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Relations of EEG and Perceived Response to Methylphenidate among Children with Attention Deficit Hyperactivity Disorder

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Relations of EEG and Perceived Response to Methylphenidate among Children with Attention Deficit Hyperactivity Disorder

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DEDICATION

For Alvin.

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ABSTRACT

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Methylphenidate (MPH) is a common stimulant medication that has demonstrated efficacy in treatment among individuals with attention deficit hyperactivity disorder (ADHD) as well as those with co-occurring oppositional defiant disorder (ODD) symptoms (Connor et al., 2002, Cortese et al., 2018). However, there are currently no known reliable markers to predict response to MPH (Kim et al., 2015) and current approaches rely on trial-and-error by patients. Electroencephalographic (EEG) methods show promise as one tool to identify and predict MPH response. The current study examined relations between EEG frequencies and perceived response to MPH across both ADHD and ODD symptoms utilizing caregiver report on the Strengths and Weaknesses of Attention-Deficit/Hyperactivity Symptoms and Normal Behaviors (SWAN; Swanson et al., 2012). Participants included 30 children with ADHD (70% male) between the ages of 7 -11 years (M_{Age} = 121.27 months, *SD* = 16.47 months) and their primary caregivers. Children's absolute power frequencies were gathered during a resting state EEG paradigm. Caregivers completed measures regarding their child's medication history, and retrospectively rated their child's ADHD and ODD symptoms across pre-MPH and optimal MPH dosage timepoints. Results indicated that alpha frequency was marginally predictive of SWAN scores at optimal-MPH dosage while controlling for SWAN scores prior to MPH (p = .058). No other frequency bands examined demonstrated significant relations. Given the small sample size and low statistical power of this study, the results may underestimate relations between EEG

frequencies and SWAN scores. These findings provide preliminary support for EEG spectral power as a potential predictor of MPH response, lending credence for future investigation and potential clinical utility.

Keywords: ADHD; stimulant response; biomarkers; electroencephalography

CHAPTER I - INTRODUCTION

Attention Deficit Hyperactivity Disorder (ADHD) is a common psychiatric disorder evident in the early developmental period and characterized by symptoms of inattention, hyperactivity-impulsivity, or both across a variety of settings (American Psychiatric Association [APA], 2013). ADHD symptoms are associated with poorer academic, social, and occupational outcomes compared to those with typical development (Fredriksen et al., 2014; Owens & Jackson, 2017; Sciberras et al., 2009). Current estimates indicate a worldwide prevalence rate of 5.3 percent (Polanczyk et al., 2014), with diagnostic rates in the United States rising over the past 20 years (Xu et al., 2018). It is estimated up to 60% of individuals diagnosed with ADHD present with comorbid oppositional defiant disorder (ODD; Burke et al., 2002; Noordermeer et al., 2017), suggesting etiological overlap.

Despite the heterogeneity of this disorder, effective treatments for ADHD symptoms exist. The most validated of these are: (1) psychopharmacological treatments and (2) behavioral interventions, with the two modalities often used in conjunction to target impairment (MTA Cooperative Group, 2004). The extant literature on psychostimulant medications to address impairing ADHD symptoms is abundant, surpassing any other body of literature addressing childhood psychiatric disorder treatment (Greenhill et al.,1999; Greenhill et al., 2002). Both methylphenidate (MPH) and mixed amphetamine salts are within the psychostimulant medication class, each uniquely targeting synaptic dopamine availability (Volkow et al., 2002). MPH is the most common stimulant used for individuals with ADHD and is effective for approximately 65-70% of children for whom it is prescribed (Cortese et al., 2018).

While most individuals with ADHD demonstrate significant symptom improvement utilizing MPH, a substantial percentage (approximately 30%) report little alleviation across impairing ADHD symptoms and thus are considered "non-responders" (Hodgkins et al., 2012). Other available stimulant medications such as amphetamine salts or non-stimulant medications are generally trialed when individuals are considered MPH non-responders. Less is known about individual differential response to medications, as investigations comparing medication effects across stimulants are sparse (Faraone & Buitelaar, 2010). Even less is known about response to MPH when individuals with ADHD present with concurrent ODD symptoms. Within the framework of precision medicine, much is left to be explored in predicting which medication may work best—and for whom—among individuals diagnosed with ADHD.

Electroencephalography (EEG) has shown promise as a viable clinical tool to understand the heterogeneity of ADHD through neurophysiological markers. Recently, EEG methods have been employed to identify biomarkers of ADHD diagnosis and medication response (Lenartowicz & Loo, 2014). EEG is a non-invasive technique to study brain dynamics at the millisecond-level (Puce & Hämäläinen, 2017). EEG data are wide-ranging; information that can be extracted includes: (1) the absolute magnitude of oscillations (e.g., quantifying the spectral power signal), which broadly measures brain state; (2) event-related potentials (ERPs); and (3) scalp topography, measuring numerous electrical contributions across electrodes (Lenartowicz & Loo, 2014). Investigations of frequency bands (e.g., alpha, beta, theta, delta) are calculated through EEG; the term *frequency* signifies the number of oscillations or cycles within a time period, generally calculated as oscillations per second (Hz). In existing literature, the common ranges for

each frequency band are as follows: The alpha band is denoted by 8-12 Hz range, the beta band is denoted by a range of 13 – 30 Hz. The theta band is denoted by 4-7 Hz range, and the delta band is denoted by a range of 4 Hz or less.

Literature examining relations between neurophysiology, ADHD symptoms, and medication response has emerged within the past 20 years, with much yet to be explored. EEG investigations demonstrate consistent findings of increased frontal and central theta among individuals with ADHD, however, there are considerably mixed findings across other bands (Loo & Barkley, 2005). The effects of MPH among ADHD individuals have been demonstrated to improve abnormal EEG activity, with consistent findings that MPH decreases theta activity (Clarke et al., 2002). However, findings across other bands appears quite mixed, likely due to varied methods and age ranges examined (for a review, see Loo & Barkley, 2005). MPH appears to be effective for patients with ADHD and coexisting ODD (Connor, 2015; Kolko et al., 1999). Yet, little is known about which biological markers may predict MPH response in this population. Examining the role of EEG spectral power on children's clinical presentations—both off MPH and at optimal MPH dosage—would substantially build upon the existing literature.

The study's overall goal is to determine potential biomarker associations of MPH response (via neurophysiological data) and retrospective parent reported changes in ADHD and ODD symptoms (both pre-MPH and at optimal dosage). This investigation is unique in examining concurrent dimensional symptoms of ODD, the most common coexisting psychiatric disorder within this population. I aim to investigate whether EEG spectral power demonstrates relations to improvements in ADHD and ODD symptoms at optimal MPH dosage among children in middle childhood.

In the following sections, I outline the theoretical reasoning for this investigation. First, I provide an overview of ADHD. I then outline ODD symptoms among ADHD populations. Following this, I provide an overview of EEG as a potential clinical tool to understanding fundamental neurophysiology among ADHD populations and provide current findings as it pertains to this study. Next, I discuss empirical investigations of MPH as a treatment for ADHD symptoms. Finally, I provide evidence for investigating EEG spectral power as a potential marker for MPH response.

Attention Deficit Hyperactivity Disorder

ADHD is a neurodevelopmental disorder characterized by at least 6 of 9 outlined impairing symptoms of inattention and/or hyperactivity-impulsivity domains across multiple settings (APA, 2013). Nearly 70% of individuals diagnosed with ADHD in childhood continue to demonstrate impairing symptoms in adulthood (Sibley et al., 2022), underscoring the importance of identifying effective treatments. Symptom profiles and severity can vary across the lifespan; inattention domain symptoms often persist within adulthood while hyperactive-impulsive symptoms are often present in early childhood and attenuate to subthreshold clinical levels in adulthood (Lahey et al., 2005). However, the subject of hyperactive-impulsive symptom remission is debated (for a review, see Polanczyk & Rohde, 2007).

Additionally, the presence of coexisting psychiatric diagnoses across internalizing and externalizing disorders is well-documented within this population. Genomic studies suggest a partial etiological overlap for coexisting externalizing symptoms including ODD (Brikell et al., 2018; Hamshere et al., 2013). Recent literature indicates that 6 in 10 children with ADHD have at least one concurrent psychiatric

diagnosis, which may contribute to further and more severe impairment in functioning (Danielson et al., 2018). Broadly, coexisting disorders among ADHD populations are associated with a myriad of health impairments, including increased hospitalization rates and suicidality (Biederman et al., 2008a).

Heterogeneity of ADHD

ADHD is a considerably heterogenous disorder that can vary in symptom severity across the lifespan. Generally, hyperactive-impulsive symptoms attenuate across adolescence and into adulthood (Molina et al., 2009); however, this remittance does not appear to influence global symptom severity across inattentive and coexisting ODD symptoms (Sibley et al., 2012). This heterogeneity has provided difficulties in categorization attempts within the *Diagnostic and Statistical Manuel of Mental Disorders, Fifth Edition* (DSM-5; APA, 2013). Currently, the DSM-5 lists three subtypes of the disorder in order to capture an individual's unique behavioral presentation: *Predominantly Inattentive Subtype*, *Predominantly Hyperactive-Impulsive Subtype*, and *Combined Presentation* (APA, 2013). However, studies examining diagnostic classification have demonstrated challenges validating these subtypes through biological markers, and inconsistencies in identifying differences across subtypes (Rowland et al., 2008). These classifications also do not predict the course of impairing symptoms across development (Loo et al., 2018). Overall, the current delineation of subtypes within the DSM-5 do not appear to have particular clinical utility, nor do these subtypes outlined predict treatment response. A biologically based approach may prove more useful to understanding this neurodevelopmental disorder and psychiatric medication response.

Epidemiology

To date, 9.4 percent children in the United States have received a diagnosis of ADHD within their lifetime; 8.4% of U.S. children have a current diagnosis of ADHD (Danielson et al., 2018). A recent investigation by the National Survey of Children's Health found that 63.8 percent of children with a diagnosis of ADHD have at least one coexisting psychiatric condition (Danielson et al., 2018). While the DSM-5 previously estimated ADHD prevalence to be between 3 and 5 percent (APA, 2013), a weighted prevalence estimate of diagnosed ADHD from 2015 to 2016 was 10.2 percent (Xu et al., 2018). Importantly, the extant literature provides a clear consensus that ADHD is not overdiagnosed within the United States, contrary to popular belief (Sciutto & Eisenberg, 2007). Numerous factors are implicated in the diagnostic prevalence increase, including increased awareness of the disorder, increased health care accessibility through the Affordable Care Act, changes to diagnostic criteria within the DSM to reflect a subtype of predominantly inattentive symptoms, decreased stigma, and increased consensus surrounding recommendation for early identification among professionals (Xu et al., 2018).

Investigations of sex differences consistently demonstrate the disorder is more prevalent among males, with a 3:1 male-to-female ratio in community-based samples (Willcutt, 2012). Theories of this higher prevalence rate vary. from age-related explanations of attenuation of hyperactive-impulsive symptoms, to delayed diagnostic identification among females with ADHD, to a later onset of symptoms among females (Agnew-Blais et al., 2016; Murray et al., 2019; Williamson & Johnston, 2015). Notably, meta-analysis indicates that during the school years, females are less likely to be referred for ADHD assessment due to confounding psychiatric symptoms that receive greater or

more immediate attention, such as depression or anxiety (Gershon & Gershon, 2002). Further, males are more likely to demonstrate impairing externalizing and/or disruptive behavior during school years and are more likely to be referred for diagnostic assessment (Martel, 2013). Recent theories of the male-to-female ratio include both the mean difference model, in which the mean symptom severity for males is closer to clinical diagnostic threshold, as well as the variance difference model, in which males demonstrate more extreme severities of symptom presentation across the distribution (Arnett et al., 2015). Results from an investigation by Arnett and colleagues (2015) indicate that the 3:1 male-to-female ratio appears to be valid and not the result of measure invariance (Arnett et al., 2015).

Etiology

The etiological mechanisms of ADHD are multifactorial. Currently, the etiology of this disorder can be conceptualized as a constellation of genetic, neurobiological, and environmental risk factors. The heritability for ADHD has been previously shown via twin studies, varying between 77 to 88% (Faraone & Larsson, 2019). Numerous studies investigating twin zygosity and ADHD also lend credence to a genetic etiology, with previous estimates of monozygotic concordance rates at nearly 80% (for an overview, see Biederman, 2005). Methods to examine genetic etiology can employ several approaches, such as genome scans with no *a priori* hypotheses, and theoretically driven candidate gene investigations. A genomewide linkage analysis of 204 families (853 individuals and 270 affected sibling pairs) suggests particular chromosomal locations (namely, *16p13* and *17p11*) are regions "likely to harbor risk genes for ADHD" (Ogdie et al., 2003). Further, meta-analyses of ADHD candidate genes implicate *DRD4*, the D4 dopamine receptor

gene (Gizer et al., 2009). In particular, common polymorphisms among individuals with ADHD include the dopamine receptor D4 4-repeat allele (*DRD4*4)*, the 2-repeat allele (*DRD4*2)*, and the 7-repeat allele (*DRD4*7)*, with prevalence rates at 65.1%, 8.8%, and 19.2%, respectively (Chang et al., 1996). *DRD4*7*, the 7-repeat allele of dopamine receptor D4, has been of particular interest among ADHD etiological investigations, given the high prevalence of the polymorphism and increased odds ratios of hyperactivity and inattention scores (Tovo-Rodrigues et al., 2013). Interestingly, this polymorphism appears to be region-specific (Hawi et al.,2000). However, results from genetic investigations have yielded inconsistent findings, with theories that the genotype must interact with a particular environmental risk to yield impairing symptoms (Kieling et al., 2008).

Environmental Risk Factors

While genetic and biological factors are strongly implicated in etiology, additional influences conferring risk for ADHD include several perinatal factors such as maternal infection and maternal immune activation (Strickland, 2014) and perinatal exposure to nicotine or alcohol (Milberger et al., 1998). Other environmental factors demonstrated to increase risk for ADHD symptoms include exposure to polychlorinated biphenyl compounds, pregnancy or delivery complications, poor maternal health, maternal age, labor duration, low birth weight, eclampsia, or hemorrhage (Banerjee et al., 2007). While there are clear indications for a genetic basis, the etiology of ADHD strikes similarities to the etiology of autism spectrum disorder; for both neurodevelopmental disorders, no single risk factor has been identified as the sole causal mechanism (Kieling

et al., 2008). Thus, while existing literature points heavily to genetic contributions, the consensus is that the disorder is likely due to gene-environment interactions.

Comorbid Oppositional Defiant Disorder

Coexisting psychiatric disorders are the rule, rather than the exception, among ADHD populations, and are considered a "key clinical feature of ADHD" (Biederman, 2005). ODD is the most common coexisting psychiatric disorder among individuals with ADHD, with prevalence rates upwards of 50% (Nock et al., 2007). The DSM-5 outlines ODD symptoms as "a pattern of angry and irritable mood, argumentative and defiant behavior, or vindictiveness, demonstrated at least once per week over a period of six months for children 5 years and older" (APA, 2013, p. 462). Severity (*mild, moderate, or severe*) is dependent on the number of settings in which symptoms occur (APA, 2013). Both ADHD and ODD symptoms frequently manifest during the preschool years (Lavigne et al., 2009; Riddle et al., 2013), and demonstrate adverse developmental outcomes (Forehand et al., 2016). To date, only a few studies have examined bidirectional relations between symptoms of ADHD and ODD across youth populations. Overall, the existing literature suggests ADHD symptoms predict later ODD symptoms, but ODD symptoms do not prospectively predict later symptoms of ADHD among school-age children (Burke et al., 2005; Burns & Walsh, 2002). Literature investigating these relations in preschool-aged children demonstrated mixed findings: ADHD symptoms predicted later ODD and CD symptoms in some investigations (Lahey et al., 2009; Wåhlstedt et al., 2008). However, these conclusions are limited, given reduced effect sizes when early conduct problems are controlled for in analyses. More recently, a longitudinal investigation of preschoolers suggests ADHD symptoms predict later

argumentative and defiant symptoms (Harvey et al., 2016). Overall, the relations between these diagnostic symptoms are yet to be well-understood.

Etiology

The shared etiology between ODD and ADHD is currently unknown, but literature demonstrates some heritability (Faraone et al., 1998). Common genetic risk factors appear to explain covariation of ADHD and ODD (Dick et al., 2005; Nadder et al., 2002). It is important to note, however, that genetic studies indicate the development of ODD symptoms is less likely to be genetically influenced than the development of ADHD symptoms alone, marking the importance of understanding ODD symptoms from a gene-by-environment interaction (Burt et al., 2001). A recent investigation found that family histories of ADHD and ODD/CD symptoms uniquely predict ADHD and coexisting anger/irritable symptoms in children (Harvey et al., 2016). Tuvblad and colleagues (2009) found that covariation of ADHD, ODD, and CD symptoms among 9-to-10-year-old children were explained by a latent externalizing behavior factor; with 57% of the total variance in the latent factor explained by a common genetic risk factor (Tuvblad et al., 2009). The authors assert their findings suggest that a common genetic influence marks liability for the co-occurrence of ADHD, ODD and CD symptoms among those in middle childhood.

Animal models of gene-environment interactions of ADHD and coexisting psychiatric symptoms suggest an interaction between tobacco exposure during the perinatal period with the *DAT1* dopamine transporter gene, providing the catalyst to up-regulate nicotine receptors (for a review, see Russell, 2011). Kahn and colleagues (2003) prospectively investigated children ages 6 months to 60 months to examine both

independent and joint contributions of *DAT1* polymorphisms and maternal prenatal smoking on ADHD and ODD symptoms (Kahn et al., 2003). The authors found that independent contributions of *DAT1* and prenatal maternal smoke exposure did not significantly account for increased ODD symptoms; however, children who were homozygous for the *DAT1* 10-repeat allele and also exposed to prenatal smoking demonstrated increased risk of hyperactive-impulsive and ODD symptoms (Kahn et al., 2003). Given biological factors implicated in ADHD etiology and partial heritability of ODD, examining the link between biological indices and treatment outcomes in this population is crucial. The following section will describe the use of EEG to denote neurophysiological differences within ADHD populations and review the extant literature.

Electroencephalography

EEG is a neurophysiological method that allows for the temporal evaluation of electrical activity stemming from the brain and can determine relative electrical activity across brain regions (Davidson et al., 2000). EEG recordings have been employed to study human behavior since Hans Berger used radio equipment to examine brain electrical activity in the early 1920's (Britton et al., 2016). The concept of brain waves was verified through Adrian and Matthews' (1934) investigation, in which the authors identified alpha rhythms—that is, oscillations between 10 to 12 Hz (Adrian & Matthews, 1934). EEG is both non-invasive and cost-effective (Bailey, 2014). It is most commonly used as a tool to assess seizure activity and diagnose epilepsy; however, clinical and research purposes for EEG vary widely and include sleep disorder physiology, biological

indices of neurodevelopmental disorders, and assessment of medication effects (Davidson et al., 2000)

Broadly, brain electrophysiology can be examined in three ways: 1) event related potentials, in which the average of EEG signals is time- and phase-locked to a stimulus or subject response; 2) continuous EEG, in which the absolute or relative magnitude of oscillations is calculated; and 3) scalp topography, providing a visualization of the brain regions implicated in both continuous EEG and ERP (Britton et al., 2016). EEG waveforms are measured and generated via differential amplification, in which one active exploring electrode site is compared with another neighboring or distant reference electrode, thus measuring electrical potential (Britton et al., 2016).

Neurodevelopmental research employing EEG methodology often aims to clarify underlying mechanisms and biological markers of neurodevelopmental disorders (Lau-Zhu et al., 2009). Among investigations of individuals diagnosed with ADHD, relations have been found between frontal cortical abnormalities and ADHD symptoms (Barry et al., 2003; Cortese, 2012; Monastra, 2008), as well as differences in ERP waveforms (Kaiser et al., 2020), however, results of spectral topography investigations have been highly variable (Thome et al., 2012). Overall, biological indices of ADHD remain elusive with no clear consensus. The use of EEG may provide further clarification to the etiology.

EEG Power Investigations in ADHD Populations

EEG has been employed as a tool to examine ADHD since Jasper and colleagues' (1938) seminal investigation (Lenartowicz & Loo, 2014). Investigations of EEG differences among children and adolescents with ADHD consistently demonstrate

increased theta activity among these populations (Clarke et al., 2003; Clarke et al., 2008). This increased theta activity is posited to be reflective of cortical hypoarousal (Loo & Barkley, 2004). The most consistent finding across investigations suggests that both children and adults diagnosed with ADHD demonstrate increased absolute and relative theta, decreased absolute and relative beta, and decreased absolute alpha compared to their typically developing peers (Kirkland & Holton, 2019, Lenartowicz & Loo, 2014). Significant group differences have also been found among adolescent populations as well as adult populations, such that beta activity was significantly reduced compared to typically-developing controls (Hermens et al., 2005; Lenartowicz & Loo, 2014), which is posited to be reflective of reduced concentration or active thinking (Baumeister et al., 2008). However, some studies suggest no differences in global or relative spectral power (Skirrow et al., 2015; Clarke et al., 2002; Clarke et al., 2003). It is important to note that EEG differences in alpha frequency (associated with an idle, relaxed state and associated with creativity) demonstrate inconsistent findings between ADHD and typically developing controls; relative power is often decreased among individuals with ADHD (Clarke et al., 2002; Clarke et al., 2003; Clarke et al., 2008), although other investigations found no significant differences among groups (Huang et al., 2018).

Prior to 2010, numerous investigations examined a potential "theta-to-beta ratio" to differentiate ADHD diagnosis, with initial results demonstrating large (range = 0.62 - 3.08) effect sizes (Snyder & Hall, 2006). However, recent evidence examining the theta-to-beta ratio points to replication errors across age ranges; overall findings indicate no significant group differences between ADHD versus typically developing peers (Arns et al., 2013; Saad et al., 2018). Finally, a meta-analysis by Arns and colleagues (2013)

reported decreased effect sizes in the theta-to-beta ratio comparing patients with ADHD and typically-developing controls. Interestingly, the decreased effect sizes across years was found to be driven by an increase in the theta-to-beta ratio among typically developing groups, and not due to a decreased ratio among the ADHD groups (Arns et al., 2013). Barring theta activity, the literature appears mixed given brain regions and age ranges investigated.

Stimulant Medications

Stimulant medications are considered the first line of treatment for ADHD; of these, MPH formulations are generally the first line of stimulant medications employed (Briars & Todd, 2016). MPH alters dopaminergic neural transmission, increasing dopamine and norepinephrine in the synaptic cleft (Capp et al., 2005). MPH is an FDA-approved medication to treat symptoms of ADHD, with well-documented efficacy (Schachter et al., 2001). Several older studies raise the question of whether childhood stimulant treatment demonstrates causal relations to later substance use disorder (Kollins et al., 2001); however, numerous studies have debunked this theory (Barkley et al., 2003; Biederman et al., 2008b; Loney et al., 2002).

EEG Relations of MPH Response in Children with ADHD

MPH has been demonstrated to improve abnormal EEG activity among individuals with ADHD, with the most common finding demonstrating that MPH attenuates absolute theta activity and increases absolute beta activity (Clarke et al., 2002). However, the literature is inconsistent, and results across frequency bands demonstrate mixed findings (Loo & Barkley, 2005).

Kirkland and Holton (2019) provide an excellent overview of the extant literature investigating stimulant treatment effects, although not particular to MPH. Previous investigations suggest that MPH use among children results in increased alpha activity in both central and parietal regions during baseline conditions (Loo et al., 2004; Loo et al., 2018). The authors found that among those who exhibited medication response, there was an associated increased frontal beta activity; whereas non-responders demonstrated decreased frontal beta activity (Loo et al., 2004). Further, increased frontal beta activity following medication administration appears to be associated with medication-related improvement in parent behavior ratings across both inattentive and hyperactive-impulsive symptoms (Loo et al., 2004). Decreased right frontal theta activity also demonstrates relations with improvements in parent-rated IA (Loo et al., 2004).

Few investigations have examined baseline neurophysiological predictors of MPH response, which would provide outstanding clinical utility for children and families in identifying medication treatment course. Gokten and colleagues (2019) provides the most similar methodological approach to the current study: The authors examined the relationship between initial EEG absolute power frequency bands (prior to the initiation of methylphenidate treatment) and difference scores, as measured by the Conner's Parent Rating Scale short form, following 13 months of MPH treatment among children with ADHD. The authors found that absolute frontal delta, frontal and central theta negatively correlated with parent-reported Conner's hyperactivity difference scores, that is, elevations were related to symptom improvement. Additionally, the authors found that absolute frontal beta and parietal beta positively correlated to parent-reported Conner's hyperactivity difference scores, that is, decreased beta power was related to more

improvement. Overall, among the stimulant class, decreased absolute theta and increased absolute beta has been demonstrated to be associated to treatment response, whereas treatment effects relations to alpha are mixed.

ODD symptoms have been examined through EEG methods in MPH response investigations among individuals with ADHD. However, these symptoms are often examined through broadband and categorical measures, such as the Child Behavior Checklist (CBCL; Achenbach & Rescorla, 2001). While the CBCL is often employed to determine standard scores across a variety if behaviors and accordingly maps items to DSM-5 symptom domains, items reported are not exhaustive to the diagnostic criteria, and do not capture a continuum of symptom presentation and severity and are prone to social-cultural bias (Brites et al., 2015). Categorical scales utilized by measures such as the CBCL or Conner's Parent Rating Scales provide items reflective to the extent which a specific psychopathology is present, which has the potential to exclude subtler variations of symptom presentation. For example, item 10 on the CBCL reads, "*Can't sit still, restless, or hyperactive*" that is rated on the extent to which this behavior is present on a 0-2 scale and does not reflect the extent to which a child has relatively strong behavioral control. Evaluation of disruptive or socially unacceptable behavior can vary across cultures (Brites et al., 2015), thus, a dimensional approach to examining these symptoms is warranted. The Strengths and Weaknesses of Attention-Deficit/Hyperactivity Symptoms and Normal-behaviors (SWAN; Swanson et al., 2012) provides a culturally-responsive approach, to better reflect symptom variability at the adaptive ends of attention and activity regulation as well as at the symptomatic levels of these dimensions. For example, the SWAN asks caregivers to rate how well their child "listens when

spoken to" (rating attentional skills) or "awaits turn" (rating activity regulation). Dimensional discrimination from the SWAN is ascertained from the average (level zero), such that extremes are represented both at the high (−1, −2, −3), and low (+1, +2, +3) end of the spectrum (Brites et al., 2013).

Given that ODD symptoms often manifest in the preschool years and are associated with poor developmental outcomes among individuals with ADHD, it is surprising that neurophysiological relations of ODD symptoms have not been robustly examined on and off-stimulants from a dimensional perspective. While differential behavioral profiles have been previously demonstrated among children across EEG frequencies, I am unaware of any research to date that has examined EEG predictors of MPH response utilizing the SWAN. An examination of EEG predictors of MPH response utilizing the SWAN provides the unique research opportunity to discern the degree to which a child's adaptive behavioral presentation (e.g., strengths in sustained attention, attention to detail, behavioral inhibition) may be enhanced or degraded following MPH. That is, use of the SWAN provides valuable information regarding the utility of MPH among those with maladaptive behavioral profiles *and* those presenting with adaptive strengths at baseline.

Current Study and Hypotheses

I will investigate the relations between EEG absolute frequencies and caregiver-reported changes in ADHD and ODD symptoms among school-age young children with ADHD. Overall, the goal of this study is to examine potential biomarkers linked to caregiver perceptions of MPH response among young children with ADHD. This study extends upon previous MPH response literature by examining dimensional symptoms and

is unique in its examination of continuum ODD symptoms in addition to ADHD symptoms. The methodological approach aligns with NIMH RDoC criteria, such that biologically-based groups are provided a dimensional phenotype. The results of this study may illuminate the clinical utility of EEG to predict perceived MPH response among school-age children with ADHD. Based on previous literature, the following hypotheses were made:

Hypothesis 1: Baseline absolute alpha frequency will be significantly predictive of change in caregiver-reported ADHD and ODD symptoms from pre-MPH to optimal MPH dosage. Specifically, it was hypothesized that reduced alpha frequency would predict greater symptom improvement (i.e., a significant negative relation between variables of interest). While literature regarding alpha frequency and MPH response is mixed, several investigations of baseline EEG profiles suggest that children with ADHD demonstrate decreased absolute alpha frequency compared to typically-developing peers (Kirkland & Holton, 2019, Lenartowicz & Loo, 2014).

Hypothesis 2: Baseline absolute beta1 frequency will be significantly predictive of change in caregiver-reported ADHD and ODD symptoms from pre-MPH to optimal MPH dosage. Specifically, it was hypothesized that decreased beta1 frequency would predict greater symptom improvement (i.e., a significant negative relation between variables of interest). One previous investigation found significant negative relations between absolute beta frequency within the parietal and frontal regions and improvement in Conner's hyperactivity difference scores (Gokten et al., 2019).

Hypothesis 3: Baseline absolute beta2 frequency will be significantly predictive of change in caregiver-reported ADHD and ODD symptoms from pre-MPH to optimal

MPH dosage. Specifically, it was hypothesized that decreased beta2 frequency would predict greater symptom improvement (i.e., a significant negative relation between variables of interest) based similarly on the beta1 frequency band findings by Gokten and colleagues (2019) described above.

Hypothesis 4: Baseline absolute theta frequency will be significantly predictive of change in caregiver-reported ADHD and ODD symptoms from pre-MPH to optimal MPH dosage. Specifically, it was hypothesized that elevated theta frequency would predict greater symptom improvement (i.e., a significant positive relation between variables of interest). This hypothesis is based on substantial literature suggesting individuals with ADHD demonstrate elevated baseline absolute and relative theta, further, elevated frontal and central theta have demonstrated relations to symptom improvement (Kirkland & Holton, 2019, Lenartowicz & Loo, 2014).

This study employs a cross-sectional, residualized change model. My independent variables across separate hypotheses are the following: average alpha, beta1, beta2, and theta frequencies. Given that I am examining residualized change scores derived from the SWAN as a dependent variable, retrospective parent reported pre-MPH SWAN ratings will serve an independent variable.

The residualized change models can be expressed as the following equation:

$$RS_{n2}=\beta_0+\beta_1 RS_{n1}+\beta_2 C_n+e_{n2}.$$

The subscript *n* is representative of each participant, and subscripts 1 and 2 represent timepoints. RS_{n2} represents participant's SWAN score at optimal MPH (i.e., timepoint 2), RS_{n1} represents participant's SWAN score pre-MPH (i.e., at timepoint 1), and C_n represents spectral power at the requency band (i.e., alpha. beta1, beta2, or theta). It is

important to note that both ANCOVA and multiple regression models are represented by this equation. Castro-Schilo and Grimm (2018) describe that the measurement scale of C_n (either grouping or continuous) determines if the data should be examined through ANCOVA or a multiple regression model, respectively. Following recommendations from Castro-Schilo and Grimm (2018) for analyzing two-occasion (e.g., repeated measures) data, and given that each C_n across my four hypotheses represents a continuous variable, multiple linear regression analyses was employed for the purposes of this investigation. Multiple linear regression models are used to estimate relationships between two or more independent variables and one dependent variable.

CHAPTER II – METHOD

Participants

This investigation was conducted as a subset of larger investigation examining neurophysiological correlates among school-age children with a clinical diagnosis of ADHD. The larger investigation and this sub-investigation were approved by the Institutional Review Board at the University of Washington (STUDY00004534). Participants in the larger investigation included children with ADHD and typically-developing controls as well as their primary caregivers. Exclusion criteria for the larger study was the following: Diagnosis of autism spectrum disorder, known genetic syndrome(s), intellectual disability or global developmental delay, IQ < 80, perinatal trauma, gestational age less than 32 weeks, prenatal exposure to substances, history of seizures, or colorblindness. Children were administered a brief measure assessing their cognitive abilities (WASI-II; Weschler, 2011) to verify IQ inclusion criteria. Participants within the ADHD group from the larger study were eligible to complete this sub-investigation if they had ever been treated with a methylphenidate medication, which was assessed during recruitment via a one-item screener.

A total of 31 children and their parents participated in this investigation. One participant (n =1) was later disqualified and removed from analyses due to identification of right central temporal discharges that were suggestive of Rolandic epilepsy or epilepsy with centro-temporal spikes, thus meeting exclusion criteria. The final sample of participants included 30 children (70% male, 30% female) ages 7-11 years old (M =

121.27 months; *SD*= 16.47 months) and their caregivers. Sample characteristics are further detailed below in Table 1 and Table 2.

Table 1

Sample Demographics

	Frequency	Percentage
Sex		
Male	21	70.0
Female	9	30.0
Ethnicity		
European American/White	21	70.0
Multiracial	6	20.0
European American, Hispanic	3	6.7
African-American	1	3.3
Currently Prescribed MPH		
Yes	14	46.7
No	16	43.3
Primary Caregiver Education		
High School or Equivalent	2	6.7
Some College	1	3.3
4-year college	11	36.7
Master's Level	10	33.3
Doctorate (PhD/MD)	6	20.0

Procedures

Families were recruited for the parent investigation from ADHD diagnostic clinics, research centers, community settings, and relevant social media posts within the greater Seattle area. Caregivers completed demographic, medical, and other behavioral measures during the larger main visit, including information regarding their child's psychiatric symptoms and health history. Children completed a 1-hour EEG session that included resting and task-based paradigms, and underwent neuropsychological testing lasting approximately 2 hours. During neuropsychological testing, children were

administered a brief cognitive assessment via a 2-subtest FSIQ from the *Wechsler Abbreviated Scale of Intelligence, Second Edition* (WASI-II; Weschler, 2011) to ensure inclusion criteria were met. A licensed clinical psychologist then reviewed the available data and confirmed diagnostic status as part of the larger investigation.

Primary caregivers of participants within the ADHD group who had consented to recontact for future research through the larger study were then recruited via phone and email within two years of their child's participation for the purposes of the current investigation. Caregivers were provided a list of methylphenidate brand names and completed a one-item screener, "*Has your child ever taken methylphenidate, even if it was a brief medication trial?*" to discern MPH medication history. Those who responded, "*Yes, my child is currently taking a methylphenidate medication*" or "*Yes, but not currently*" were invited to participate in the study. Caregivers consented to the use of their child's resting state data (acquired during the larger investigation), completion of a one-time HIPAA-compliant online questionnaire containing 2 repeated measures (SWAN, NICHQ Vanderbilt Performance subscales) and 1 measure of medication side effects (NICHQ Vanderbilt Side Effects subscale), and a brief clinical phone interview to provide specific examples pertaining to their survey responses. Caregivers were provided a survey link to the online questionnaire and were instructed to retrospectively rate their child's ADHD and ODD symptoms prior to MPH treatment, and then were instructed to rate their child's ADHD and ODD symptoms at optimal MPH dosage. Among those who did not achieve an optimal dosage or those who discontinued MPH prior to one month, caregivers were instructed to rate their child's ADHD and ODD symptoms at the highest

dose received for longer than three days. Caregivers then completed a brief phone interview following completion of the questionnaire to further provide examples of their child's pre-MPH and optimal-MPH functioning and behaviors. Caregivers were offered a $20 gift card in compensation for their participation for completing both the questionnaire and the brief follow-up interview.

EEG Acquisition

Children underwent a one-hour EEG visit consisting of 5 paradigms as part of the larger study. Participants were comfortably seated at 70cm from the presentation screen throughout EEG collection. A high-density 128-channel EGI Phillips GSN Hydrocel net and Netstation Acquisition software (version 4.5.6) with a 400-series high impedance amplifier (Electric Geodesics Inc., EGI, Eugene, OR) was used to collect continuous EEG data. At the start of the session, electrode impedances were reduced to below 50 kOhms to minimize signal-to-noise ratio. Additionally, examiners monitored and re-wet electrodes with saline solution throughout the EEG session. The vertex electrode—analog filtered (0.1 Hz high-pass, 100 Hz elliptical low-pass), amplified, and digitized with a sampling rate of 1000 Hz—served as reference for EEG signals. Timing of the presentation of the visual stimuli during the resting state, lights-on, eyes open tasks on the subject monitor was recorded using a Cedrus Stimtracker (Cedrus Corporation, San Pedro, CA).

Measures

Diagnostic Status

ADHD diagnosis of participants were confirmed as part of the larger investigation by a licensed clinical psychologist through review of caregiver report on the CBCL 6-18 (Achenbach & Rescorla, 2001), caregiver report on the KSADS-COMP (Townsend et al., 2019), clinical interview with the caregiver, an ADHD checklist, and/or behavioral observations during the larger study visit. Diagnostic status informed eligibility criteria for this sub-investigation.

Cognitive Abilities

Participants completed the WASI-II (Weschler, 2011) during the larger study visit. The WASI is a brief assessment of cognitive abilities for individuals ages 6 years 0 months to 90 years 11 months. The larger study utilized the Vocabulary and Matrix Reasoning subtests to derive a 2-subscale full scale IQ for each child. Each child's FSIQ-2 standard score was used to assess his or her cognitive abilities and included as a potential covariate in the current study. An FSIQ score below 80 was exclusionary for the parent study. The WASI-II was normed using 2,300 individuals aged 6 years 0 months to 90 years 11 months utilizing a representative sample of the United States population based on age, sex, race, ethnicity, educational level, and region. The alpha coefficient of the WASI-II FSIQ-2 composites was $\alpha = .94$. The WASI-II was also tested against other measures of intelligence (WASI, WISC-IV, WAIS-IV); correlations ranged from acceptable (.71) to excellent (.92).

Demographic Variables

Primary caregivers completed a demographic questionnaire as part of the larger study, detailing primary caregiver education level, child age, child sex, and ethnicity as

part of a Brief Medical History Questionnaire. Potential covariates were examined from the demographic questionnaire and analyzed to determine if they should be controlled for in subsequent analyses. Primary caregivers also completed brief survey items detailing if their child was currently taking MPH, the MPH medication brand prescribed, and approximate length of time the medication was taken.

EEG Spectral Analysis

A 5-minute, continuous resting state lights-on paradigm was selected for the purposes of this investigation and in accordance with previous literature. Resting state EEG provides a measure of overall brain activity in non-aroused or evoked states, noting function in the absence of instructions and task demands (Bai et al., 2017). Other paradigms from the larger study (e.g., easy event-related potential task, hard event-related potential task, auditory oddball task) were thus not examined, as my investigation aims to examine children's passive fundamental brain state.

Raw EEG spectral power were processed through the larger study following procedures similar to the Batch EEG Automated Processing Platform software (BEAPP; Levin et al., 2018). BEAPP is MATLAB-based, free software program available through GitHub, and has been employed to identify biomarkers of neurodevelopmental disorders, including neurophysiological indices of autism spectrum disorder in infancy (Gabard-Durnam et al., 2019). EEG data was processed via Matlab R2018b using EEGLAB 15 and functions and extensions. Initial processing involved all resting state data, 112 channels remained following exclusion of 14 rim channels and eye electrodes. Data were first downsampled to 250 Hz and bandpass filtered at 0.3-80 Hz. Next, the EEGLAB

Cleanline plugin was employed and removed electrical line noise from 55-65 Hz. Bad channels were then automatically deleted and subsequently interpolated following HAPPE preprocessing pipeline methods outlined by Gabard-Durnham and colleagues (2018). Average referencing preceded channel interpolation. Extended independent component analysis (ICA) was conducted, utilizing primary component analysis dimension reduction in order to identify and remove artifact components following the BEAPP pipeline methods (Levin et al., 2018). Welch's method was utilized to perform Fast Fourier Transformation (FFT) FFT is a mathematical method for transforming a function of time into a function of frequency and is frequently employed in EEG analyses (Nunez et al., 1997). Power values were log-transformed to facilitate direct comparisons with other investigations and in order to run parametric analyses (Cohen, 2014). Spectral power was calculated for 4 frequency bands: alpha (8-12 Hz), beta1 (13-20 hz), beta2 (21-30 Hz), and theta (4-7 Hz). Delta was not included as part of this analyses due to significant artifact conflation (e.g., eye movements, tongue movements, talking, chewing, movement artifacts). As a practical constraint, frequency bands (alpha, beta1, beta2, theta) were separately averaged across anterior frontal, frontal, central, and parietal regions of the scalp to serve as the primary variables of interest.

ADHD and ODD Symptoms

Parent-reported ADHD and ODD symptom severity pre-MPH and at the optimal/highest dosage were assessed via the Strengths and Weakness in ADHD Symptoms and Normal Behavior Scale (SWAN; Swanson et al., 2006). The SWAN measures the 18 ADHD symptoms as outlined through the *DSM-5*, as well as comorbid

ODD symptoms across 8 items. The SWAN uses a balanced, 7-point Likert scale, with anchors ranging from -3 = *far below (relative to same-aged peers)* to 3= *far above (relative to same-aged peers).* Items marked "*below*" or "*far below"* indicate clinical impairment. For ease of interpretation in this study, SWAN scores were reverse coded such that greater scores indicated greater clinical impairment. The SWAN has demonstrated high internal consistency (Cronbach's alpha > .90; Lakes et al., 2013) and strong external validity (Arnett et al., 2013). In this study, Cronbach's alpha for pre-MPH SWAN scores were .95 for the Inattention subscale, .94 for the Hyperactivity-Impulsivity subscale, .92 for the ODD subscale, and .88 for total SWAN scores. Cronbach's alpha for optimal-MPJH SWAN scores were .95 for the Inattention subscale, .93 for the Hyperactivity-Impulsivity subscale, .97 for the ODD subscale, and .95 for the total SWAN scores at optimal MPH. A total score of averaged ratings across ODD and ADHD symptoms were then computed from the SWAN for the purposes of this investigation.

Data Entry and Preparation

Data were entered into the Statistical Package for the Social Sciences (SPSS) Version 27.0 software and were cross-checked for accuracy. Primary variables of interest included averaged alpha, beta1, beta2, and theta frequencies (separate independent variables), children's ADHD and ODD symptoms prior to MPH (covariate; SWAN Timepoint 1), and children's ADHD and ODD symptoms at optimal MPH (dependent variable; SWAN Timepoint 2). All variables were continuous data.

Power Analysis

An *a priori* power analysis was conducted using G*Power (Faul et al, 2007) to determine adequate power and appropriate sample size for the current investigation. Pre-MPH SWAN scores served as a covariate in the model; no other covariates were detected. Using standard parameters of power at .8 and alpha set at .05, results indicated that a sample size of 68 was needed for a moderate Cohen's F^2 effect size of .15. The current study analyses were thus underpowered. Practical constraints limiting study recruitment are further outlined within the discussion section.

Preliminary Analyses

Preliminary data pre-screening evaluated assumptions of multiple regression and reviewed the data for missingness and outliers. No missingness was detected. Outliers were examined using histograms and box-and-whisker plots. No clear reasons for exclusion were identified and thus these datapoints were retained to represent variability within the clinical sample. No demographic variables (age, sex, ethnicity, primary caregiver highest level of education) were significantly correlated with variables of interest, nor were children's abbreviated IQ scores, and thus these variables were not controlled for in subsequent analyses. Prior to data analysis, the data were examined for the following violations of the assumptions of multiple regression, as outlined below:

Linearity

This assumption states that the relation of the independent variable (IV) and the dependent variable (DV) must be linear. Data were examined graphically using a scatter-plot with a best fitting line to determine linearity, and to ensure the data do not follow

other trajectories (e.g., cubic, quadratic). Data appeared randomly and evenly dispersed, thus the assumption was met.

Homoscedasticity

This assumption refers to the variance of the residuals being constant across all values of the independent variables (Field, 2009). This assumption was tested via visual inspection by plotting predicted values and residuals. To meet the assumption, data should appear evenly dispersed, with no significant outliers. If a funneling pattern emerges with the data, in which there are various levels of diffusion at different values of the IV, it would represent heteroscedasticity, violating this assumption. Data appeared evenly dispersed with no significant outliers.

Independence

The assumption of independence states that the errors of estimation are statistically independent; meaning a residual from one observation is not related to the residual of another observation. To test this, I conducted the Durbin-Watson test (Field, 2009). Values less than one or greater than three indicate residual dependence within the sample (Cohen et al., 2003). Durbin-Watson values were found to be within the appropriate range.

Normality

This assumption states there is normal distribution in the errors in estimation of the outcome variable. Accordingly, residuals distribution should be in concordance with a normal distribution (Field, 2009). To inspect this, I examined the data visually with a histogram as well as a probability-probability plot (P-P plot). The histogram of the

residuals revealed a normal distribution, and the P-P plot shows the z-scores plotted tightly along the diagonal line, which was sufficient evidence to conclude that the residuals of the data are normally distributed (Field, 2009)

Multicollinearity

Multicollinearity occurs when there is high covariance between two predictor variables (Field, 2009). I assessed multicollinearity through preliminary correlational analyses. If two of my predictor variables are highly correlated with one another ($r > .80$), I may consider combining the two predictors. Other tests of multicollinearity may include the VIF (value greater than 10) or a tolerance statistic (value less than .20; Field, 2009). It is important to note that while the EEG frequency variables were found to be highly correlated with one another, this did not present a multicollinearity issue because each EEG band was tested within a separate model, and thus the assumption of multicollinearity was not violated.

CHAPTER III – RESULTS

Descriptive and Correlational Analyses of Study Variables

Means and standard deviations of relevant demographic variables and primary variables of interest can be found in Table 2. Pearson's bivariate correlations among the study variables are presented in Table 3.

Table 2

Means and Standard Deviations

Variable	Range		*M*	*SD*
	Min	Max		
Age (in months)	87.93	144.23	121.27	16.47
FSIQ-2	92	128	108.53	9.69
SWAN T1	.74	2.81	1.62	.55
SWAN T2	-1.33	1.48	.10	.79
Alpha	.07	1.44	.49	.32
Beta1	.03	.47	.17	.10
Beta2	.02	.48	.12	.10
Theta	.14	1.25	.53	.28

Note. SWAN T1 = Caregivers' retrospective ratings of children's ADHD and ODD symptom severity pre-MPH. SWAN T2 = Caregivers' ratings of children's ADHD and ODD symptom severity at optimal MPH dosage. Greater SWAN scores indicate more clinically significant symptoms.

Table 3

Bivariate Correlations among Study Variables

Variable	1	2	3	4	5	6	7	8
1. Age (months)	—							
2. FSIQ-2	.22	—						
3. Alpha	.18	-.08	—					
4. Beta1	.04	.18	.71***	—				
5. Beta2	.13	.23	.56***	.87***	—			
6. Theta	.06	-.02	.77***	.68***	.51***	—		
7. SWAN T1	-.12	-.19	.15	.02	.04	-.03	—	
8. SWAN T2	.00	-.20	-.35*	-.23	-.07	-.25	-.04	—

Note. * $p < .10$, ** $p < .05$, *** $p < .01$

Test of Hypotheses

Multiple linear regressions were performed to determine the predictive ability of EEG frequencies on SWAN scores at optimal-MPH dosage while controlling for SWAN scores prior to MPH.

Alpha Frequency

Results of the multiple regression analysis indicated that the two predictors explained 12.8% of the variance ($F(2,27)=1.98$, $p <.15$, $R^2 =.12$). As can be seen in Table 4, it was found that alpha frequency was marginally statistically significantly predictive of SWAN scores at optimal-MPH dosage while controlling for SWAN scores prior to MPH, $\beta = -.35$, $t(27) = -1.97$, $p = .058$. Thus, with each one-unit increase in alpha power (i.e., alpha frequency elevation), SWAN scores at optimal-MPH dosage decreased by -.86 (i.e., improvement in symptoms) when controlling for pre-MPH SWAN scores.

Table 4

Results of Multiple Regression in Alpha Frequency Band

Variable	*B*	SE(*B*)	β	*t*	*p*	95% CI	
						LL	UL
Constant	.51	.46		1.10	.27	-.44	1.46
SWAN T1	.01	.25	.09	.04	.96	-.51	.54
Alpha	-.86	.43	-.35	-1.97	.06	-1.76	.03

Note. $*p < 0.05$.

Beta1 Frequency

Results of the multiple regression analysis indicated that the two predictors explained 5.6% of the variance ($F(2,27)=.80$, $p <.45$, $R^2 =.05$). As can be seen in Table 5, it was found that beta1 frequency was not significantly predictive of SWAN scores at

optimal-MPH dosage while controlling for SWAN scores prior to MPH, β = -.03, *t*(27) = - .20, *p* = .839.

Table 5

Results of Multiple Regression in Beta1 Frequency Band

						95% CI	
Variable	*B*	SE(*B*)	β	*t*	*p*	LL	UL
Constant	.50	.51		.98	.33	-.54	1.56
SWAN T1	-.05	.26	-.03	-.20	.83	-.60	.49
Beta1	-1.81	1.45	-.23	-1.24	.22	-4.80	1.17

Note. *$p < 0.05$.

Beta2 Frequency

Results of the multiple regression analysis indicated that the two predictors explained 0.8% of the variance ($F(2,27)=.10$, $p <.90$, $R^2 =.008$). As can be seen in Table 6, it was found that beta2 frequency was not significantly predictive of SWAN scores at optimal-MPH dosage while controlling for SWAN scores prior to MPH, β = -.07, t(27) = - .38, *p* = .702.

Table 6

Results of Multiple Regression in Beta2 Frequency Band

						95% CI	
Variable	*B*	SE(*B*)	β	*t*	*p*	LL	UL
Constant	.27	.49	--	.54	.58	-.74	1.28
SWAN T1	-.05	.27	-.04	-.21	.83	-.62	.50
Beta2	-.55	1.42	-.07	-.38	.70	-3.47	2.37

Note. *$p < 0.05$.

Theta Frequency

Results of the multiple regression analysis indicated that the two predictors explained 6.9% of the variance ($F(2,27)=1.10$, $p < .30$, $R^2 = .069$). As can be seen in Table 7, it was found that theta frequency was not significantly predictive of SWAN scores at optimal-MPH dosage while controlling for SWAN scores prior to MPH, $\beta = -.05$, $t(27) = -1.30$, $p = .174$.

Table 7

Results of Multiple Regression in Theta Frequency Band

						95% CI	
Variable	*B*	SE(*B*)	β	*t*	*p*	LL	UL
Constant	.61	.53	--	1.14	.26	-.48	1.72
SWAN T1	-.07	.26	-.05	-.29	.77	-.62	.46
Theta	-.71	.51	-.25	-1.39	.17	-1.76	.33

Note. $*p < 0.05$.

CHAPTER IV – DISCUSSION

In this study, I investigated the relations between EEG frequencies and changes in inattentive, hyperactive-impulsive, and oppositional defiant symptoms at optimal dosage in a sample of children diagnosed with ADHD and previously trialed on MPH. Examining these relations may lead to potential identification of biosignals that may inform families of potential MPH response prior to initiating medication. In the sections below, I will interpret the results of my multiple regression analyses, discuss implications of these results, outline the limitations of this investigation, and discuss future directions within this discussion and conclusion.

Overall, no frequency bands examined within this study met traditional statistical significance levels ($p < .05$) to reject the null hypothesis, however, the alpha frequency band approached statistical significance, which warrants further examination in future studies. Hypothesis 1 postulated that reduced alpha frequency would predict greater symptom improvement (i.e., a significant negative relation between variables of interest) based on previous literature suggesting youth with ADHD demonstrate decreased absolute alpha frequency compared to typically-developing peers (Kirkland & Holton, 2019, Lenartowicz & Loo, 2014). The alpha frequency multiple regression result from this investigation appears to be in concordance with several previous investigations which have demonstrated reduced baseline alpha (Barry et al., 2009; Clarke et al., 2002; Clarke et al., 2003; Clarke et al, 20008) among ADHD populations. These results and the extant literature are also congruent with neurophysiological literature suggesting that resting alpha power reflects attentional processes such as alertness and hypervigilance (Klimesch, 1999) as well as creative ideation (Schwab et al., 2014).

Surprisingly, Beta1, Beta2, and Theta frequencies were not predictive of retrospective perceived change in ADHD and ODD symptoms at optimal MPH dosage. These results are counter to Loo and colleagues' (2004) results, which found a significant positive relation between frontal beta and ADHD symptom improvement, as well as a significant negative relation between frontal theta and improvements in inattention symptoms. However, there are several caveats to consider in making this comparison, namely, that Loo and colleagues' (2004) investigation examined both baseline neurophysiology and re-tested while on stimulant medication. The results of the current investigation are also counter to Gokten and colleagues (2019), who found that decreased beta and increased frontal delta, frontal theta, and central theta were related to caregiver-reported symptom improvement on MPH.

From a neurophysiological perspective, an important caveat is that each frequency band was averaged across regions for the purposes of the current study as a practical constraint. Given marginally significant results within the alpha frequency band, it is possible that specification of region-specific variables may yield statistically significant findings and allow for further comparisons with other investigations. Further, given that only baseline neurophysiology was measured, it is likely that a re-test of the EEG paradigm with MPH administration would further illuminate these relations and allow for direct comparisons. However, methodological differences are likely to exist within medication administration procedures, complicating direct comparisons. The numerous inconsistent findings within the EEG literature investigating ADHD populations are thought to reflect methodological differences, such as eyes-open versus eyes-closed paradigms or cognitive activation tasks (Loo et al., 2004).

The current study has several notable strengths. First, this investigation examined change in both ADHD and ODD symptoms utilizing a dimensional, continuum measure which captures both adaptive and maladaptive presentations. The use of the SWAN serves as an attempt to more accurately examine an individual's behavioral presentation in the context of their culture-specific and age-related norms, rather than categorical ratings of psychopathology, as intended by the authors (Brites et al., 2015, Swanson et al., 2009). The SWAN been used in investigations across cultures; tests of statistical stability by translation and validation for other languages has yielded promising results, overall reports suggest excellent specificity, excellent stability, and good internal consistency among translated versions of the scale (Brites et al., 2015).

Second, this investigation examined a population of children in middle childhood (ages 7-12) years, reflective of the average range in which most children diagnosed with ADHD initiate a stimulant medication trial (Swanson & Volkow, 2009). Third, this study utilized a residualized change score model based on theoretical reasoning and recommendations from Castro-Schilo and Grimm (2018) to reduce statistical bias for two-occurrence continuous data. I am aware of several investigations that have examined ADHD change score outcomes, however, most have examined this change by calculation of difference scores, which are noted to be highly prone to statistical bias (Castro-Schilo & Grimm, 2018).

Despite these outlined strengths, there were several limitations of the current study. The small sample size of this investigation impacted statistical power and thus was more susceptible to Type II error, or the failure to reject the null hypotheses. It is possible that low statistical power may be responsible for null results, given that a sample size of

68 was recommended. Additionally, although sample demographics were reflective of the region, participants in this investigation were predominantly European American, limiting generalizability. Future research should examine correlates of MPH response among participants and caregivers from diverse racial, ethnic, socioeconomic, and gender identity backgrounds. Perhaps the most important caveat of this investigation, this study employed retrospective caregiver ratings, which should be interpreted with caution due to the high potential for caregiver recall bias (Miller et al., 2009).

It is also important to note that a majority of the data for this investigation was collected during the height of the COVID-19 pandemic. While research methods were not altered for the purposes of this investigation, it is possible that this may have influenced the selection of caregivers who enrolled in the study as well as caregiver's retrospective ratings of their child's ADHD and ODD symptoms. Results from a recent investigation of the impact of the COVID-19 pandemic on caregivers of those with developmental disabilities such as ADHD found that COVID-19 related difficulties with childcare resources significantly predicted higher caregiver burden scores on the Burden Scale for Family Caregivers (Iovino et al., 2021). There exists the possibility that those with greater caregiver burden were not included in this study due to caregiver-related time constraints. Crucially, this study did not examine caregivers' symptoms of ADHD. It is possible that inattentive and/or hyperactive-impulsive symptoms among caregivers could have influenced their ratings of their child's ADHD and ODD symptoms. A 2009 investigation by Miller, Newcorn, and Halperin examining retrospective recall inaccuracies among parents of adolescent youth diagnosed with ADHD further supports this possibility. The authors found that current symptom severity in late adolescence and

early adulthood influenced both youth and parents recall of childhood symptoms (Miller et al., 2009). Future research examining MPH response would likely benefit from additional raters within other settings, such as participants' teachers, utilizing a prospective design with multiple informants.

Additionally, while the investigation examined baseline neurophysiological predictors that may predict MPH response, children did not undergo a re-test of the resting state EEG paradigm while on their optimal MPH dosage. Although all children refrained from prescribed ADHD medications during a 48-hour medication washout, some literature suggests that prior use of stimulants may alter baseline neurophysiological functioning (Pertermann et al., 2019; Robertson et al., 2019). Relatedly, this study employed a cross-sectional design, thus, no causation can be inferred from study findings.

Conclusions

The study's primary goal was to examine associations of EEG frequency bands and caregiver perceived change in children's ADHD and ODD symptoms at optimal MPH dosage**.** Although no frequency bands reached traditional statistical significance levels, results suggest the alpha band frequency should be examined in future investigations of behavioral changes following stimulant medication. These findings provide novelty to the extant literature examining neurophysiological indices of MPH response with the inclusion of ODD symptoms. A trial-and-error approach to stimulant medications have the potential to cause worry and distress within families and can potentially lead to early discontinuation of effective treatment (Toomey et al., 2012)

These preliminary results should be further explored to identify neurophysiological stimulant response phenotypes among children with ADHD.

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