivity in distinguishing ADHD from healthy control participants (Chabot, di Michele, Prichep, & John, 2001; Chabot, Merkin, Wood, Davenport, & Serfontein, 1996; Chabot & Serfontein, 1996; Mann et al., 1992; Monastra, Lubar, & Linden, 2001; Monastra et al., 1999). Excess slow-wave activity coupled with decreased fast wave activity, favoring the cortical hypoarousal model, was first observed in "ADHD" in the early 1970s (Loo & Makeig, 2012; Satterfield et al., 1974). This work sparked the interest in determining EEG abnormalities in ADHD children, and much research has been carried out since, to replicate the findings (Alexander et al., 2008; Arns, 2011; Barry, Johnstone, & Clarke, 2003; Hermens, Kohn, et al., 2005; Hermens, Soei, et al., 2005; Lazzaro, Gordon, Whitmont, Meares, & Clarke, 2001; Monastra et al., 2001; Ogrim, Kropotov, & Hestad, 2012; Snyder & Hall, 2006; Snyder et al., 2008). Chabot and Serfontein (1996) found that the "overwhelming majority" of resting EEG profiles among 400 ADHD children showed a homogeneous pattern (despite the clinical heterogeneity) of neurophysiological dysfunction with the variance being accounted for by normal/abnormal dimensions and not by IQ or the presence of hyperactivity or learning problems.

Thus, ADHD has been consistently characterized by an elevation in low frequency activity (i.e., both absolute and relative theta), during resting (EC or EO) conditions, especially when recorded from frontal sites (Abibullaev & An, 2012; Barry, Clarke, & Johnstone, 2003; Boutros et al., 2005; Bresnahan, Anderson, & Barry, 1999; Chabot & Serfontein, 1996; Clarke, Barry, McCarthy, & Selikowitz, 1998; Clarke, Barry, McCarthy, & Selikowitz, 2001c; Clarke, Barry, McCarthy, Selikowitz, & Brown, 2002; DeFrance et al., 1996; Dupuy, Clarke, Barry, McCarthy, & Selikowitz, 2013; Lazzaro et al., 1999; Lazzaro et al., 1998; Loo & Makeig, 2012; Mann et al., 1992; Ogrim et al., 2012;

Quintana, Snyder, Purnell, Aponte, & Sita, 2007; Snyder et al., 2008). There has been some discrepancy as to whether the theta elevation is localized to the frontal brain, as predicted by the maturational view (Clarke et al., 1998; Mann et al., 1992), or instead represents a more widespread phenomenon (DeFrance et al., 1996). Fast wave EEG markers in ADHD have also been revealed, with evidence of decreased alpha and beta activities in ADHD (Callaway, Halliday, & Naylor, 1983). Monastra et al.'s (2001) study measured the power of theta and beta bands spectra, with 90% sensitivity and 94% specificity in differentiating ADHD from non-ADHD individuals. Similarly, two studies have reported high specificity and sensitivity (87% and 94%, respectively) of TBR recorded at a single electrode site Cz (Monastra et al., 2001; Snyder et al., 2008). Decreased relative beta activity, increased absolute and relative theta activity, or increased theta/beta ratio has also differentiated ADHD from controls (Bresnahan et al., 1999; Bresnahan & Barry, 2002; Clarke, Barry, McCarthy, & Selikowitz, 2001a; Clarke, Barry, McCarthy, & Selikowitz, 2002; Lubar, 1991; Mann et al., 1992; Monastra et al., 1999). In contrast, other studies have also revealed increased beta power in ADHD, with the interpretation that this may reflect a distinct subgroup (e.g., combined subtype with poor IQ) of ADHD (Chabot & Serfontein, 1996; Kuperman, Johnson, Arndt, Lindgren, & Wolraich, 1996). Poil et al. (2014) reported higher beta and lower alpha power in adult ADHD combined type group compared with controls; however, this was inconsistent with their observations of ADHD combined type children. This highlights the variability in EEG differences in ADHD individuals both developmentally and in the nature of the heterogeneous condition in terms of a deviation from expected developmental trajectory.

Clarke, Barry, McCarthy, and Selikowitz (2001b) determined EEG-defined subtypes (as opposed to *Diagnostic and Statistical Manual of Mental Disorders* [4th ed.; *DSM-IV*; American Psychiatric Association [APA], 1994] subtypes) by identifying three distinct EEG clusters of ADHD. The first showed increased slow wave and deficient fast wave, high theta, and reduced delta and theta EEG associated with cortical hypoarousal; the second showed increased high amplitude theta with deficient beta activity suggestive of maturational lag; and the third showed excessive beta activity, which also may be suggestive of cortical hyperarousal. While Groups 1 and 2 displayed similarities of increased theta and decreased beta, unlike Group 1, Group 2 EEG was characterized by developmental differences in posterior relative delta and alpha and central beta compared with normal profiles, which lends support to the maturational lag theory.

Despite encouraging results in EEG-based research of ADHD, findings remain inconclusive due to factors such as study design, EEG technology, type of analysis, sample size, and variations in fixed frequency bands to support the evidence of increased theta in previous findings (Arns et al., 2013; Liechti et al., 2013; Loo & Makeig, 2012). While TBR has consistently been found to be abnormal in ADHD populations, its reliability has not been replicated in several recent studies (Arns et al., 2013; Arns & Gordon, 2014; Loo & Makeig, 2012; Murias et al., 2007; Poil et al., 2014). Arns et al. (2013) recently conducted a meta-analysis and found that heterogeneity among studies was very high and therefore suggests that the overall effects sizes may be an overestimation. They argue that although TBR may be utilized as a measure to discriminate a substantial proportion of ADHD patients from controls, it does not have the reliability to support diagnosis (Arns et al., 2013). Despite such data and commentary, clinicians can now utilize the TBR as part of the diagnosis for ADHD thanks to the very recent FDA approval.

FDA Approval of Theta/Beta as an ADHD Marker and NEBA

In 2013, the FDA approved the use of the NEBA system for diagnostic purposes in the assessment of ADHD. The NEBA process involves using a single electrode recording from the vertex (i.e., the central-midline site; Cz) and a ground electrode at the frontal-midline location (Fz) to obtain the TBR, utilized as a diagnostic marker of ADHD (NEBAHealth, 2013). Although a very limited number of clinical studies are available to confirm the efficacy of the NEBA system, a growing number of practitioners in the United States have incorporated this diagnostic tool into their patient assessments. The availability of an objective brain-based assessment of ADHD is attractive to clinicians as a method to help reduce diagnostic error and refine treatment prediction. Importantly, NEBA is not marketed as a standalone diagnostic tool, but rather as one that is to be used in conjunction with current gold standard ADHD assessment measures including clinician assessment and patient self-report measures. Despite this, there is some degree of skepticism from clinicians with regard to the value of an EEG tool such as NEBA in the current ADHD assessment model. Moreover, clinicians and researchers alike seek further clarification toward the validity of the TBR as a diagnostic measure in ADHD. NEBA (NEBAHealth, 2013) have made available on their website (www.nebahealth.com) a summary of their two clinical studies designed to test the efficacy of the TBR as a diagnostic marker for ADHD. While their first study is double blinded, with blind break handled by an independent third party, their second study was a review of deidentified patient files by a multidisciplinary clinical team (NEBAHealth, 2013). To date, it is difficult to ascertain the necessary data to review NEBA's study as information available on public domain is limited; specifically, information pertaining to the EEG band ranges (i.e., for theta and

beta power) used by the NEBA system is not readily available or clear (not a specific mention of the power band cutoffs defined in another NEBA study; NEBAHealth, 2013).

Despite the promise of the NEBA system, the data on which it is based remain inconclusive warranting further validation studies to determine clinical efficacy of TBR as a biomarker of ADHD and the use of EEG as a diagnostic instrument (Ogrim et al., 2012). Critically, the vast majority of evidence in support of TBR as a biomarker of ADHD has been based on the use of traditional fixed frequency bands. Given the heterogeneity of EEG findings in the ADHD literature and that fixed frequency bands are based on adult EEG findings, the previous research remains limited in terms of its clinical application and support for the proposed biomarker (Thome et al., 2012). There are many factors that influence EEG power measures such as scalp thickness, volume of cerebrospinal fluid, age, arousal, and type of cognitive demands (Klimesch, 1999). Although a number of such factors (e.g., sex, subtype, and comorbidity) have been found to moderate TBR, one of the most impactful factors is age (Arnold, 2013; Hermens, Kohn, et al., 2005; Hermens et al., 2004). The following section highlights how age-related changes in the EEG could be the single-most important factor with respect to the limitations of TBR as a diagnostic marker of ADHD.

Important Considerations for EEG-Based Markers Due to the Effects of Age

As ADHD was previously viewed as (primarily) a childhood disorder, earlier classifications did not fully account for or characterize the nature of symptoms in adults with the disorder. However, with increasing awareness, clinical observations of the progression of the disorder into adulthood have become highly relevant, and the clinical insights gained (e.g., hyperactivity transforming into "feelings of restlessness" with adulthood) have helped redirect ADHD research toward a better understanding of the broader effects of age (Bresnahan et al., 1999; Klimesch, 1999). The range of symptoms present in adults varies from mild impairment in daily functioning to significant impairment, often compounded by the onset of comorbid conditions such as depression and anxiety (Bresnahan et al., 1999). Consequently, those who present with moderate to significant impairment experience instabilities across employment, social, and relationship areas leading to a reduction in quality of life. Hence, greater awareness of the developmental trajectory of ADHD may assist in the reduction of adult symptoms through better treatment management. Thus, age effects are fundamental to improving our understanding of ADHD, specifically from an etiological perspective, as an appreciation of such effects will provide important insights for the refinement of the theoretical models examining maturational lag, developmental deviation, and cortical arousal.

Neurobiological measures such as MRI and EEG have been able to elicit information that is imperative to observations of age effects in ADHD, providing further insight into the maturational lag and cortical hypoarousal models. Bresnahan et al. (1999) found that, compared with their age-matched healthy controls, ADHD children, adolescents, and adults consistently showed increased theta EEG; however, decreased beta EEG was less evident in the older patient groups. Interestingly, this pattern of EEG "changes" with age in ADHD was interpreted as neurophysiological evidence for the developmental trajectories of both impulsivity (i.e., theta EEG is persistent) and hyperactivity (i.e., beta EEG normalizes with age; Clarke et al., 1998). Noting that theta EEG decreases with age in the normal population, Hermens et al. (2004) found that adult ADHD males display enhanced global theta EEG, whereas adult ADHD females showed only a decrease in a measure of autonomic arousal (i.e., skin conductance level [SCL]). Such findings were interpreted as providing little support for the maturational lag hypothesis, as raised theta activity appears to have persisted into adulthood in ADHD males. However, findings in other adult ADHD studies have been inconsistent with reports of null findings with respect to theta and/or TBR levels as well as reduced sensitivity of TBR accuracy to discriminate adult ADHD (Liechti et al., 2013; Ogrim et al., 2012; van Dongen-Boomsma et al., 2010).

One major factor that may be contributing to the mixed findings across ADHD age groups is the assumption that the EEG frequency bands used may be different in children as compared with adults. In other words, there may be normal developmental features of the EEG that are actually confounding our understanding of what it means to have anomalous fluctuations across the four fixed frequency bands. In general, longitudinal studies of healthy normal children have found that between 4 and 17 years of age, slow EEG (i.e., delta, theta) power decreases and fast EEG (i.e., alpha, beta) power increases with increasing age (Benninger, Matthis, & Scheffner, 1984; Harmony, Marosi, Díaz de León, Becker, & Fernández, 1990). Accordingly, slow-wave EEG (in particular, theta) is considered a robust measure of immature brain development, with peaks in theta activity typically disappearing in adulthood (Klimesch, 1999). Changes observed in the EEG spectra with increasing age are not necessarily linear (i.e., different aspects of the EEG spectra follow different patterns—for example, linear and biphasic—with development). Indeed, some EEG power spectra studies have revealed gradual changes in EEG spectral power with "growth spurts" at around ages 6 and 10 years in absolute and relative EEG power (Somsen, van't Klooster, van der Molen, van Leeuwen, & Licht, 1997; Thatcher, 1991). Furthermore, the developmental velocity (i.e., change per year) of EEG is different in boys

and girls (Benninger et al., 1984). Alpha wave activity is also age dependent suggesting that alpha peak frequency (which is often a prominent feature of EEG recorded under EC condition) is also an important measure of brain maturation and has been linked to reaction time and working memory (Richard Clark et al., 2004). Developmental changes in alpha and theta are observed in early childhood until late adulthood where there is an increase in upper alpha and decrease in theta. Critically, after determining the longitudinal nature of the various EEG power bands in normal children, Benninger et al. (1984) concluded that although age effects were prominent, participants' individual characteristics accounted for 2 to 3 times more variance (in the EEG; than age), and this may help to explain the inconsistencies in the literature. Given the effects of age and individual characteristics, the TBR (as a research and diagnostic tool) may benefit from a reconceptualization. An opportunity to redefine the TBR exists through the application of individualized frequency bands that utilize the "transition frequency" cutoff, as proposed by Klimesch (1999); this approach is described further in the following section.

Transition Frequency (TF) as a Marker for ADHD

As discussed above, a dependency on traditional fixed frequency bands may be problematic in the classification of ADHD, and alternative approaches, such as the use of individual alpha peak frequency (IAF) as a reference point for individually determined power bands, have been proposed (Lansbergen, Arns, van Dongen-Boomsma, Spronk, & Buitelaar, 2011). Critically, Lansbergen et al. (2011) found that TBR in ADHD children and adolescents was significantly increased compared with controls when traditional fixed power bands were used (i.e., theta = 4-7.5 Hz; beta = 12.5-25 Hz); however, when IAF was used as an anchor point to determine theta and beta power bands for each participant, TBR in the ADHD group did not significantly differ from healthy controls. The interpretation of these findings was that when using the traditional fixed-band approach, for some individuals, the "theta band" EEG power actually contained some "slow alpha" activity. The IAF methodology adopted by Lansbergen et al. (2011) was based on the work of Klimesch (1999) and colleagues (Doppelmayr, Klimesch, Pachinger, & Ripper, 1998) who, in a series of experiments with healthy adult populations, highlighted the importance of IAF in terms of its relationship with subsequent cognitive processes (in particular, memory; Basar, Schurmann, Basar-Eroglu, & Karakas, 1997; Goljahani et al., 2012; Klimesch, Vogt, & Doppelmayr, 1999). Defined as the individual dominant (i.e., peak or gravity) EEG frequency within the alpha "range," the IAF of some individuals may be difficult to detect; for example, an individual may have multiple peaks with the alpha range, or there may be a plateau whereby the maximum power extends across a wide frequency range. Indeed, for some cases in the Lansbergen et al. (2011) study, it was not possible to determine the IAF despite the additional criterion of alpha desynchronization (i.e., the decrease in alpha activity from EC to EO conditions) to help determine the IAF location.

Within Klimesch's methodology, there is an additional (and probably more reliable) way to determine power band cutoffs (as well as the IAF itself) for a given individual (Klimesch, 1999). The TF, according to Klimesch (1999), represents the true boundary between theta and alpha oscillations; this index is essentially the point at which superimposed resting-state (e.g., EC) and event-related (e.g., during a working memory task) EEG spectra intersect. The theory behind TF is based on the evidence that while alpha activity desynchronizes with increasing cognitive load, theta activity synchronizes in a similar (albeit opposite) linear fashion (Klimesch, 1999). Hence, TF represents an important physiological criterion for the determination of individual power bands (e.g., theta is 2Hz below TF to TF; alpha is TF to TF plus 6 Hz; beta is TF plus 6 Hz to TF plus 16 Hz, and so on—see Klimesch, 1999). Importantly, TF has been shown to have a robust linear relationship with IAF, such that the latter is consistently 4 Hz beyond the former (Klimesch, 1999). Thus, TF also offers a solution to determining IAF when it may be difficult to detect as a single "peak." Perhaps as a result of its inconsistency or difficulty to measure, IAF has been excluded from much of the ADHD research to date, which has clearly favored the reporting of spectral power measures (Arns, 2011).

The use of individually determined power bands with TF as the anchor point would be particularly crucial in the assessment of ADHD for several reasons. First, this approach can better address maturational factors (in both ADHD and control groups) by determining the TF, which in young samples is likely to be slower than the standard 7 Hz cut point used in the majority of the (typically adult) literature. Second, by utilizing both resting and high-cognitive load conditions, this technique would provide important information as to the relative state of ADHD patients who may be unnecessarily engaging cognitive effort when they have been asked to sit quietly in a resting state; in other words, in some circumstances, an increase in "resting state" theta in a young patient with ADHD may actually stem from mental activity that is closer to that observed under higher-cognitive load (when theta is expected to synchronize/increase). Inversely, decreased theta activity in the resting state has been linked to increases in subsequent cognitive performance (Hermens, Soei, et al., 2005). There is a body of research showing that when task demands (particularly with respect to working memory) lead to increases in cognitive load, there is a corresponding increase in frontal theta power (Goljahani et al., 2012; Klimesch, 1997;

Raghavachari et al., 2001). However, such research has primarily been in non-ADHD adult samples.

It is not unreasonable to assume that previous EEG-based research of ADHD (in the resting state) may be somewhat limited due to the simple notion that one individual's "theta power" may be another individual's "alpha power" because of arbitrarily applied power band cutoffs. Thus, the TBR as a diagnostic marker for ADHD may benefit from a reconceptualization around the idea that the theta and beta power bands (or any other power bands for that matter) should be determined objectively and at the individual level; hence, the incorporation of the TF as an anchor point for TBR may provide the field with new insights into the brain state of patients with this condition. Until individually determined TBR is utilized, interpretations of increased TBR in ADHD that focus on brain maturation versus developmental deviation may be confounded. Future research around this individual-based approach could also investigate the effects of gender, ADHD subtype, and comorbidity and their interactions with age to identify psychophysiological subtypes.

Conclusion

To date, objective assessment of ADHD has been hampered by limitations in various diagnostic tools, and as a result, there is some skepticism with regard to the clinical utility of such tools. Recently, the EEG power ratio of theta over beta band activity has been touted and subsequently approved as a diagnostic marker for ADHD. Such a marker has the capacity to not only help classify patients but also help clinicians determine the type and timing of pharmacological and psychological treatment, as well as help to predict clinical outcomes. However, as identified in this article, there are limitations around the use of traditional fixed-band analyses in EEG. These limitations may lead to misinterpretations of a patient's brain state whether it is in the context of maturational and/or cortical arousal status. Therefore, a reconceptualization of markers, such as TBR, based on individually determined cut points in the EEG is warranted. In the case of TBR, we argue that the determination of the TF between theta and alpha band activities with respect to both resting and high-cognitive load conditions is crucial to a better classification of ADHD patients, of all ages.

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