EEG Power Spectral Slope differs by ADHD status and stimulant medication exposure in early childhood.

Running Title: EEG Power Spectral Slope in Early Childhood ADHD

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ABSTRACT

Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder characterized by hyperactivity/impulsivity and inattentiveness. Efforts towards the development of a biologically based diagnostic test have identified differences in the EEG power spectrum, most consistently reported is an increased ratio of theta to beta power during resting-state in those with the disorder, compared to controls. Current approaches calculate theta/beta ratio using fixed frequency bands, but the observed differences may be confounded by other relevant features of the power spectrum, including shifts in peak oscillation frequency, and altered slope or offset of the aperiodic 1/f-like component of the power spectrum. In the present study, we quantify the spectral slope and offset, peak alpha frequency, and band-limited and band-ratio oscillatory power in the resting-state EEG of 3-7-year-old children with and without ADHD. We found that medication-naïve children with ADHD had higher alpha power, greater offsets, and steeper slopes compared to typically developing children. Children with ADHD who were treated with stimulants had comparable slopes and offsets to the typically developing group despite a 24-hour medication washout period. We further show that spectral slope correlates with traditional measures of theta/beta ratio, suggesting the utility of slope as a neural marker over and above traditional approaches. Taken with past research demonstrating that spectral slope is associated with executive functioning and excitatory/inhibitory balance, these results suggest that altered slope of the power spectrum may reflect pathology in ADHD.

NEW & NOTEWORTHY. This manuscript highlights the clinical utility of comprehensively quantifying features of the EEG power spectrum. Using this approach, we identify for the first

time, differences in the aperiodic components of the EEG power spectrum in children with ADHD, and provide evidence that spectral slope is a robust indictor of an increase in low relative to high frequency power in ADHD.

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder characterized by hyperactivity/impulsivity and inattentiveness. Children with ADHD are more likely to exhibit poor educational outcomes (Loe and Feldman 2007), social-emotional problems (Wehmeier et al. 2010) and substance use disorders (Wilens et al. 2011) that persist into adulthood. Recent estimates place the worldwide prevalence of ADHD between 5.3-7.2% (Polanczyk et al. 2007; Polanczyk et al. 2014; Thomas et al. 2015), though the rate of diagnosis in the United States is higher, estimated at 7.7% for 4-11-year-olds, and 13.5% for 12-17-year-olds (Xu et al. 2018). In addition to varying by age, diagnostic rates vary by gender, race, and ethnicity. Specifically, females and Hispanic and African American children are diagnosed at lower rates than Caucasian males (Polanczyk et al. 2014; Visser et al. 2014; Xu et al. 2018). These inconsistencies appear to reflect disproportionate diagnosis rather than true differences in prevalence between these populations (Bruchmuller et al. 2012; Merten et al. 2017).

One potential solution to the misdiagnosis of ADHD is a sensitive and specific biologically based diagnostic test. Towards this, a large body of research has sought to identify biomarkers of ADHD diagnosis and symptomology. Many of these efforts have focused on resting state electroencephalography (EEG), due in part to the clinical accessibility and cost-effectiveness of EEG. One of the more consistent findings differentiating ADHD from controls comes from analysis of the EEG power spectrum. Children with ADHD tend to have relatively greater power in the low frequency theta range along with relatively reduced power in the high frequency beta range compared to typically developing children; this is referred to as the theta/beta ratio and has commonly been proposed as a potential biomarker of ADHD (Barry et al. 2003; Loo and Makeig 2012; Monastra et al. 2001; Monastra et al. 1999; Snyder and Hall 2006).

111 In addition to elevated theta/beta ratio in ADHD, a recent study found reductions in theta/beta
112 ratio following treatment with methylphenidate, a common stimulant used to treat ADHD, which
113 persisted after a 24-hour medication washout (Isiten et al. 2017). This finding is consistent with
114 reports that treatment with stimulant medications ameliorates EEG and cortical structure
115 abnormalities in ADHD patients (Clarke et al. 2017; Clarke et al. 2003; Nakao et al. 2011; Shaw
116 et al. 2009; reviewed in Spencer et al. 2013).

117 Despite the fact that reduced theta/beta ratio is one of the more consistently observed
118 differences between ADHD and control subjects, its diagnostic utility is low due to failed
119 replications and diminishing effect sizes over time (Arns et al. 2013; Loo and Makeig 2012; Saad
120 et al. 2018). One potential explanation for this variability is that current approaches calculate
121 theta/beta ratio using fixed frequency bands, defining theta as EEG power between 4-8 Hz, and
122 beta as EEG power between 13-21 Hz (Monastra et al. 1999). Importantly, observed group
123 differences in theta/beta ratio could be explained not just by differences in narrowband
124 oscillatory power, but by other dynamic and physiologically relevant features of the power
125 spectrum, including a shift in peak oscillation frequencies, and altered slope or offset of the
126 aperiodic, 1/f-like, component of the power spectrum (Gao 2016; Haller et al. 2018).

127 Differences in oscillatory power across conditions are the most extensively studied
128 feature of the EEG power spectrum (Fig.1A). Differences in oscillatory power have been linked
129 both to disease states, as well as to a wide variety of cognitive processes (Basar et al. 1999; 2001;
130 Klimesch 1999; Makeig et al. 2002). For example, studies have linked task-related increases in
131 theta oscillations with enhanced cognitive performance, including working memory (Hsieh and
132 Ranganath 2014), and attention (Makeig et al. 2002). Conversely, chronic elevations in theta
133 power have been associated with cognitive impairment observed in old age (reviewed in

Klimesch 1999), and in disease states, including ADHD (Barry et al. 2003) and Alzheimer's disease (Fernandez et al. 2002). In addition to differences in oscillatory power, the peak frequency within these frequency bands can also vary (Fig.1B). For example, the location of the peak frequency within the alpha band increases with age during childhood (Epstein 1980; Marshall et al. 2002), peaks in early adulthood, and then decreases during older adulthood (Aurlien et al. 2004) at which point a lower peak frequency is associated with diminished executive function (Grandy et al. 2013). Furthermore, oscillatory peaks within defined frequency bands exist atop an aperiodic signal reflecting diminished power with increasing frequency, which varies in terms of slope and offset (He 2014). The slope of the aperiodic signal, or rate of decline in power with increasing frequency (Fig. 1C) fluctuates with cognitive state (Podvalny et al. 2015), and is associated with aging, executive function (Voytek et al. 2015), and synaptic excitatory/inhibitory balance (Gao et al. 2017). In contrast, the offset, or broadband power of the signal (Fig. 1D), may reflect the firing rate of neuronal populations (Manning et al. 2009). Thus, typical EEG approaches that do not fully characterize the power spectrum may conflate differences in the ratio of low frequency to high frequency oscillations with shifts in peak frequencies, power spectral slope and/or offset. For example, increased power in a low frequency band (theta) relative to a higher frequency band (beta) may be better assessed by measuring the slope of the aperiodic signal, as this would implicitly measure the relative power in high and low frequencies without relying on arbitrarily defined frequency bands.

In the present study, we took such a comprehensive approach, and compared the slope, offset, peak alpha frequency, and band-limited and band-ratio relative power of the resting-state EEG signal in a sample of 3-7-year-old, medication-naïve children with ADHD (n=50), and age and gender matched typically-developing controls (TD; n=50). In addition, we compared these

aspects of the EEG power spectra in 3-7-year-old children with ADHD and a history of stimulant treatment (*n*=26), to age and gender matched medication-naïve children with ADHD (*n*=26) and typically developing controls (*n*=26). Given previous literature documenting theta/beta ratio differences associated with childhood ADHD and suggesting normalization of the EEG power spectra with stimulant treatment, we hypothesized that medication-naive children with ADHD would have steeper slopes compared to typically developing controls, and that treatment with stimulants would flatten the EEG power spectral slope. We further hypothesized that slope estimates would correlate with traditional estimates of theta/beta ratio, reflecting the utility of measuring EEG power spectral slope as a robust indicator of relative low to high frequency power in children with ADHD.

MATERIALS AND METHODS

Participants

A total of 127 children (26.8% female) between the ages of 3 years 0 months and 7 years 4 months (*M*=5 years 9 months, *SD*=1 year 2 months) participated in the present study from a sample of children (*N*=197) in a longitudinal study evaluating stability of ADHD diagnosis. Participants were recruited from schools, community events, and databases consisting of children seen for ADHD at Boston Children's Hospital, or whose families expressed interest in participating in research within the Labs of Cognitive Neuroscience at Boston Children's Hospital. From the larger sample, we excluded participants due to parent report of genetic abnormalities (*n*=1), prenatal substance exposure (*n*=2), parent report of autism spectrum disorder confirmed during study assessments (*n*=1), parental language barriers (*n*=1), refusal to participate after time of consent (*n*=1), active use of a non-stimulant psychotropic medication (*n*=19), or insufficient artifact-free EEG data as determined by a trained experimenter (*n*=18*;* 11

ADHD, 7 Control). Of the remaining participants, 76 met criteria for ADHD and 78 were classified as typically developing controls. Of those who met criteria for ADHD, 50 were medication naïve (ADHD-), and 26 were actively treated with stimulant medications but underwent a 24-hour medication washout prior to study procedures (ADHD+). The 24-hour wash-out period was determined based on parent-report, and is the standard washout period used for stimulants given their short half-life (Cole et al. 2008; Isiten et al. 2017; Valera et al. 2010; Wigal et al. 2007). A group of 50 typically developing (TD) participants was selected to match the ADHD- group regarding both age and gender, and a subset of participants from the TD and ADHD- groups were selected to age and gender match the group of 26 ADHD+ participants. See Table 1 for demographics. All study procedures complied with the Helsinki Declaration and were approved by the Institutional Review Board at Boston Children's Hospital. All child participants provided verbal assent, and their primary caregivers provided written informed consent.

ADHD Diagnosis

ADHD diagnosis was determined during the study visit using the Diagnostic Structured Interview Schedule– young child version (DISC-IV; Shaffer et al. 2000) . In some cases, additional information was obtained from the Achenbach child behavior checklist (CBCL 1.5-5 or 6-18 depending on age; Achenbach 1994), and the Swanson Nolan and Pelham Checklist (SNAP-IV; Swanson 2011). Children included in the ADHD group either met diagnostic criteria on the DISC-IV (n=64), or received a subthreshold score on the DISC-IV (n=8) but met clinical thresholds on either the CBCL (ADHD subscale t-score $\geq$ 70, n= 3), the SNAP-IV (caregiver endorsed 6/9 inattention or hyperactivity symptoms, n=4), or both (n=1). In addition, two

participants met neither clinical nor subclinical threshold on the DISC-IV but met clinical threshold on the SNAP-IV (n=1) or both the SNAP-IV and the CBCL (n=1). Further, due to technical difficulties, two participants did not have DISC-IV scores, but met criteria on both the CBCL and the SNAP-IV (n= 2).

Teacher report of ADHD symptoms was assessed using either the Teacher Report Form of the CBCL (TRF; Achenbach 1994) or the Conners-3 Teacher Rating Scale (Conners 2001) in 48% of participants (N=61) due to complications in data collection. There was no difference in ADHD symptoms between participants with and without teacher report on either the DISC, CBCL, or SNAP-IV (*p's*>0.40). ADHD symptoms by group membership for each of the measures is shown in Table 2 for the full ADHD- and TD samples, and Table 3 for the ADHD+ sample and the age- and gender- matched TD and ADHD- subsamples.

EEG Acquisition

EEG data was obtained during eyes open and eyes closed resting state conditions for a total of 7 minutes. During the recording period, the participants cycled through 30 seconds of eyes open data collection in which the child directed their attention toward a cartoon image of open eyes; a 15 second break in which a research assistant encouraged the child's continued compliance; and 30 seconds of eyes closed data collection in which the child was instructed to sit calmly with their eyes closed. This process was repeated seven times. While this is a non-standard procedure for collecting resting state EEG data, it was designed to maximize the amount of artifact-free data given the young age of the children participating in the study and similar procedures have been used elsewhere with children in this age range (Vuga et al. 2008). Even within this specially designed procedure, young children were unable to follow the

direction to sit calmly with their eyes closed. Specifically during the eyes closed section, children tended to squeeze their eyes shut, squint, or open and close their eyes repeatedly to observe the room. This resulted in an excessive amount of muscle and movement artifact for the eyes closed segments, thus these were excluded from further analysis and only eyes open segments were used.

EEG data was recorded with a 128-channel HydroCel Geodesic Sensor Net System (Electrical Geodesics Inc., Eugene, OR) with a NetAmps 200 Amplifier and NetStation software at an effective sampling rate of 250 Hz. Electrodes were maintained such that at least 90% of the 128 electrodes had impedances below 50 kΩ prior to initiating the resting state recording.

EEG Pre-Processing

Data were preprocessed using NetStation. Recordings were high-pass filtered to 0.1 Hz and low-pass filtered to 100 Hz. Then, data was segmented into the eyes open and eyes closed conditions. The best 2-4 eyes open segments were selected, and these were concatenated to form a 1-2-minute block of eyes open resting state data. While data length did not differ between the ADHD+ group and the age and gender-matched TD and ADHD- subgroups ($F_{(2,75)}$=0.833, p=0.439), there was a trend level group difference in length of data between the full ADHD- group (M=111.97 seconds, SD=18.28) and TD group (M=117.99 seconds, SD=11.91; $t_{(84.26)}$ = 6.02, p=0.054). As a result, we controlled for data length in all analyses.

After segmenting and concatenating the data, any electrodes with artifacts outside of a ±80 mV range were removed, and were replaced with data interpolated from the remaining electrodes. Eye and other radial electrodes were removed from all analyses. Finally, all channels

were re-referenced to the average reference (Liu et al. 2015), and exported to MATLAB (MathWorks Inc., Natick MA) for further processing.

We identified and removed eye-blinks and muscle movements using Independent Components Analysis (ICA) in EEGLAB (Delorme and Makeig 2004). Prior to ICA, recordings were high-passed filtered to 1 Hz due to evidence that this improves artifact detection (Winkler et al. 2015). Electrode locations from the 128-channel montage were mapped and reduced to the 10-10 International System (Luu and Ferree 2005) to account for highly correlated signal from nearby electrodes (Onton and Makeig 2006). Then, the ICA decomposition was calculated in EEGLAB and we used the MARA EEGLAB plug-in (Winkler et al. 2014; Winkler et al. 2011). MARA is a supervised machine-learning algorithm that has been pre-trained to identify and label independent components of the EEG signal as artifact or neural activity based on six features described in Winkler et al. (2014). Of the 71 components derived from ICA, only the first 12 accounted for more than 1% of the variance each. As such, a trained experimenter (SF) visually inspected these first 12 components to verify MARA's artifact classification. In the rare instances when it differed from MARA's classification, the experimenter's classification by visual inspection was used. The remaining 59 components were classified solely based on MARA's calculated probabilities, with those assigned a probability greater than 0.50 were marked as artifact, and their time series were subtracted from the overall signal creating a cleaned signal that is used for further analysis.

Data Analysis

We first estimated power spectral density (PSD) using Welch's method with a Hamming window length of 1 second, and 50% overlap (Gao et al. 2017). To independently examine the

four components of the electrophysiological power spectrum (Fig. 1. A-D), we used the Fitting Oscillations & One Over f (FOOOF) toolbox to calculate slope and offset (Haller et al. 2018), and visually detected each individual's peak alpha frequency (PAF), which was then used to estimate individualized narrow-band power (Doppelmayr et al. 1998). We assessed each of these parameters at 12 midline electrodes across the frontal, central, parietal and occipital regions (FCZ, FZ, F3, F4, C3, C4, CZ, P3, P4, PZ, O1, O2).

Individualized Peak Alpha Frequency. We determined PAF though visual inspection of the plot of the power spectrum. PAF detection was performed within the predefined alpha band of 5.5–13 Hz (Klimesch 1999; Marshall et al. 2002), and defined as the average point of highest amplitude within that range for the 12 channels tested. Two researchers (MR and MK) independently identified the peak within the alpha range to the nearest 0.25 Hz with 83% concordance. In those instances where the researchers differed in their classifications, the PAF was re-evaluated to ensure accurate selection. Cases of discordance were due to either split peaks, or minimal deviation from the aperiodic background scaling. If, upon re-evaluation, the researchers could not agree upon a dominant peak, split peaks were averaged together to estimate PAF, whereas those with minimal deviation from background scaling were regarded as having no PAF and were excluded from PAF analysis. Of 100 participants, 91 had a clear alpha peak. Of the nine individuals without an alpha peak, four were in the TD group and five were in the ADHD- group. Those with and without alpha peaks did not differ in regards to group ($t_{(98)}$=0.346, p=0.730), age ($t_{(98)}$=0.534, p=0.595), or data length ($t_{(98)}$=1.090, p=0.278), but there was a trending difference in gender ($t_{(98)}$=1.947, p=0.054) with females being more likely to not have an alpha peak.

295

296 *Frequency Band Analysis.* In order to account for observations that frequency
297 bandwidths vary based on PAF, individualized frequency bands were calculated as a percentage
298 of the PAF as follows: theta [PAF × 0.4 – PAF × 0.6] and alpha [PAF × 0.6 – PAF × 1.2]
299 (Doppelmayr et al. 1998). Previous work has shown that this approach better accounts for
300 variations in bandwidth that occur as a function of PAF (Doppelmayr et al. 1998), which in turn
301 varies with age (Aurlien et al. 2004; Epstein 1980; Marshall et al. 2002). For the nine
302 participants with no clear alpha peak, we instead calculated individualized frequency bands using
303 the average PAF for the ADHD- and TD groups, which were 8.43 and 8.84, respectively. To
304 account for differences in the amplitude of the EEG signal due to noise including skull thickness
305 and electrode impedance, we calculated relative power by dividing the power within each band
306 by the total power (Gasser et al. 1982; Kappenman and Luck 2010). To allow for direct
307 comparison with existing literature, theta/beta ratio was calculated using standard methods
308 described in Monastra et al. (1999), which divides theta band power between 4-8 Hz by beta
309 band power between 13-21 Hz.

310

311 *Slope and Offset.* We used the FOOOF toolbox (Haller et al. 2018) to calculate the slope
312 (Fig. 1C) and offset (Fig. 1D) of the PSD between 4 and 50 Hz. Briefly, we first modeled the
313 aperiodic slope, then found the oscillatory peaks and fit them with Gaussians. We then subtracted
314 the Gaussians iteratively until all peaks were removed. We then refit the aperiodic slope of the
315 power spectrum with the peaks removed using an exponential function in semi-log power space.
316 This procedure provides an estimate for each EEG channel of two key aperiodic features of the
317 power spectrum: slope and offset.

Statistics. Data were analyzed using IBM SPSS Statistics version 25, and SAS version 9.4. To examine electrophysiological differences related to ADHD diagnoses, we conducted a single factor analysis of covariance (ANCOVA). To evaluate the relationship between slope and theta/beta ratio, we conducted a partial correlation. All analyses controlled for data length and were corrected for multiple comparisons. Between-group main effects were Bonferroni corrected to $p<0.05$. In order to account for account for collinearity amongst EEG electrodes and reduce the risk of Type II errors, between-group comparisons of the individual EEG electrodes were instead False Discovery Rate (FDR) corrected to $p<0.05$.

RESULTS

Electroencephalographic Results

Slope of the Power Spectrum. We tested whether the aperiodic spectral slope, averaged across electrodes, differed between the ADHD- and TD groups using ANCOVA, controlling for data segment length. Average slopes were significantly steeper in the ADHD- group (M=1.67, SD=0.27) compared to the TD group (M=1.51, SD=0.32; $F_{(1,97)} = 9.58$, $p=0.003$, $\eta^2=0.088$; Fig. 2A). This pattern was consistent across all tested electrode pairs, with statistically significant group differences in electrode pairs Cz ($p=0.008$), F3 ($p=0.03$), FCz ($p=0.008$), O1 ($p=0.003$), O2 ($p=0.008$), P4 ($p=0.005$), and Pz ($p=0.008$) after FDR correction (Fig. 2B).

Power Spectrum Offset. Next, we evaluated between-group differences in offset of the power spectrum. A single-factor ANCOVA found that the average offsets were greater for

ADHD- (M=1.67, SD=0.43) than for TD (M=1.41, SD=0.48; $F_{(1, 97)}$=8.708, p=0.004, η^2=0.082; Fig. 2C). This pattern was consistent across all electrodes tested with C3 (p=0.042), Cz (p=0.005), F3 (p=0.042), FCz (p=0.012), O1 (p=0.005), O2 (p=0.005), P4 (p=0.01), and Pz (p=0.005) surviving FDR correction (Fig. 2D).

Individual Peak Alpha Frequency. Individual peak alpha frequencies ranged from 5.75 – 11.25 Hz (Fig. 3A). We tested for a difference in the peak alpha frequency between the full TD and ADHD- groups with an ANCOVA, and found no significant difference in average peak alpha between the ADHD- (M=8.43, SD=1.25) and TD (M=8.84, SD=1.03) groups ($F_{(1, 88)}$=2.80, p=0.098; η^2=0.031; Fig. 3B).

Narrowband Alpha and Theta. We estimated the individualized alpha and theta power bands based on the location of each person's peak alpha frequency. Using ANCOVA, we found no significant between-group differences in individualized theta power (Fig. 4A; $F_{(1,97)}$=2.15 , p=0.15). We did find a significant group-difference in individualized alpha power (Fig. 4B; $F_{(1,97)}$=4.38 , p=0.039, η^2=0.030), with greater alpha power in the full ADHD- group (M=0.06, SD=0.018) compared to the TD group (M=0.05, SD=0.018). This pattern was evident across all electrode pairs; group differences at F3 (p=0.027), Fz (p=0.015), O1 (p=0.032), O2 (p=0.006), and P4 (p=0.031) were statistically significant, although none survived FDR correction (Fig. 4C).

Theta/Beta Ratio. Theta/beta ratios have been widely used to compare children with ADHD to TD children. Thus, we evaluated theta/beta ratio in this sample to allow direct comparison to data in the literature and to evaluate the relationship between this established metric and the novel EEG measures reported here. We found no overall difference in theta/beta ratio between the full ADHD- (M=8.66, SD=3.10) and TD groups (M=8.47, SD=2.55; $F_{(1, 97)}$=0.371, p=0.544, η^2=0.004; Fig. 5A). We did observe a significant correlation between theta-beta ratio and aperiodic slope, (Fig. 5B; r=0.293, p=0.003).

Treatment with Stimulant Medications

Because this is the first report of power spectrum slope and offset differences between medication naïve children with or without ADHD, we sought to test whether these differences were modified by exposure to stimulant medication. Specifically, we evaluated power spectrum slope and offset in a subsample of the TD and medication-naive (ADHD-) groups that were age and gender matched to a sample of 26 children with ADHD currently treated with stimulants, who underwent a 24-hour medication washout prior to completing the study (ADHD+). An ANCOVA found a main effect of group on mean slope ($F_{(2,74)}$ = 4.76, p=*0.011*; η^2=0.112; Figure 6A). As in the larger sample, the ADHD- group (M=1.71 SD=0.26) had significantly steeper slopes than the TD group (M=1.48, SD=0.36, p=0.019 Bonferroni corrected), and also had steeper slopes than the ADHD+ group (M=1.49, SD=0.31, p=0.044, Bonferroni corrected). This pattern held across all electrodes (Fig. 6B), with the ADHD- group having significantly steeper slopes than the TD group at Cz (p=0.024), FCz (p=0.019), O1 (p=0.019), P4 (p=0.019) and Pz (p=0.019), and significantly steeper slopes than the ADHD+ group at Cz (p=0.019), FCz (p=0.019), O1 (p=0.019), P4 (p=0.019) and Pz (p=0.019) after FDR correction. In contrast, the slopes did not differ between the TD and ADHD+ groups at any electrodes (p's>0.642).

385 We also found a main effect of group on offset ($F_{(2,74)}$ = 5.65, p=0.005; η^2=0.132; Fig.
386 6C), with higher average offset in the ADHD- group (M=1.74 SD=0.41) relative to both the TD
387 group (M=1.31, SD=0.54, p=0.007 Bonferroni corrected) and the ADHD+ group (M=1.38,
388 SD=0.52, p=0.038 Bonferroni corrected). In contrast, there were no significant differences in
389 offset between the ADHD+ and TD groups (ps>0.9). Amongst individual electrode pairs (Fig.
390 6D), the TD group had significantly lower offset than the ADHD- group for C3 (p=0.028), with
391 Cz (p=0.008), FCz (p=0.011), O1 (p=0.008), P4 (p=0.015), and Pz (p=0.008) withstanding FDR
392 correction. The ADHD+ group had significantly lower offset than the ADHD- group with Cz
393 (p=0.008), FCz (p=0.023), O1 (p=0.015), P4 (p=0.023), and Pz (p=0.015) withstanding FDR
394 correction. Again, there were no significant differences in offset between the TD and ADHD+
395 groups for any of the electrode pairs (p's>0.50).

396

397 **DISCUSSION**

398 By quantifying four distinct features of the EEG power spectrum, including aperiodic slope
399 and offset, peak alpha frequency, and power within individualized alpha and theta bands, we
400 identified a novel neural correlate of ADHD. Moreover, our findings may explain discrepancies
401 in the ADHD literature regarding theta/beta ratios. To summarize, we found that medication
402 naïve children with ADHD had steeper spectral slopes and elevated offsets compared to typically
403 developing children. While this is the first report evaluating spectral slope in children with
404 ADHD, it is consistent with reports of elevated low frequency: high frequency power captured
405 by commonly used theta/beta ratio. While we did not find a significant group difference in
406 theta/beta ratio in this sample, spectral slope positively correlated with theta/beta ratio,
407 suggesting that band-limited theta/beta ratio calculations may inconsistently capture the shift in

low relative to high frequency EEG power in ADHD. In contrast, spectral slope considers the full EEG spectrum and may be a better metric as it is not confounded by shifts in aperiodic offset, peak frequencies, or narrow-band power. Together, our findings support the use of spectral slope as a measure of a shift in low relative to high frequency power in ADHD. These results are consistent with another recent study which also found relative band power or power ratios predict ADHD diagnosis with only moderate success, while entropy measures, which capture non-frequency specific global activity, are more successful at predicting ADHD diagnosis (Chen et al. 2019).

Stimulant treatment and normalization of aberrant brain activity

As our initial group comparison included only ADHD patients that were medication naïve, we next tested whether our observed electrophysiological group differences were modified by treatment with stimulant medication, which improve behavioral symptoms in children with ADHD, and are the most common medicinal treatment for the disorder (Storebo et al. 2015). We found aperiodic slopes and offsets in stimulant-treated children with ADHD were similar to those of typically developing controls, but were significantly different from the medication naïve ADHD group. These findings are consistent with a growing body of literature showing that stimulant treatment can normalize structural and functional brain abnormalities associated with ADHD (Clarke et al. 2017; Clarke et al. 2003; Nakao et al. 2011; Shaw et al. 2009; Spencer et al. 2013). Perhaps most pertinent is a recent study showing a significant reduction in theta/beta ratio in children with ADHD after 1.5 years of stimulant treatment (Isiten et al. 2017); consistent with our results, this normalization persisted even after a 24-hour medication washout period. This finding taken in conjunction with our work supports the idea that flatter slopes in the stimulant-

treated and typically developing groups compared with the medication naïve ADHD group could reflect a post-treatment reduction in low relative to high frequency power and a normalization of brain physiology.

Relative power across the EEG power spectrum

What underlies an abnormal ratio of low relative to high frequency power in the brain EEG spectrum? Understanding the relative power across frequencies in brain dynamics is an active area of research, and recent studies evaluating the physiological underpinnings of spectral slope suggest that it reflects neural signal to noise ratio (Voytek et al. 2015) and that the spectral slope is an index of the excitatory/inhibitory (E/I) balance of the recorded brain circuits (Gao et al. 2017). Thus, our results may reflect abnormal E/I balance in the cortical circuitry of children with unmedicated ADHD. This interpretation is consistent with observations of altered E/I balance in clinical and preclinical models of ADHD, which have shown reductions in GABA signaling (Edden et al. 2012) and/or increases in glutamate signaling (Courvoisie et al. 2004; Hammerness et al. 2012; Zimmermann et al. 2015). While steeper slope has generally been regarded as reflecting enhanced signal to noise ratio and thus increased GABA or reduced glutamate signaling (Gao et al. 2017; Voytek et al. 2015), perhaps there is a range of cognitively optimal spectral slopes at different developmental stages, with slopes that are either too flat or too steep yielding cognitive impairments. Moreover, similar findings have been noted in a clinical study evaluating 1/f slope in patients with schizophrenia. Despite the association of schizophrenia with reduced GABAergic inhibition in the cortex (Lewis et al. 2005), elevated 1/f slopes during an attention task were found in schizophrenia patients compared to controls, which was proposed to reflect a compensatory increase in GABAergic activity (Peterson et al. 2018).

Thus, it is possible that the steeper 1/f slopes in medication naïve children with ADHD reflects a compensatory mechanism of some sort. For example, our EEG was collected in a quiet resting state, which may have required substantially more cognitive control in the children with ADHD. However, the fact that the previously medicated ADHD group did not show evidence of such compensation argues against this idea. Still, studies assessing E/I balance using transcranial magnetic stimulation (TMS) have shown that stimulants like methylphenidate, which inhibit reuptake of dopamine and norepinephrine, may rectify E/I balance in ADHD (Buchmann et al. 2006; Moll et al. 2000), consistent with the idea that normalization of slope could reflect normalization of E/I balance. Further work is needed to confirm that the effects we observed reflect a stimulant-induced change in E/I balance.

Study limitations

Our results indicate a difference in power spectral slope in young children with ADHD compared to typically developing controls, which could represent a transdiagnostic risk factor or an intermediate phenotype, rather than an ADHD specific feature. Previous work has reported variations in spectral slope associated with age (Voytek et al. 2015), and with other clinical diagnoses, including schizophrenia (Peterson et al. 2018). Additionally, evidence that spectral slope may reflect differences in E/I balance (Gao et al. 2017) suggests that spectral slope differences may be present in other disorders with underlying E/I imbalance, such as autism, epilepsy, and alcohol use disorders (reviewed in Fritschy 2008; Gao 2015; Rubenstein and Merzenich 2003; Selten et al. 2018; Wackernah et al. 2014). While the specificity of this difference in spectral slope remains to be tested, our results do suggest that spectral slope more appropriately captures a shift in low relative to high frequency power in ADHD as compared to

the theta/beta ratio, which has been frequently reported as an EEG biomarker in children with ADHD (Barry et al. 2003; Loo and Makeig 2012; Monastra et al. 2001; Monastra et al. 1999; Snyder and Hall 2006).

We acknowledge certain limitations of this study. First, diagnosis in this study was based on parent report of symptoms, which could be subject to inconsistencies. While we did collect teacher report of symptoms in a subset of participants to confirm diagnostic status, we were unable to do so for all participants. Second, we used a non-traditional EEG data acquisition paradigm; however, this paradigm was chosen due to its superior robustness to the excess movement that occurs in very young study participants (Vuga et al. 2008). Third, in evaluating the chronic impact of stimulant treatment on aperiodic slope and offset, we used a relatively short wash-out period of 24 hours. Previous studies have used a similar washout period (Cole et al. 2008; Isiten et al. 2017; Valera et al. 2010), and given the short half-life of stimulants, even in young children (Wigal et al. 2007), it is unlikely that normalized aperiodic slope and offset in stimulant-treated children are driven entirely by acute drug effects. Still, it is important to note that we did not measure drug levels or compliance with the 24-hour medication wash-out, which was determined by parental report. Thus, we cannot rule out the possibility that acute drug action or stimulant withdrawal could at least partly explain our results.

Conclusion

In summary, this study highlights the potential clinical utility of comprehensively quantifying features of the EEG power spectrum. Using this approach, we found that medication naïve children with ADHD had steeper EEG power spectrum slopes and greater EEG power spectrum offsets than typically developing children. Moreover, we show that spectral slope correlates with

traditional measures of theta/beta ratio, although theta/beta ratio itself did not differ between groups. This is consistent with spectral slope and offset as a robust and complete measure of relative contributions of low and high frequencies to the overall power spectrum. Interestingly, this difference was not apparent in stimulant-treated children with ADHD, despite a 24-hour medication washout. Thus, spectral slope may reflect pathology in the brains of children with ADHD that is normalized by stimulant medication. Future studies should evaluate whether these group differences in spectral slope and offset can be replicated in older children and adults with ADHD, determine whether there are interaction effects of age and gender, and assess normalization of slope and offset after stimulant treatment using random assignment.

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FIGURE LEGENDS

Figure 1. Schematic of the four components of the electrophysiological power spectrum. (A) Low (solid) and high (dashed) power in the alpha range. (B) Low (dashed) and high (solid) peak alpha frequency. (C) Flat (solid) and steep (dashed) slopes. (D) Low (solid) and high (dashed) offsets.

Figure 2. Comparisons of slope (A-B) and offset (C-D) in the full TD (black/solid) and ADHD- (white/dashed) samples. Error bars reflect +/- SD. (A) ADHD- has steeper slopes compared to TD when averaging across participants and electrodes. (B) Slopes were steeper in ADHD- for all electrodes tested, with asterisks denoting statistical significance after FDR correction. (C) ADHD- has greater offset compared to TD when averaging across participants and electrodes. (D) This pattern holds when considering electrodes individually, with asterisks denoting statistical significance after FDR correction.

Figure 3. Individual alpha frequency as determined by visual inspection of the power spectrums for the sample of TD (black) and ADHD- (white) participants. (A) Cumulative frequency plot showing the proportion of peaks which fall at various points across the alpha range. (B) Peak alpha frequency group averages showed no significant differences between TD and ADHD-. Error bars reflect +/- SD.

Figure 4. Theta (A) and alpha (B-C) power for the full sample of TD (black/solid) and ADHD- (white/dashed) participants calculated using individualized frequency bands based on peak alpha. Error bars reflect +/- SD. (A) There is no significant group difference in theta power. (B) ADHD- has elevated alpha power compared to TD. (C) While ADHD- had higher alpha power than TD in all tested electrodes, this group difference was not significant for any individual electrode pairs after FDR correction.

Figure 5. Theta/beta ratio for the full sample of TD (black) and ADHD- (white) participants. (A) There was no significant group difference in theta/beta ratio between TD and ADHD-. Error bars reflect +/- SD. (B) Theta/beta ratio was significantly correlated with slope.

Figure 6. Slope (A-B) and offset (C-D) for the ADHD+ group (gray), and the age- and gender-matched TD (black) and ADHD- (white/dashed) subgroups. Error bars reflect +/- SD. Asterisks denotes significant difference between TD and ADHD-, while pound signs denote significant differences between ADHD- and ADHD+. (A) ADHD- has steeper slopes compared to both TD and ADHD+ when averaging across participants and electrodes. (B) Slopes were steeper in ADHD- for all electrodes tested, with symbols denoting statistical significance after FDR correction. (C) ADHD- has greater offset compared to TD and ADHD+ when averaging across participants and electrodes. (D) This pattern holds when considering electrodes individually, with symbols denoting statistical significance after FDR correction.

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TABLES

Table 1. Group demographics for the full ADHD- and TD samples, as well as the subgroups selected for age and gender matching with the ADHD+ group.

	ADHD- (n=50)	***TD (n=50)***	***ADHD- (n=26)***	***ADHD+ (n=26)***	***TD (n=26)***
	% (n)	**% (n)**	**% (n)**	**% (n)**	**% (n)**
Female	28 (14)	28 (14)	23.1 (6)	23.1 (6)	23.1 (6)
Handedness (R)	86 (43)	90 (45)	84.6 (22)	76.9 (20)	96.2 (25)
Race					
White	66 (33)	62 (31)	69.2 (18)	88.5 (23)	73.1 (19)
Black/African American	12 (6)	12 (6)	11.5 (3)	3.8 (1)	11.5 (3)
Asian	0 (0)	6 (3)	0 (0)	0 (0)	3.8 (1)
Other/ Multiracial	18 (9)	20 (10)	15.5 (4)	7.7 (2)	11.5 (3)
Hispanic/ Latino	18 (9)	6 (3)	23.1 (6)	15.4 (4)	7.7 (2)
	M ± SD	***M ± SD***	***M ± SD***	***M ± SD***	***M ± SD***
Age (months)	67.70 ± 14.66	67.76 ± 14.76	74.50 ± 10.38	74.88 ± 9.71	74.81 ± 10.12

Values presented as a percent of total group, with the raw number in parenthesis. Age is expressed as mean ± standard deviation. ADHD-, mediation naive ADHD group; TD, typically developing control group; ADHD+, stimulant treated ADHD group after 24-hour medication washout.

Table 2. Average ADHD symptoms for the complete ADHD- and TD samples.

	ADHD- vs TD			
	ADHD- (n=50)	***TD (n=50)***	**Group Differences**	
	M ± SD (N)	***M ± SD (N)***	***t***	***p***
DISC Symptoms (0-23)	16.31 ± 4.10 (48)	3.78 ± 3.84 (45)	-15.2	<0.001*
CBCL Attention Problems t-score	66.88 ± 6.97 (50)	52.00 ± 3.47 (49)	-13.41	<0.001*
SNAP-IV (0-9)				
Inattentiveness	5.47 ± 2.53 (47)	0.69 ± 1.13 (48)	-11.94	<0.001*
Hyperactivity	6.21 ± 2.56 (48)	1.25 ± 1.71 (48)	-11.17	<0.001*
Teachers Conners				
Inattention t-score	61.25 ± 11.77 (16)	46.69 ± 8.53 (13)	-3.73	0.001*
Hyperactive t-score	74.69 ± 12.97 (16)	53.64 ± 16.93 (11)	-3.66	0.001*
TRF ADHD t-score	58.83 ± 11.91 (6)	53.25 ± 4.30 (8)	-1.237	0.24

Values are presented as mean ± standard deviation. The number of participants with scores for each measure is listed in parenthesis. As expected, the ADHD- (medication naïve ADHD) group had significantly more ADHD symptoms compared to TD (typically developing) on all measures with the exception of the TRF (Teacher Report Form), which was completed in a small number of total cases. DISC, the Diagnostic Structured Interview Schedule– young child version; CBCL, Child Behavior Checklist; SNAP-IV, Swanson Nolan and Pelham Checklist.

Table 3. Average ADHD symptoms for the ADHD+ group, and the TD and ADHD- subgroups.

	ADHD- vs ADHD+ vs TD					
	ADHD- (n=26)	***ADHD+ (n=26)***	***TD (n=26)***	**Group Differences**		
	Mean ± SD (N)	***M ± SD (N)***	***M ± SD (N)***	***ADHD- vs. ADHD+***	***ADHD- vs TD***	***ADHD+ vs TD***
DISC Symptoms (0-23)	17.27 ± 3.08 (26)	18.31 ± 3.67 (26)	3.88 ± 3.70 (25)	0.862	<0.001*	<0.001*
CBCL Attention Problems t-score	67.31 ± 6.45 (26)	68.78 ± 5.74 (23)	52.04 ± 3.87 (26)	>0.99	<0.001*	<0.001*
SNAP-IV (0-9)						
Inattentiveness	5.67 ± 2.24 (24)	7.46 ± 2.11 (24)	0.46 ± 1.14 (24)	0.005*	<0.001*	<0.001*
Hyperactivity	6.0 ± 2.71	7.54 ± 2.23	0.75 ± 1.29	0.045*	<0.001*	<0.001*

Values are presented as mean ± standard deviation. The number of participants with scores for each measure is listed in parenthesis. The ADHD+ (stimulant treated ADHD after medication washout) and ADHD- (medication naïve ADHD) groups have significantly more symptoms on all parent report measures as compared to TD (typically developing). However, ADHD-, but not ADHD+, had significantly more symptoms than TD on teacher report measures, likely due to effects of medication during school hours. Abbreviations as reported in Table 2.

	(25)	(24)	(24)			
Teachers Conners						
Inattention t-score	59.27 ± 11.73 (11)	53.92 ± 8.39 (12)	44.82 ± 5.33 (11)	0.473	0.002*	0.059
Hyperactive t-score	74.47 ± 13.02 (11)	62.08 ± 16.04 (12)	51.00 ± 12.85 (9)	0.137	0.003*	0.261
TRF ADHD t-score	50 (1)	60.2 ± 7.92 (5)	54.0 ± 4.95 (5)			0.176

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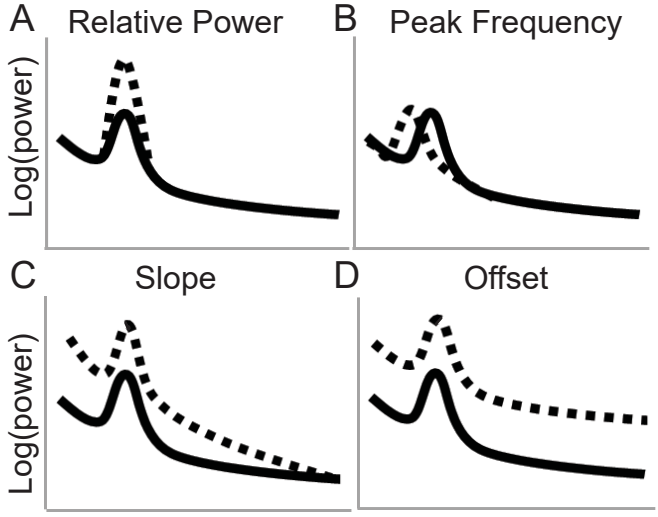

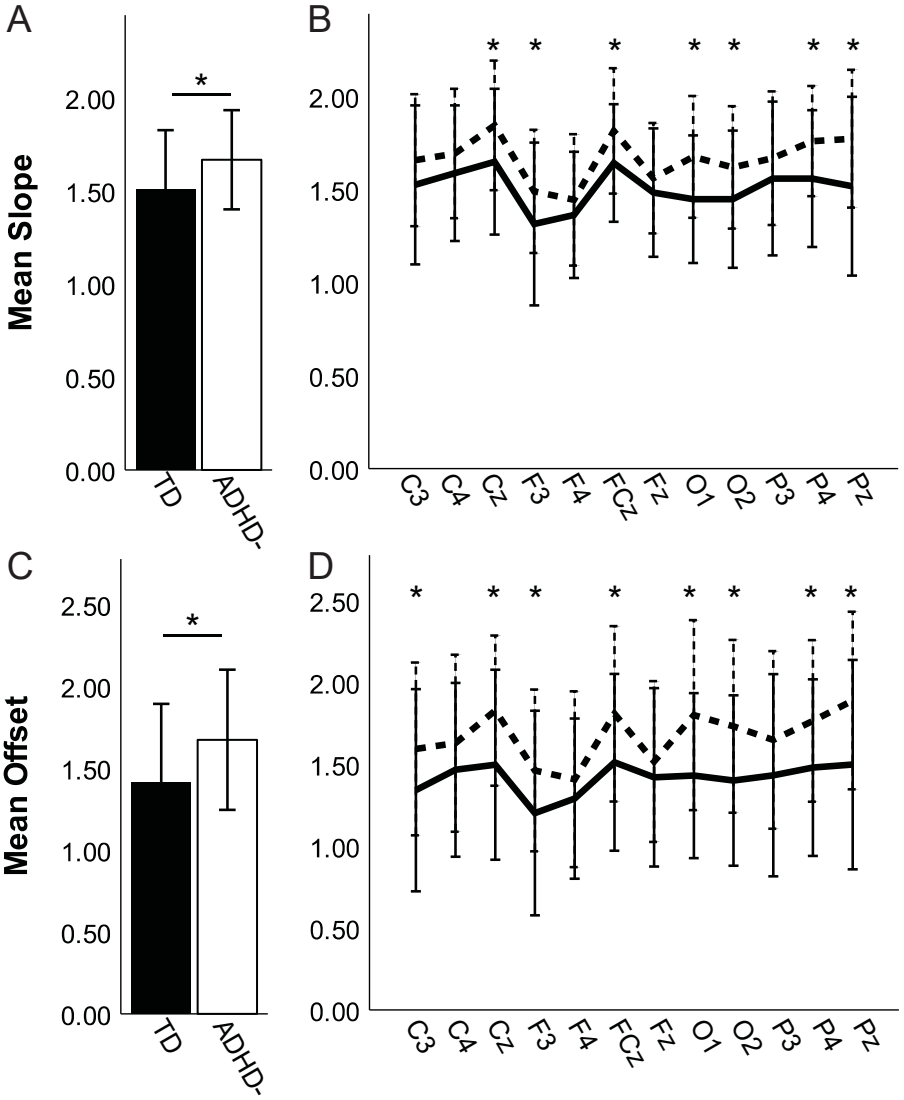

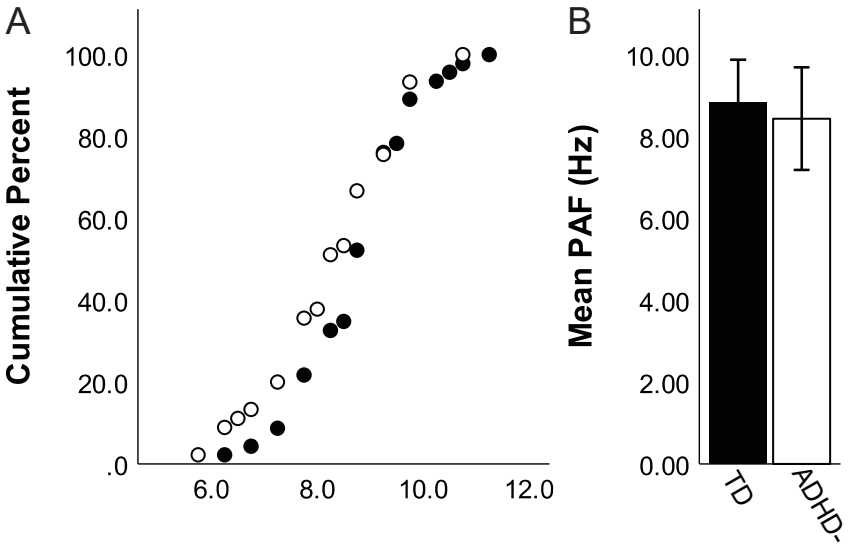

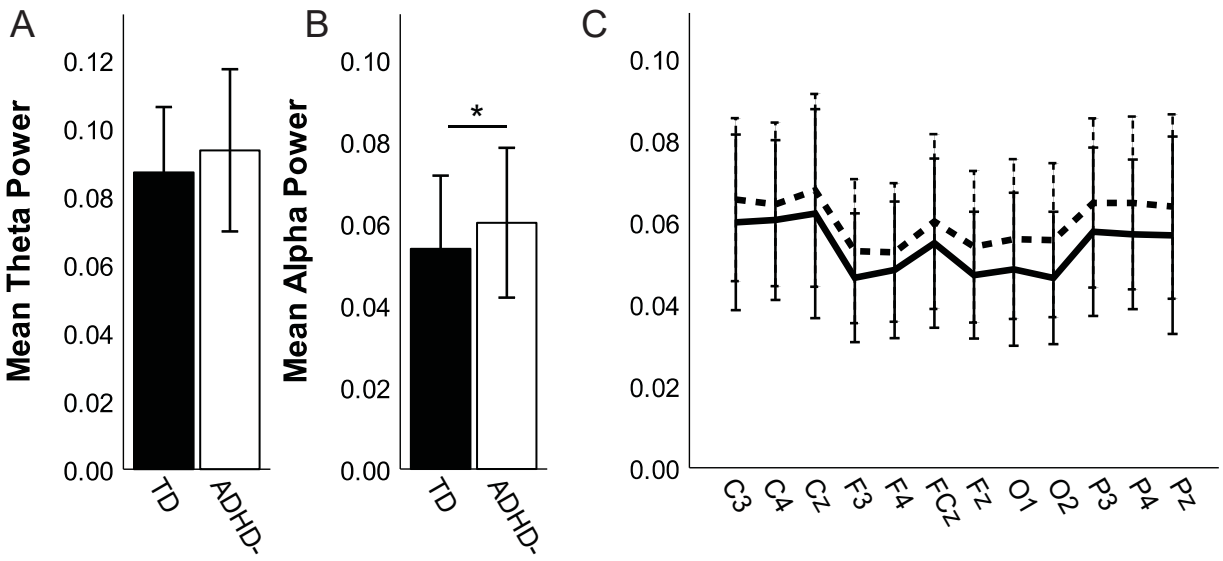

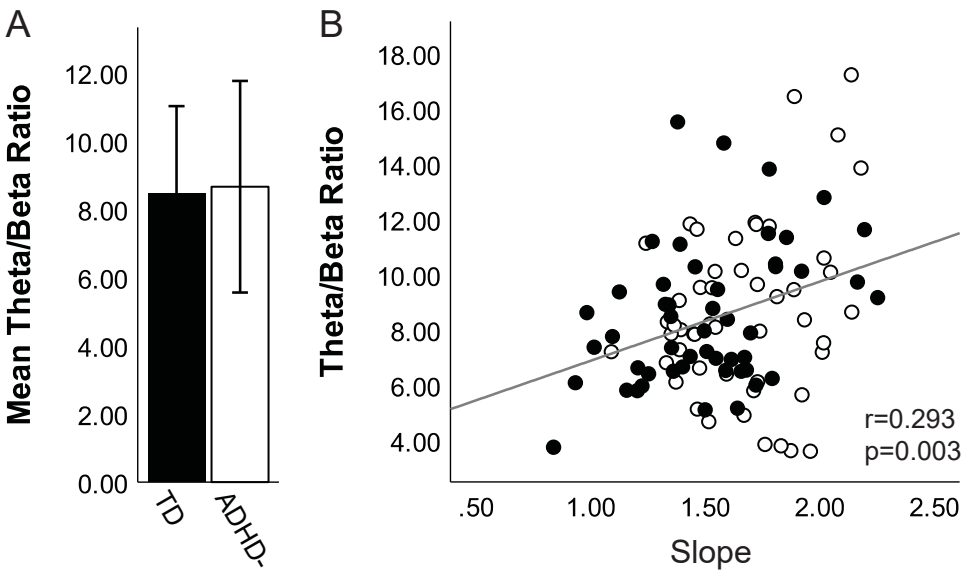

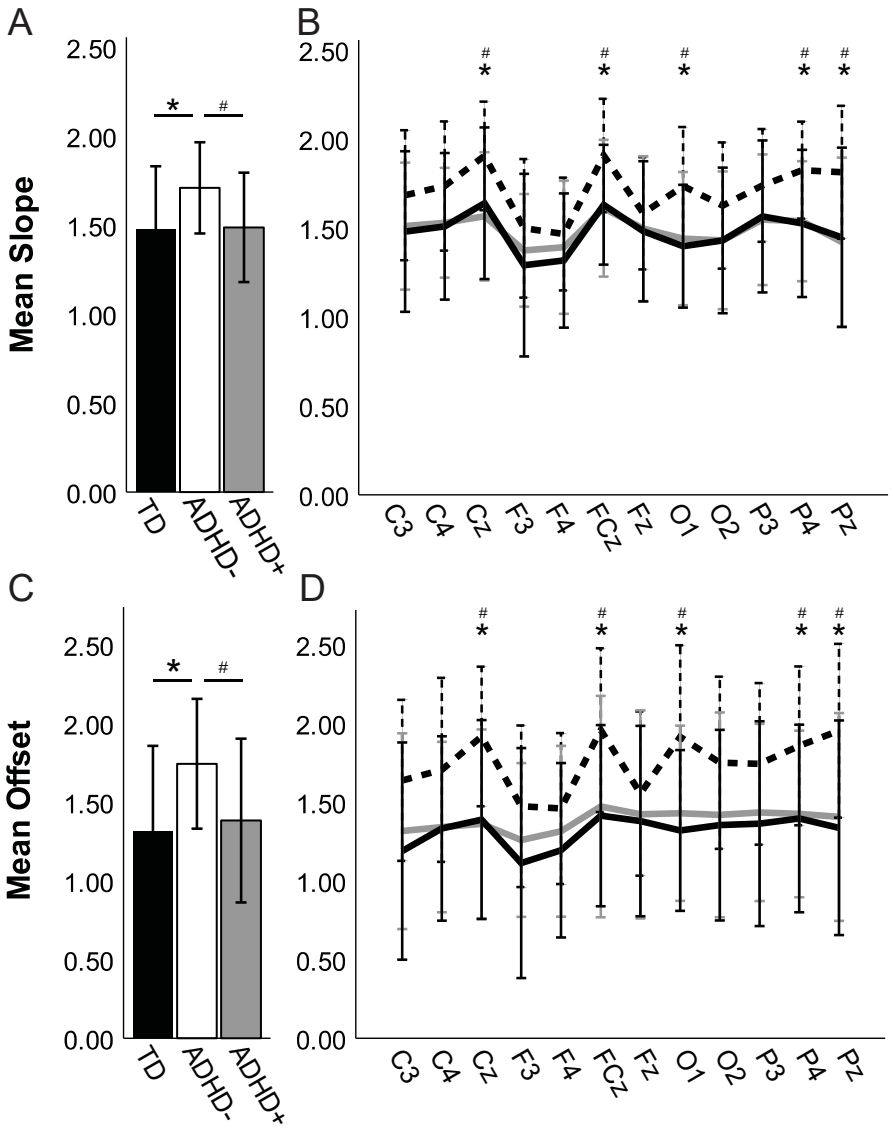

Table 1. Group demographics for the full ADHD- and TD samples, as well as the subgroups selected for age and gender matching with the ADHD+ group.

	ADHD- (n=50)	***TD (n=50)***	***ADHD- (n=26)***	***ADHD+ (n=26)***	***TD (n=26)***
	% (n)	**% (n)**	**% (n)**	**% (n)**	**% (n)**
Female	28 (14)	28 (14)	23.1 (6)	23.1 (6)	23.1 (6)
Handedness (R)	86 (43)	90 (45)	84.6 (22)	76.9 (20)	96.2 (25)
Race					
White	66 (33)	62 (31)	69.2 (18)	88.5 (23)	73.1 (19)
Black/African American	12 (6)	12 (6)	11.5 (3)	3.8 (1)	11.5 (3)
Asian	0 (0)	6 (3)	0 (0)	0 (0)	3.8 (1)
Other/ Multiracial	18 (9)	20 (10)	15.5 (4)	7.7 (2)	11.5 (3)
Hispanic/ Latino	18 (9)	6 (3)	23.1 (6)	15.4 (4)	7.7 (2)
	M ± SD	***M ± SD***	***M ± SD***	***M ± SD***	***M ± SD***
Age (months)	67.70 ± 14.66	67.76 ± 14.76	74.50 ± 10.38	74.88 ± 9.71	74.81 ± 10.12

Values presented as a percent of total group, with the raw number in parenthesis. Age is expressed as mean ± standard deviation. ADHD-, mediation naive ADHD group; TD, typically developing control group; ADHD+, stimulant treated ADHD group after 24-hour medication washout.

Table 2. Average ADHD symptoms for the complete ADHD- and TD samples.

	ADHD- vs TD			
	ADHD- (n=50)	***TD (n=50)***	**Group Differences**	
	M ± SD (N)	***M ± SD (N)***	***t***	***p***
DISC Symptoms (0-23)	16.31 ± 4.10 (48)	3.78 ± 3.84 (45)	-15.2	<0.001*
CBCL Attention Problems t-score	66.88 ± 6.97 (50)	52.00 ± 3.47 (49)	-13.41	<0.001*
SNAP-IV (0-9)				
Inattentiveness	5.47 ± 2.53 (47)	0.69 ± 1.13 (48)	-11.94	<0.001*
Hyperactivity	6.21 ± 2.56 (48)	1.25 ± 1.71 (48)	-11.17	<0.001*
Teachers Conners				
Inattention t-score	61.25 ± 11.77 (16)	46.69 ± 8.53 (13)	-3.73	0.001*
Hyperactive t-score	74.69 ± 12.97 (16)	53.64 ± 16.93 (11)	-3.66	0.001*
TRF ADHD t-score	58.83 ± 11.91 (6)	53.25 ± 4.30 (8)	-1.237	0.24

Values are presented as mean ± standard deviation. The number of participants with scores for each measure is listed in parenthesis. As expected, the ADHD- (medication naïve ADHD) group had significantly more ADHD symptoms compared to TD (typically developing) on all measures with the exception of the TRF (Teacher Report Form), which was completed in a small number of total cases. DISC, the Diagnostic Structured Interview Schedule– young child version; CBCL, Child Behavior Checklist; SNAP-IV, Swanson Nolan and Pelham Checklist.

Table 3. Average ADHD symptoms for the ADHD+ group, and the TD and ADHD- subgroups.

	ADHD- vs ADHD+ vs TD					
	ADHD- (n=26)	***ADHD+ (n=26)***	***TD (n=26)***	**Group Differences**		
	Mean ± SD (N)	***M ± SD (N)***	***M ± SD (N)***	***ADHD- vs. ADHD+***	***ADHD- vs TD***	***ADHD+ vs TD***
DISC Symptoms (0-23)	17.27 ± 3.08 (26)	18.31 ± 3.67 (26)	3.88 ± 3.70 (25)	0.862	<0.001*	<0.001*
CBCL Attention Problems t-score	67.31 ± 6.45 (26)	68.78 ± 5.74 (23)	52.04 ± 3.87 (26)	>0.99	<0.001*	<0.001*
SNAP-IV (0-9)						
Inattentiveness	5.67 ± 2.24 (24)	7.46 ± 2.11 (24)	0.46 ± 1.14 (24)	0.005*	<0.001*	<0.001*
Hyperactivity	6.0 ± 2.71 (25)	7.54 ± 2.23 (24)	0.75 ± 1.29 (24)	0.045*	<0.001*	<0.001*
Teachers Conners						
Inattention t-score	59.27 ± 11.73 (11)	53.92 ± 8.39 (12)	44.82 ± 5.33 (11)	0.473	0.002*	0.059
Hyperactive t-score	74.47 ± 13.02 (11)	62.08 ± 16.04 (12)	51.00 ± 12.85 (9)	0.137	0.003*	0.261
TRF ADHD t-score	50 (1)	60.2 ± 7.92 (5)	54.0 ± 4.95 (5)			0.176

Values are presented as mean ± standard deviation. The number of participants with scores for each measure is listed in parenthesis. The ADHD+ (stimulant treated ADHD after medication washout) and ADHD- (medication naïve ADHD) groups have significantly more symptoms on all parent report measures as compared to TD (typically developing). However, ADHD-, but not ADHD+, had significantly more symptoms than TD on teacher report measures, likely due to effects of medication during school hours. Abbreviations as reported in Table 2.