Adult Attention-Deficit/Hyperactivity Disorder: Investigation of Neurophysiological Models

Dissertation

zur Erlangung des Grades eines Doktors
der Naturwissenschaften

der Mathematisch-Naturwissenschaftlichen Fakultät
und
der Medizinischen Fakultät
der Eberhard-Karls-Universität Tübingen

vorgelegt
von

Sarah Nicole Wyckoff
aus Phoenix, Arizona, United States of America

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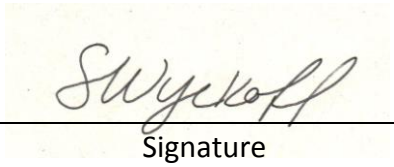
Declaration

I hereby declare that I have produced the work entitled: “Adult ADHD: Investigation of Neurophysiological Models”, submitted for the award of a doctorate, on my own (without external help), have used only the sources and aids indicated and have marked passages included from other works, whether verbatim or in content, as such. I swear upon oath that these statements are true and that I have not concealed anything. I am aware that making a false declaration under oath is punishable by a term of imprisonment of up to three years or by a fine.

Tübingen, 24.6.2013 

Date Signature

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Abstract - English

Introduction. Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by symptoms of inattention, impulsivity, and hyperactivity that are observed across the lifespan. Deviant electroencephalographic (EEG) patterns of activity have been repeatedly observed in children with ADHD during resting-state conditions. However, the research in adult populations is limited and several neurophysiological models investigated in children with ADHD have not been examined in adults. Thus, the primary aim of this thesis was to investigate neurophysiological models of ADHD in an adult population, as well as to explore the relation between resting-state brain oscillations and core ADHD behaviors. The neurophysiological models investigated in this thesis were quantitative EEG (QEEG) using fixed frequency bands and individualized frequency bands based on individual alpha peak frequency (iAPF), phenotype classification, and vigilance classification.

Methods. Continuous 21-channel EEG was acquired from 48 adult participants with DSM-IV defined ADHD and 48 age and sex matched healthy control participants. To investigate QEEG differences between populations the EEG was Fourier transformed and pooled into nine regions by averaging the power at several electrode sites. For each frequency band (delta, theta, alpha, beta, theta/alpha, and theta/beta power), power analysis (absolute and relative power), and condition (eyes-closed and eyes-open), a mixed ANOVA was used to examine the effects of region and group using fixed and individualized frequency bands. To investigate the EEG phenotype model, EEG files were individually reviewed and hand scored for the presence or absence of identifiable EEG patterns including frontal slowing, low iAPF, high iAPF, beta spindling, frontal alpha, persistent eyes-open alpha, temporal alpha, and paroxysmal activity. A Pearson's chi-squared test was used to investigate the relationship

between group (ADHD, Control) and phenotype (present, absent) in a series of 2x2 cross-tabulation tables. To investigate the EEG vigilance model, eyes-closed EEG vigilance stages (O, A1, A2, A3, B1, and B2/3+) were classified using the latest version of Vigilance Algorithm Leipzig (VIGALL) macro. Differences in the amounts of vigilance stages and stage transitions in ADHD and control participants were tested using a Mann-Whitney *U*-test. Correlations were calculated between ADHD behavioral measures, QEEG data, and classification sub-groups.

Results. Compared to control participants, the ADHD group presented with significantly enhanced relative theta, absolute beta, theta/alpha power, and attenuated relative alpha during the eyes-closed condition, as well as significantly enhanced absolute and relative theta and attenuated relative alpha during the eyes-open condition when using fixed-frequency bands for the QEEG analysis. Despite non-significant differences in iAPF values between groups, QEEG differences were influenced using individualized frequency bands. Consequently, the ADHD group presented with significantly attenuated relative alpha and relative beta during the eyes-closed condition, as well as significantly enhanced absolute and relative theta, theta/alpha power, and attenuated relative alpha during the eyes-open condition. EEG phenotype classification revealed a significantly greater prevalence of the frontal slow and high iAPF subtypes in the ADHD group compared to the control group. EEG vigilance classification revealed that ADHD participants spent more time in lower vigilance stages (B2/3) than control participants did (ADHD = 21.2%, Control = 14.2%). No consistent relationship was found between resting-state brain oscillations and ADHD behaviors, with the exception of a weak positive correlation between iAPF and inattention.

Discussion. The present investigation confirmed and extended many of the findings reported in children with ADHD in an adult ADHD population; namely enhanced theta and attenuated alpha activity. Theta and alpha power abnormalities were further evidenced by an increased prevalence of ADHD individuals with the frontal slow (theta) and high iAPF phenotypes (alpha) and lower vigilance stage dominance (theta/alpha). The results support the hypothesis that imbalances or deviations within septal-hippocampal circuits and thalamocotical loops may lead to the disturbances of theta and alpha activity, expression of ADHD subtypes, and neurobiological deficits linked to the dopaminergic system, altered reinforcement mechanisms, and changes in vigilance and arousal. Further, these findings may account for discrepant QEEG findings within ADHD research, as EEG activity in ADHD appears to be mediated by iAPF values. Future research should investigate the role of iAPF in ADHD, as well as determine whether these neurophysiological models are reliable discriminants of ADHD or predictive of treatment response.

Abstract - German

Einführung. Die Aufmerksamkeitsdefizit-/ Hyperaktivitätsstörung (ADHS) ist eine neurobiologisch verursachte Entwicklungsstörung. Symptome der Unaufmerksamkeit, Impulsivität und Hyperaktivität werden bei Kindern und auch bei Erwachsenen beobachtet. Im Ruhe-Elektroenzephalogramm (EEG) wurden wiederholt abweichende Aktivitätsmuster bei Kindern mit einer ADHS beobachtet. ADHS bei Erwachsenen ist bisher nur wenig untersucht und neurophysiologische Modelle der ADHS wurden bisher nur für Kinder entwickelt. Daher ist das Hauptziel der vorliegenden Arbeit, die neurophysiologischen Modelle der ADHS an Erwachsenen zu überprüfen. Außerdem soll die Beziehung zwischen den Oszillationen des Gehirns im Ruhezustand und den Hauptsymptomen der ADHS untersucht werden. Im Einzelnen wurden folgende Modelle in dieser Arbeit untersucht: Abweichungen im quantitativen EEG (QEEG), wobei feste und individuelle Frequenzbänder anhand von individueller Alpha-Peak Frequenz (iAPF) betrachtet werden, die Phänotypen-Klassifikation und die Vigilanz-Klassifikation.

Methode. Achtundvierzig Erwachsene mit einer DSM-IV ADHS Diagnose und 48 in Alter und Geschlecht gematchte, gesunde Probanden wurden mit einem 21-Kanal EEG gemessen. Für die Untersuchung etwaiger Unterschiede zwischen den Probanden mit und ohne ADHS wurde das EEG Fourier transformiert und in neun Regionen aufgeteilt, indem das durchschnittliche Powerspektrum von mehreren Elektrodenpositionen gebildet wurde. Die Effekte von Region und Gruppe wurden mit Hilfe von Varianzanalysen einmal für feste und einmal für individualisierte Frequenzbänder bestimmt (Delta, Theta, Alpha, Beta, Theta/Alpha und Theta/Beta Power absolute und relative Power) jeweils für die Bedingungen (Augen offen (A-O) und Augen geschlossen(A-G). Für die Untersuchung des

EEG Phänotypen-Models wurden die EEG-Daten für jeden Probanden einzeln überprüft. Es wurde per visueller Inspektion geprüft, ob folgende EEG-Muster vorhanden waren: frontale Verlangsamung, niedrige iAPF, hohe iAPF, Beta-Spindeln, frontales Alpha, fehlender Alpha-Block bei geöffneten Augen, temporales Alpha und paroxysmale Aktivität. Ein Pearson's Chi-Quadrat Test wurde mit 2x2 Kreuztabellen berechnet, um die Beziehung zwischen der Gruppe und dem Phänotyp zu untersuchen. Um das EEG Vigilanz-Model zu untersuchen, wurden die EEG-Vigilanzstadien bei geschlossenen Augen (O, A1, A2, A3, B1 und B2/3+) mit der neuesten Version des Vigilanz Algorithmus Leipzig (VIGALL) Macro klassifiziert. Die Unterschiede in der Menge der Vigilanz-Stadien und den Übergängen in die verschiedenen Stadien, wurde mit dem Mann-Whitney *U*-test analysiert. Korrelationen wurden zwischen den Symptomen, den QEEG-Daten und den Klassifikationssubtypen berechnet.

Ergebnisse. Im Vergleich zu den Probanden der Kontrollgruppe zeigte die ADHS-Gruppe in der QEEG-Analyse mit festen Frequenzbändern signifikant größere Anteile im relativen Theta, absoluten Beta und in der Theta/Alpha Power sowie ein verringertes relatives Alpha während der A-G Bedingung. In der A-O Bedingung war Theta absolut und relativ stärker, sowie Alpha relativ geringer ausgeprägt. Obwohl in den iAPF-Werten keine signifikanten Gruppenunterschiede gefunden wurden, ergab sich ein anderes Bild als bei der Betrachtung der festen Frequenzbänder. Die ADHS-Gruppe zeigte signifikant weniger relatives Alpha und weniger relatives Beta in der A-G Bedingung. Außerdem zeigten sich in der A-O Bedingung signifikante Erhöhungen im absoluten und relativen Theta und in der Theta/Alpha Power sowie eine Verringerung des relativen Alpha. Die EEG-Phänotypen-Klassifikation ergab in der ADHS-Gruppe eine signifikant häufigere Prävalenz der frontalen Verlangsamung und des Subtypus mit hoher iAPF. Die EEG Vigilanz-Klassifikation zeigte, dass die ADHS Gruppe mehr

Zeit in niedrigeren Vigilanzstadien (B2/3) verbrachte als die Kontrollgruppe (ADHS = 21.2%, Kontrollen = 14.2%). Bis auf eine schwache positive Korrelation zwischen der iAPF und Unaufmerksamkeit, fanden sich keine konsistenten Beziehungen zwischen den Oszillationen im Ruhezustand des Gehirns und den Symptomen.

Diskussion. Die hiervorliegende Arbeit bestätigt und erweitert viele Befunde aus der ADHS-Forschung an Kindern für Erwachsene, vor allem die erhöhte Theta- und niedrigere Alpha-Aktivität. Diese Befunde werden auch durch die erhöhte Prävalenz der Phänotypen frontale Verlangsamung und hohe iAPF, sowie der Dominanz der niedrigeren Vigilanzstadien in der ADHS Gruppe bestätigt. Die Ergebnisse unterstützen die Hypothese, wonach ein Ungleichgewicht oder Abweichungen in den septo-hippokampalen Verbindungen und den thalamisch-kortikalen Schleifen zu einer Störung von Theta- und Alpha-Aktivität, dem Auftreten von ADHS-Subtypen und neurobiologischen Defiziten führen, welche mit dem dopaminergen System, veränderten Verstärkungsmechanismen und Veränderungen in der Vigilanz und Erregung verbunden sind. Ferner können die Ergebnisse dazu beitragen, widersprüchliche Befunde zu der Aktivität einzelner Frequenzbänder zu klären, da der iAPF-Wert anscheinend die EEG-Aktivität anders darstellt. Zukünftig sollte die iAPF bei einer QEEG-Betrachtung stärker berücksichtigt werden. Außerdem sollte untersucht werden, welchen Beitrag die neurophysiologischen Modelle zur Diagnose und Vorhersage des Therapieerfolgs bei ADHS leisten können.

Adult Attention-Deficit/Hyperactivity Disorder: Investigation of Neurophysiological Models

1. Introduction

Attention–deficit/hyperactivity disorder (ADHD) is one of the most common disorders of childhood with a worldwide-pooled prevalence of 5.29% and a range of 2-12% (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007). Despite the misconception that most individuals with ADHD mature out of the disorder, 30-65% of children take their symptoms into adulthood (Faraone, Biederman, & Mick, 2006). The primary symptoms of adult ADHD include persistent inattentiveness, impulsivity, and hyperactivity. The estimated prevalence of clinician-assessed adult ADHD in the United States is 4.4-5.2%, with a range of 1.2-7.3% in European populations (Goodman & Thase, 2009). Impairment in educational, occupational, neuropsychological, and social functioning are reported (Rostain, 2008) and patient profiles indicate histories of school failure, employment problems, and traffic accidents (Faraone et al., 2000). Comorbid psychiatric disorders are reported by 65-89% of adults with ADHD (Sobanski, 2006), including diagnosis of mood, anxiety, and substance abuse disorders (Spencer, 2009).

The core symptoms of ADHD have been linked to several neurophysiologic deficits, some reflected by pathological electroencephalographic (EEG) activity. Spontaneous EEG activity is defined in frequency bands and identified by the number of cycles per second of the waveform. The traditional frequency bands include delta (0.5-4 Hz), theta (4-8 Hz), alpha (8-12 Hz), sensorimotor rhythm or SMR (12-15 Hz), beta (13- 30 Hz), and gamma (30-100 Hz). EEG activity presents as synchronized or desynchronized and reflects the summation of excitatory and inhibitory postsynaptic potentials in the pyramidal cells of the cerebral

cortex, with additional contributions from granular and glial cell activity (for reviews, see Lopes da Silva, 1991; Speckmann & Elger, 1999). Surface EEG electrodes capture large field potentials generated by the coordinated action of glial networks (Fellin et al., 2009) and the synchronous extracellular current flow of neurons with a similar spatial orientation radial to the scalp. Synchronized high-amplitude oscillations of slow EEG frequencies can be observed during relaxed eyes-closed conditions, whereas desynchronized lower-amplitude oscillations of faster frequencies dominate during visual attention and eyes-open conditions (Steriade, Gloor, Llinás, Lopes da Silva, & Mesulam, 1990). Table 1 provides a summary of the basic EEG frequency bands and the mental states most commonly associated with the prevalence of each bandrange.

Table 1

Frequency Bandwidths and Associated States

Name	Range	Description	Waveform (3 second epoch)
Delta	0.5 – 4 Hz	Deep Sleep, Repair, Coma	
Theta	4 – 8 Hz	Drowsy, Creative	
Alpha	8 – 12 Hz	Relaxed, No Visual Processing	
SMR	12 – 15 Hz	Motor Relation, Alert	
Beta	13 – 30 Hz	Cognitive Processing	
Gamma	30 – 45+ Hz	Problem Solving	

Note. Individual bandranges filtered from eyes-open resting state data. Hz = hertz, the SI unit of frequency defined as the number of cycles per second of the electrophysiological waveform. Adapted from, Sherlin, L. H. (2009). Diagnosing and treating brain function through the use of low resolution brain electromagnetic tomography (LORETA). In T. H. Budzynski, H. K. Budzynski, J. R. Evens, & A. Abarbanel (Eds.), *Introduction to quantitative EEG and neurofeedback: Advanced theory and applications* (2nd. ed.) (pp. 87). Oxford, UK: Elsevier.

1.1. EEG in the Diagnostic and Prognostic Domain

For decades, EEG has been recorded and visually inspected by neurologists and researchers to detect abnormal waveforms and peak activity; assess consciousness, coma, or brain death; locate areas of damage following injury, stroke, or tumors; and investigate paroxysmal activity and seizure foci. Over time, technological advancements in data collection and signal processing afforded the opportunity for spectral components of the EEG to be extracted and quantified. Quantitative EEG (QEEG) analysis is defined as the mathematical processing of frequency and amplitude components of EEG that may be transformed into a variety of numerical measures, providing precise, quantitative descriptions of many indices of brain function (Hammond et al., 2004). Typically, QEEG data is derived from a 19-channel EEG recording utilizing the standardized International 10-20 system of electrode placement. EEG is recorded during standardized conditions, such as eyes-closed resting, eyes-opened staring at a focal point, or other auditory and visual tasks. The EEG signal is digitized, visually inspected, and edited to remove muscle movements, eye rolls and blinks, electrocardiogram (EKG), and other corrupting factors. Finally, the refined data is subjected to spectral analysis using the fast Fourier transform (FFT) algorithm. Individual QEEG recordings are compared to a “normal” group or to a defined “clinical” population. A variety of statistical computations, such as relative and absolute power, power ratios, coherence, phase lag, hemispheric asymmetries may be calculated. QEEG analyses yield a variety of color-coded topographic maps and numerical tables with raw and standardized data, which may have diagnostic and prognostic applications. For example, in the diagnostic domain, QEEG analyses may aid trained clinicians in assessment, differential diagnosis, identification of “signature” patterns of electrical activity in the cerebral cortex,

and serve as a discriminant of pathology. The diagnostic application of QEEG assumes homogeneity among the clinical population under investigation. In the prognostic domain, QEEG analyses may aid in medication selection, treatment outcome prediction, and development of targeted neurofeedback-training protocols. The prognostic application of QEEG assumes heterogeneity among the clinical population under investigation.

1.2. EEG Correlates of ADHD

Table 2

Resting state EEG Findings in Childhood ADHD Compared to Healthy Controls

	Ratio			Absolute Power				Relative Power			
Study	θ/β	θ/α	δ/θ	δ	θ	α	β	δ	θ	α	β
Eyes-Open											
Amer et al. (2010)				*ns*	*ns*	↓	*ns*	↑	*ns*	↓	*ns*
Bresnahan et al. (1999)*	↑			↑	↑	*ns*	*ns*	↑	↑	*ns*	↓
Lazzaro et al. (1998)				*ns*	↑	*ns*	*ns*	*ns*	*ns*	*ns*	↓
Lazzaro et al. (1999)				*ns*	↑	↑	*ns*	*ns*	↑	↑	↓
Monastra et al. (1999)*	↑										
Monastra et al. (2001)*	↑										
Eyes-Closed											
Barry et al. (2009)	↑							*ns*	↑	↓	↓
Chabot & Serfontein (1996)				*ns*	↑	*ns*	*ns*	*ns*	↑	↑	*ns*
Clarke at al. 1998				*ns*	↑	*ns*	*ns*	*ns*	↑	↓	↓
Clarke et al. 2001a	↑	↑		↑	↑	*ns*	*ns*	*ns*	↑	↓	↓
Clarke et al. 2001b	↑							↓	↑	↓	*ns*
Clarke et al. 2001c	↑	↑	↓	*ns*	↑	↓	↓	*ns*	↑	↓	↓
Clarke et al. 2001d				↑	↑	*ns*	*ns*	*ns*	↑	↓	↓
Clarke et al. 2002	↑	↑		*ns*	↑	↓	↓	↑	↑	↓	↓

Note. The definition of frequency bands may differ. * Analysis included adolescent and adult participants θ/β = theta/beta ratio; θ/α = theta/alpha ratio; δ/θ = delta/theta ratio; δ = delta; θ = theta; α = alpha; β = beta; ↑ = increased activity; ↓ = decreased activity; *ns* = non-significant; blank = not assessed.

EEG activity and abnormalities during resting state conditions have been investigated for over 40 years in childhood ADHD populations. Several signature patterns of activity have emerged. Table 2 provides a summary of key EEG studies investigating childhood ADHD. Although the investigation of resting state EEG activity in adult ADHD populations is limited,

similar patterns of activity have emerged. Table 3 provides a summary of key EEG studies investigating adult ADHD.

Table 3

Resting state EEG Findings in Adult ADHD Compared to Healthy Controls

	Ratio		Absolute Power				Relative Power			
Study	θ/β	θ/α	δ	θ	α	β	δ	θ	α	β
Eyes-Open										
Bresnahan et al. (1999)*	↑		↑	↑	*ns*	*ns*	↑	↑	↓	↓↑
Bresnahan et al. (2006)	↑		↑	↑	*ns*	*ns*	*ns*	↑	*ns*	↓
Bresnahan & Barry (2002)	↑		↑	↑	↑	↑	*ns*	↑	*ns*	*ns*
Loo et al. (2009)				*ns*	*ns*	↑				
Monastra et al. (1999)*	↑									
Monastra et al. (2001)*	↑									
Woltering et al. (2012)	↑	↑		↑	↓	↓		↑	↓	↓
Eyes-Closed										
Clarke et al. (2008)			↓	*ns*	*ns*	↓↑	*ns*	↑	*ns*	↓
Hermens et al. (2004)			↑	↑	*ns*	↓				
Koehler et al. (2009)	*ns*	*ns*	*ns*	↑	↑	*ns*				
Loo et al. (2009)				*ns*	↓	*ns*				
Woltering et al. (2012)	↑	↑		↑	↓	↓		↑	↓	↓

Note. The definition of frequency bands may differ. * Analysis included children and adolescent participants; θ/β = theta/beta ratio; θ/α = theta/alpha ratio; δ = delta; θ = theta; α = alpha; β = beta; ↑ = increased activity; ↓ = decreased activity; *ns* = non-significant; blank = not assessed.

Overall, increased theta activity has been the most common and consistently reported EEG abnormality in childhood ADHD research (Amer, Rakhawy, & El Kholy, 2010; Barry, Clarke, Johnstone, McCarthy, & Selikowitz, 2009; Bresnahan, Anderson, & Barry, 1999; Chabot & Serfontein, 1996; Clarke, Barry, McCarthy, & Selikowitz, 1998; 2001a; 2001b; 2001c; 2001d; 2002; Lazzaro et al., 1998; Lazzaro et al., 1999; Monastra et al., 1999; Monastra, Lubar, & Linden, 2001). Decreased beta activity (Bresnahan et al., 1999; Clarke et al., 1998; 2001a; 2001c; 2001d; 2002; Lazzaro et al., 1998; Lazzaro et al., 1999) and increased theta/beta ratios (Barry et al., 2009; Bresnahan et al., 1999; Clarke et al., 2001a; 2001b; 2001c; 2002; Monastra et al., 1999; Monastra et al., 2001) have also been reported

in childhood populations without discrepancy. However, this does not hold true for the EEG findings in adult ADHD research.

Although increased theta, decreased beta, and elevated theta/beta ratios have been reported in some adult ADHD populations, other studies failed to report classic deviations in beta (Bresnahan & Barry, 2002; Koehler et al., 2009; Loo et al., 2009) and theta/beta ratio (Koehler et al., 2009). The increase of slow wave activity coupled with reduced fast wave activity has led to the development of several EEG-based models of ADHD including the *Maturational Lag* model, *Developmental Deviation* model, and *Hypoarousal* model (review, see Barry, Clarke, & Johnstone, 2003). However, differences in the EEG presentation of children and adults may expose several shortcomings of these models across the lifespan.

1.3. Current EEG Models of ADHD

According to Barry et al. (2003), the maturational lag model is defined as a developmental lag in central nervous system (CNS) functioning in which children with ADHD present as developmentally inappropriate for their age and act in a manner fitting of a younger age cohort. From an electrophysiological standpoint, this model requires that EEG of children with ADHD fall within the activity range of a younger population. Specifically, the presence of elevated slow wave activity (delta and theta) and deficient fast wave activity (alpha, beta, and total power) are interpreted as representing maturational lag in the CNS (Clarke et al., 2001b; 2011; Mann, Lubar, Zimmerman, Miller, & Muenchen, 1992). The presence of increased theta activity and theta/beta ratios is commonly interpreted as a marker of maturational lag (Clarke et al., 1998; Lazzaro, et al., 1998). The developmental deviation model of ADHD asserts that the disorder is the result of abnormal functioning of CNS, in which the EEG activity is not considered normal in children of any age and not likely

to mature in a normal fashion (Barry et al., 2003). The work of Chabot and Serfontein (1996) and Clarke et al. (2001d) supports this hypothesis, as differences in EEG activity for children with ADHD deviated from the activity of younger controls. Additionally, Bresnahan et al. (1999) indicated that ADHD adults showed age related changes and normalization of some EEG parameters, but persistent elevated slow wave activity. Finally, the hypoarousal model proposes that ADHD behavior is the result of under-arousal in the CNS, which has been supported by electrodermal, cerebral blood flow, positron emission tomography, and EEG studies (Barry et al., 2003). Again, this model has lead researchers and clinicians to conceptualize the prevalence of increased theta, decreased beta, and increased theta/beta activity as a marker of cortical hypoarousal (Clarke et al. 2001; 2011).

While the majority of childhood ADHD cases may fit one or more of the models introduced, each has its limitations. Barry et al. (2003) assert that both the maturational and developmental deviation model fail to explain adult ADHD, emphasizing that behavioral research supports maturational improvement in hyperactivity with age, but persistent impairments in attention/impulsivity that support developmental deviation (Bellak & Black, 1992; Kinsbourne, 1973, as cited in Barry et al. 2003). Investigation of EEG parameters has led to a similar maturational lag/developmental deviation paradox. Bresnahan et al. (1999) analyzed the EEG of children, adolescents, and adults with ADHD, concluding that the maturational model accounted for the reduction of hyperactivity and beta deficits with increased age, whereas persisting inattention and elevated theta activity in adults support a developmental deviation.

The classification of the theta/beta ratio as a marker or discriminant for ADHD is questioned not only because of discrepant findings in adult ADHD research, but also for its

failure to explain behavior and its lack of reliability across studies. The first criticism is evidenced by EEG studies reporting a reduction of the theta/beta ratio in ADHD individuals across the lifespan to near normalized levels (Bresnahan et al., 1999; Monastra et al., 1999; Monastra et al., 2001), despite developmentally deviant symptoms. Additionally, several meta-analyses have investigated the diagnostic value of the theta/beta ratio in ADHD compared with healthy controls (Boutros, Fraenkel, & Feingold, 2005; Snyder & Hall, 2006). The most recent meta-analysis sought to correct statistical inaccuracies, standardize the electrode location, and assess the reliability of theta/beta ratio differences across studies (Arns, Conners, & Kraemer, 2012). Large effect sizes (ES) for increased theta/beta ratios among ADHD children 6-13 years (ES = 0.75) and 6-18 years old (ES = .62) were reported. However, a significant heterogeneity test revealed increased variance of ES across studies. Arns et al. (2012) concluded that an excessive theta/beta ratio cannot be considered a reliable diagnostic measure of ADHD, as the ESs were misleading and overestimated, and other explanatory variables for the effects have to be assumed.

Further, the work of Barry et al. (2009) provided evidence opposing the linkage between the theta/beta ratio and the hypoarousal model by investigating the correlation of the measure with skin conductance – a standard measure of CNS arousal. They concluded skin conductance was significantly negatively correlated with relative alpha, rather than the theta/beta ratio in children. In an adult ADHD population, Hermens and colleagues (2004) indicated a double dissociation of EEG and skin conductance levels in male and female adults with ADHD. Specifically, males presented with greater enhancement of absolute theta activity then females, while females alone presented with autonomic hypoarousal evidenced by lower skin conductance levels.

Finally, Lansbergen, Arns, van Dongen-Boomsma, Spronk, and Buitelaar (2011) investigated the efficacy of the theta/beta ratio as an ADHD discriminant when differences in individual alpha peak frequency (iAPF) were controlled, as individuals with a slower iAPF value often inflate the findings of increased theta activity (Arns et al. 2008). They reported that under the traditional frequency band definitions, the theta/beta ratio proved to be significantly higher in a group of ADHD children as compared to a sample of healthy children in a control group. However, this difference was no longer significant when iAPF based frequency band classification was used, indicating that iAPF may serve as a better marker for the maturational lag model.

As a whole, the findings presented support that individuals with ADHD do not represent a homogenous population, thus a single marker or model cannot accurately capture the behavioral and physiologic components of the disorder across the lifespan. Accordingly, researchers have moved beyond the search for a diagnostic discriminant and have begun to investigate alternative theories using QEEG analysis. In an attempt to develop theory-driven and prognostic oriented models for EEG interpretation, neurofeedback protocol selection, and medication response prediction, the *EEG Phenotype* model (Johnstone, Gunkelman, & Lunt, 2005) and *EEG Vigilance* models (Bente, 1964; Hegerl, Olbrich, Schönknecht, & Sander, 2008a) have emerged to explain trait and state differences in clinical populations.

1.4 EEG Phenotypes Model

The EEG phenotype model is an evidenced-based method for the classification of neurobehavioral syndromes based on the categorization of individual “trait” components using psychometric and QEEG measures (Johnstone et al., 2005). Upon review of clinical EEG

and QEEG studies, Johnstone and colleagues (2005) asserted that several commonly seen neurophysiological profiles or "phenotypes" emerged within the EEG literature, having specific implications in guiding treatment. Specifically, the following phenotype characteristics were observed: normal EEG, frontal slow, low iAPF, frontal beta spindles, low voltage, frontal alpha, persistent occipital alpha with eyes-open, temporal alpha, and high iAPF among others.

Table 4

EEG Phenotype Classifications and Definitions

Classification	Definitions
Normal EEG	EEG does not meet the criteria for classification of any other phenotype, no paroxysmal abnormalities
Frontal slow	Presence of slow activity in the frontal leads, activity is not considered frontal alpha or a slowed iAPF
Slow iAPF	Presence of an iAPF $\leq$ 9 Hz at Pz, dependent on age (> 10 years). For ages < 9, iAPF below 8.5, interpreted with caution
Frontal beta spindles	Presence of multiple occurrences of frontal beta spindles with an amplitude of 20μV and a center frequency > 14 Hz
Low voltage	Presence of reduced EEG power in all frequency bands, as evidenced by significantly decreased activity in discrete bands according to the subjects individual QEEG report
Frontal alpha	Presence of frontal alpha and significant increase in the alpha activity according to the subjects individual QEEG report, not due to high iAPF
Persistent alpha EO	Alpha power does not attenuate (<50%) during EO as compared to EC, with Pz as the site of primary analysis
Temporal Alpha	Presence of alpha in the temporal sites in the raw EEG data, independent of occipital and parietal alpha
High iAPF	Presence of an iAPF of $\geq$ 11 Hz at Pz

Note. Adapted from "EEG Phenotypes Predict Treatment Outcome to Stimulants in Children with ADHD," by M. Arns, J. Gunkelman, M. Breteler, and D. Spronk, 2008, *Journal of Integrative Neuroscience, 7*(3), p. 427,

Table 4 provides a summary of the EEG phenotypes and the neurophysiologic characteristics associated with each classification. Current literature supports the classification of EEG defined sub-types of ADHD (Chabot & Serfontein, 1996; Clarke et al., 1998; Clarke et al., 2001b; 2001d; 2011) and neurophysiological support for sub-types of

maturational lag, developmental deviation, and hypoarousal. However, the variability of treatment response within these sub-types prompted Arns et al. (2008) to investigate the presence and prognostic power of EEG phenotypes in childhood ADHD. Phenotype classification was determined by two independent raters (Kappa > 0.90) based on the presence of phenotype profile characteristics (outlined by Johnstone et al., 2005) in eye movement corrected eyes-open and eyes-closed EEG tracings.

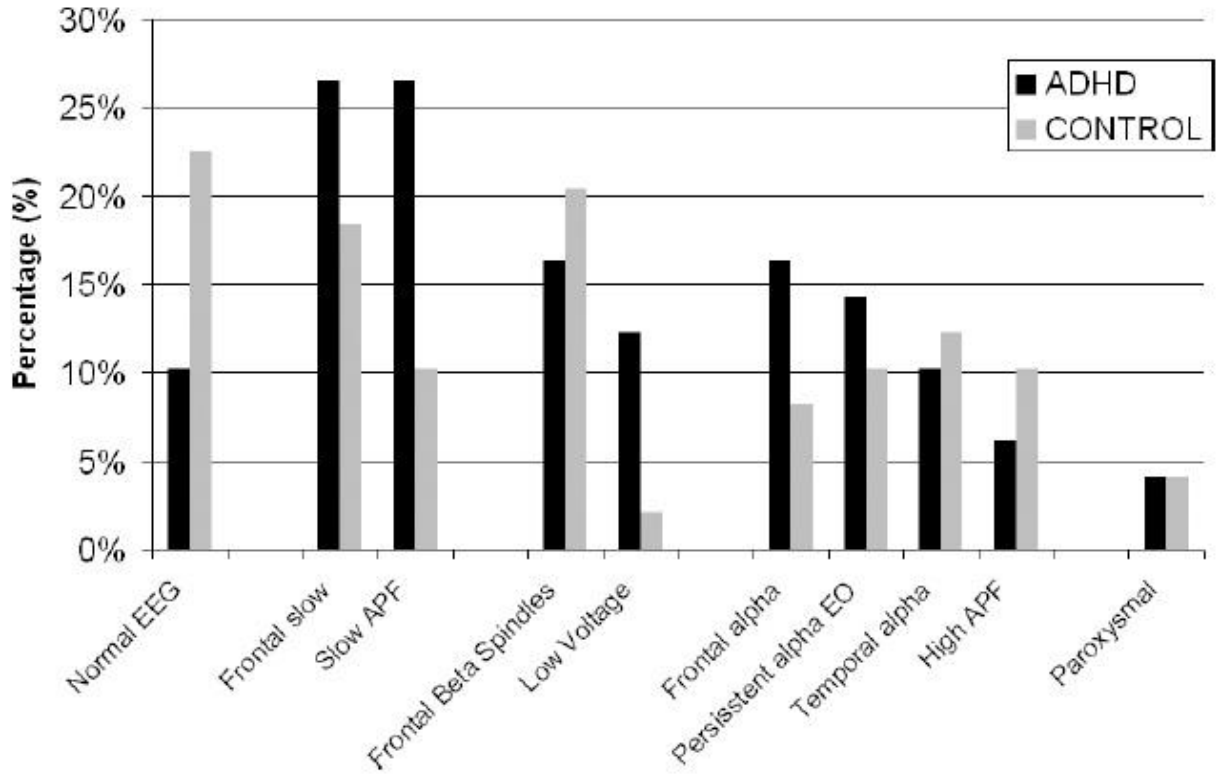

Figure 1. Occurrence of EEG phenotypes in a childhood ADHD and control group. Note the higher occurrence of frontal slow, slow alpha peak frequency, and low voltage EEG in the ADHD group. Also, note that the control group had occurrences of several EEG phenotypes. Only 25% displayed a "normal" EEG. Reprint from "EEG Phenotypes Predict Treatment Outcome to Stimulants in Children with ADHD," by M. Arns, J. Gunkelman, M. Breteler, and D. Spronk, 2008, Journal of Integrative Neuroscience, 7(3), p. 429. © Copyright (2008) World Scientific Publishing Company; http://www.worlkdscinet.com/jin/

Arns et al. (2008) indicated that although there were no significant differences between the EEG phenotypes of ADHD versus healthy control participants, ADHD children tended to

have a higher occurrence of frontal slow, slow iAPF, and low voltage EEG compared to controls. The occurrence of different EEG phenotypes for both ADHD and control participants as observed by Arns et al. (2008) is presented in Figure 1. Arns et al. (2008) highlighted the potential risk of combining frontal slow and slow iAPF phenotypes into the same category based on deviations in traditional frequency bands, as both may present with excessive frontal theta. The clinical impact of misclassification was further supported by the finding that ADHD participants with frontal slow responded to stimulant medication (common treatment for excessive slow wave activity) with clinically relevant reductions in the number of false negative errors on a continuous performance task, while individuals with slow iAPF did not.

1.5. EEG Vigilance Model

The EEG vigilance model is another personalized approach to EEG classification that focuses on "state" dependent changes in the raw data. EEG vigilance stages refer to the pattern of distinct states of global brain activation observable on the continuum from full wakefulness to sleep onset during an extended eyes-closed resting state recording (Olbrich et al., 2009). For the analysis of vigilance states, the power and temporal dynamics of the EEG in the four main frequency bands (delta, theta, alpha, and beta) are compared against specific criteria and classified in 1-second epochs in accordance with the latest version of the *Vigilance Algorithm Leipzig* (VIGALL) originally presented by Hegel and colleagues (2008a). For a visual of vigilance stage classifications and criteria, refer to Figure 2. Once classified, clinicians may calculate the percentage of time spent in each vigilance stage, frequency of stage shifts, and plot the time course of the data to gain insight about vigilance regulation patterns. This model has been utilized in the evaluation of adult patients with manic behavior (Hegerl et al., 2008a; Hegerl, Sander, Olbrich, & Schönknecht, 2009),

borderline personality disorder, and obsessive-compulsive disorder (Hegerl et al., 2008b). According to these studies, vigilance instability (faster descent into lower vigilance stages, more frequent stage shifts) may result in cognitive and attention deficits and/or auto-stabilization behaviors, including hyperactivity, sensation seeking, and distractibility – core ADHD symptoms (Hegerl, Himmerich, Engmann, & Hensch, 2010).

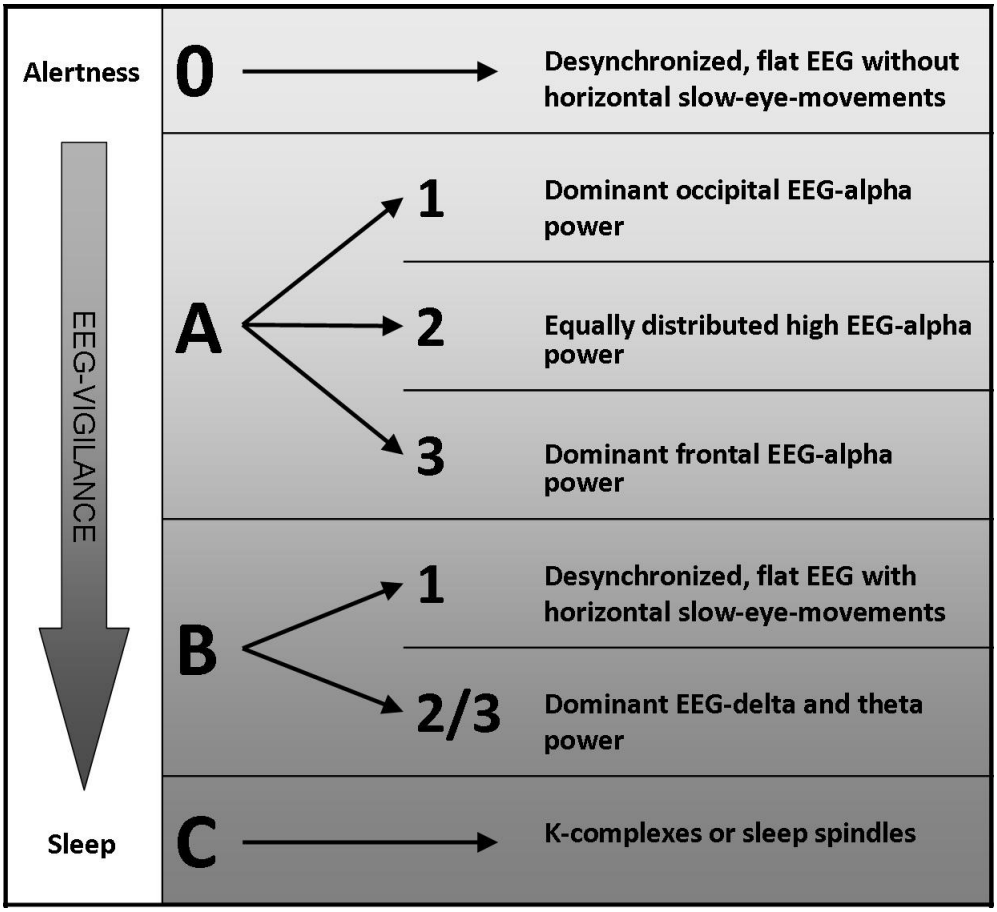

Figure 2. EEG-vigilance stages on the continuum from high to low vigilance levels (left column): The main criteria of the EEG-vigilance classification algorithm are given in seven distinct EEG-vigilance stages (middle columns). Adapted from "EEG-vigilance and BOLD effect during simultaneous EEG/fMRI measurement," by S. Olbrich, Mulert, C., Karch, S., Trenner, M., G., Leicht, O. Pogarell, and Hegerl, U., 2009, NeuroImage, 45(2), p.321, © 2008 by Elsevier, Inc.

Sander, Arns, Olbrich, and Hegerl (2010) investigated EEG vigilance regulation and stage dominance in a sample of children with ADHD, assessing the prognostic value of the model for determining stimulant medication response. They hypothesized that the common finding of increased frontal theta and reduced alpha activity in QEEG studies was the

product of rapid declines in vigilance and unstable regulation patterns. For the investigation, two minutes of artifact free eyes-closed data were classified into six vigilance stages; A1, A2, A3 with dominant alpha activity, stages B1, B2/3 with low amplitude non-alpha and increasing levels of theta and delta activity, and stage C characterized by sleep onset. Compared to non-ADHD controls, children with ADHD were classified as having unstable vigilance regulation, as they spent less time in the higher A1 stages and had stage changes more frequently. Sanders et al. (2010) also found that ADHD children with less stable vigilance showed worse pre-treatment performance on a computerized task, but better post-treatment improvements following a course of stimulant medication.

1.6. Proposed Study

To summarize, EEG has been used as a tool to search for the neurophysiologic markers of ADHD for over 40 years. Signature patterns of activity have been identified, theoretical models have been developed and tested, and new methods of classification have emerged, all with diagnostic and prognostic implications. However, the investigation and testing of these models have focused heavily on childhood ADHD, with limited research focused on an adult ADHD population. Of the studies targeting adult ADHD populations, one focused only on male participants (Clarke et al., 2008), several assessed a narrow set of QEEG variables (Koehler et al., 2009; Monastra et al., 1999; Monastra et al., 2001) or were limited to a single condition. Others included children and adolescents within group statistics (Bresnahan et al., 1999; Monastra et al., 1999; Monastra et al., 2001), utilized single electrode recordings (Monastra et al., 1999; Monastra et al., 2001), or assessed a narrow age range (Woltering et al., 2012). These studies presented contradictory findings or failed to yield any significant differences in comparisons to control groups. Additionally,

review of the current body of literature failed to identify any studies using iAPF-adjusted bandranges or EEG phenotype and EEG vigilance approaches in the assessment of adult ADHD. Given the limitations of the current EEG literature on adult ADHD and the need to evaluate the effectiveness of emerging methods of EEG classification in an expanded population, the following hypotheses were tested.

1.6.1. Hypothesis 1. ADHD adults will present with increased theta activity, decreased beta activity, and elevated theta/beta ratios as compared to an age and gender matched control population.

1.6.2. Hypothesis 2. QEEG differences between the adult ADHD and control group derived from the traditional frequency band definitions will differ from bandranges calculated based on individual alpha peak frequency.

1.6.3. Hypothesis 3. ADHD adults will present with an increased prevalence of the frontal slow phenotype and low iAPF phenotypes, compared to an age and gender matched control population.

1.6.4. Hypothesis 4. ADHD adults will present with a pattern of unstable EEG vigilance regulation, characterized by lower vigilance stage dominance and a greater number of stage changes compared to an age and gender matched control population.

2. Method

2.1. Participants

2.1.1. Inclusion criteria. Participants included adults 18 years and older with:

1. Diagnosis of Attention Deficit Disorder (inattentive, hyperactive, or combined type) according to DSM-IV criteria.
2. No additional serious physical, neurological, or psychiatric disorders with the exception of moderate depression, moderate anxiety, and personality disorders (excluding borderline personality disorder or anti-social disorder).
3. A full scale IQ > 80

Healthy control participants had to fulfill the same criteria, with the exception of an ADHD diagnosis, and were gender and age (+/- 1 year) matched to the clinical population. All participants were required to be proficient in written and spoken German language skills, with Basic English language speaking skills.

2.1.2. Recruitment. Study participants were recruited from the University of Tübingen student population, online ADHD support groups and forums, and the Tübingen community sample. Interested participants were screened over the phone for exclusion criteria and invited to participate in three to four hours of pre-assessment testing and EEG acquisition.

2.2. Psychometric Assessments

2.2.1. Demographic questionnaire. The demographic questionnaire assessed the following variables: gender, age, handedness, current year in college, years of education, occupation, previous episodes of head injury and unconsciousness, prior experience with

EEG, current medication and dosage history, and for female participants, menstrual cycle, and oral contraceptive information.

2.2.2. ADHS-Selbstbeurteilungsskala (ADHS-SB). The ADHS-SB is a 22-item sub-scale questionnaire of the Homburger ADHS-Skalen für Erwachsene (HASE; Rösler et al., 2008). The self-report questionnaire assesses the participant's current symptoms, according to the 18 diagnostic criteria for ADHD listed in the DSM-IV and ICD-10-R, on a 0 – 3 Likert-Scale (cut-off score for inclusion: > 18).

2.2.3. Beck-Depression-Inventory (BDI-II). The BDI-II is a 10-minute self-reported questionnaire assessing depression symptoms during the last two weeks (Beck, 1996; cut-off score for exclusion > 28).

2.2.4. Borderline Symptom Liste - Kurzform (BSL-23). The BSL-23 is a 23 item self-report questionnaire used to measure presence of Borderline Personality Disorder symptoms on a 0 - 4 Likert-Scale (Bohus et al., 2009; cut-off score for exclusion > 47).

2.2.5. Culture Fair Test-20-Revised (CFT-20-R). The CFT-20-R is a nonverbal intelligence test (Weiss, 2008; cut-off for exclusion < 80).

2.2.6. Edinburgh Handedness Inventory. The Edinburgh Handedness Inventory is a self-rated questionnaire that assesses right or left hand dominance for 10 activities (Oldfield, 1971).

2.2.7. Positive and Negative Affect Schedule (PANAS). The state version of the PANAS is a self-rated 20-item questionnaire that assesses momentary positive and negative emotions on a 1 – 5 Likert-Scale (Krohne, Egloff, Kohlmann, & Tausch, 1996).

2.2.8. Schlaffragebogen A (SF-A) und B (SF-B). The SF-A and SF-B is a 25-item German sleep questionnaire that assesses sleep quality and quantity for the previous night

of sleep, summarizing responses into five items: sleep quality, feeling of being well rested after sleeping, being psychologically well balanced before sleeping, being psychologically exhausted after sleep, and psychosomatic symptoms during sleep. Time of sleep onset and waking are also assessed (Görtelmeyer, 1981).

2.2.9. Stanford Sleepiness Scale (SSS). The SSS is a self-rated 1-item questionnaire assessing momentary sleepiness/alertness on 0 – 7 scale (Hoddes et al., 1973).

2.2.10. State-Trait Anxiety Questionnaire (STAI). The STAI is a self-rated 40-item questionnaire about temporary and long-term anxiety with a range of four possible responses (Spielberger, Gorusch, & Lushene, 1970; cut-off score for exclusion > 57).

2.2.11. Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I). The SCID-I is a semi-structured interview for the assessment of major DSM-IV Axis I diagnoses (First et al., 1997).

2.2.12. Wender-Reimherr Interview (WRI). The WRI is the structured interview of the sub-scale of the HASE (Rösler et al., 2008). The interview investigates the 28 psychopathological characteristics associated with adult ADHD. Responses are rated on a 0 – 2 Likert-Scale.

2.2.13. Wender Utah Rating Scale - Kurzform (WURS-K). The WURS-K is a 25-item sub-scale questionnaire of the HASE (Rösler et al., 2008). The questionnaire establishes a retrospective diagnosis of childhood ADHD symptoms for adult ADHD evaluation using a 0-4 Likert scale (cut-off score for inclusion: > 30).

2.3. EEG Recording

Continuous EEG was recorded during the following tasks:

- 8 min alternating eyes-open/eyes-closed alpha asymmetry

- 15 min eyes-closed resting state
- 5 min eyes-open resting state
- 10 min eyes-closed active auditory P300a/b
- 8 min eyes-closed passive auditory P300
- 13 min eyes-closed active auditory contingent negative variation (CNV)

Although all tasks were recorded, only the asymmetry task and resting state conditions were analyzed for the purposes of this study. EEG was recorded from 22 electrode sites (FP1, FP2, F7, F3, Fz, F4, F8, T7, C3, Cz, C4, T8, P7, P3, Pz, P4, P8, O1, Oz, O2, A1, and A2) according to the International 10-20 system, using an EEG cap system with Silver/Silver Chloride (Ag/AgCl) electrodes, referenced in common average, with the ground electrode located between Fz and Cz. Four additional latex-free adhesive Ag/AgCl electrodes collected electro-oculogram activity. Vertical electro-oculographic (VEOG) activity was recorded with an electrode attached 1 cm above and 1 cm below the left eye. Horizontal electro-oculographic (HEOG) activity was recorded with an electrode attached 1 cm beyond the external canthi of the right and left eye. All head electrodes were activated with conductive gel. When applicable, the impedance values assessed were kept below 5 kΩ (cross-equilibrated within 1 kΩ) or the DC offset was monitored and kept below $\pm$ 25,000 µV peak-to-peak. Additional physiological sensors collected data throughout the recording and included the following: respiration, electrodermal activity, electrocardiogram, and skin temperature. Only data from the EEG recordings were analyzed for the purpose of this investigation.

All participants were asked to refrain from drinking alcohol or taking ADHD medications twenty-four hours before the EEG measurement and refrain from drinking

coffee and smoking cigarettes for two hours before the EEG measurement. Upon arrival, all participants provided written informed consent to participate in the study, in accordance with the convention of Helsinki and the approval of the Ethics Committee of the Faculty of Medicine at the University of Tübingen. During the fitting of the EEG and physiological sensors, participants were informed about all measures and familiarized with the study protocol. For the EEG procedure, participants were seated comfortably in a reclining chair located in a private, climate controlled, light and sound attenuated recording suite. All task instructions were given verbally by the EEG technician in English and repeated in German in a pre-recorded audio file embedded in the acquisition protocol for standardization and clarity. Participants were requested to remain relaxed and keep their eyes focused in a fixed direction throughout the recording to reduce electromyographic and EOG artifacts – respectively.

EEG data was recorded using two different acquisition units, the Nexus-32 amplifier and BioTrace+ software, version V2011A1 (Mind Media B.V., Netherlands; 24 bit A/D conversion, 512 Hz sampling rate, bandpass = 0.01 and 70 Hz) and the Brain Amp Standard (Brain Products GmbH, Germany; 16 bit A/D conversion, 200 Hz sampling rate, bandpass = 0.05 and 70 Hz, 50 Hz notch filter). Once the recording was completed, the data and event markers for the alpha asymmetry and eyes-closed/eyes-open resting state tasks were exported in EDF+ format for analysis specific processing procedures in third-party software packages. Once all data files were exported and imported into Brain Vision Analyzer software, version 2.0 (Brain Products GmbH, Germany), the files were down sampled and filtered to the same technical specifications. A repeated measures analysis of variance (ANOVA) with group (ADHD and control) and amplifier (Brain Products and Mind Media) as

between-subjects factors, and within-subjects factors of frequency (delta, theta, alpha, and beta) and electrode site (9 pooled regions) was undertaken separately for each condition (eyes-closed and eyes-open) and spectral analysis (absolute and relative power). No group by amplifier by frequency by electrode site interaction was observed for eyes-closed absolute power, $F(1, 88) = 3.136$, $p = .080$, $\eta_p^2 = .003$, eyes-closed relative power, $F(1, 88) = 1.513$, $p = .222$, $\eta_p^2 = .017$, eyes-open absolute power, $F(1, 88) = 1.874$, $p = .175$, $\eta_p^2 = .021$, or eyes-open relative power, $F(1, 88) = 3.143$, $p = .080$, $\eta_p^2 = .034$ (Bonferroni adjusted α, $p < .001$).

2.4. Data Processing Procedures

To test each hypothesis, several analysis specific processing procedures were employed using a variety of third-party software packages.

2.4.1. QEEG. To test *Hypothesis 1,* the EDF+ EEG file was imported to the Brain Vision Analyzer software, version 2.0 (Brain Products GmbH, Germany) for pre-processing. When applicable, data were down sampled to 200 Hz, re-referenced to linked ears, bandpass filtered at 1.5–25 Hz, and segmented into individual 5 min eyes-closed and eyes-open data files. Data from FP1, FP2, F7, F3, Fz, F4, F8, T7, C3, Cz, C4, T8, P7, P3, Pz, P4, P8, O1, and O2 were exported in ASCII format. The individual eyes-closed and eyes-open files were imported into the WinEEG Advanced software, version 2.84.44 (WinEEG, St. Petersburg, Russia 2005) for two-phase visual inspection, artifact rejection, and spectral analysis. Artifact rejection was based on visual and computer selection. During phase-one of the artifact rejection, each 1 s epoch was visually inspected for technical artifacts and marked. Computer based artifact rejection was completed using the independent component analysis (ICA) method. During ICA correction, the EEG was decomposed into 19

signal components. Only components that reflected VEOG, HEOG, EKG, and EMG artifacts, without reducing non-artifact signals, were removed. The file was visually inspected a second time to ensure all major artifacts were removed. Files required a minimum of 200 artifact free epochs for inclusion in the Fourier analysis. The EEG was analyzed (1 s epochs, 0% Hanning window) in four frequency bands: delta (1.5-3.5 Hz), theta (3.5-7.5 Hz), alpha (7.5-12.5 Hz), beta (12.5-25 Hz) for both absolute and relative power. Theta/alpha and theta/beta power ratios were calculated by dividing the absolute power of the lower frequency band by the power of the higher frequency band. To test *Hypothesis 2*, a second Fourier analysis was completed using frequency bandranges calculated using iAPF values. The following formulas were used to calculate each frequency band (Doppelmayr, Klimesch, Pachinger, & Ripper, 1998). When f(i) = alpha peak frequency, delta (f(i) – 8 to f(i) – 6), theta (f(i) - 6 to f(i) – 4), alpha (f(i) - 4 to f(i) + 2), beta (f(i) + 2 to 25 Hz.

2.4.2. EEG phenotype. Phenotype classification pre-processing was identical to the procedure for QEEG analysis, with artifact rejection and spectral analyses completed using Brain Vision Analyzer software. After a low pass filter (< 70 Hz), high pass filter (< 0.5 Hz), and a notch filter (50 Hz) was applied, the data were segmented into individual 2 min eyes-closed and eyes-open data files. For each participant, the difference overlay between the eyes-closed and eyes-open frequency spectra was calculated. The occipital or parietal site showing the maximum difference peak between 6.0-13.5 Hz for alpha suppression was defined as the iAPF value (Arns, Drinkenburg, Fitzgerald, & Kenemans, 2012; Arns, Drinkenburg, & Kenemans, 2012). The EEG tracings of the eyes-closed and eyes-open data were visualized in 10 s epochs per page and saved as PDF documents for hand scoring. Independent raters for this study included a combination of the first author and researchers

from Johnstone et al. (2005) and Arns et al. (2008). A high inter-rater reliability (Kappa > 0.90) was established for the senior researchers. Subsequently, the same training method was used to ensure consensus with the third rater.

The training procedure included review of seminal papers on the classification of iAPF (Doppelmayr et al., 1998; Klimesch, 1999; Niedermeyer, 1999) and EEG phenotype classification (Arns et al., 2008; Johnstone et al., 2005), followed by hand scoring exercises of non-study related EEG (30+) to establish agreement between the novice and expert raters. During the scoring exercises, the 2 min of raw data were inspected epoch by epoch to get an overall picture of the participants EEG characteristics followed by inspection of activity characteristics for each frequency band. Paroxysmal activity was also evaluated during the initial inspection. First, the difference overlay map was reviewed to determine the iAPF value. Then, a classification of “low” (< 9 Hz) or “high” (> 11 Hz) iAPF phenotype was assigned if applicable. Second, alpha activity characteristics were observed for classification of frontal alpha, temporal alpha, and persistent eyes-open occipital alpha phenotypes when applicable. Third, theta/delta activity characteristics were observed for classification of frontal slow phenotype when applicable. Finally, the record was inspected for multiple bursts of beta spindles (amplitude of 20μV and a center frequency > 14 Hz) over the frontal and central regions for classification of beta spindle phenotypes when applicable. If the record was free of paroxysmal activity or the dominance of any of the frequency specific characteristics, the files was assigned to the normal EEG phenotype (unremarkable). Following successful completion of the training phase, one or more phenotypes were assigned by two independent raters in accordance with the classification procedure and criteria used by Arns et al. (2008), as reported in Table 4. Raters were blind to the

assignment and diagnosis of participants that composed the healthy population published by Arns et al. (2010), but not blind to diagnosis for the classification of the ADHD participants.

2.4.3. EEG vigilance. Vigilance classification pre-processing was identical to the procedure for QEEG analysis, with artifact rejection and spectral analyses completed using Brain Vision Analyzer software. After a low pass filter (< 70 Hz), high pass filter (< 0.5 Hz), and a notch filter (50 Hz) were applied, the 15 min eyes-closed recording was segmented into 900, 1 s epochs. Data from FP1, FP2, F7, F3, Fz, F4, F8, T7, C3, Cz, C4, T8, P7, P3, Pz, P4, P8, O1, Oz, and O2 were included in the analysis. EEG vigilance stages (O, A1, A2, A3, B1, and B2/3+) were classified using the latest version of VIGALL macro (Hegerl et al., 2008a; Olbrich et al., 2009) within the Brain Vision Analyzer software. VIGALL uses a frequency spectrum from 2-25 Hz and calculates power in the four frequency bands (delta, theta, alpha, and beta). The bandwidths for the theta, alpha, and beta frequencies were determined based on the occipital iAPF of each participant. The alpha band was then defined as iAPF +/- 2 Hz, theta from 4.0 Hz to the beginning of the alpha band, and beta from the end of the alpha band to 25.0 Hz. For each 1 s epoch, the respective vigilance stage was defined based on the proportion of power in the four frequency bands. Vigilance levels decline as the power of dominant occipital alpha decreases and migrates towards the frontal lobes (A1, A2, and A3), is replaced by desynchronized flat EEG (B1), and followed by dominant theta and delta power (B2/3). Stage C vigilance was hand scored through visual inspection of each epoch for signs of sleep including K-complexes and sleep spindles. For a reference of the vigilance stages and classification criteria, refer to Figure 2.

2.5. Data Analysis

2.5.1. Demographic/psychometric assessments. A one-way ANOVA was used to compare questionnaire scores and individual demographic information between the ADHD group and control group for all hypotheses.

2.5.2. QEEG. To test *Hypotheses 1*, the frequency band output for each of the 19 electrode channels of both the eyes-closed and eyes-open data sets were pooled into nine regions by averaging the power at several electrode sites. The following regions were defined, left frontal (FP1, F3, F7), midline frontal (Fz), right frontal (FP2, F4, F8), left central (T7, C3), midline central (Cz), right central (T8, C4), left posterior (P7, P3, O1), midline posterior (Pz), and right posterior (P8, P4, O2). These regions formed a 3 x 3 grid across the scalp, permitting the analysis of topographic effects in a sagittal and lateral dimension. For each frequency band (delta, theta, alpha, beta, theta/alpha, and theta/beta power) and power analysis (absolute and relative power), the normal distribution of the data was inspected. Variables showing substantial skew (> 2) were log transformed on a band-by-band basis.

A mixed ANOVA was used to examine the effects of region and group for each frequency band, power analysis, and resting condition. The effects of region were examined in two orthogonal three-level repeated measures factors (sagittal and lateral), with planned Helmert contrasts within each factor. Within the sagittal factor, the first contrast compared the activity of the central (C) region with the mean of the frontal and posterior (F/P) region. The second contrast compared the activity between the frontal (F) and posterior (P) regions. Within the lateral factor, the first contrast compared the activity of the midline (M) with the mean of the left and right (L/R) hemispheres. The second contrast compared the activity

between the left (L) and right (R) hemisphere. These planned contrasts allowed for optimal clarification of electrode region effects within the sagittal and lateral dimensions. No Bonferroni-type correction to the significance level (α, p < .05) was applied, as each analysis only included planned group comparisons, topographic contrasts and interactions, and the total number of comparisons did not exceed the degrees of freedom for effect (Tabachnick & Fidell, 1989). A mixed analysis of covariance (ANCOVA) was used to examine the effects of region and group interactions controlling for age. As the directional nature of each comparison was not hypothesized, two-tailed probabilities are reported for all statistics. For significant between group effects and topographic interactions, the partial eta squared (η_p^2) was reported to describe the proportion of variance that the variable explained, independent of other variables in the analysis.

Effect size: $$\eta_p^2 = \frac{SS_{effect}}{SS_{effect} + SS_{residual}}$$

For all significant group by region interactions, bivariate or partial (age as a covariate when applicable) correlation coefficients were calculated between baseline ADHD behavioral measures and mean frequency band activity (mean power across 3 x 3 electrode grid) to investigate the relationship between resting state brain activity and behavior (Bresnahan & Barry, 2002; Koehler et al., 2009). Bonferroni-type adjustments to the statistical significance level (α, *p* < .05/number of significant frequency band interactions) were applied to control for Type I errors for multiple comparisons.

To test *Hypothesis 2,* the same mixed ANOVA procedure was used to examine the effects of region and group for iAPF derived frequency bands, power analyses, and resting conditions. Additionally, the same procedure for calculation of bivariate or partial

correlation coefficients was followed to examine the relationship between iAPF derived frequency band activity and baseline ADHD behaviors.

2.5.3. EEG phenotype. To test *Hypothesis 3*, a categorical variable was created to indicate the presence or absence of each phenotype classification. As the phenotype classification method is not an automated process and requires additional time, expense, and resources, a limited investigation was performed to evaluate whether a large-scale analysis of EEG phenotypes is justifiable in an adult ADHD population. For this analysis only, the control group differed from the participants used for the QEEG and EEG vigilance analyses. An age and gender matched control group was drawn from a healthy population published elsewhere (Arns, 2011; Arns, Gunkelman, Olbrich, Sander, & Hegerl, 2010). Phenotype classification for this population was completed by the same independent raters, with high inter-rater reliability (Kappa > 0.90). Accordingly, baseline differences for the ADHS-SB questionnaire were not available for this analysis. A Pearson's chi-squared test was used to investigate the relationship between group (ADHD, Control) and phenotype (present, absent) in a series of 2x2 cross-tabulation tables. For each significant association, an odds ratio was calculated and reported.

Odds ratio: $odds = \frac{P(Event\ Y)}{P(No\ Event\ Y)}$

When, $P\ (Event\ Y) = \frac{1}{1+ e^{(b_0 + b_1 x_1)}}$ and $P\ (No\ Event\ Y) = 1 - P\ (Event\ Y)$

A Bonferroni-type adjusted one-way ANOVA was used to compare questionnaire scores (α, $p < .01$) and mean frequency band activity (α, $p < .005$) between phenotype subgroups of the ADHD participants for the eyes-closed and eyes-open conditions.

2.5.4. EEG vigilance. To test *Hypothesis 4*, the mean percentage of all non-artifact segments were calculated for each vigilance stage. Due to a lack of normal distribution in the data, differences in the amounts of vigilance stages (O, A1, A2, A3, B1, B2/3, and C) and stage transitions (stage, sub-stage) in ADHD and control participants were tested using a Mann-Whitney *U*-test. As the directional nature of some comparison were hypothesized, one-tailed probabilities were reported when applicable. Bonferroni-type adjustments to the statistical significance level (α, $p = .007$) were applied to control for Type I errors for multiple comparisons. For significant comparisons, *z*-scores were converted into the effect size estimate, *r* (Rosenthal, 1991), in which a value of >.1 indicates a small effect, >.3 a medium effect, and >.5 a large effect.

Effect size: $r = \frac{Z}{\sqrt{N}}$

The same procedure for calculation of partial correlation coefficients was followed to examine the relationship between vigilance classification and baseline ADHD behaviors. A Bonferroni-type adjusted one-way ANOVA was used to compare questionnaire scores (α, $p < .01$) and mean iAPF adjusted frequency band activity (α, $p < .005$) between “low” and “high” vigilance subgroups of the ADHD group for the eyes-closed condition. ↜

3. Results

The results will be presented according to the hypothesis under investigation. As the population variables for each analysis differs, demographic, psychometric, and physiological information will be reported separately. The study flow is presented in Figure 3. Forty-eight adults with ADHD and 48 healthy controls initially met the study criteria and completed the EEG assessment. One study pair was excluded from the data pre-processing due to technical issues and excessive artifact epochs.

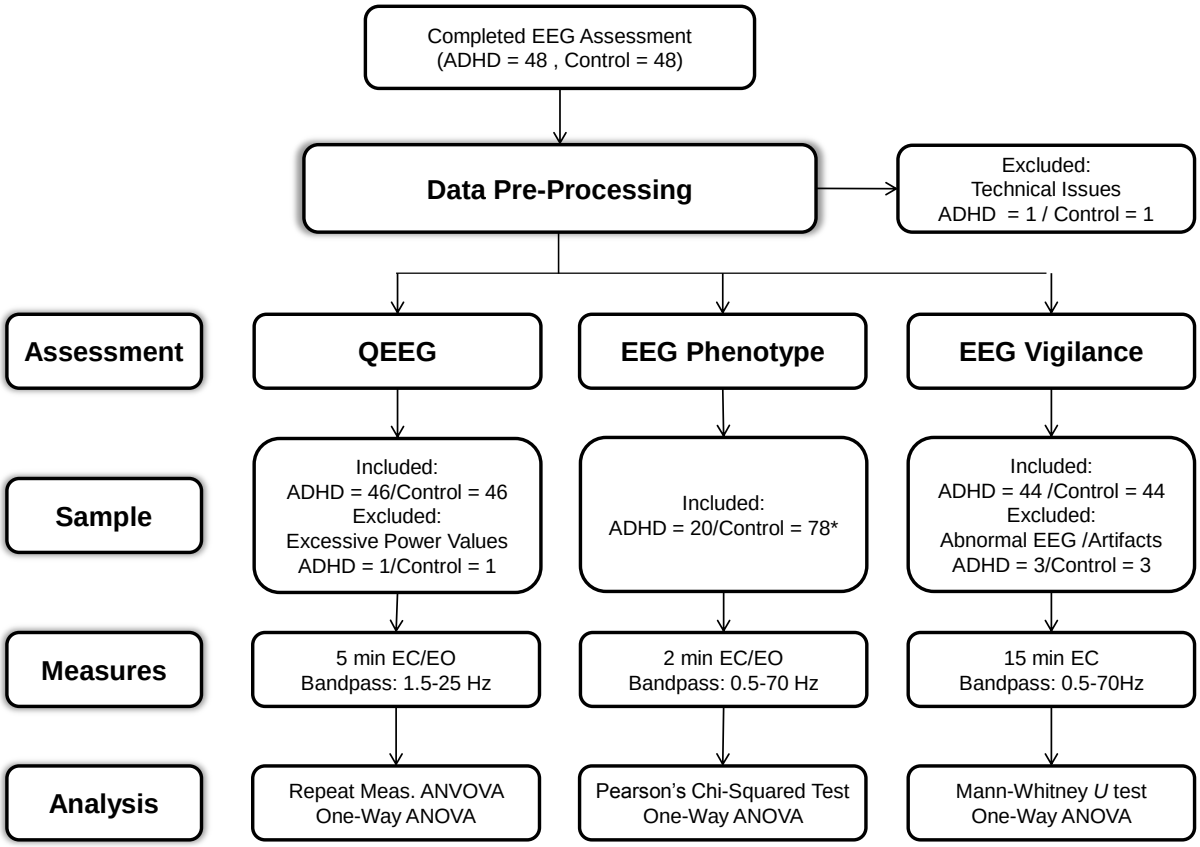

Figure 3. Flow of participants throughout the recruitment and analysis processes. Note: *The control group used for the phenotype classification comparison was age and gender matched and selected from the healthy control population published by Arns, Gunkelman, Olbrich, Sander, and Hegerl (2010).

3.1. Standard Frequency QEEG – Hypothesis 1

3.1.1. Demographics. Of the 47 matched pairs included in the data pre-processing steps, the EEG data of 46 ADHD adults and 46 healthy controls (male-to-female ratio, 1.4:1.0) were included in the QEEG analysis. One study pair was excluded from the final analysis due to the ADHD participant exhibiting excessive global alpha power, possibly due to the effects of an illicit drug. Means and standard deviations for demographic and psychometric data are presented in Table 5. No significant differences were found for age or iAPF values.

Table 5

Hypotheses 1and 2 - Mean (Standard Deviation) Demographic and Psychometric Data

Variables	ADHD	Control	*df*	*F*	*p*
Demographics	*n* = 46	*n* = 46			
iAPF [Hz]	10.4 (1.1)	10.1 (.91)	1,90	2.669	.106
Age [years]	35.4 (11.2)	35.5 (11.3)	1,90	.002	.963
Gender	27 Male	27 Male			
Time Variables					
Appointment Time [time]	13:38 (3:36)	14:05 (2:54)	1,91	.514	.475
Hours of Sleep [hours]	7:15 (1:55)	7:33 (1:15)	1,80	.686	.410
SSS [score]	3.1 (1.1)	2.6 (1.3)	1,83	3.751	.056
Psychometrics					
ADHS_total [score]	31.1 (7.3)	7.2 (5.4)	1,90	317.483	<.001
ADHS_attn [score]	16.6 (4.4)	3.8 (3.0)	1,90	265.221	<.001
ADHS_imp [score]	6.3 (3.0)	1.6 (1.7)	1,90	85.577	<.001
ADHS_hyp [score]	8.2 (3.0)	1.9 (1.9)	1,90	142.694	<.001
BDI-II_total [score]	13.2 (8.1)	3.5 (3.7)	1,90	55.118	<.001
PANAS_pos [score]	24.3 (6.4)	26.9 (6.0)	1,89	3.764	.056
PANAS_neg [score]	13.4 (3.3)	11.2 (2.0)	1,89	14.106	<.001

Note. ADHS = ADHS-Selbstbeurteilungsskala (Rösler et al., 2008), attn = inattention sub-scale, imp = impulsivity sub-scale, hyp = hyperactivity sub-scale, BDI-II = Beck-Depression-Inventory (Beck, 1996), PANAS = Positive and Negative Affect Schedule (Krohne et al., 1996), SSS = Stanford Sleepiness Scale (Hoddes et al., 1973).

3.1.2. Psychometrics. All participants in the ADHD group had a confirmed diagnosis of ADHD (DSM-IV) assessed by the HASE, which required the presence of ADHD in childhood and current symptoms of ADHD in adulthood evaluated by clinical interviews and ADHD rating scales. The cut-off for inclusion in the ADHD group required a rating of > 18. As expected, significant differences were observed between baseline scores of ADHD and mood ratings between the ADHD and control participants. Adults with ADHD scored significantly higher on all ADHD and mood questionnaires, with exception of the positive emotion subscale of the PANAS. No significant differences were observed between groups for time of appointment, total hours of sleep the night before the experiment, or momentary sleepiness at the start of the experiment. The Stanford Sleepiness Scale revealed that participants in both groups reported feeling between, (2) *"Functioning at high level, but not at peak, able to concentrate"* or (3) *"Awake, but relaxed, responsive but not fully alert"*.

3.1.3. Mixed ANOVA. Figures 4, 5, 6, and 7 provide a summary of differences between the ADHD and control group across the sagittal and lateral dimension during the eyes-closed and eyes-open conditions. Table 6 provides a summary of the significant group interactions for each traditionally defined frequency bandrange. The assumption of sphericity was violated for each frequency band ANOVA. As the sample size was sufficiently large and multivariate analysis of variance (MANOVA) is not dependent upon the assumptions of sphericity, the Wilks' Lambda multivariate test statistics are reported (O'Brien & Kaiser, 1985).

Delta. During the eyes-closed condition, no effects in absolute delta or relative delta power were observed, $F(1, 90) = 2.486$, $p = .118$, $\eta_p^2 = .027$ and $F(1, 90) = 2.717$, $p = .103$, $\eta_p^2 = .029$, respectively.

Similarly, during the eyes-open condition, no effects of absolute delta or relative delta power were observed, $F(1, 90) = 3.579$, $p = .062$, $\eta_p^2 = .038$ and $F(1, 90) = .107$, $p = .744$, $\eta_p^2 = .001$, respectively.

Theta. No effects in absolute theta power were observed during the eyes-closed condition, $F(1, 90) = 2.782$, $p = .099$, $\eta_p^2 = .030$. However, a significant group main effect was observed in relative theta power, $F(1, 90) = 4.350$, $p = .040$, $\eta_p^2 = .046$. The ADHD group ($M = 3.18$, $SD = .43$) presented with significantly greater global relative theta power compared to the control group ($M = 3.01$, $SD = .46$). In the sagittal dimension, relative theta activity was enhanced in the central compared to the frontal/posterior regions (C > F/P), $F(1, 90) = 43.864$, $p < .001$, $\eta_p^2 = .328$, and in the frontal compared to the posterior region (F > P), $F(1, 90) = 65.333$, $p < .001$, , $\eta_p^2 = .421$, across groups. In the lateral dimension, relative theta was enhanced in the midline compared to the hemispheres, (M > L/R), $F(1, 90) = 42.362$, $p < .001$, $\eta_p^2 = .320$, across groups. Group differences in the comparison of the two hemispheres were greater in the posterior than frontal region (group by F vs. P by L vs. R), $F(1, 90) = 7.150$, $p = .009$, $\eta_p^2 = .074$, with the ADHD group (2.99 ln-μV^2) showing enhanced right posterior relative theta compared to the control group (2.80 ln-μV^2).

During the eyes-open condition, there appeared to be global enhancement of absolute theta power in the ADHD group ($M = 1.39$, $SD = .48$) compared to the control group ($M = 1.20$, $SD = .62$). However, the group main effect failed to reach significance, $F(1, 90) = 3.201$, $p = .077$, $\eta_p^2 = .034$. In the sagittal dimension, absolute theta was enhanced in the

frontal compared to the posterior region (F > P), $F(1, 90) = 112.096$, $p < .001$, $\eta_p^2 = .555$, across groups. In the lateral dimension, midline activity was enhanced compared to the hemispheres (M > L/R), $F(1, 90) = 531.946$, $p < .001$, $\eta_p^2 = .855$, across groups. Group differences were observed for the comparison of central and frontal/posterior regions between the two hemispheres (group by C vs. F/P by L vs. R), $F(1, 90) = 4.718$, $p = .032$, $\eta_p^2 = .050$. Specifically, the ADHD group showed enhanced central activity in left hemisphere and enhanced frontal/posterior activity in the right hemisphere compared to the control group. No effects of relative theta power were observed, $F(1, 90) = .238$, $p = .627$, $\eta_p^2 = .003$ during the eyes-open condition. However, a significant group by sagittal by lateral interaction was observed, $V = .896$, $F(4,87) = 2.538$, $p = .046$, $\eta_p^2 = .104$. Across groups, relative theta activity was maximal in the frontal region (C > F/P; F > P), $F(1, 90) = 15.032$, $p < .001$, $\eta_p^2 = .143$ and $F(1, 90) = 130.348$, $p < .001$, $\eta_p^2 = .592$, and greater in the left than right hemisphere (L > R), $F(1, 90) = 43.047$, $p < .001$, $\eta_p^2 = .324$. The difference between the central region and the frontal/posterior regions was greater on the midline than in the hemispheres (C vs. F/P by M vs. L/R), $F(1, 90) = 9.721$, $p < .003$, $\eta_p^2 = .097$, across groups. Between groups, the ADHD group presented with significantly enhanced relative theta activity across the midline (group by C vs. F/P by M vs. L/R), $F(1, 90) = 4.558$, $p < .035$, $\eta_p^2 = .048$, left hemisphere dominance of central region activity, and enhanced right posterior activity (group by C vs. F/P by L vs. R), $F(1, 90) = 4.646$, $p < .034$, $\eta_p^2 = .049$.

Alpha. No effects in absolute alpha power were observed during the eyes-closed condition, $F(1, 90) = .614$, $p = .435$, $\eta_p^2 = .007$. Although there appeared to be a global reduction in relative alpha power in the ADHD group ($M = 3.68$, $SD = .44$) compared to the control group ($M = 3.83$, $SD = .37$), the group main effect failed to reach significance, $F(1, 90)$

= 3.752, *p* =.056, η_p^2 = .040. In the sagittal dimension, relative alpha was dominant in the posterior region (F < P; C < F/P), *V* = .479, *F*(2, 89) = 48.408, *p* < .001, η_p^2 = .521, across groups. A significant group by sagittal by lateral region interaction effect was observed, *V* = .847, *F*(4, 87) =3.940, *p* = .005, η_p^2 = .153, in which the control group demonstrated enhanced activity across both regional dimensions compared to the ADHD group. Group differences in the comparison of the two hemispheres were greater in the posterior than frontal region (group* by F vs. P by L vs. R) with the ADHD group (3.79 ln-μV^2) showing a trend toward deficient right posterior activity compared to the control group (3.94 ln-μV^2), *F*(1, 90) = 3.775, *p* =.055, η_p^2 = .040, **ns*.

During the eyes-open condition, no effects of absolute alpha or relative alpha power were observed, *F*(1, 90) = .203, *p* = .654, η_p^2 = .002 and *F*(1, 90) = 1.065, *p* = .305, η_p^2 = .012, respectively. However, in relative power a significant group by sagittal by lateral interaction was observed in which the ADHD group (3.66 ln-μV^2) showed decreased posterior midline activity compared to the control group (3.78 ln-μV^2; group by F vs. P by M vs. L/R), *F*(1, 90) = 4.164, *p* = .044, η_p^2 = .044.

Beta. Although there appeared to be globally enhanced eyes-closed absolute beta power in the ADHD group (*M* = 1.25, *SD* = .52) compared to the control group (*M* = 1.21, *SD* = .73), the group main effects failed to reach significance, *F*(1, 90) = 0.91, *p* = .763, η_p^2 = .001. In the lateral dimension, absolute beta activity was enhanced in the midline compared to the two hemispheres, *F*(1, 90) = 197.899, *p* < .001, η_p^2 = .687, across groups. Group differences in the enhancement of midline activity were observed between the frontal and posterior region (group by F vs. P by M vs. R/L), *F*(1, 90) = 4.749, *p* = .032, η_p^2 = .050, with the ADHD group showing significantly greater posterior midline activity, as well as diffuse frontal

enhancement compared to the control group. No significant effects were observed for relative beta power, $F(1, 90) = .176$, $p = .676$, $\eta_p^2 = .002$.

During the eyes-open condition, no effects of absolute beta or relative beta power were observed, $F(1, 90) = 3.078$, $p = .083$, $\eta_p^2 = .033$ and $F(1, 90) = .473$, $p = .493$, $\eta_p^2 = .005$, respectively.

Theta/alpha power. A significant main effect was observed for theta/alpha power during the eyes-closed condition, $F(1, 90) = 4.579$, $p = .035$, $\eta_p^2 = .048$, with the ADHD group ($M = .84$, $SD = .68$) showing enhanced ratios compared to the control group ($M = .59$, $SD = .51$). In the sagittal dimension, the theta/alpha ratio was enhanced in the central compared to frontal/posterior regions (C > F/P), $F(1,90) = 13.494$, $p < .001$, $\eta_p^2 = .130$, and in the frontal compared to the posterior regions (F > P), $F(1,90) = 67.950$, $p < .001$, $\eta_p^2 = .430$, across groups. In the lateral dimension, midline theta/alpha ratios were enhance compared to the hemispheres (M > L/R), $F(1,90) = 21.206$, $p < .001$, $\eta_p^2 = .191$, across groups. Between groups, this difference was significantly greater in the ADHD group (1.05 μV^2) compared to the control group (.65 μV^2; group by M > L/R), $F(1,90) = 4.485$, $p = .037$, $\eta_p^2 = .047$.

During the eyes-open condition, no main effect for theta/alpha was observed, $F(1, 90) = 1.640$, $p = .204$, $\eta_p^2 = .018$.

Theta/beta power. No effects in theta/beta power were observed during the eyes-closed or eyes-open conditions, $F(1, 90) = .272$, $p = .603$, $\eta_p^2 = .003$ and $F(1, 90) = .348$, $p = .556$, $\eta_p^2 = .004$, respectively.

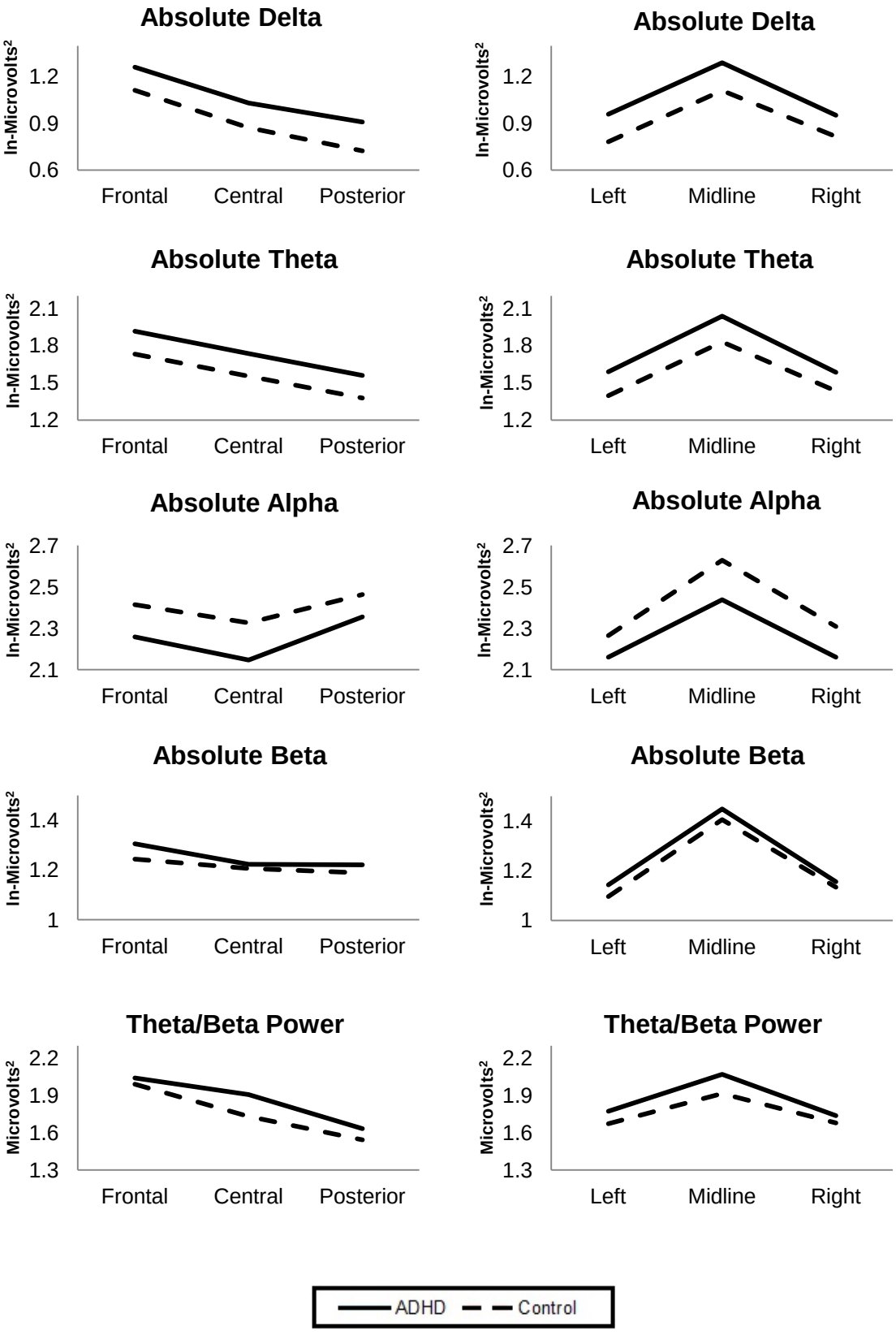

Figure 4. Absolute and theta/beta power (ln-transformed) using traditional frequency bands as a function of scalp region for the ADHD and Control group during eyes-closed condition. The left column reflects the sagittal regions and the right column reflects the lateral regions.

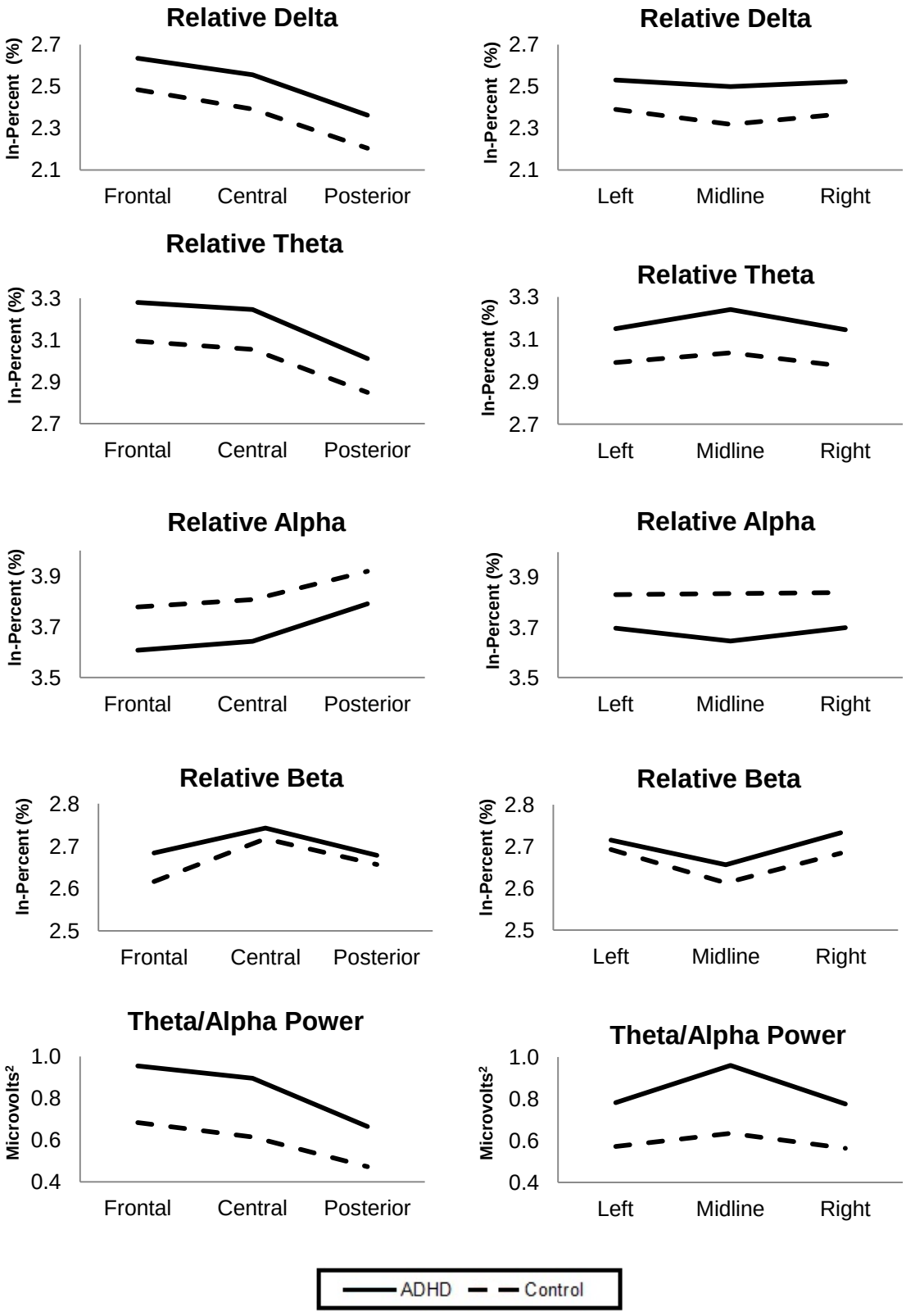

Figure 5. Relative and theta/alpha power (ln-transformed) using traditional frequency bands as a function of scalp region for the ADHD and Control group for eyes-closed condition. The left column reflects the sagittal regions and the right column reflects the lateral regions.

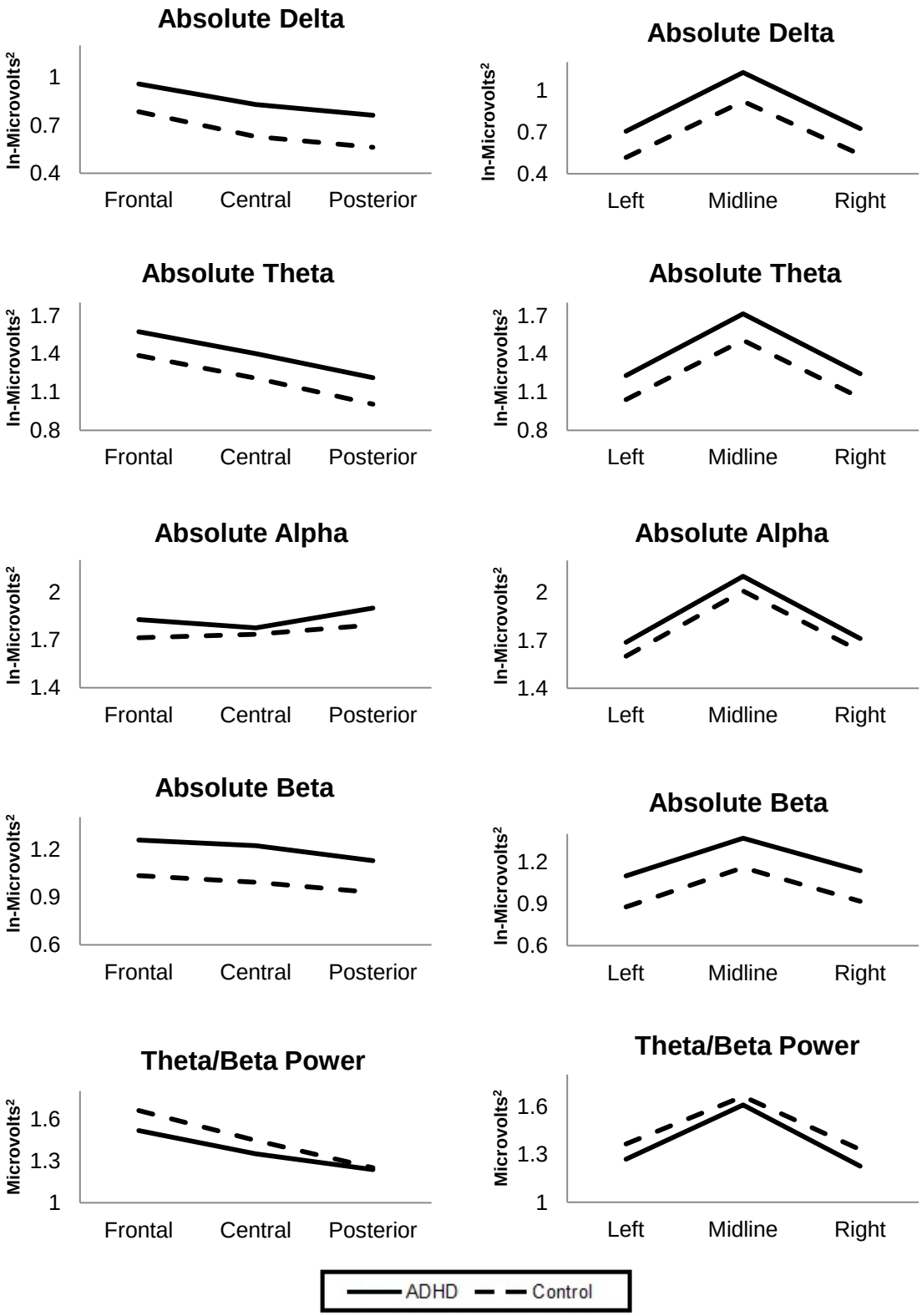

Figure 6. Absolute and theta/beta power (ln-transformed) using traditional frequency bands as a function of scalp region for the ADHD and Control group for eyes-open condition. The left column reflects the sagittal regions and the right column reflects the lateral regions.

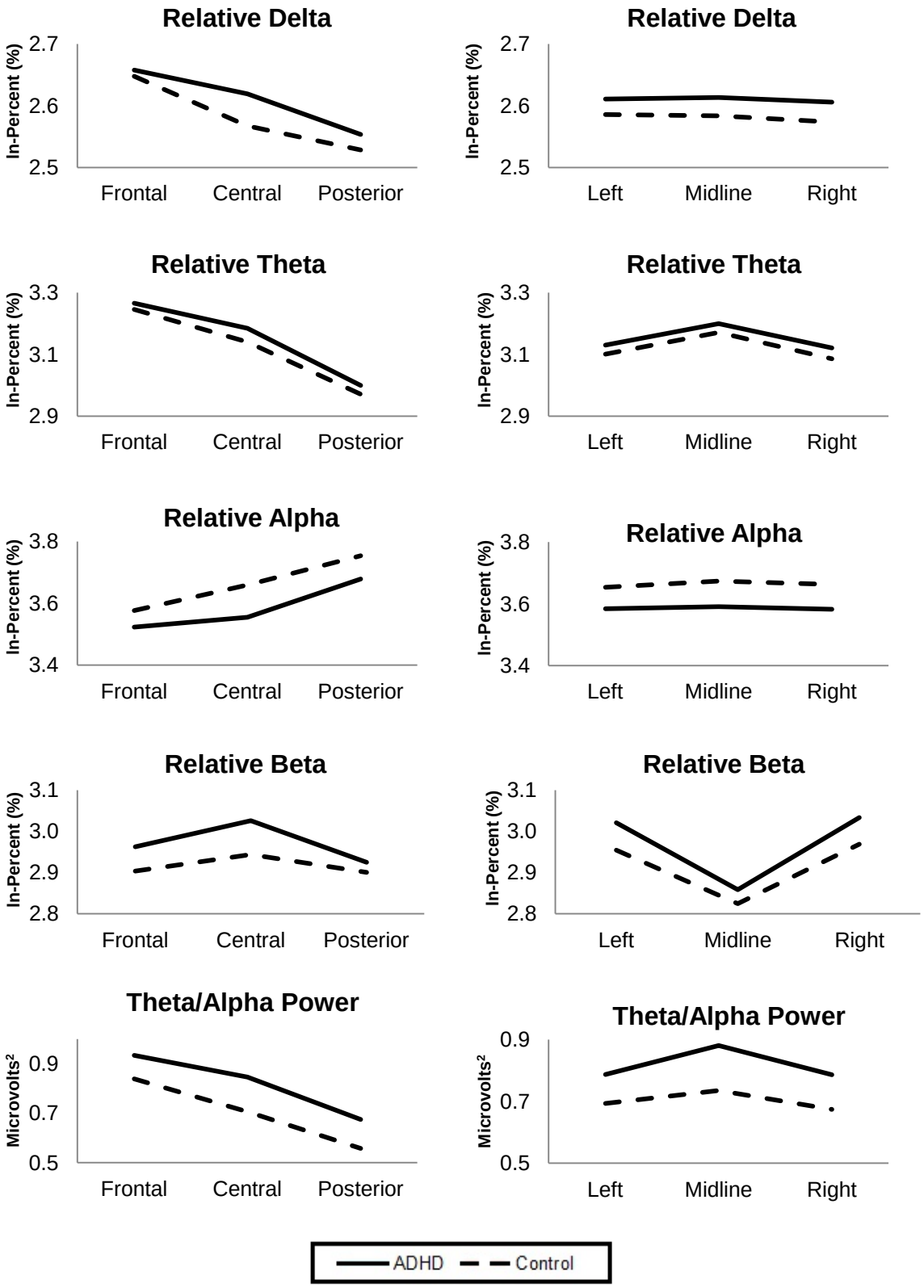

Figure 7. Relative and theta/alpha power (ln-transformed) using traditional frequency bands as a function of scalp region for the ADHD and Control group for eyes-open condition. The left column reflects the sagittal regions and the right column reflects the lateral regions.

Table 6

Summary of Significant Group Interactions with Traditional Frequency Bands

Condition/Frequency/Comparison	Absolute power				Relative power				
	df	*F*	*p*	η_p^2	*V*	*df*	*F*	*p*	η_p^2
Eyes Closed									
Theta									
Group main effect						1,90	4.350	.040	.046
Grp × Sag × Lat					.891	4,87	2.647	.039	.109
Grp × Sag × Lat - F vs. P × L vs. R						1,90	7.150	.009	.074
Alpha									
Grp × Sag × Lat					.847	4,87	3.940	.005	.153
Beta									
Grp × Sag × Lat - F vs. P × M vs. L/R	1,90	4.749	.032	.050					
Theta/Alpha									
Group main effect	1,90	4.579	.035	.048					
Grp × Lat – M vs. L/R	1,90	4.485	.037	.047					
Eyes Open									
Theta									
Grp × Sag × Lat					.896	4,87	2.538	.046	.104
Grp × Sag × Lat - C vs. F/P × M vs. L/R						1,90	4.558	.036	.048
Grp × Sag × Lat – C vs. F/ P × L vs. R	1,90	4.718	.032	.050		1,90	4.646	.034	.049
Alpha									
Grp × Sag × Lat - F vs. P × M vs. L/R						1,90	4.164	.044	.044

Note. Grp = group, Lat = lateral, Sag = sagittal, vs. = versus, F = frontal, P = posterior, C = central, L = left hemisphere, R = right hemisphere, M = midline, F/P = mean of the combined frontal and posterior regions, L/R = mean of the combined left hemisphere and right hemisphere regions

3.1.4. Analysis of covariance with age. Table 7 provides a summary of retained significant group interactions after controlling for age as a covariate. During the eyes-closed condition, age was significantly related to absolute delta, $F(1, 89) = 5.913$, $p = .017$, $\eta_p^2 = .062$, absolute theta, $F(1, 89) = 5.502$, $p = .021$, $\eta_p^2 = .058$, and theta/beta power, $F(1, 89) = 7.919$, $p = .006$, $\eta_p^2 = .082$. During the eyes-open condition, age was significantly related to absolute delta, $F(1, 89) = 5.124$, $p = .026$, $\eta_p^2 = .054$, absolute theta, $F(1, 89) = 4.798$, $p = .031$, $\eta_p^2 = .051$, relative beta, $F(1, 89) = 6.457$, $p = .013$, $\eta_p^2 = .068$, and theta/beta power,

$F(1, 89) = 11.502$, $p = .001$, $\eta_p^2 = .114$. However, there were no changes in the reported significant interactions in any frequency band after controlling for age.

Table 7

Summary of significant group interactions with traditional frequency bands, age (covariate)

Condition/Frequency/Comparison	Absolute power				Relative power				
	df	*F*	*p*	η_p^2	*V*	*df*	*F*	*p*	η_p^2
Eyes Closed									
Theta									
Group main effect						1,89	4.356	.040	.047
Grp × Sag × Lat					.887	4,86	2.742	.034	.113
Grp × Sag × Lat - F vs. P × L vs. R						1,89	7.583	.007	.079
Alpha									
Grp × Sag × Lat					.846	4,86	3.902	.006	.154
Beta									
Grp × Sag × Lat - F vs. P × M vs. L/R	1,89	5.003	.028	.053					
Theta/Alpha									
Group main effect	1,89	4.616	.034	.049					
Grp × Lat – M vs. L/R	1,89	4.435	.038	.047					
Eyes Open									
Theta									
Grp × Sag × Lat					.894	4,86	2.556	.044	.106
Grp × Sag × Lat - C vs. F/P × M vs. L/R						1,89	4.582	.035	.049
Grp × Sag × Lat – C vs. F/ P × L vs. R	1,89	4.831	.031	.051		1,89	4.602	.035	.049
Alpha									
Grp × Sag × Lat - F vs. P × M vs. L/R						1,89	4.124	.045	.044

Note. Grp = group, Lat = lateral, Sag = sagittal, vs. = versus, F = frontal, P = posterior, C = central, L = left hemisphere, R = right hemisphere, M = midline, F/P = mean of the combined frontal and posterior regions, L/R = mean of the combined left hemisphere and right hemisphere regions.

3.1.5. Correlation between behavioral and QEEG data. Figure 8 provides a summary of significant correlations between the mean power of traditional defined frequency bands and ADHD behavioral data for the entire study population. Based on the significant group by region interactions between the ADHD and control group, the mean power of traditionally defined eyes-closed relative theta, relative alpha, absolute beta, and theta/alpha power, as well as eyes-open absolute and relative theta, and relative alpha

were correlated with the behavioral data (Bonferroni adjusted α, $p < .007$). After controlling for age, when applicable, no significant partial correlation coefficients were observed between QEEG activity and behavioral measures during the eyes-closed condition. During the eyes-open condition, a significant relationship between mean absolute theta power and ADHD-SB total score (small), $r = .30$, $p = .004$ and men absolute thetapower and ADHD-SB hyperactive score (small), $r = .30$, $p = .005$ were observed. The correlations were in the positive direction, indicating that as the mean power increased, core symptoms of ADHD increased.

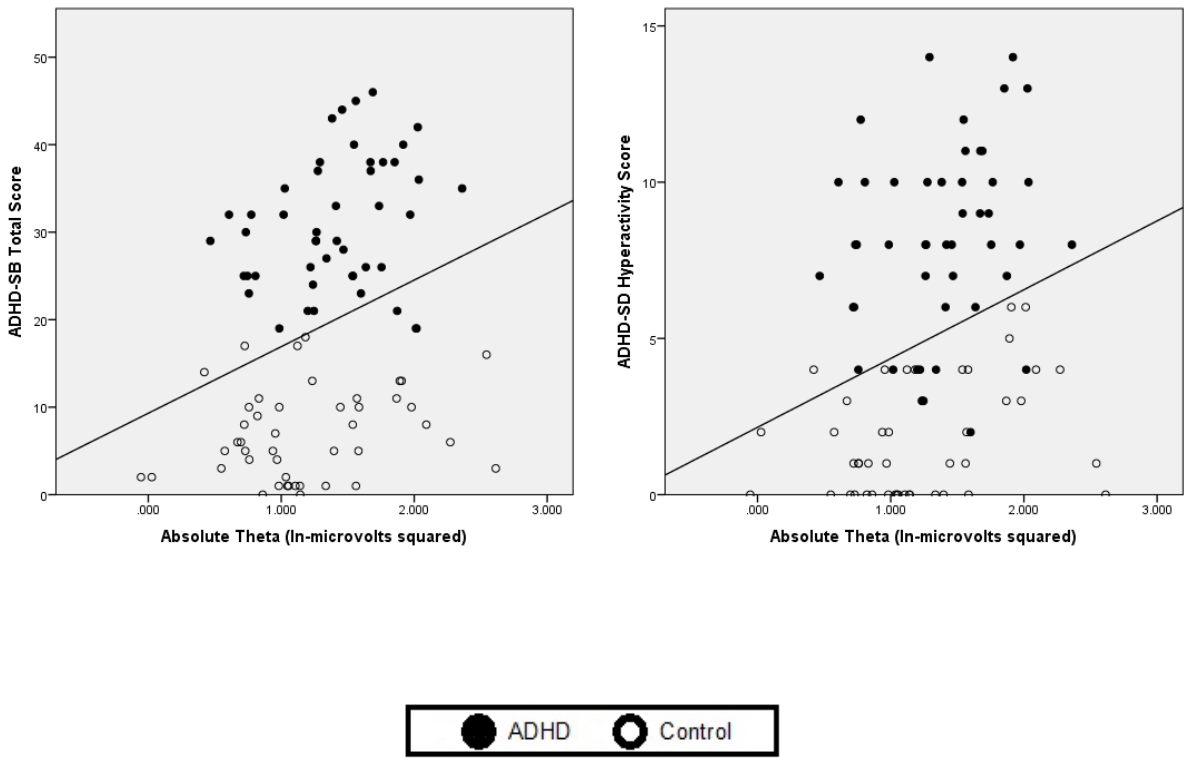

Figure 8. Age controlled partial correlation scatterplots of significant correlations between traditionally defined frequency bands and ADHD-SB behavioral questionnaires during the eyes-open condition. ADHD participants indicated with solid circle, control participants indicated with outlined circle. Note, age was negatively correlated with absolute theta, therefore, the residual values of frequency activity controlled for age was reported on the x – axis.

3.2. Individualized APF QEEG – Hypothesis 2

3.2.1. Demographics and psychometrics. The demographic and psychometric data presented for *Hypothesis 1* apply to *Hypothesis 2,* as the EEG was reanalyzed using individualized frequency bandranges.

3.2.2. QEEG analysis. Figure 9 provides a summary of the iAPF value distribution in the study population, as well as the iAPF-adjusted alpha frequency range. During phase two of the iAPF analysis, the frequency bands were recalculated according the iAPF and reanalyzed with a mixed ANOVA. The frequency bandranges assessed in *Hypothesis 1* included delta (1.5-3.5 Hz), theta (3.5-7.5 Hz), alpha (7.5-12.5 Hz), beta (12.5-25 Hz), theta/alpha, and theta/beta for both absolute and relative power. The iAPF values observed in the study population fell within the range of 8-14 Hz (*M* = 10.31, *SD* = 1.02). Accordingly, the iAPF bandranges assessed in *Hypothesis 2* included delta (1.5 $\pm$ 4.5 Hz to 5 $\pm$ 3 Hz), theta (5 $\pm$ 3 Hz to 7 $\pm$ 3 Hz), alpha (7 $\pm$ 3 Hz to 13 $\pm$ 3 Hz), and beta (13 $\pm$ 3 Hz to 25 Hz; Doppelmayr et al., 1998; Klimesch, 1999). Table 8 provides a summary of significant group interactions. Figures 10, 11, 12, and 13 provide a summary of iAPF defined EEG bandrange differences between the ADHD and control group, across the sagittal and lateral regions, during the eyes-closed and eyes-open conditions.

iDelta. During the eyes-closed condition, no significant effects of absolute delta or relative delta power were observed, $F(1, 90) = 3.561$, $p = .062$, $\eta_p^2 = .038$ and $F(1, 90) = 2.774$, $p = .099$, $\eta_p^2 = .030$, respectively.

During the eyes-open condition, no significant effects of absolute delta or relative delta power were observed, $F(1, 90) = 1.968$, $p = .164$, $\eta_p^2 = .021$ and $F(1, 90) = .066$, $p = .798$, $\eta_p^2 = .001$, respectively.

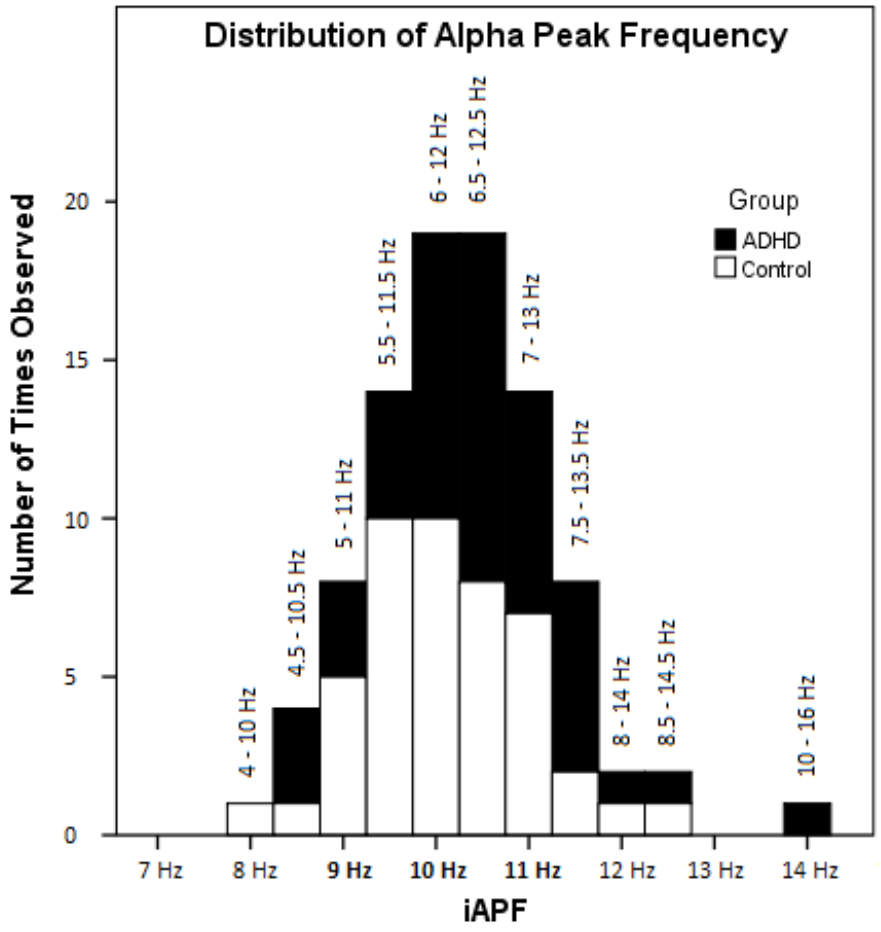

Figure 9. Distribution of iAPF in the study population. The iAPF values are plotted on the x-axis and the occurrence of the observed iAPF value across the entire study population are plotted along the y-axis. Individual group distributions of iAPF values are indicated (ADHD represented in black, control group represented in white). See the iAPF-adjusted alpha frequency range above the frequency plots, bold values indicate traditional alpha range that is not considered slow iAPF (< 9 Hz) or high iAPF activity (>11 Hz).

iTheta. No significant effects were observed for absolute and relative theta during the eyes-closed condition, $F(1, 90) = 1.773$, $p = .186$, $\eta_p^2 = .019$ and $F(1, 90) = 1.490$, $p = .225$, $\eta_p^2 = .016$, respectively.

During the eyes-open condition, no significant main effect of absolute theta power was observed, $F(1, 90) = .415$, $p = .521$, $\eta_p^2 = .005$. Group differences in the comparison of the central and frontal/posterior regions between the two hemispheres were observed (group by C vs. F/P by L vs. R), $F(1,90) = 4.004$, $p = .048$, $\eta_p^2 = .043$. Specifically, the ADHD group

showed enhanced central activity in the left hemisphere and enhanced right frontal activity compared to the control group. No significant main effect of relative theta power was observed, *F*(1, 90) = .545, *p* = .462, η_p^2 = .006. However, group differences in the comparison of the central and frontal/posterior regions between the hemispheres were observed (group by C vs. F/P by L vs. R), *F*(1,90) = 4.112, p = .046, η_p^2 = .044. Although the ADHD group (2.4 ln-μV^2) presented with a global reduction of relative theta power compared to the control group (2.5 ln-μV^2), the global activity of the control group was equipotential. The ADHD group presented with enhanced central activity in the left hemisphere.

iAlpha. No significant effects in absolute alpha power were observed during the eyes-closed condition, *F*(1, 90) = 3.82, *p* =.538, η_p^2 = .004. Although there appeared to be a global reduction in relative alpha power in the ADHD group (*M* = 3.87, *SD* = .48) compared to the control group (*M* = 4.02, *SD* =.28), the group main effect failed to reach significance, *F*(1, 90) = 3.297, *p* =.073, η_p^2 = .035. In the sagittal dimension, central relative alpha activity was reduced compared to the frontal/posterior regions (C < F/P), *F*(1, 90) = 21.499, *p* = < .001, η_p^2 = .193, and enhanced in the frontal compared to the posterior region (F > P), *F*(1, 90) = 27.338, *p* = < .001 , η_p^2 = .233, across groups. In the lateral dimension, activity in the right hemisphere was greater compared to the left (L < R), *F*(1, 90) = 7.091, *p* = .009, η_p^2 = .073, across groups. Between groups, a significant sagittal by lateral interaction was observed, with the control group (4.02 ln-μV^2) presenting with enhanced activity across both dimensions compared to the ADHD group (3.87 ln-μV^2), *V* = .896 *F*(4, 87) = 2.516, *p* =.047, η_p^2 = .104.

No significant effects in absolute alpha power were observed during the eyes-open condition, *F*(1, 90) = .382, *p* =.538, η_p^2 = .004. In relative alpha power, no group main effect

was observed, *F*(1, 90) = .335, *p* = .564, η_p^2 = .004. However, in the sagittal dimension, activity was reduced in the central region compared to the frontal/posterior regions (C < F/P), *F*(1, 90) = 23.874, *p* < .001, η_p^2 = .210, and greater in the posterior compared to the frontal regions (F < P), *F*(1, 90) = 62.772, *p* < .001, η_p^2 = .411, across groups. The reduction of central activity differed significantly between the groups (group by C by F/P), *F*(1, 90) = 10.906, *p* = .001, η_p^2 = .108. Specifically, the ADHD group (3.77 ln-μV^2) presented with significantly reduced central activity compared to the control group (3.84 ln-μV^2).

iBeta. No significant effects in absolute or relative beta power were observed during the eyes-closed condition, *F*(1, 90) = .039, *p* =.845, η_p^2 < .001 and *F*(1, 90) = .046, *p* =.830, η_p^2 < .001, respectively. However, in the sagittal dimension, central relative beta power was enhanced compared to the frontal/posterior regions (C > F/P), *F*(1, 90) = 30.019, *p* < .001, η_p^2 = .250, across groups. In the lateral dimension, midline activity was decreased compared to the two hemispheres (M < L/R), *F*(1, 90) = 51.337, *p* < .001, η_p^2 = .363, across groups. Group differences in the enhancement of central activity at the midline were observed (group by C vs. F/P by M vs. L/R), *F*(1, 90) = 4.282, *p* = .041, η_p^2 = .045, with the ADHD group presenting with less central and posterior relative beta activity compared to the control group.

During the eyes-open condition, no significant effects of absolute beta or relative beta power were observed, *F*(1, 90) = 1.667, *p* = .200, η_p^2 = .018 and *F*(1, 90) = .132, *p* = .717, η_p^2 < .001, respectively.

iTheta/alpha power. No significant effect in theta/alpha power was observed during the eyes-closed or eyes-open condition, *F*(1, 90) = 2.623, *p* = .109, η_p^2 = .028 and *F*(1, 90) = .084, *p* = .773, η_p^2 = .001, respectively. However, a significant group by sagittal interaction was observed during the eyes-open condition. Across groups, central theta/alpha ratios

were greater in the central than frontal/posterior regions (C > F/P), $F(1, 90) = 4.854$, $p = .030$, $\eta_p^2 = .051$, but maximal in the frontal compared to posterior regions (F > P), $F(1, 90) = 139.312$, $p < .001$, $\eta_p^2 = .608$. Between groups, the enhancement of central theta/alpha power was greater in the ADHD group (.32 μV^2) compared to the control group (.31 μV^2).

iTheta/beta power. No significant effects in theta/beta power were observed during the eyes-closed or eyes-open conditions, $F(1, 90) = .998$, $p = .320$, $\eta_p^2 = .011$ and $F(1, 90) = 1.387$, $p = .242$, $\eta_p^2 = .015$, respectively.

Table 8

Summary of Significant Group Interactions with iAPF Frequency Bands

Condition/Frequency/Comparison	Absolute power					Relative power			
	df	*F*	*p*	η_p^2	*V*	*df*	*F*	*p*	η_p^2
Eyes Closed									
iAlpha									
Grp × Sag × Lat					.896	4,87	2.516	.047[t]	.104
iBeta									
Grp x Sag × Lat – C vs. F/P × M vs. R/L						1,90	4.282	.041	.045
Eyes Open									
iTheta									
Grp × Sag × Lat – C vs. F/ P × L vs. R	1,90	4.004	.048[t]	.043		1,90	4.112	.046[t]	.044
iAlpha									
Grp × Sag					.892	2,89	5.396	.006	.108
Grp × Sag – C vs. F/P						1,90	10.906	.001	.108
iTheta/Alpha									
Grp x Sag - C vs. F/P	1,90	6.147	.015	.064					

Note. Grp = group, Lat = lateral, Sag = sagittal, vs. = versus, F = frontal, P = posterior, C = central, L = left hemisphere, R = right hemisphere, M = midline, F/P = mean of the combined frontal and posterior regions, L/R = mean of the combined left hemisphere and right hemisphere regions, [t] same interaction was significant using the traditional frequency bands.

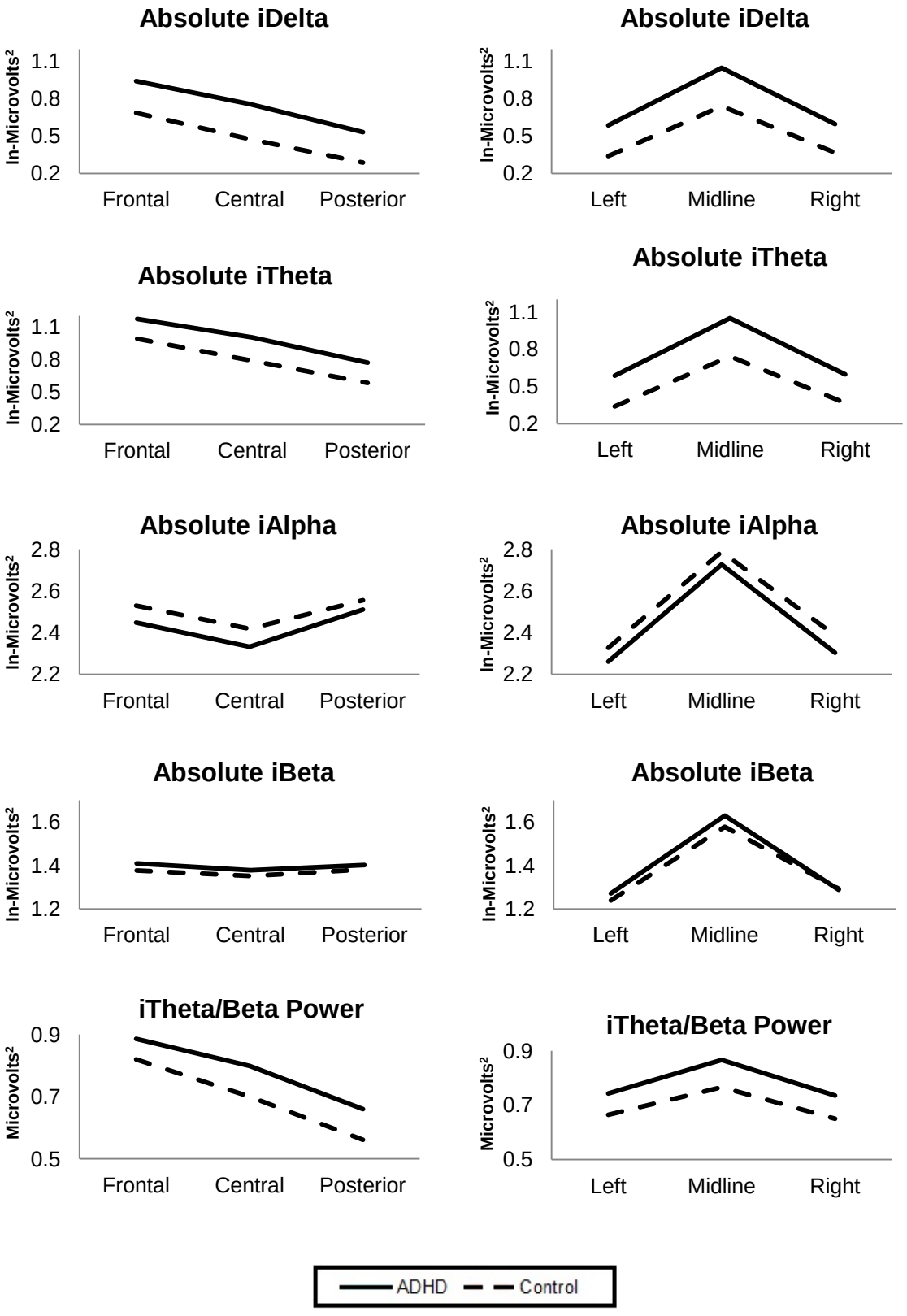

Figure 10. Absolute and theta/beta power (ln-transformed) using iAPF band calculation as a function of scalp region for the ADHD and Control group during eyes-closed condition. The left column reflects the sagittal regions and the right column reflects the lateral regions.

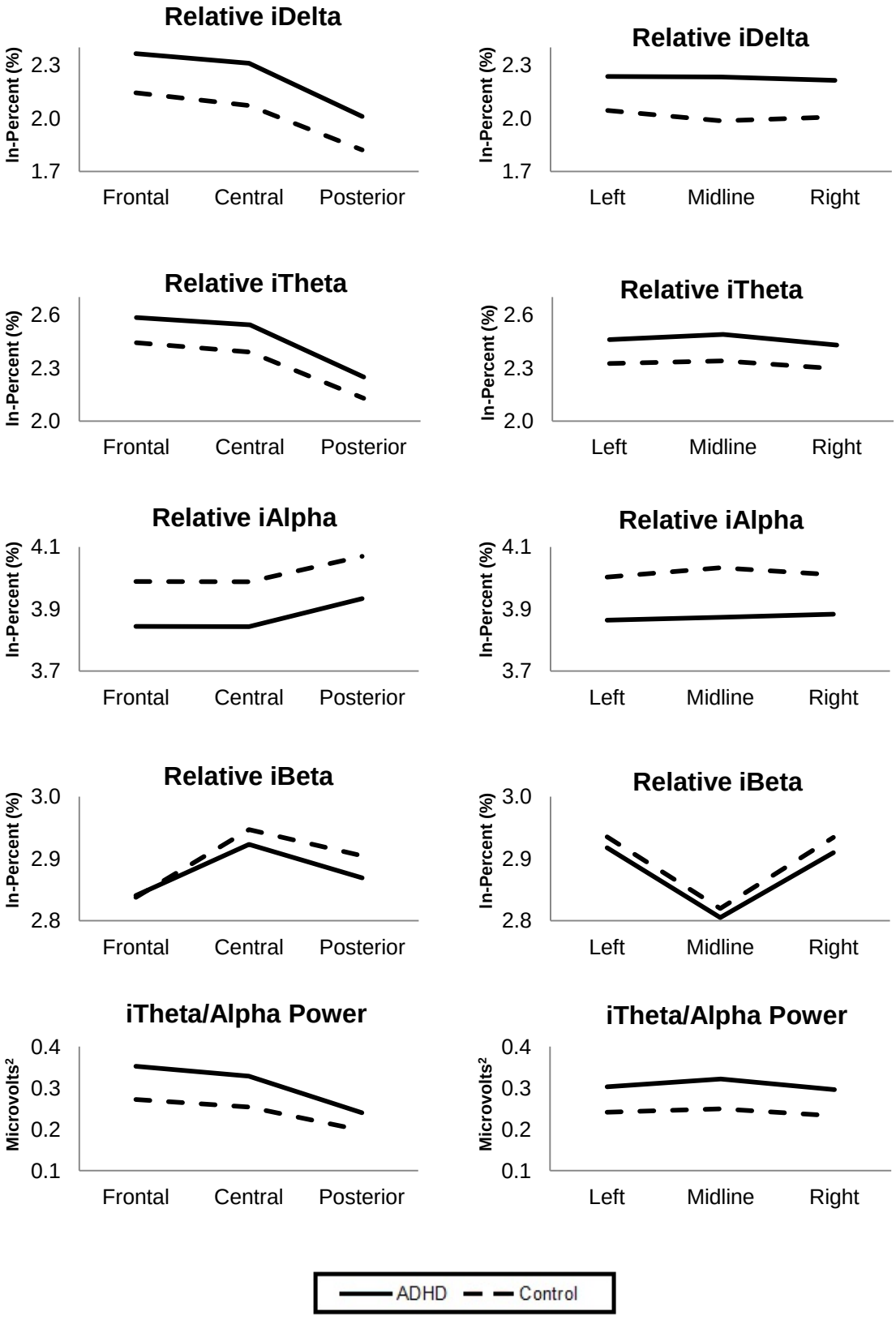

Figure 11. Relative and theta/alpha power (ln-transformed) using iAPF band calculation as a function of scalp region for the ADHD and Control group for eyes-closed condition. The left column reflects the sagittal regions and the right column reflects the lateral regions.

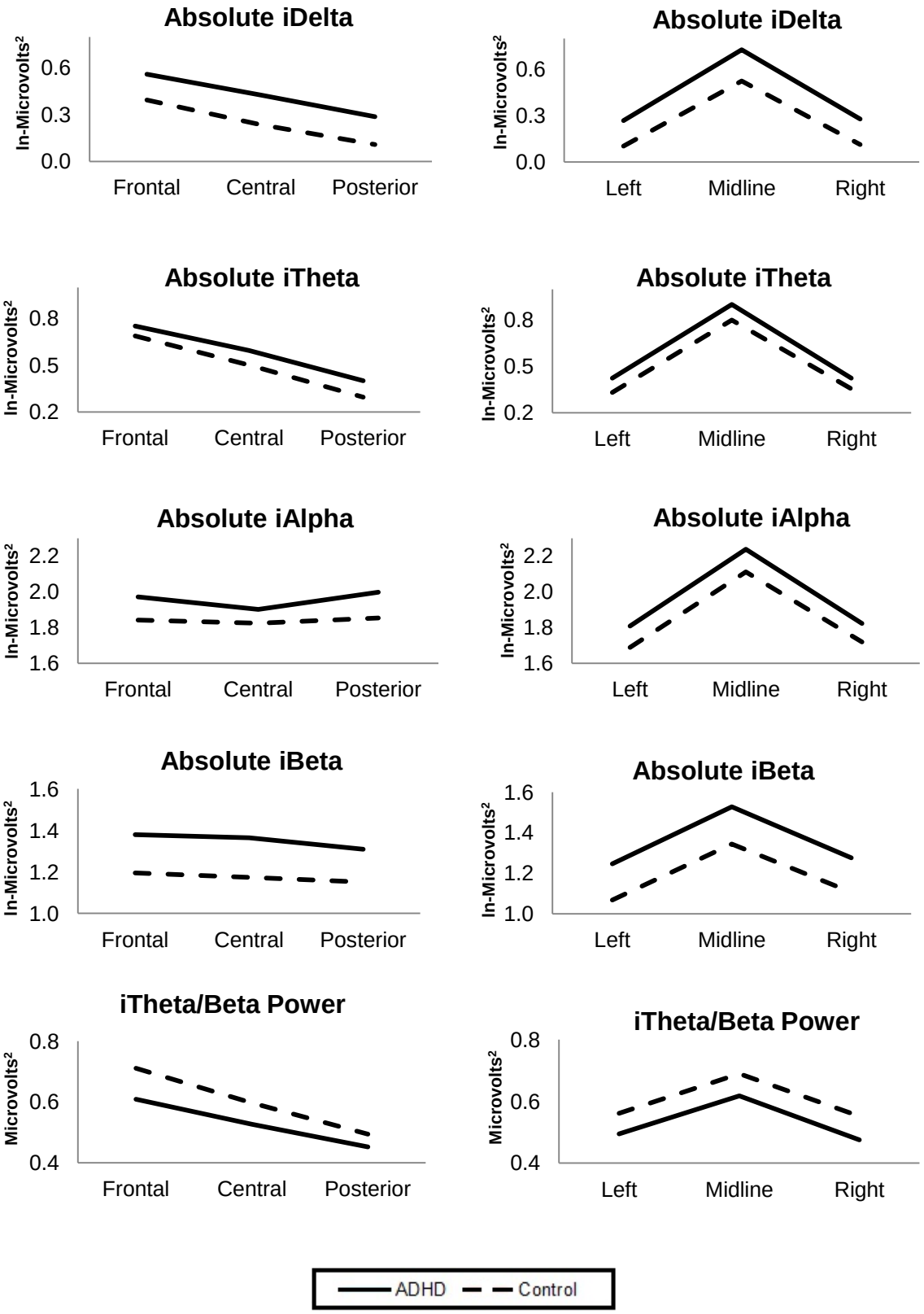

Figure 12. Absolute and theta/beta power (ln-transformed) using iAPF band calculation as a function of scalp region for the ADHD and Control group during eyes-open condition. The left column reflects the sagittal regions and the right column reflects the lateral regions.

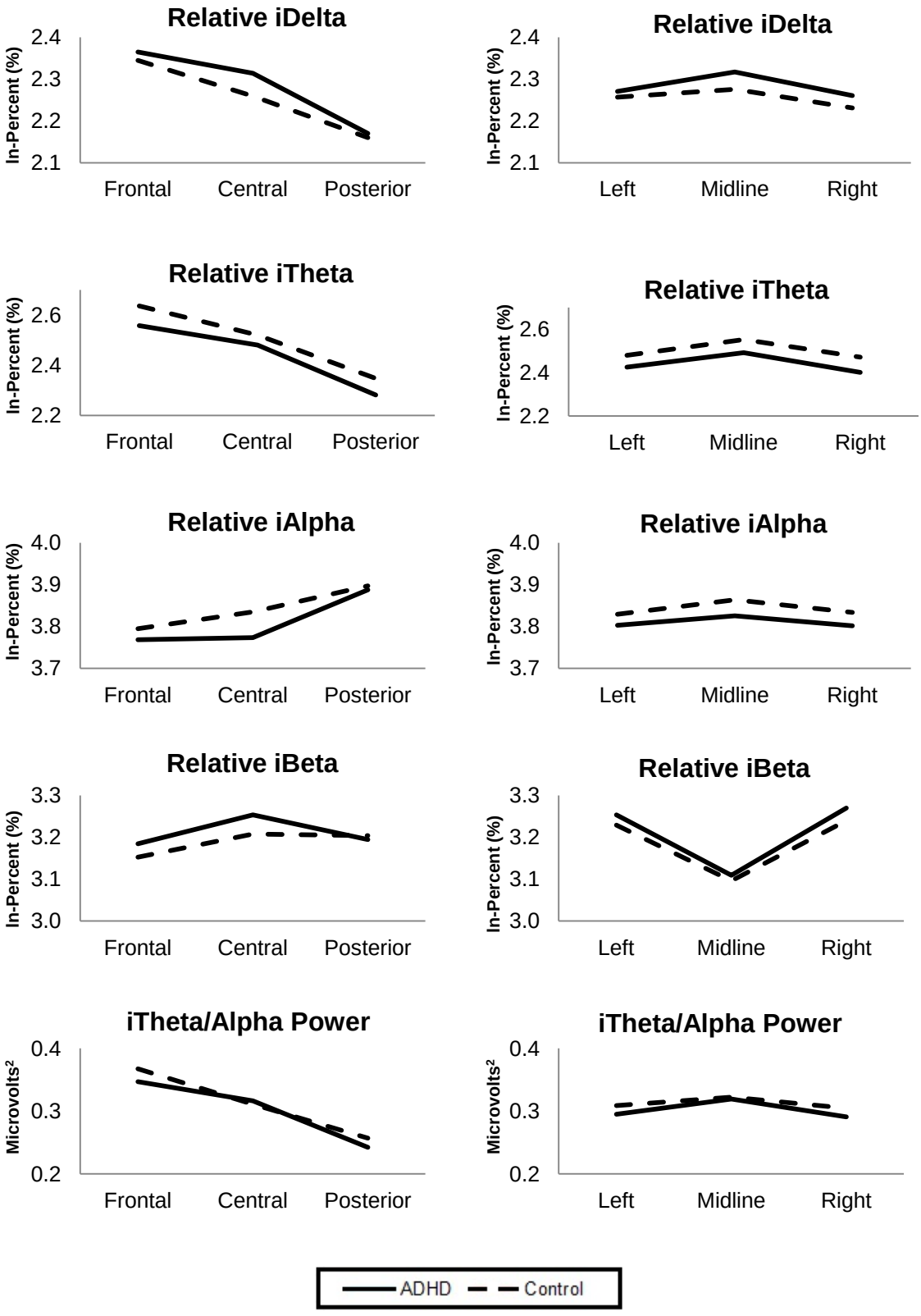

Figure 13. *R*elative and theta/alpha power (ln-transformed) using iAPF band calculation as a function of scalp region for the ADHD and Control group for eyes-open condition. The left column reflects the sagittal regions and the right column reflects the lateral regions.

3.2.3. Analysis of covariance with age. Table 9 provides a summary of retained significant group interactions after controlling for age as a covariate. During the eyes-closed condition, age was significantly related to absolute delta, $F(1, 89) = 5.097$, $p = .026$, $\eta_p^2 = .054$, relative beta, $F(1, 89) = 10.533$, $p = .002$, $\eta_p^2 = .106$, and theta/beta, $F(1, 89) = 6.985$, $p < .010$, $\eta_p^2 = .073$. During the eyes-open condition, age was significantly related to absolute delta, $F(1, 89) = 5.854$, $p < .018$, $\eta_p^2 = .062$, relative delta, $F(1, 89) = 4.109$, $p = .046$, $\eta_p^2 = .044$, relative beta, $F(1, 89) = 20.323$, $p < .001$, $\eta_p^2 = .186$, and theta/beta, $F(1, 89) = 11.812$, $p < .001$, $\eta_p^2 = .117$. However, there were no changes in the reported significant interactions in any frequency band after controlling for age.

Table 9

Summary of significant group interactions with iAPF frequency bands, age (covariate)

Condition/Frequency/Comparison	Absolute power				Relative power				
	df	*F*	*p*	η_p^2	*V*	*df*	*F*	*p*	η_p^2
Eyes Closed									
iAlpha									
Grp × Sag × Lat					.891	4,86	2.623	.040[t]	.109
iBeta									
Grp x Sag × Lat – C vs. F/P × M vs. R/L						1,89	4.454	.038	.048
Eyes Open									
iTheta									
Grp × Sag × Lat – C vs. F/ P × L vs. R	1,89	3.979	.049[t]	.043		1,89	4.103	.046[t]	.044
iAlpha									
Grp × Sag					.889	2,88	5.472	.006	.111
Grp × Sag – C vs. F/P						1,89	11.064	.001	.111
iTheta/Alpha									
Grp x Sag - C vs. F/P	1,89	6.513	.012	.068					

Note. Grp = group, Lat = lateral, Sag = sagittal, vs. = versus, F = frontal, P = posterior, C = central, L = left hemisphere, R = right hemisphere, M = midline, F/P = mean of the combined frontal and posterior regions, L/R = mean of the combined left hemisphere and right hemisphere regions, [t] same interaction was significant using the traditional frequency bands.

3.2.4. Correlation between behavioral and QEEG data. Based on the significant group by region interactions between the ADHD and control group, the mean power of iAPF defined eyes-closed relative alpha and relative beta, as well as eyes-open absolute and relative theta, relative alpha, and theta/alpha power were correlated with the behavioral data for the entire study group. After controlling for age, when applicable, no significant bivariate or partial correlation coefficients were observed between QEEG activity and behavioral measures during the eyes-closed or eyes-open condition (Bonferroni adjusted α, $p < .008$). A significant relationship between iAPF values and baseline ADHD-SB inattention sub-scores, $r = .27$, $p = .008$, was observed (see Figure 14). The correlations were in the positive direction, indicating that as iAPF values increased, inattention scores also increased.

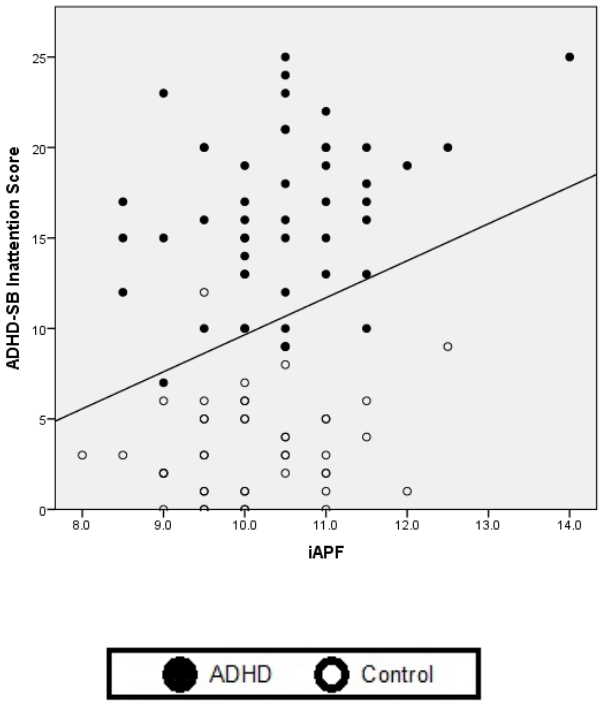

Figure 14. Correlation scatterplot of significant relationships between individual alpha peak frequency values and ADHD-SB behavioral questionnaire data. ADHD participants indicated with solid circle, control participants indicated with outlined circle.

3.3. EEG Phenotype – Hypothesis 3

3.3.1. Demographics. Because the phenotype classification is not an automated procedure and requires additional time, expense, and resources, a limited investigation was performed. Of the ADHD adults included in the initial data pre-processing steps, only the first 20 ADHD participants were included in the phenotype analysis. An age and gender matched control group was selected from the healthy population published by Arns et al. (2010), which had previously been phenotype classified by study collaborators. No significant differences were observed between groups for age. Additionally, each group consisted of a male-to-female ratio of 1.5:1.

3.3.2. Psychometrics. All participants in the ADHD group met the same diagnostic criteria as described in the QEEG analysis. However, baseline differences in ADHD and mood questionnaire data between the ADHD and control participants could not be calculated, as the same assessments were not available for the healthy population classified by Arns et al. (2010). Means and standard deviations for psychometric data are presented in Table 10.

3.3.3. Phenotype classification. Figure 15 displays the prevalence of different EEG phenotypes for the adult ADHD and matched control populations. There was a significant association between the presence of an ADHD diagnosis and the classification of the frontal slow phenotype, χ^2 (1) = 7.372, p = .007. Based on the odds ratio, the odds of having a frontal slow phenotype classification was 5.17 times higher among individuals diagnosed with ADHD than for those without an ADHD diagnosis. Similarly, there was an association between the presence of an ADHD diagnosis and the classification of the high iAPF phenotype, χ^2 (1) = 11.887, p = .001. Based on the odds ratio, the odds of having the high iAPF phenotype classification was 6.29 times higher among individuals diagnosed with adult

ADHD than for those without an ADHD diagnosis. Conversely, an association was also observed between the presence of an ADHD diagnosis and the classification of central beta spindles, χ^2 (1) = 4.028, *p* = .045. Based on the odds ratio, the odds of having the central beta spindles classification was 6.51 times greater among individuals without an adult ADHD diagnosis than for those with a diagnosis.

Table 10

Hyp 3 - Mean (Standard Deviation) Demographic, Psychometric, and Phenotype Data

Variables	ADHD		Control		*df*	*Statistic*	*p*
Demographics	*n* = 20		*n* = 78				
Age [years]	32.7 (9.7)		35.37 (9.8)		1,96	1.187	.279
Gender	12 Male		46 Male				
Time Variables					*n*		
Appointment Time [time]	13:09 (3:57)		*N/A*		19		
Hours of Sleep [hours]	6:42 (1:25)		*N/A*		11		
SSS [score]	3.15		*N/A*		13		
Psychometrics					*n*		
ADHS_total [score]	33.8 (7.9)		*N/A*		19		
ADHS_attn [score]	18.7 (3.5)		*N/A*		19		
ADHS_imp [score]	6.1 (3.0)		*N/A*		19		
ADHS_hyp [score]	9.1 (4.0)		*N/A*		19		
BDI-II_total [score]	12.0 (7.9)		*N/A*		19		
PANAS_pos [score]	21.4 (4.9)		*N/A*		17		
PANAS_neg [score]	14.0 (3.4)		*N/A*		17		
Chi-Squared Tests	*n*	%	*n*	%	*df*	χ^2	*p*
Normal EEG	1	5.0	4	5.1	1	.001	.981
Frontal alpha	9	45.0	42	53.8	1	.499	.480
Frontal slow	6	30.0	6	7.7	1	7.372	.007
Low iAPF	0	0	9	11.5	1	2.541	.111
High iAPF	9	45.0	9	11.5	1	11.887	.001
Frontal beta spindles	5	25.0	14	17.9	1	.506	.477
Central beta spindles	1	5.0	20	25.6	1	4.028	.045
Other beta spindles	0	0	6	7.7	1	1.639	.200
Low Voltage	3	15.0	11	14.1	1	.010	.918
Persistent EO alpha	4	20.0	14	17.9	1	.045	.833

Note. ADHS = ADHS-Selbstbeurteilungsskala (Rösler et al., 2008), attn = inattention sub-scale, imp = impulsivity sub-scale, hyp = hyperactivity sub-scale, BDI-II = Beck-Depression-Inventory (Beck, 1996), PANAS = Positive and Negative Affect Schedule (Krohne, et al., 1996), SSS = Stanford Sleepiness Scale (Hoddes et al., 1973), N/A = data not collected, Chi-Squared N-values and percentages are reported for the presence of a phenotype.

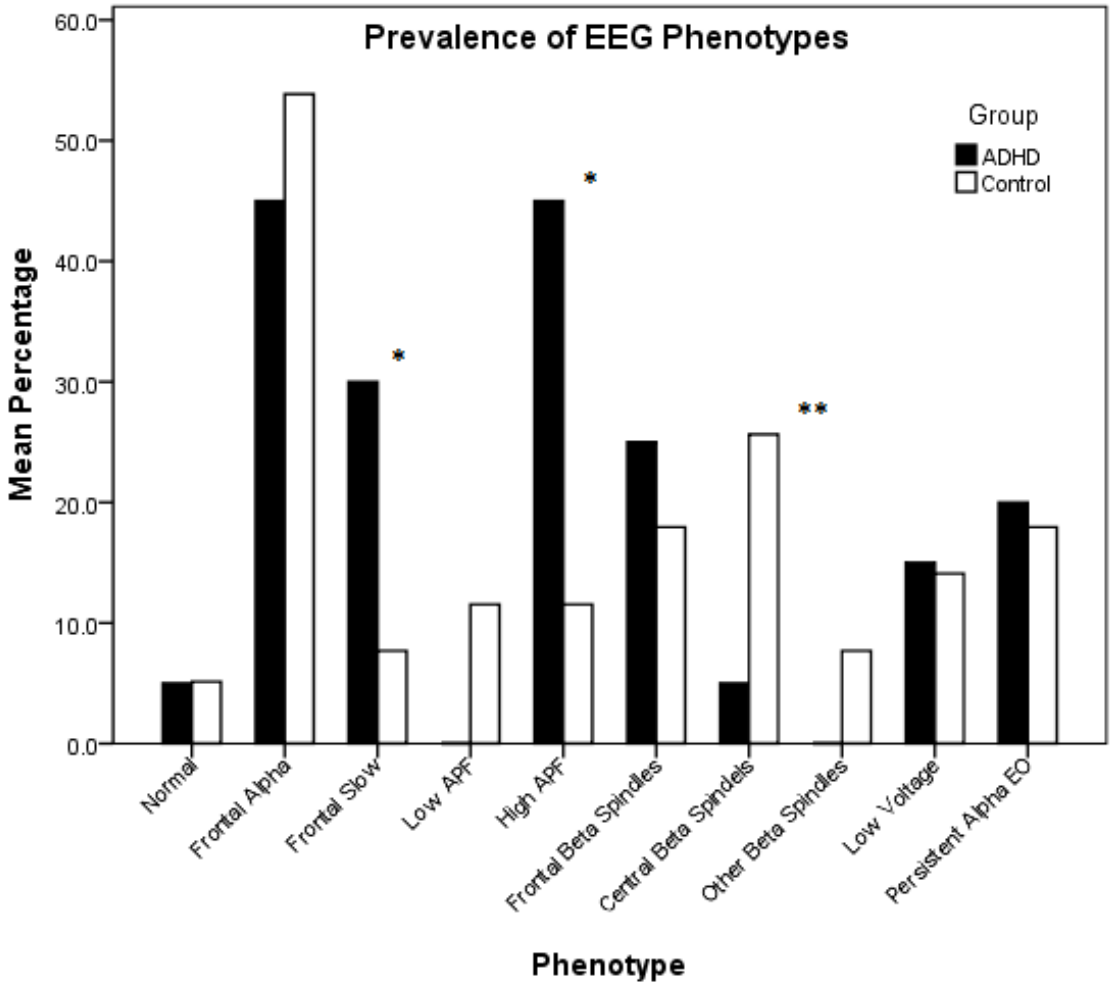

Figure 15. Occurrence of the different EEG phenotypes for both adult ADHD and control groups. Note the significantly higher occurrence of Frontal Slow (*p = .007) and High APF (*p = .001) in the ADHD population and Central Beta Spindles (**p = .045) in the control population. Note that the control group had occurrences of several EEG phenotypes, with only 5% displaying a "normal" EEG.

3.3.4. Relation between behavior, QEEG, and phenotype subgroup. Of the 20 ADHD participants classified, six presented with the frontal slow phenotype and nine presented with the high iAPF phenotype. No significant differences were observed between the phenotype subgroups for baseline ADHD behavior questionnaires. During the eyes-closed and eyes-open condition, no significant differences were observed between the phenotype subgroups for absolute or relative power, theta/alpha power, or theta/beta power.

3.4. EEG Vigilance – Hypothesis 4

3.4.1. Demographics. Of the 47 matched pairs included in the data pre-processing steps, the EEG data of 44 ADHD adults and 44 healthy controls (male-to-female ratio, 1.6:1.0) were included in the vigilance analysis. Three study pairs were excluded from the final analysis due to excessive technical artifacts and frequent eye opening. No significant differences were observed between groups for age or iAPF activity.

3.4.2. Psychometrics. All participants in the ADHD group met the same diagnostic criteria as described in the QEEG analysis. As expected, significant differences were observed between baseline scores of ADHD and mood ratings among ADHD and control participants. Adults with ADHD scored significantly higher on all ADHD and mood questionnaires, with exception of the positive emotion subscale of the PANAS. No significant differences were observed between groups for time of appointment, total hours of sleep the night before the experiment, or momentary sleepiness at the start of the experiment. The Stanford Sleepiness Scale revealed that participants in both groups reported feeling between, (2) *"Functioning at high level, but not at peak, able to concentrate"* or (3) *"Awake, but relaxed, responsive but not fully alert."* Means and standard deviations for demographic and psychometric data are presented in Table 11.

3.4.3. Vigilance classification. Means and standard deviations of vigilance measures are also presented in Table 11. On average participants with ADHD spent less time at the highest vigilance stages O, A1, and A2, and more time in the lowest vigilance stages A3, B1, B2/3, and C compared to control participants. Using the Mann-Whitney *U*-test, this difference was significant for vigilance stage B2/3, $z = -1.957$, $p = .025$, $r = .21$. However, this

difference was not significant after Bonferroni correction ($\alpha = .007$). Both groups showed an equal amount of vigilance stage and sub-stage transitions.

Table 11

Hyp 4 - Means (Standard Deviation) Demographic, Psychometric, and Vigilance Measures

Variables	ADHD	Control	*df*	*Statistic*	*p*
Demographics	*n* = 44	*n* = 44		*F*	
iAPF [Hz]	10.4 (1.1)	10.1 (.92)	1, 86	2.262	.136
Age [years]	34.8 (11.2)	34.9 (11.1)	1, 86	.003	.955
Gender	27 Male	27 Male			
Time Variables				*F*	
Appointment Time [time]	13.37 (3:38)	14:06 (2:57)	1, 85	.682	.411
Hours of Sleep [hours]	7:15 (1.56)	7:33 (1:17)	1, 75	3.615	.061
SSS [score]	3.0 (1.1)	2.5 (1.2)	1, 77	3.615	.061
Psychometrics				*F*	
ADHS_total [score]	31.8 (7.0)	7.2 (5.2)	1, 86	345.830	< .001
ADHS_attn [score]	17.0 (4.1)	3.7 (3.0)	1, 86	301.928	< .001
ADHS_imp [score]	6.5 (3.0)	1.7 (1.7)	1, 86	86.999	< .001
ADHS_hyp [score]	8.3 (3.1)	1.8 (1.8)	1, 86	143.233	< .001
BDI-II_total [score]	12.4 (7.9)	3.4 (3.7)	1, 84	47.161	< .001
PANAS_pos [score]	24.3 (6.7)	27.1 (6.1)	1, 83	4.100	.046
PANAS_neg [score]	13.3 (3.3)	11.2 (2.1)	1, 83	12.417	.001
Vigilance Stages				*z-values*	
Stage O [%]	15.1 (19.1)	21.3 (26.6)		-.685	.494
Stage A1 [%]	9.0 (13.1)	13.0 (17.4)		-.906	.365
Stage A2 [%]	13.8 (15.9)	15.4 (17.8)		-.480	.631
Stage A3 [%]	15.8 (16.0)	12.4 (13.0)		-.689	.491
Stage B1 [%][1]	20.6 (17.8)	20.3 (21.2)		-.655	.256
Stage B2/3 [%][1]	21.2 (19.5)	14.2 (16.3)		-1.957	.025[b]
Stage C [%][1]	4.6 (11.6)	3.4 (9.1)		-.840	.201
Stage Transitions				*F*	
Stages [amount]	18.3 (10.7)	18.7 (10.1)	1, 86	.023	.879
Sub-stages [amount]	40.2 (14.1)	38.3 (15.2)	1, 86	.358	.551

Note. ADHS = ADHS-Selbstbeurteilungsskala (Rösler et al., 2008), attn = inattention sub-scale, imp = impulsivity sub-scale, hyp = hyperactivity sub-scale, BDI-II = Beck-Depression-Inventory (Beck, 1996), PANAS = Positive and Negative Affect Schedule (Krohne et al., 1996), SSS = Stanford Sleepiness Scale (Hoddes et al., 1973), [1]1-tailed significance level reported, [b] Not significant after Bonferroni Correction (*p* = .007).

3.4.4. Relation between behavior, QEEG, and vigilance. After controlling for age, no significant relationships were observed between the percentage of time in each vigilance stage (O, A1, A2, A3, B1, B2/3, C) and baseline ADHD behavior data for the entire study population. Within the ADHD group, no significant differences were observed between "high" (sum of O, A1, A2, and A3; n=23) and "low" (sum of B1, B2/3, and C; n=20) vigilance subgroups for baseline ADHD behavior questionnaires. During the eyes-closed condition, a significant difference was observed between "high" (*M* = .23, *SD* = .15) and "low" (*M* = .39, *SD* = .22) vigilance subgroups for iAPF adjusted mean theta/alpha power activity, $F(1, 41) = 9.579$, $p = .004$, $\eta_p^2 = .189$. ↜

4. Discussion

The aim of the current investigation was to replicate QEEG findings reported in adult ADHD populations and to extend the application of the EEG phenotype and EEG vigilance model beyond a childhood ADHD population.

4.1. Hypothesis 1 - Partially Confirmed

"*ADHD adults will present with increased theta activity, decreased beta activity, and elevated theta/beta ratios as compared to an age and gender matched control population.***"** In support of the hypothesis, the ADHD group presented with elevated absolute and relative theta activity across lateral and sagittal topographic dimensions during the eyes-closed and eyes-open conditions, as well as enhanced theta/beta ratios across lateral and sagittal topographic dimensions during the eyes-closed condition. Supporting previous findings, these differences were significant for eyes-closed relative theta power (Clarke et al., 2008) and eyes-open absolute and relative theta power (Bresnahan et al., 1999; Bresnahan, Barry, Clarke, & Johnstone., 2006; Bresnahan & Barry et al., 2002). In opposition of the proposed hypothesis, the ADHD group also presented with elevated absolute and relative beta activity across lateral and sagittal topographic dimensions during the eyes-closed and eyes-open conditions, as well as reduced theta/beta ratios across sagittal and lateral dimensions during the eyes-open condition. These differences were only significant for eyes-closed relative beta power, a finding that has not been consistently reported in an adult ADHD sample.

To test for potential age confounds and gender by group interactions in the eyes-closed and eyes-open condition, the data were reanalyzed with an ANCOVA to control for age/iAPF and a two-way ANOVA to assess for gender by group interactions. The results of

the ANCOVA revealed that age was significantly related to delta, theta, beta, and theta/beta power activity across eyes-closed and eyes-open conditions. However, the significant effects and interactions reported using ANOVA persisted even after the association with age was controlled. Gender by group interactions were assessed with a two-way ANOVA (not reported), and no significant group main effects were reported for any frequency band or condition. However, a gender by group by region interactions was observed within absolute and relative delta, relative theta, and absolute and relative alpha. As the interactions observed were not the same as those reported in the ANOVA analysis, participant gender was not determined to drive significant group effects.

4.1.1. Delta. The analysis of power differences in delta has produced variable findings across childhood and adult ADHD studies. Although significant power differences were not reported in the present study, enhanced eyes-open delta activity was observed and has been consistently reported in ADHD children (Amer et al., 2010; Bresnahan et al., 1999) and adults (Bresnahan et al., 1999; 2006; Bresnahan & Barry, 2002). This finding was partially supported by the small positive correlation of eyes-open absolute delta activity with ADHS-SB total score and impulsivity sub-scores. As delta activity increased, so did the core ADHD symptoms. Enhanced activity has also been reported in the majority of eyes-closed delta power analyses (Clarke et al., 2001a; 2001d; 2002; Hermens et al., 2008), with the exception of two studies (Clarke et al, 2001b; 2008). Compared to control participants, Hermens et al. (2010) reported adult ADHD participants produced significantly enhanced absolute delta activity, while Koehler et al. (2010) reported enhanced activity that failed to reach significance. In the current study, the enhanced absolute delta activity observed in the ADHD group also failed to reach significance. However, a small effect size was observed (r =

.20) for eyes-closed absolute delta, as a group by sagittal by lateral interaction approached significance, *F*(1, 90) = 3.369, p = .070, η_p^2 = .036.

Conversely, in the eyes-closed condition, Clarke et al. (2008) reported reduced absolute delta activity in adults and Clarke et al. (2001b) reported reduced relative delta activity in children. The key to understanding the discrepant findings within delta power may be linked to differences in population sampling procedures. For example, the study population investigated by Clarke et al. (2008) included only adult male participants (N = 40) within a restricted age range of 18 and 26 years and Clarke et al. (2001b) included only young males (N=224) within the age range of 8 to 12. The current study included both male and female participants in an extended age range (21-65 years). Therefore, the finding of reduced absolute delta activity observed by Clarke and colleagues may also have been the direct result of excluding female participants from these studies and using a restricted age range.

Koehler et al. (2009) investigated gender and group differences in an adult population. Although they did not report any significant gender by group by frequency interactions, they did detect significant main effects for gender on absolute delta power. Specifically, female participants showed increased delta activity compared to males. Clarke et al. (2001a) investigated gender by age by group differences in a childhood population, reporting delta activity decreased more slowly with age in ADHD females compared to control groups or their male ADHD counterparts. Taken together, these findings provide a plausible hypothesis to explain the discrepancies observed between the current study and the previously reported eyes-closed delta activity. More importantly, they highlight the lack

of homogeneity of delta activity within an adult ADHD population, making it an unreliable diagnostic marker of ADHD.

4.1.2. Theta. The analysis of differences in theta power has produced the most consistent findings across childhood and adult ADHD studies. In childhood ADHD populations, enhanced activity has been reported in eyes-open/eyes-closed absolute theta (Barry et al., 2009; Bresnahan et al, 1999; Chabot & Serfontein, 1996; Clarke et al., 1998; 2001a; 2001c; 2001d; 2002; Lazzaro et al., 1998; 1999) and eyes-open/eyes-closed relative theta (Barry et al., 2009; Bresnahan et al., 1999; Clarke et al., 1998; 2001a; 2001b; 2001c; 2001d; 2002; Lazzaro et al., 1999). Similarly, in an adult ADHD population, enhanced activity has been reported in eyes-open/eyes-closed absolute theta (Bresnahan et al., 1999; 2006; Bresnahan & Barry, 2002; Hermens et al., 2004; Koehler et al., 2009; Woltering et al., 2012) and eyes-open/eyes-closed relative theta (Bresnahan et al., 1999; 2006; Bresnahan & Barry, 2002; Clarke et al., 2008; Woltering et al., 2012). These findings were replicated in the current study.

In terms of topography, the ADHD group displayed enhancement of theta activity in the midline, left central region, and right frontal/posterior regions during the eyes-open condition. During the eyes-closed condition, the ADHD group showed enhanced global and right posterior activity. These results support findings of central elevations (Bresnahan et al., 2006; Clark et al. 2008) and asymmetries observed in children with ADHD reported in previous studies (Hermens et al., 2005). Despite evidence supporting that theta activity decreases with age (Bresnahan et al., 1999), the persistence of this activity is hypothesized as representative of continued ADHD symptoms in adulthood. This was supported by the finding that eyes-open absolute theta negatively correlated with age, while positively

correlating with the ADHD-SB total and Hyperactivity behavioral sub-scores. Post-hoc analysis revealed this correlation was driven by enhanced central midline absolute theta in the ADHD group, $r = .443$, $p = .002$, further supporting the correlation observed between posterior theta and the inattention subscale of the Adult ADHD Self-Report Scale (Koehler et al., 2009). The fact that these interactions remained significant after controlling for age covariance supports the view that enhanced theta activity during resting state conditions is a reliable EEG marker of ADHD, irrespective of age.

4.1.3. Alpha. The adult ADHD literature has reported a limited number of significant differences in faster frequency bands, along with mixed findings. In ADHD adults, enhanced absolute alpha activity has been reported in eyes-closed (Koehler et al., 2009) and eyes-open (Bresnahan & Barry, 2002) conditions, while deficient absolute and relative power has been reported in eyes-closed (Loo et al., 2009; Woltering et al., 2012) and eyes-open (Bresnahan & Barry, 1999; Woltering et al., 2012) conditions as well. Similarly, incongruent findings have been observed in childhood ADHD populations, as both enhanced alpha power (Chabot & Serfontein, 1996; Lazzaro et al., 1999) and decreased alpha power (Amer et al., 2010; Barry et al., 2009; Clarke et al., 1998; 2001a; 2001b; 2001c; 2001d; 2002) have been reported. In the current study, the ADHD group presented with significantly decreased eyes-closed relative alpha activity across both regional dimensions.

Decreased alpha appears to be one of the most consistent findings in childhood ADHD research. Clarke and colleagues (2001) hypothesized that reduced alpha activity in combination with enhanced theta and posterior delta was indicative of a maturational lag. This is supported by research indicating that the mature brain (at or beyond 16 years) is characterized by an increase in absolute power in the upper alpha band and a decrease in

theta and delta power as compared to a less developed brain in younger children (for review, see Klimesch, 1998). A maturational lag has also been hypothesized in a series of other studies showing that children with poor education, reading and writing disabilities, spelling disabilities, and other neurological disorders also show significantly enhanced delta and theta but less alpha power (for review, see Fuller, 1978). However, due to the age of the study population (21-65 years) and the lack of simultaneously enhanced posterior delta and theta activity, the likelihood of a maturational lag accounting for ADHD symptoms and QEEG differences is unlikely. This was further evidenced by the lack of correlation between age and alpha power, as well as, the lack of correlation between baseline ADHD-SB symptoms and alpha power. For these reasons, deficient alpha activity observed during resting state conditions cannot be considered a reliable EEG marker of ADHD.

4.1.4. Beta. As with the investigation of other frequency band differences, the power analyses of beta activity have produced variable findings. In the investigation of eyes-closed absolute beta, ADHD participants were reported having decreased posterior activity (Hermens et al., 2004), decreased midline with enhanced right posterior activity (Clarke et al., 2008), attenuated central and right hemisphere activity (Woltering et al., 2012), and globally enhanced sagittal midline activity that failed to reach significance (Koehler et al., 2009). In the analysis of eyes-closed relative beta, Clarke et al. (2008) observed attenuated midline hemispheric activity, while Woltering et al. (2012) observed attenuated right posterior activity. During eyes-open recordings, enhanced absolute beta (Bresnahan & Barry, 2002; Loo et al., 2009) and attenuated relative beta (Bresnahan et al., 1999; 2006; Woltering et al., 2012) power have been reported. In the present study, significant topographic differences were observed in the eyes-closed condition only. Absolute beta was

enhanced in the posterior midline region for the ADHD group compared to the control group.

A variety of factors contributes to the lack of cohesive findings. First, the electrode pooling dimensions were not standardized between studies. Hermens et al. (2004) and Koehler et al. (2009) collapsed frequency activity into a three level orthogonal sagittal factors for ANOVA, while Woltering et al. (2012) extracted and compared data from 66 individual electrode sites for t test comparison. The adoption of the statistical procedure outlined by Clarke et al. (2008) allowed for the inclusion of both sagittal and lateral factors, while reducing the likelihood of Type 1 errors, leading to a more sensitive investigation of topographical variations in power.

Second, age and gender differences were implicated in the Clarke et al. (2008) data set. As presented in the discussion of delta power inconsistencies, Clarke and colleagues included a population of young (18-26) males in their investigation of eyes-closed absolute and relative power differences. Although their investigation targeted absolute and relative activity during the eyes-open condition, Barry et al. (1999) reported age related beta power changes for ADHD and healthy controls. Within the analysis of absolute beta, a significant linear reduction of activity with age was observed, with ADHD adults (20-42 years old) showing enhanced absolute beta activity along the sagittal midline compared to controls. Within the analysis of relative beta, a linear increase in activity with age was observed, in which ADHD adults showed enhanced relative beta power along the sagittal midline compared to the control group. In both power analyses, children and adolescents with ADHD showed decreased levels of beta power. Therefore, a young adult sample may not reflect the beta enhancement observed with maturation.

Lastly, gender differences between the groups should be addressed. Koehler et al. (2009) investigated gender and group differences in an adult population. Although they did not report any significant gender by group by frequency interactions, they did detect significant main effects for gender in absolute beta power. Specifically, female participants showed increased central and posterior beta activity compared to males. Clarke et al. (2008) used a sample of all males while the other studies utilized a male-to-female ratios of 3:2 (Hermens et al., 2004), 1:1 (Koehler et al., 2009), and 1.4:1 in the current study. Taken together, these findings provide a plausible hypothesis to explain the discrepancies observed between the current study and the previously reported beta activity. Additionally, they highlight the lack of homogeneity of beta activity across the lifespan.

The linear increase and normalization of beta activity with age is at the heart of the maturational lag model, as the normalization of beta deficits with age is hypothesized to correlate negatively with the reduction of hyperactivity symptoms across the ADHD lifespan (Bresnahan et al., 1999). However, this hypothesis has not been supported by investigations that have correlated EEG activity with core ADHD symptoms in adult ADHD populations (Koehler et al, 2009; van Dongen-Boomsma). In these previous studies, no significant beta frequency interactions were observed between the ADHD and control populations, therefore correlations with core ADHD symptoms were not assessed post-hoc. While this supports the normalization of beta deficits in adult ADHD populations, the hypothesized relationship between beta enhancement and symptom reduction has not been thoroughly investigated. In another investigation, Bresnahan and Barry (2002) reported that adults with sub-clinical ADHD presented with greater enhancement of relative beta compared to individuals in a clinical population, possibly accounting for a lesser degree of symptoms.

However, contrary to the maturational lag hypotheses, both the clinical and sub-clinical populations produced greater symptoms and beta activity than the control group. This finding was supported in the current investigation, as an interaction was observed between groups for eyes-closed absolute beta activity. Despite the observation of enhanced absolute beta activity in the ADHD group, this activity was not positively correlated with age or negatively correlated with core ADHD behaviors. Therefore, beta activity does not appear to reliably discriminant clinical and control populations or correlate with core ADHD symptoms, making it an unreliable diagnostic marker of adult ADHD.

4.1.5. Theta/alpha power. Enhanced central theta/alpha power has been reported in child (Clarke et al., 2001a; 2001c; 2002) and adult (Woltering et al., 2012) ADHD populations. The current study supported these findings, as a significant group main effect for enhanced theta/alpha ratios was observed. This finding is not surprising due to the presence of enhanced eyes-closed absolute theta and attenuated absolute alpha were observed in the ADHD group during the eyes-closed condition. Despite findings that theta/alpha activity was able to differentiate between combined and inattentive subtypes of ADHD (Clarke et al., 2001a; 2001c) and ADHD and reading disorders (Clarke et al., 2002), no relationship between alpha/theta power and baseline ADHD symptoms were observed.

4.1.6. Theta/beta power. The finding of enhanced theta/beta ratios among children and adults (Woltering et al., 2012) with ADHD was not supported by the current study. This finding is not surprising, given the presence of enhanced posterior midline activity in the ADHD group during the eyes-closed condition and the lack of beta activity differences between groups in the eyes-open condition. To account for the inconsistencies in the theta/beta power, the age related limitations previously discussed should be

considered. Specifically, Woltering et al. (2012) assessed college students, which may reflect lesser maturational beta enhancement as observed in an older cohort. It is also important to note that several studies have used a lifespan (children, adolescent, and adult) population in their calculation of enhanced ratios (Bresnahan et al., 1999; Monastra et al., 1999; 2001).

Additionally, study tasks have been variable in the calculation of enhanced theta/beta ratios. For example, Monastra et al. (1999; 2001) only reported theta/beta ratios from Cz and assessed activity during a combined eyes-fixed baseline, reading, listening, and drawing task. In this case, elevations in the theta/beta ratio may demonstrate activation and processing deficits rather than "resting state" hypoarousal as hypothesized. These reasons, along with the lack of correlation between the theta/beta ratio and core ADHD symptoms, do not permit the use of this metric as a diagnostic marker in adult ADHD.

4.2. Hypothesis 2 – Partially Confirmed

"QEEG differences between the adult ADHD and control group derived from the traditional frequency band definitions will differ from bandranges calculated based on individual alpha peak frequency". The impact of iAPF was explored in a two-phase process. First, iAPF values were used as a covariate in an ANCOVA analysis. Despite having no significant differences between the groups in iAPF, iAPF was correlated with several frequency bands including eyes-closed absolute and relative alpha and relative beta, theta/alpha power, and theta/beta power, as well as, eyes-open relative delta, relative theta, absolute and relative alpha, relative beta, theta/alpha power, and theta/beta power. Once controlling for iAPF, the group main effect and group by sagittal by lateral effect for relative theta and group main effect for theta/alpha power were no longer significant in the eyes-closed condition. Additionally, the group by sagittal by lateral interaction (group by F

vs. P by M vs. L/R) observed for relative alpha power was no longer significant in the eyes-open condition after controlling for iAPF. The other significant group by sagittal by lateral interactions within eyes-closed relative theta, alpha, absolute beta, and theta/alpha power, and eyes-open absolute theta persisted after ANCOVA. These findings supported the investigation of iAPF defined QEEG differences in Hypothesis 2.

In general, alpha is the dominant frequency of the mature brain, predominant in the posterior region. EEG maturation follows a gradual frequency increase with age, reaching a mean of 10 Hz around age 10, plateaus with declines in intermixed posterior slow wave activity between ages 20 to 30, and then tends to decline in late adulthood (Niedermeyer, 1999). However, there is a fair amount of interindividual variability in alpha activity causing significant portions of alpha power to fall outside of traditional fixed frequency bands (Doppelmayr et al., 1998). For example, in an individual with a low iAPF of 8.5 Hz, the lower range of alpha activity would fall below the fixed frequency window and be misinterpreted as theta activity. At the same time, some portions of lower beta activity would be misinterpreted as higher range alpha activity. The reverse situation is also possible. For example, in an individual with a high iAPF of 12 Hz, the higher range alpha activity would fall above the fixed frequency window and be misinterpreted as lower range beta activity, while delta activity may be interpreted as low frequency theta activity.

The purpose of the adjusted power analysis was to test the impact of differences in iAPF on QEEG analysis. Specifically, the goal of this investigation was to test the robustness of the findings of *Hypothesis 1* (observed, enhanced – absolute and relative theta, absolute beta, reduced relative alpha, and enhanced theta/alpha power), after controlling for interindividual differences in alpha peak frequencies. Of the significant interactions

observed in *Hypothesis 1,* three remained significant after testing for the covariance of iAPF and re-analysis of iAPF-adjusted frequency differences. First, was the finding of attenuated eyes-closed sagittal and lateral relative alpha (group by sagittal by lateral). The second and third, were the findings of enhanced central left hemisphere relative and absolute theta during the eyes-open condition. Thereafter, all other significant findings differed from those presented in the fixed frequency ANOVA.

4.2.1. iDelta. It is important to note that iAPF delta was not analyzed by Lansbergen et al. (2011) in their analysis of iAPF mediation by slow alpha peak frequency. Delta was not investigated because it was not essential to the investigation of "robust" markers of childhood ADHD – theta, beta, and theta/beta ratio (Arns, M., personal communication, March 13, 2013). However, differences in traditional versus iAPF based delta bands were investigated by Doppelmayr et al. (1998) using the method adopted by the current investigation.

Overall, absolute delta power was reduced with iAPF adjustment. After correcting for iAPF differences within the delta frequency band, no significant group main effects were observed for absolute and relative power during the eyes-closed and eyes-open condition. In both power analyses, the ADHD group produced enhanced delta power across the sagittal and lateral dimension, compared to the control population. Similar trends were observed using traditional frequency bands, which also did not reach the level of significance. Despite a reduction in power across regional dimensions, conditions, and groups, the trends towards a group main effect in absolute and relative delta were enhanced during the eyes-closed condition and reduced during the eyes-open condition following iAPF re-calculation. In the eyes-closed condition, the significant enhancement of delta appears to be driven by the

individuals with higher iAPF values (11 – 14 Hz, 29.4 %), as the delta band for these individuals included activity that was previously misinterpreted as lower range theta activity. Prior to iAPF frequency adjustment, theta activity was enhanced in the midline and right posterior regions for the ADHD group. After the recalculation, these significant findings were minimized and activity was interpreted as part of the delta range.

Interestingly, before iAPF correction, a weak positive correlation was observed between eyes-open mean absolute delta and the ADHD-SB total and impulsivity sub-scores, despite the lack of a significant group effect. After correction, this relationship disappeared as the group differences diminished and activity moved further away from the level of significance. Overall, these findings may provide an explanation for the contradictory findings in delta activity among ADHD children and adults. Individuals with lower iAPF values may be presenting with excessive delta activity that is in fact the lower range of theta activity, while individuals with higher iAPF values may show reduced delta activity as the true delta activity may cycle faster than the fixed range definition. In any case, delta activity does not appear to be a robust discriminant of adult ADHD or predictor of core ADHD symptoms. Delta activity should be interpreted within the context of iAPF and age maturation due to the impact of iAPF correction on fixed frequency interactions and the correlation of age with eyes-closed and eyes-open absolute and relative power.

4.2.2. iTheta. Overall, absolute theta power was reduced with iAPF adjustment. Major changes to theta band interactions were observed after iAPF adjustment. Although the ADHD group continued to show enhanced eyes-closed activity across both dimensions, all significant group effects observed using fixed frequency bands normalized after iAPF correction. This was also observed to a lesser degree during the eyes-open condition.

Following iAPF correction, ADHD participants continued to show left hemisphere dominance of central absolute and relative theta power compared to the control group, as well as enhanced absolute right posterior activity. Interestingly, the ADHD group actually presented with attenuated relative theta activity during the eyes-open condition. This was reflected in the weakening of the group by sagittal by lateral interaction (C vs. F/P by L vs. R) for both absolute and relative theta. During the fixed frequency analysis, absolute theta accounted for 5.0% of the variance not assumed by other factors, but only 4.3% after iAPF correction. Similarly, relative theta accounted for 4.9% of the variance not assumed by other factors, but only 4.4% after iAPF correction. The weak positive correlation between eyes-open absolute theta and baseline ADHD-SB total scores was also no longer significant following iAPF correction.

As stated previously, individuals with higher iAPF values have delta, theta, and alpha ranges that cycle above fixed frequency ranges, while individuals with lower iAPF values (8-9.5 Hz, 14%) have activity that cycles below the lower bound of fixed frequency bands. Due to the relative distribution of iAPF values above and below the established fixed frequency band means, iAPF reclassification appears to normalize group differences in activity within the theta band. This supports the hypothesis of Arns et al. (2008) which asserts that the finding of enhanced theta in childhood ADHD populations is blurred by the presence of true frontal slow (excessive theta) and or deviant iAPF values. In childhood populations, excessive fixed frequency band theta appears to be enhanced by individuals with lower iAPF values, as true alpha range extends into the upper range of fixed theta band activity. The opposite is true in individuals with high iAPF values, as excessive theta appears to be reduced by the reclassification of fixed frequency upper theta as iAPF adjusted lower range

alpha activity. Overall, iAPF changes (upward or downward) reduced the overall absolute and relative power in both groups under both conditions. Therefore, the finding of excessive fixed band theta activity, with the possible exception of enhanced left hemisphere central activity and right posterior absolute activity, should be evaluated within the context of iAPF maturation when used as a discriminant of ADHD or as a predictor of core ADHD symptoms.

4.2.3. iAlpha. Overall, absolute alpha power remained stable with iAPF adjustment. Moderate changes were observed in the alpha interactions after iAPF correct. The ADHD group continued to show significantly reduced relative alpha activity along the sagittal and lateral dimensions during the eyes-closed condition. However, this effect was weakened. Under the fixed frequency band analysis, the group by sagittal by lateral interaction accounted for 15.3% of the variance not assumed by other factors, but only 10.4% after iAPF correction. The clustering of iAPF values within the traditional fixed frequency band activity led to minimal changes after correction of individuals with lower or higher iAPF values during the eyes-closed condition.

Interindividual differences in iAPF had a greater impact during the eyes-open condition. Before iAPF adjustment, the ADHD group presented with significantly attenuated posterior midline relative power activity compared to the control group. After iAPF adjustment, the ADHD group presented with significantly attenuated activity in the central region (group by C < F/P). This topographic change in activity appears to be driven by individuals with high iAPF values, as all frequency ranges are shifted upwards. For example, in the fixed frequency eyes-open analysis, posterior relative theta appeared to be enhanced and posterior relative alpha reduced. Once correcting for individuals with higher iAPF

values, posterior theta enhancement was normalized (reduced), while posterior attenuation also normalized (enhanced).

Absolute power differences remained non-significant, with the ADHD group presenting with reduced activity in the eyes-closed condition and enhanced activity in the eyes-open condition. Overall, the activity between groups was equipotential despite the differences observed in relative power. According to Klimesch (1999), the reason for this difference in absolute and relative power is related to the fact that relative power measurements tend to produce larger estimates for the dominant frequency range where the absolute power is the largest and lower estimates for frequencies that fall outside of this dominant range. In the control group, the absolute power was the dominant alpha band and relatively low in all other bandranges. Therefore, minor differences in absolute power may be amplified in relative power analyses.

4.2.4. iBeta. Overall, absolute beta power increased with iAPF adjustment. Thus, group differences and distributions of beta activity changed dramatically after iAPF adjustment. Prior to iAPF adjustment, the ADHD group presented with enhanced absolute beta activity in the eyes-closed condition, leading to significantly enhanced absolute beta in the posterior midline. After iAPF correction, this interaction was no longer significant, as eyes-closed absolute power was equipotential between the ADHD and control group in the sagittal and lateral dimensions. However, changes in absolute power distributions led to changes in relative power interactions. Specifically, the ADHD group presented with less central and posterior relative beta activity compared to the control group. Despite this interaction, eyes-closed relative beta did not correlation with any baseline ADHD behavioral sub-scales.

Using a fixed frequency range, individuals with lower iAPF values appear to overinflate alpha band activity, as frequency bands should be shifted downward. Therefore, iAPF adjusted beta ranges would capture activity traditionally included in the upper alpha range of fixed frequency bands, increasing overall activity in the beta band. Conversely, correction for individuals with higher iAPF values would shift frequency bands upward, expanding the alpha range and pull activity traditionally classified as lower frequency beta into the upper alpha range. This would decrease the overall activity within the beta band. This may explain the discrepancies in alpha and beta activity across lifespan populations of ADHD. This is evidenced in the current study by the enhancement of sagittal midline relative alpha power; at the expense of reduce sagittal midline relative beta power in the ADHD group.

4.2.5 iTheta/alpha power. Overall, theta/alpha power decreased with iAPF adjustment. This was driven by the normalization of theta activity and stability of the alpha activity across the eyes-closed and eyes-open conditions. In the eyes-closed condition, the enhanced theta/alpha activity observed in the ADHD group was normalized with the reduction of theta activity in the ADHD group. In the eyes-open condition, theta/alpha power became significantly enhanced in the central region for ADHD group after iAPF correction. This interaction was driven by the finding of enhanced central absolute theta activity and focal reduction of relative alpha activity over the central midline.

4.2.6. iTheta/beta power. Overall, theta/beta power decreased with iAPF adjustment. Despite changes in iAPF adjusted theta and beta power, theta/beta power was not significantly different between the ADHD and control group. During the eyes-closed condition, ADHD participants presented with elevated theta/beta ratios compared to

controls. After iAPF correction, the overall power of both groups was reduced due to the normalization of theta and beta power. Before and after iAPF adjustment, ADHD participants presented with non-significantly enhanced theta/beta ratios during the eyes-closed condition. During the eyes-open condition, control participants presented with non-significantly elevated theta/beta ratios compared to ADHD participants, which is contradictory to most models of the disorder. After controlling for differences in iAPF, enhanced absolute theta power was observed during the eyes-open condition for the ADHD group. This was also true for absolute beta activity. Although absolute beta differences between the groups failed to reach the level of significance, the enhanced activity in the ADHD group was large enough to produce lower theta/beta ratios.

4.3. Hypothesis 3 - Partially Confirmed

"ADHD adults will present with an increased prevalence of the frontal slow phenotype and low iAPF phenotypes, compared to an age and gender matched control population." This investigation was a pilot attempt to identify specific EEG phenotypes (Johnstone et al., 2005) in an adult ADHD population that have been previously observed in ADHD children (Arns et al., 2008). Arns et al. (2008), reported that ADHD children had a tendency towards an increased prevalence of the frontal slow (excess theta), slow iAPF (peak frequency alpha < 9Hz), and low voltage EEG phenotypes compared to healthy controls. Despite a lack of significant group differences in phenotype classification, the researchers effectively demonstrated how variability in alpha peak frequency could overestimate theta activity by misclassifying low frequency alpha within traditional fixed frequency bands (basis for *Hypothesis 2*). As enhanced theta is considered the most robust marker of adult ADHD, a frontal slow phenotype group was expected. The potential for a

slow iAPF phenotype contributing to enhanced theta power also seemed likely. The presence of this phenotype was investigated as a potential marker of maturational lag in adult ADHD.

The hypothesis was partially confirmed as ADHD adults presented with a significantly increased prevalence of the frontal slow phenotype. The presence of this phenotype is supported by the significant theta enhancement reported in *Hypothesis 1 and 2,* as well as by the findings reported in other investigations of adult ADHD (Arns et al., 2008; Bresnahan et al., 1999; 2006; Bresnahan & Barry, 2002; Clarke et al., 2008; Hermens et al., 2004; Koehler et al., 2009; Loo et al., 2009; Woltering et al, 2012). Conversely, the presence of the slow iAPF phenotype was not confirmed. Although some ADHD individuals were classified with the low iAPF phenotype, this did not differ from the number of cases observed in the healthy control group. Alternatively, ADHD participants showed a greater prevalence for the high iAPF phenotype. This was a surprising finding.

As stated, alpha is the dominant frequency of the mature brain and follows a gradual frequency increase with age and decline in late adulthood (Niedermeyer, 1999). The same pattern is true of iAPF values. Köpruner et al. (1984) reported that a young adult in their 20s would have an iAPF around 11 Hz, while a 70-year old would show an iAPF drop of 2.65 Hz to a frequency of 8.24 Hz (as cited in Doppelmayr et al., 1998). In the current study, age was negatively correlated with iAPF values. As participants increased in age, their iAPF values decreased. However, compared to an age matched control group, the ADHD group had a higher prevalence of higher iAPF, beyond the expected 10-11Hz. Because iAPF values mature in a curvilinear fashion, increasing in childhood/adolescents and decreasing in adulthood, and at different rates per individual, it is conceivable that interindividual

differences have contributed to inconsistent findings of alpha and beta in adult ADHD. For example, studies reporting “excess beta” might have been referring to “excess alpha” due to individuals with faster alpha peak frequencies, as observed in *Hypothesis 2.*

The second goal of this investigation was to determine if classification of specific phenotypes were correlated with behavioral symptoms and QEEG data in an adult ADHD population. Heterogeneity of EEG phenotypes were present in both ADHD and control populations and cannot be explained by diagnostic differences (ADHD / non-ADHD) alone, as each group showed equal rates of “normal EEG activity” and some percentage of all other phenotypes. Accordingly, no significant differences were observed between the phenotype subgroups for baseline ADHD behavior questionnaires. During the eyes-closed and eyes-open condition, no significant differences were observed between the phenotype subgroups for absolute or relative power, theta/alpha power, or theta/beta power calculated with traditional frequency bands.

These findings do not support the maturational lag hypothesis of ADHD, as iAPF values appear to mature overtime without a reduction in symptoms. Rather, they may indicate different developmental trajectories for individuals with ADHD compared to controls. This is evidenced by the fact that ADHD children have a tendency to have lower iAPF values than age matched peers in childhood (Arns et al., 2008), ADHD adults show a maturational “normalization” of EEG in young adulthood (Bresnahan et al., 1999), and a potential overshoot of iAPF activity in older ADHD adult populations before maturational decline with old age. These changes appear to occur without consequent symptom reduction or phenotype differences. In fact, correlation coefficients demonstrated a weak positive relationship between iAPF values and baseline ADHD-SB inattention sub-scores,

indicating as iAPF values increased, so did inattention scores. Further longitudinal research is required, using multimodal imaging techniques to follow a single cohort of children with ADHD into adulthood, before this hypothesis can be addressed. Until then, these findings support the use of iAPF frequency bands to minimize interindividual difference in QEEG analysis.

4.4 Hypothesis 4 - Partially Confirmed

"ADHD adults will present with a pattern of unstable EEG vigilance regulation, characterized by lower vigilance stage dominance and a greater number of stage changes compared to an age and sex matched control population". This investigation sought to assess vigilance regulation patterns in an adult ADHD population that have been previously observed in ADHD children (Sander et al., 2010) and adult psychopathology. Hegerl et al. (2010) suggest unstable vigilance regulation is a trait characteristic of ADHD that elicits auto-stabilization behavior (hyperactivity, impulsivity) and accounts for cognitive and attentional deficits. Sander et al. (2010) supported this hypothesis, reporting that ADHD children tended to spend less time in the highest (A1) vigilance stage compared to healthy controls. Additionally, Sander and colleagues indicated that ADHD children with less stable vigilance showed worse pre-treatment CPT performance but achieved better post-treatment response to stimulant medications compared with individuals with more stable vigilances. In the current study, ADHD adults had a marginally (before Bonferroni correction) significant higher prevalence of B2/3 stage dominance but an equal amount of stage/sub-stage transitions compared to the control group. Additionally, ADHD adults showed a lower prevalence of A1 and A2 stages, and higher prevalence of A3, B1 and C stages, although these differences did not reach significant levels.

The second goal of this investigation was to evaluate differences in symptom presentation across vigilance stages. Heterogeneity of EEG vigilance was present in both ADHD and control populations. This result cannot be explained by diagnostic differences alone, as each group showed equal rates of stage transitions and some percentage of all vigilance stages. Hegerl et al. (2010) hypothesized that a degree of unstable vigilance regulation is present in both inattentive and combined subtypes of ADHD, with both subtypes showing symptoms of inattention due to declining levels of vigilance. Whereas, individuals with ADHD combined subtype showed additional vigilance auto-stabilization behaviors. This hypothesis was not confirmed in the current study. After controlling for age, no significant relationships were observed between the percentage of time in each vigilance stage and baseline ADHD behavior data for the entire study population. Within the ADHD group, no significant differences were observed between “high” and “low” vigilance subgroups for baseline ADHD symptoms, despite significant QEEG differences in iAPF defined theta/alpha power enhancement. The presence of enhanced theta/alpha power in the low vigilance group was not a surprising finding, as the classification of B1 and B2/3 stage vigilance is dependent on the enhanced delta and theta activity and attenuated alpha activity in anterior and posterior electrode sites. Theta/alpha power was also significantly enhanced for low vigilance participants in the control group, to a lesser degree. Therefore, enhanced theta/alpha power may generally reflect decreased vigilance, while the severity of the ratio enhancement may discriminate ADHD and non-ADHD individuals in the eyes-open condition.

4.5. Limitations and Future Directions

Several interesting analyses were omitted from the current investigation. These included a two-way ANOVA for diagnosis by sex, and ANCOVA for IQ and subclinical symptoms of positive and negative affect, depression, and anxiety. The ADHD and control populations were matched based on age and sex for Hypotheses 1-4. Despite the ADHD and control group having an equal number of male and female participants, gender differences in EEG have been observed in normal control (Jaušovec & Jaušovec, 2010) and ADHD (Hermens et al., 2004; 2005; Koehler et al., 2009) populations. Assessment of gender differences in EEG activity among ADHD-control participants is more the exception than the rule, as most studies either have assessed males only or included matched gender samples. Gender differences in EEG were not critical to the investigation of the defined hypotheses, therefore, gender was omitted as a between subject factor for these analyses. However, this will be assessed in future analyses of this data set, as gender specific EEG characteristics may have a significant impact of treatment selection, outcome prediction, and provide clinically relevant information for diagnosticians and clinicians.

As many of the study participants were referred by other research groups, the full-scale IQ scores were not available from many (nearly 50%) of the ADHD and control participants. Thus, IQ differences between the ADHD and control groups were not assessed and an ANCOVA controlling for the effects of IQ on EEG could not be conducted. Despite inaccessibility of the full-scale IQ scores, each participant was assessed as having an IQ > 80 for inclusion or referral to the study. In previous EEG investigations of ADHD and control populations, matching participants for IQ is more the exception than the rule. Most studies included a minimum IQ requirement as part of the inclusion criteria. In mixed IQ samples,

Clarke et al. (2006; 2008) reported that IQ had no effect on significance levels of EEG differences in age-sex matched childhood and adult ADHD-control populations, respectively.

For inclusion in the study, control and ADHD participants were excluded if they presented with greater than moderate symptoms of depression and anxiety. Both ADHD and control participants presented with subclinical levels of depression assessed using the BDI-II. However, the ADHD group presented with significantly higher depression symptoms compared to control participants. The ADHD group also presented with significantly higher scores on the negative emotions subscale of the PANAS, as well as significantly lower scores on the positive emotions subscale of the PANAS. Additionally, both ADHD and control participants presented with subclinical levels of anxiety, as assessed with the STAI. Despite this, ADHD participants scored significantly higher on both the state and trait subscales compared to control participants (partial population data, not reported). Unfortunately, due to a lack of access to questionnaire data for participants referred by other research teams, the full-scale STAI state and trait scores were not available for approximately 50% of ADHD and control participants.

These findings support research reporting increased comorbid psychiatric symptomatology in the adult ADHD population (Sobanski, 2006; Spencer, 2009). However, the presence of these subclinical symptoms may influence EEG differences between the ADHD and control group. Although signature patterns of EEG activity have been reported in populations with depression (reviews see, Arns, 2011; Itil, 1983), no direct link has been established between depression scores and between-subject EEG power variability in a population of adults with clinical and sub-clinical ADHD (Bresnahan & Barry, 2002). The research of Hegerl and Hensch (2012) indicates that major depressive disorder is associated

with hyperstable vigilance regulation, whereas mania and ADHD are characterized by unstable and labile vigilance regulation. Tomarken, Davidson, Wheeler, and Doss (1992) reported a robust relationship between frontal EEG alpha asymmetries and positive and negative affect subscales of the PANAS in a healthy female population. Finally, Putman, van Peer, Maimari, and van der Werff (2010) reported that trait anxiety, as assessed with the STAI, was negatively correlated with theta/beta power in a healthy female population. Based on these findings and the lack of brain-behavior correlations in the current study, future analyses should assess the impact of comorbid symptoms on QEEG differences with an ANCOVA. Taken together, differences in the level of comorbid symptoms may have reduced the findings of unstable vigilance regulation and enhanced theta/beta ratios observed within the ADHD participants.

5. Conclusion

As previously stated, the aim of the current investigation was to replicate QEEG findings reported in adult ADHD populations and to extend the application of the EEG phenotype and EEG vigilance model beyond a childhood ADHD population. Overall, these aims were met and the results of each hypothesis provided more insight into the diagnostic and prognostic applications of EEG in the evaluation and treatment of adult ADHD. Additionally, the combination of these models helped to identify possible explanations for inconsistencies found within the existing literature.

In summary, this study was the first to investigate absolute and relative power EEG differences across sagittal and lateral dimensions of an adult ADHD population with an extended age range during eyes-closed and eyes-open conditions. Additionally, this investigation was the first to assess the impact of using traditional versus iAPF adjusted frequency bands for QEEG spectral analysis in an adult ADHD population. This study was also the first to apply the EEG phenotype and EEG vigilance classification models to an adult ADHD population. Finally, this investigation was one of the few to assess the relationship between core ADHD behavioral symptoms and aberrant EEG activity in an adult population.

Across both QEEG investigations (fixed and adjusted frequency bands), enhanced theta activity appears to be a robust neurophysiologic marker of ADHD that persists after controlling for the maturational effects of age. The finding of enhanced theta activity was further supported by the increased prevalence of the frontal slow EEG phenotype in the ADHD group. However, enhanced theta power, particularly in the eyes-closed condition, appears to be sensitive to interindividual differences in iAPF activity. Specifically, theta activity differences between ADHD and control participants were minimized after

controlling for iAPF during the eyes-closed condition and to a lesser degree during the eyes-open condition. This effect was further supported by the increased prevalence of the high iAPF EEG phenotype in the ADHD group.

While the finding of enhanced theta/beta ratios among ADHD adults was not observed in the current investigation, attenuation of fast wave activity was observed within the alpha band. Across both QEEG investigations (fixed and adjusted frequency bands), reduced alpha activity also appears to be a robust neurophysiologic marker of ADHD that persists after controlling for the maturational effects of age, as well as, interindividual differences in iAPF. The relationship of enhanced theta activity and attenuated alpha activity was further evidenced by the observation of enhanced theta/alpha ratios in the ADHD group, as well as, the finding of significantly enhanced theta/alpha ratios among ADHD individuals identified with dominant low vigilance stage activity. However, due to the impact of iAPF correction on theta band activity this combined measure proved to be sensitive to iAPF differences. Specifically, elevated ratios observed in the eyes-closed condition normalized after iAPF correction, while the ratios became enhanced in the eyes-open condition.

The finding that EEG activity is particularly vulnerable to age and iAPF variability should be of particular interest to researchers and clinicians that utilize normative databases for QEEG research. While most databases compare individual files to an age-matched cohort or strata, no corrections are made for differences in iAPF values. Lack of access to raw control participant data in many proprietary database programs makes manual iAPF correction impossible. Ultimately, as observed in the *Hypothesis 2,* differences in iAPF can influence the calculation of fixed frequency theta, alpha, and beta band activity. As

Lansbergen et al. (2011) reported, low iAPF values overestimate theta and alpha contributions in ADHD children, while the current investigation supports that high iAPF values overestimate alpha and beta contributions in ADHD adults. The findings persisted despite matching for age and non-significant group differences in iAPF.

Overall, theta band enhancement (Barry et al., 2009; Bresnahan et al., 1999; 2006; Bresnahan & Barry, 2002; Chabot & Serfontein, 1996; Clarke et al., 1998; 2001a; 2001b; 2001c; 2001d; 2002; Lazzaro et al., 1998; 1999; Hermens et al., 2004; Koehler et al., Woltering et al., 2012), alpha band attenuation (Amer et al. 2010; Barry et al. 2009; Clarke et al., 1998; 2001a; 2001b; 2001c; 2001d; 2002; Bresnahan et al., 1999; Loo et al., 2009; Woltering et al., 2012), and enhanced theta/alpha ratios (Clarke et al., 2001a; 2001c; 2002; Woltering et al., 2012) have been consistently observed in childhood and adult ADHD populations, with and without age and iAPF correction. However, the correlations between these EEG parameters and behavioral symptoms of ADHD have been less consistent, particularly in adult ADHD.

In childhood populations, Clarke et al. (2011) identified five distinct EEG cluster combinations that accounted for 88.4% of the total variance among ADHD children and correlated with distinct presentations of ADHD and comorbid symptoms. Two of the five clusters identified increased theta and reduced alpha activity as key components. The cluster with a lesser degree of EEG disturbances presented with significantly fewer ADHD behaviors and comorbid symptoms of depression and anxiety. This cluster was labeled as reflecting “hypoarousal” characterized by increased total power and relative theta and reductions in alpha and beta activity. A similar cluster with a greater degree of EEG disturbances presented with elevated levels of impulsivity, inattention, conduct issues, and

immature behaviors. This cluster was labeled as reflecting “maturational-lag” characterized by elevated delta and theta activity, reduced alpha activity, and reduced total posterior total power. These findings replicated those reported in several earlier investigations (Mann et al, 1992; Clarke et al., 2001a; 2002c). To date, a cluster based analysis of individual responses to ADHD and comorbid disorder questionnaires and EEG parameters has not been investigated in an adult ADHD population. While the findings of low/high iAPF phenotypes, altered iAPF/age maturational trajectories, and differences in vigilance regulation may better account for the maturational lag cluster in adult ADHD, additional research is needed to assess the hypoarousal model. Investigations utilizing simultaneous assessment of EEG and skin conductance measures across eyes-closed and eyes-open resting state and task conditions are needed to tease out differences between hypo-“arousal” and hypo-“activation” deficits (Barry, Clarke, Johnstone, Magee, & Rushby, 2007) and to further assess gender related dissociations in activation and arousal (Hermens et al., 2004).

Correlations of mean EEG and ADHD and subscale responses have been assessed with limited findings. Koehler et al. (2008) reported correlations between posterior theta and inattention sub-scores in ADHD adults. In the current investigation, enhanced central theta activity was positively correlated with the total scores on ADHD behavioral questionnaires. However, the attenuation of theta differences following iAPF correction diminished this correlational relationship. No correlations were observed between ADHD behavioral symptoms and alpha or theta/alpha power under traditional or adjusted frequency analyses in the current study or that of Koehler et al. (2008). Therefore, what these differences in EEG activity reflect in an adult ADHD population is still unknown,

especially in the absence of strong brain-behavior correlations between EEG activity and core ADHD symptoms.

Koziol and Stevens (2012) assert that the lack of clear brain-behavior relationships between neuropsychological parameters and the behaviorally defined disorders of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) are related to the theoretical constructs on which each is developed. Accordingly, they assert that ADHD is not a unitary "one cause/one disorder" but rather a behavioral presentation of symptoms indicative of abnormalities in multiple neural systems. For example, the DSM criterion for the diagnosis of ADHD is not exclusive to this disorder alone. Rather, it includes 18 core symptoms that overlap with a number of other disorders and can be combined in any number of ways to indicate combined, inattentive, and hyperactive subtypes. These DSM symptom combinations do not "map" directly onto functional brain networks in a 1:1 relationship, limiting their diagnostic utility and the possibility of finding a single deviant neurological system.

Accordingly, Koziol and Stevens state, "…given the now widely accepted belief of causal heterogeneity in ADHD, it would be difficult to defend the continuing expectation that all ADHD-diagnosed youth and adults should display the same type or profile of behavioral impairment on one of these numerous different types of neuropsychological tests…" (2012, p. 8). This has been observed repeatedly in the psychophysiological research, leading to the development of the neurophysiological models of ADHD that have been reviewed and assessed throughout the current investigation. At the very heart of these models, is the potential for the dysregulation in the neural systems responsible for

generating theta and alpha activity, as well as, state and trait components that blur the accurate classification of this activity.

Two distinct neural systems are involved in generating theta and alpha activity. Theta activity is generated in septal-hippocampal circuits while alpha activity is generated in thalamocotical loops (for review see, di Michele, Prichep, John, & Chabot, 2005). Any number of imbalances or deviations within these separate neural systems may lead to the enhancement or inhibition of theta and alpha activity, expression of ADHD subtypes, and neurobiological deficits linked to the dopaminergic system, altered reinforcement mechanisms, and changes in vigilance and arousal. Due to the limited spatial resolution of cortical EEG activity, QEEG analysis and classification of EEG phenotypes or vigilance regulation patterns have limited power in deciphering the origins of this activity, thus limited diagnostic power. However, these methods have been useful in medications selection, treatment response prediction, and neurofeedback selection.

From a prognostic prospective, differential effects in medication and treatment outcome have been linked to theta (Bresnahan et al., 2006), alpha (Loo, Hopfer, Teale, & Reite, 2004), and theta/alpha (Clarke et al, 2002b) activity patterns in ADHD populations. Thus, having the tools (iAPF calculation and adjustment) to define the boundaries of theta and alpha bandranges is paramount. Two studies have accounted for iAPF differences in medication response prediction. Arns et al. (2008) reported improvements of CPT parameters for individuals classified with a frontal slow EEG phenotype after stimulant medication, while individuals with a slow iAPF activity have not shown the same effects of stimulant medications (Arns et al., 2008; Chabot et al., 1999). Similarly, Saunders et al. (2010) reported improvements of CPT parameters after stimulant medication for individuals

classified with an iAPF adjusted unstable low vigilance regulation pattern, defined by enhanced theta, and reduced alpha activity. However, additional research is needed to explore the impact of high and low iAPF activity on medication response.

In the neurofeedback domain, Johnstone et al. (2005) suggest rewarding higher frequency activity, e.g., 12-18 Hz at the vertex or central sensorimotor strip to increase mean alpha frequency, while rewarding 9-10 Hz alpha activity at Pz or alpha/theta protocols over the posterior cortex for individuals with high iAPF EEG phenotypes. Gevensleben et al. (2009) indicated that individuals with lower alpha activity at baseline recordings and larger increases of alpha activity following slow cortical potential (SCP) neurofeedback were related to greater improvements across hyperactivity and impulsivity behavior subscales. Similarly, a larger enhancement of baseline theta activity and greater attenuation of theta activity following theta/beta neurofeedback were related to greater improvements on total ADHD symptoms scores. Localization of this effect over the right parietal regions was linked to a reduction of inattention sub-scales, while localization of this effect over the parietal midline was linked to the reduction of hyperactivity/impulsivity sub-scales. However, additional research is needed to explore the impact of high and low iAPF activity on neurofeedback response and protocol selection. The initial investigations have not utilized protocols to target both attenuated and enhanced iAPF activity and small sample sizes with a small occurrence of slow iAPF have limited the ability to find a clear relationship between slow iAPF values and treatment response (Arns, Drinkenburg, & Kenemans, 2012).

In conclusion, this research study investigated EEG differences in an adult ADHD population and various neurophysiological models associated with specific QEEG findings. ADHD adults presented with enhanced theta and attenuated alpha activity across resting

state conditions, after age and iAPF correction. Additionally, there is consistency of findings across QEEG and EEG phenotype or vigilance classification methods. These findings support EEG outcomes observed in childhood ADHD populations and suggest that ADHD related deficits reflect impaired theta and alpha generators and related neural systems. Despite the lack of 1:1 relationship with core ADHD symptoms, these EEG abnormalities possess diagnostic properties as they discriminate adults with ADHD from age and gender matched controls. Additionally, the type of EEG abnormalities, severity of deviation, and interindividual differences in iAPF values demonstrate prognostic properties that may enhance treatment selection and response prediction in adult ADHD populations. ↜

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