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The relationship between alpha asymmetry and ADHD depends on negative affect level and parenting practices

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ABSTRACT

Atypical frontal alpha asymmetry is associated with the approach/withdrawal and affective processes implicated in many psychiatric disorders. Rightward alpha asymmetry, associated with high approach, is a putative endophenotype for attention deficit/hyperactivity disorder (ADHD). However, findings are inconsistent, likely because of a failure to consider emotional heterogeneity within the ADHD population. In addition, how this putative risk marker interacts with environmental factors known to increase symptom severity, such as parenting practices, has not been examined. The current study examined patterns of alpha asymmetry in a large sample of adolescents with and without ADHD, including the moderating role of negative affect and inconsistent discipline. Resting-state EEG was recorded from 169 well-characterized adolescents (nADHD = 79). Semi-structured clinical interviews and well-validated rating scales were used to create composites for negative affect and inconsistent discipline. The relationship between alpha asymmetry and ADHD diagnosis was moderated by negative affect. Right asymmetry was present only for those with ADHD and low levels of negative affect. In addition, greater right alpha asymmetry predicted severity of ADHD symptoms for those with the disorder, but only in the context of inconsistent parenting practices. Results confirm right alpha asymmetry is a possible endophenotype in ADHD but highlight the need to consider emotional heterogeneity and how biological risk interacts with child environment in order to fully characterize its relationship to disorder liability and severity.

1. Introduction

Current research in attention-deficit/hyperactivity disorder (ADHD), and developmental psychopathology in general, has become increasingly focused on identifying endophenotypes— markers of disorder liability or severity that are related to etiology or developmental course (Gottesman and Gould, 2003; Lenzenweger, 2013; Singh and Rose, 2009). While there are many putative endophenotypes for ADHD (Castellanos and Tannock, 2002; Durston et al., 2009; Gau and Shang, 2010; Nigg et al., 2018), both structural and functional connectivity studies consistently identify ADHD-related differences in emotion processing networks as part of the pathophysiology of the disorder (Konrad and Eickhoff, 2010; Rubia et al., 2014; Seidman et al., 2005; Valera et al., 2007; van Ewijk et al., 2012) and behaviorally-measured emotion dysregulation mediates ADHD genetic risk (Nigg et al., *R&R*). With emotional features increasingly recognized as a core part of ADHD, the current study focuses on the role of electroencephalogram (EEG) measured patterns of atypical frontal brain laterality as a putative endophenotype in the disorder. These patterns are quantified via measurements of alpha band power at frontal electrode locations and are associated with emotional response tendencies (Davidson et al., 1990; Harmon-Jones et al., 2011; Harmon-Jones and Allen, 1997). The importance of emotional symptoms in ADHD (Bunford et al., 2015; Shaw et al., 2014) suggests alpha asymmetry may be a promising marker for the disorder.

Functionally, frontal alpha asymmetry has been interpreted in terms of an approach-withdrawal model where the approach system drives behaviors associated with maximizing reward and minimizing punishment and the withdrawal system drives behaviors associated with avoiding non-rewarding or aversive situations (Davidson et al., 1990; Harmon-Jones et al., 2011; Harmon-Jones and Allen, 1997). The approach system is often (although not always) associated with positive affect, whereas the withdrawal system is more closely associated with negative affect (Harmon-Jones et al., 2011). Alpha power is inversely related to underlying cortical activity, thus increased alpha power over the right frontal as compared to left frontal hemisphere is hypothesized to reflect decreased right hemispheric cortical activity (Allen et al., 2004a). In this framework, relatively greater left frontal alpha power is associated with withdrawal and negative affect whereas relatively greater right frontal alpha power is associated with approach and positive affect (Coan and Allen, 2003; Davidson, 2004). Thus, the proposal has been that right frontal alpha asymmetry in ADHD is a potential

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endophenotype (Hale et al., 2010) that reflects the increased approach-related behaviors often seen in this disorder (Ellis et al., 2017; Keune et al., 2015, 2011; Mitchell, 2010). This is supported by findings of an overactive behavioral activation system in ADHD (Quay, 1988) and is described in the motivation dysfunction hypothesis (Mitchell, 2010). In the current manuscript, patterns of asymmetry are described in terms of alpha power. That is, when we refer to a *right* asymmetry, it indicates greater right than left alpha power (consistent with less right as compared to left cortical activation) and vice versa for left asymmetry.

Despite its clear theoretical interest, relatively few studies have reported on frontal alpha asymmetry findings in ADHD because of a historical emphasis on cognitive rather than emotional symptoms in the disorder. Within the studies that have investigated alpha asymmetry patterns in ADHD, some have found the hypothesized right alpha asymmetry (Baving et al., 1999; Hale et al., 2010, 2009; Keune et al., 2015, 2011), including in children, adolescents, and adults. However, left alpha asymmetry has also been observed (Baving et al., 1999; Jaworska et al., 2013). Further, the largest clinical study to-date found no group difference in frontal alpha asymmetry (Gordon et al., 2010), challenging the view that it serves as a marker of ADHD-related liability. Complicating the picture further, while most studies have focused on frontal regions that can be theoretically understood in the approach/positive-withdrawal/negative framework, some studies have also found differences in posterior alpha asymmetry (Hale et al., 2010, 2009).

Several factors may contribute to the mixed picture of frontal alpha asymmetry findings. ADHD is an emotionally heterogeneous disorder (Bunford et al., 2015; Karalunas et al., 2014; Shaw et al., 2014). While some children with ADHD experience high levels of approach and dysregulation of positive affect, consistent with a hypothesized right asymmetry, others are characterized by elevated negative affect (Karalunas et al., 2019, 2014) that may be more likely to be related to left asymmetry. ADHD is also commonly comorbid with anxiety, depression, and ODD, all of which are characterized by a left (rather than right) frontal alpha asymmetry (Allen et al., 2004b; Baving et al., 2003; Davidson, 1998; Diego et al., 2001; Santesso et al., 2006; Thibodeau et al., 2006). Several studies of alpha asymmetry that control for these commonly comorbid disorders continue to find right asymmetry patterns (Baving et al., 1999; Hale et al., 2010, 2009; Keune et al., 2015). However, many individuals with ADHD experience subthreshold but still clinically-significant negative affect and at least one study emphasizing the role of subthreshold negative affect in ADHD has identified left asymmetry patterns (Jaworska et al., 2013). Overall, a growing literature on the importance of emotional heterogeneity in ADHD suggests that individuals may have either right or left asymmetry depending on their level of negative affect, but this moderation has not been formally tested.

In addition, inconsistent findings may reflect the interaction of alpha asymmetry patterns with environmental factors. Although there are a variety of environmental influences that could be considered, here we focus on discipline. Parents of children with ADHD often have inconsistent discipline practices (Bhide et al., 2016; Ellis and Nigg, 2009). Although inconsistent discipline, on its own, is not causally associated with ADHD, it is a strong predictor of ADHD symptom severity within the disorder (Bhide et al., 2016; Ellis and Nigg, 2009; Ullsperger et al., 2016). Developmental studies suggest that family environment may interact with the processes captured in frontal alpha asymmetry patterns to predict clinical outcomes (Brooker et al., 2016; Peltola et al., 2014), but this interaction of trait neurobiological markers with environment has not been tested in the context of ADHD.

The current study examined patterns of alpha asymmetry in a large sample of adolescents with and without ADHD. Primary analyses focus on the moderating role of negative affect and inconsistent discipline. Based on prior literature suggesting that emotional response tendencies are core features of the disorder, we hypothesized that negative affect would moderate the relationship between frontal alpha asymmetry and ADHD diagnosis, such that individuals with low levels of negative affect would show the expected right asymmetry patterns, but individuals with high levels of negative affect would have left asymmetry. Inconsistent parenting was hypothesized to moderate the relationship between alpha asymmetry and ADHD symptoms, consistent with prior research suggesting it is related to symptom severity. To add to the relatively sparse literature on alpha asymmetry in ADHD, we report several additional exploratory analyses. We examine whether sex moderates the relationship between alpha asymmetry and ADHD diagnosis or symptom severity but did not have hypotheses about the direction of effect. In addition, we repeated all of our frontal alpha asymmetry analyses for posterior electrode sites where effects have been inconsistently reported in the past, but again did not have specific hypotheses due to lack of clear theory for interpreting posterior alpha asymmetry effects.

2. Methods

2.1. Participants and diagnostic procedure

169 individuals ages 11–17 were recruited from a larger, ongoing longitudinal study. Participants in the larger study were recruited using a community-based strategy based on public advertising and outreach. A parent/legal guardian provided written informed consent, and adolescents provided written assent for the study. Ethics approval was obtained from the Institutional Review Board at Oregon Health & Science University. This work was carried out in accordance with the latest version of the Declaration of Helsinki.

After an initial screening phone call, a parent/guardian and teacher completed standardized rating scales, including the Conners' Rating Scales, 3rd edition (Conners, 2001), SWAN Rating Scale for ADHD (Swanson et al., 2001), and the ADHD Rating Scale (ADHD-RS) (DuPaul et al., 1998). The parent/guardian also completed a semi-structured clinical interview (Kiddie Schedule for Affective Disorders and Schizophrenia, K-SADS) administered by a Master's-level clinician who had achieved research reliability (Kaufman et al., 1997). All items on the ADHD module of the KSAD-S were queried to all participants rather than using screening questions for this module.

For diagnosis, total symptom counts were determined by combining parent (K-SADS) and teacher (ADHD-RS) report using an “OR” algorithm (Pelham et al., 2005). Following DSM, final diagnostic groups were determined as follows: Individuals with ADHD were required to have ≥ 6 hyperactive or ≥ 6 inattention symptoms, as well as parent reported impairment on K-SADS. Individuals in the control group were required to have ≤ 3 hyperactive, ≤ 3 inattention symptoms, and ≤ 4 total symptoms with no reported impairment.

For analyses, parent-reported inattention and hyperactivity/impulsivity latent variables were created using the following indicators: 1) inattention factor: parent ADHD-RS inattention raw score, Connors' inattention raw score, Connors' executive function raw score, SWAN inattention raw score, and K-SADS inattention symptom count and 2) hyperactivity-impulsivity factor: parent ADHD-RS hyperactivity raw score, Connors' hyperactivity raw score, SWAN hyperactivity raw score, and K-SADS hyperactivity symptom. Symptom models (see Fig. 1a) fit the data well (Inattention: RMSEA $< .001$, CFI $= 1.00$, $\chi^2 = .10$, $p = .95$; Hyperactivity-impulsivity: RMSEA $< .001$, CFI $= 1.00$, $\chi^2 = 3.20$, $p = .67$).

2.2. Exclusion criteria

Adolescents were excluded from the current study if they were prescribed long-acting, non-stimulant psychotropic medications; had self-reported history of neurological impairment such as seizures or head injury with loss of consciousness; had a history of substance abuse; had prior diagnosis of intellectual disability, autism spectrum disorder, or psychosis; were currently experiencing a major depressive episode; or had estimated IQ < 70.

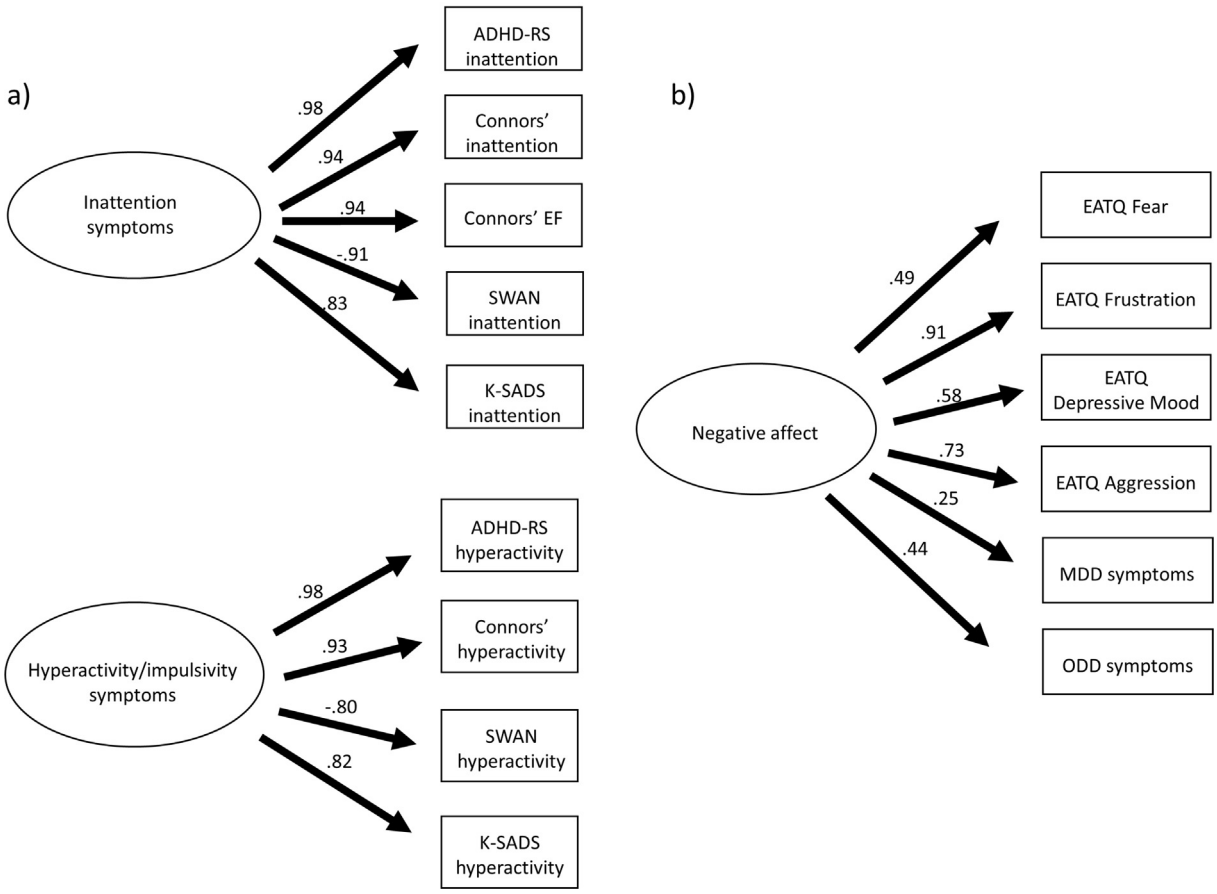

Fig. 1. Measurement models for a) inattention and hyperactivity/impulsivity symptoms and b) negative affect.

2.3. Medication washout

Adolescents with ADHD taking stimulant medications (51%) were included in the study but were required to be off medication for 24 (for short-acting preparations) to 48 hours (for long-acting preparations) prior to testing.

2.4. Negative affect

A parent/guardian completed the Early Adolescent Temperament Questionnaire (EATQ; (Ellis and Rothbart, 2001), which is derived from a well-regarded conceptual model using confirmatory factor analysis (Capaldi and Rothbart, 1992). The *fear*, *frustration*, *depressive mood*, and, *aggression* subscales were used in the current study and each have good internal consistency (all alphas > .69) (Ellis and Rothbart, 2001). EATQ measures were combined with parent-reported major depressive disorder and oppositional defiant disorder symptoms from the K-SADS to create a negative affect latent variable (see Fig. 1b). The model fit was adequate RMSEA = 0.09, CFI = 0.95, χ^2 = 21.07, p = .007.

2.5. Parenting

Inconsistent discipline was assessed using parent-report on the Alabama Parenting Questionnaire, which is a 42-item questionnaire with good internal consistency (Shelton et al., 1996). The *inconsistent discipline* scale was used in the current study due to its relevance to ADHD (Bhide et al., 2016; Ellis and Nigg, 2009).

2.6. EEG recording and processing

Resting state EEG was recorded for four, 2-min alternating blocks of eyes closed (EC) and eyes open (EO) conditions (EC, EO, EC, EO). EEG was recorded at 500 Hz with 32 Ag-AgCl active electrodes using PyCorder v1.0.9. Impedances for all electrodes were at or below 50 kΩ (mean = 23 kΩ). This maximized signal quality while minimizing cap application time in our sample. Impedance values in this range appear to have minimal effects on amplitude density in the alpha range, particularly in climate-controlled recording environments like ours (Kappenman and Luck, 2010). The electrode array was based on the international 10–20 system centered at Cz. EEG signals were amplified by a BrainVision actiCHamp2 amplifier (Cary, NC). Recordings were referenced to Cz online then re-referenced offline.

EEG data were analyzed using ERPLAB (Lopez-Calderon and Luck, 2014) and EEGLAB (Delorme and Makeig, 2004) toolboxes for MATLAB. Raw EEG data were resampled to 250 Hz and referenced offline to the average of all channels. EEG signals were filtered using an IIR bandpass filter (half-amplitude cutoffs at 0.1 and 50 Hz, 12 dB/octave roll-off). Eye artifacts were removed through independent component analysis (Jung et al., 2000). The data was segmented into 2-s non-overlapping epochs. Total possible number of epochs was 240. Trials were discarded from the analyses if they contained baseline drift or movement artifacts greater than 90 μV. Individual channels were interpolated if greater than 20% of epochs were flagged after artifact rejection. Channels responsible for the greatest percentage of trial removal were interpolated one at a time until less than 20% of the total epochs were rejected. The average number of total epochs per subject was 211 (ADHD: 205, SD: 26; Control: 215, SD: 18). No subjects were removed from analyses for having too few epochs (*a priori* threshold set at 50% rejected).

A Hanning window was applied and all artifact free 2-s epochs were analyzed using a fast Fourier transform (FFT). Power output (μV^2) was averaged across epochs within each condition and power within the

alpha band (8–13 Hz) was extracted for each subject. To increase normality, the natural log of alpha power values was calculated for each electrode site. Alpha asymmetry was calculated as the subtraction of alpha power from left electrode sites from their homologue on the right (e.g., ln(F4)-ln(F3) and ln(F8)-ln(F7)). To reduce the number of comparisons, primary analyses were restricted to two electrode pairs commonly examined in the literature (Hale et al., 2010, 2009; Keune et al., 2015, 2011): F4/3 and F8/7. Secondary analysis related to posterior effects focused on P4/3 and P8/7. Alpha asymmetry for EC and EO conditions were highly correlated (all $r > .78$) and values from each condition were averaged together to create a final alpha asymmetry score for each electrode pair.

2.7. Statistical analysis

All analyses were carried out using MPLUS (7.2) (Muthén, and Muthén, 1998). Missing data were handled using maximum likelihood methods (Graham, 2009). Power analyses revealed adequate power (> 80%) to detect medium effect sizes for as the predicted interactions. Uncorrected p values are reported below for our hypothesis-driven primary analyses consistent with recent discussion related to when multiple comparisons testing is appropriate (Rothman, 2014, 1990; Streiner, 2015; Streiner and Norman, 2011); however, we note that findings remain when a Benjamini-Hochberg correction (which is appropriate in the case of outcomes correlated < 0.50 (Blakesley et al., 2009)) is applied for each family of tests. Multiple comparisons corrections were not applied to exploratory tests related to sex and posterior electrode effects.

3. Results

3.1. Participants

Adolescents with and without ADHD did not differ in age, but individuals with ADHD tended to have a lower IQ ($p = 0.01$) and more negative affect ($p < 0.001$). As expected, based on rates of ADHD diagnosis in the population, there was also a greater proportion of males in the ADHD group than in the control group ($p = 0.003$). See Table 1 for additional description of the sample.

3.2. Relationship between alpha asymmetry and ADHD diagnosis

See Table 2 for beta weights and p values and Fig. 2 for a visual depiction of results.

Primary analyses. Frontal alpha asymmetry was not related to ADHD diagnosis (all $ps > 0.57$). However, this lack of group effect was qualified by the hypothesized negative affect × group interaction at the F8/7 electrode pair ($\beta = -0.26$, $p = 0.02$). Individuals with ADHD and low levels of negative affect had greater rightward asymmetry than controls, whereas there was no relationship between ADHD status and alpha asymmetry in individuals with high negative affect. The interaction was not significant at the F4/3 electrode pair.

Exploratory analyses. Exploratory analyses indicated that sex did not moderate the frontal alpha asymmetry effects. When posterior effects were examined, there were no group differences in posterior alpha asymmetry (all $ps > 0.31$). This lack of a group effect was qualified by a marginal sex by group interaction for the P8/7 electrode pair ($\beta = -0.17$, $p = 0.09$). Females with ADHD had more leftward posterior alpha asymmetry than females without ADHD ($\beta = -0.32$, $p = 0.005$), while males with and without ADHD did not significantly differ from each other (β = -0.008, $p = 0.94$). Negative affect did not moderate the posterior alpha asymmetry effects.

3.3. Relationship between alpha asymmetry and ADHD symptom severity

See Table 2 for beta weights and p values and Fig. 3 for a visual depiction of results.

Primary analyses. Within the ADHD group, there was no relationship between frontal alpha asymmetry and inattention or hyperactivity/impulsivity symptoms (all $ps > 0.12$). However, as hypothesized, this was qualified by a discipline x alpha asymmetry interaction for inattention symptoms at electrode sides F8/7 ($\beta = -0.31$, $p < 0.001$). In those experiencing highly inconsistent discipline, a more rightward alpha asymmetry was associated with more inattention symptoms, whereas in those experiencing consistent discipline, a greater rightward asymmetry was associated with fewer inattention symptoms. The interaction was not significant at the F4/3 electrode pair and was not significant for hyperactivity-impulsivity symptoms.

Exploratory analyses. Sex did not moderate the relationship between frontal alpha asymmetry and ADHD symptom severity. There was no relationship between posterior alpha asymmetry and ADHD symptoms (all $ps > 0.48$). Interactions with sex and parenting were

Table 1
Demographics and asymmetry scores (mean (SD)).

	Control	ADHD	F	Effect Size (95% CI)
n	90	79		
age (years)	13.98 (1.28)	13.94 (1.49)	0.003	0.01 (−0.47 – 0 .45)
IQ	115.29 (13.28)	109.63 (15.17)	6.09*	0.41 (1.16–10.52)
sex (male:female)	51:39	62:17	$X^2 = 9.04$*	
Inattention Symptoms				
ADHD-RS inattention T-score	47.17 (8.74)	70.08 (10.64)	214.00**	2.42 (−26.38 – −20.10)
Connors' inattention T-score	47.55 (10.14)	73.87 (11.71)	220.53**	2.46 (−30.15 – −23.07)
K-SADS inattention symptom count	0.16 (0.54)	6.58 (2.16)	672.50**	4.30 (−6.86 – −5.89)
Hyperactivity/impulsivity symptoms				
ADHD-RS hyperactivity T-score	46.39 (8.28)	63.46 (13.30)	84.73**	1.52 (−20.25 – −13.09)
Connors' hyperactivity T-score	47.92 (8.66)	68.23 (15.52)	98.69**	1.64 (−24.37 – −16.28)
K-SADS hyperactivity symptom count	0.17 (0.50)	2.87 (2.55)	77.86**	1.46 (−3.12 – −1.98)
Negative Affect				
K-SADS depression symptom count	0.82 (2.62)	1.54 (3.54)	2.75	0.27 (−1.80 – 0.16)
K-SADS ODD symptom count	0.27 (0.85)	1.47 (1.82)	30.32**	0.91 (−1.58 – −0.74)
Alpha Asymmetry				
F4/3	0.05 (0.22)	0.03 (0.26)	0.09	0.06 (−0.07 – 0.09)
F8/7	0.04 (0.33)	0.02 (0.37)	0.03	0.03 (−0.12 – 0.10)
P4/3	0.13 (0.45)	0.07 (0.36)	0.53	0.13 (−0.19 – 0.09)
P8/7	0.18 (0.50)	0.12 (0.42)	0.24	0.09 (−0.12 – 0.19)

*p < .01; **p < .001.

Table 2
Alpha asymmetry relationships to ADHD diagnosis and symptoms.

	Electrode	Moderations											
		no moderation			sex			negative affect			inconsistent discipline		
		β	SE	*p*	β	SE	*p*	β	SE	*p*	β	SE	*p*
ADHD Diagnosis	F4/3	−0.05	0.08	0.57	−0.07	0.07	0.33	0.003	0.08	0.97	−0.01	0.10	0.95
	F8/7	−0.02	0.06	0.79	0.05	0.12	0.69	**−0.26**	**0.11**	**0.02**	0.04	0.11	0.73
	P4/3	−0.07	0.07	0.31	−0.08	0.10	0.45	−0.06	0.09	0.50	0.08	0.10	0.38
	P8/7	−0.07	0.07	0.38	−0.17	0.10	0.09	−0.05	0.10	0.62	−0.02	0.11	0.84
Inattention symptoms	F4/3	0.11	0.14	0.44	−0.05	0.06	0.41	0.02	0.22	0.95	−0.05	0.09	0.59
	F8/7	−0.16	0.13	0.22	−0.06	0.11	0.59	−0.01	0.13	0.92	**0.31**	**0.09**	**< 0.001**
	P4/3	−0.003	0.13	0.98	0.09	0.09	0.34	−0.11	0.12	0.36	0.06	0.12	0.65
	P8/7	−0.03	0.14	0.81	0.05	0.08	0.51	0.009	0.10	0.93	−0.06	0.08	0.50
Hyperactivity/impulsivity symptoms	F4/3	0.12	0.12	0.44	0.02	0.12	0.89	−0.09	0.11	0.42	−0.05	0.10	0.74
	F8/7	−0.14	0.09	0.22	−0.10	0.09	0.27	0.00	0.09	1.00	0.10	0.08	0.24
	P4/3	−0.08	0.13	0.98	0.07	0.11	0.51	0.002	0.10	0.98	0.06	0.13	0.66
	P8/7	0.08	0.11	0.81	0.01	0.10	0.92	0.04	0.08	0.67	−0.06	0.09	0.51

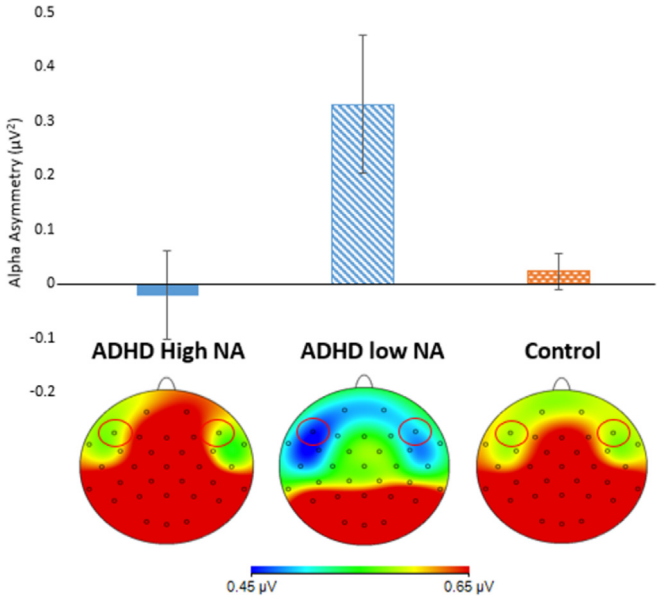

Fig. 2. Group differences in alpha asymmetry and the topographical distribution of alpha power (8–13 Hz) for each group. Red circles appear around electrodes F8 and F7 where alpha was measured. NA = negative affect. *Of note*: ADHD high and low negative affect groups were dichotomized (± 1SD from the mean) for depiction purposes. Means and SEMs show ln transformed values, topographic heads show raw alpha power.

also not significant for posterior sites (all *ps* > 0.34).

4. Discussion

The current study examined the relationship between ADHD and alpha asymmetry, a proposed endophenotype for the disorder. Overall, results are consistent with the proposal that alpha asymmetry is an important marker of ADHD liability and is related to ADHD severity but highlight several crucial caveats. Between-group analyses found no alpha asymmetry differences between adolescents with and without ADHD and no relationship to symptom severity. However, this apparent lack of effect was qualified by interactions with negative affect and parenting practices. Consistent with hypotheses based on the growing literature related to emotional heterogeneity in ADHD, those with low levels of negative affect showed a more rightward asymmetry, while this relationship was not seen in those with ADHD and high levels of negative affect. Further, a more frontal rightward asymmetry predicted severity of ADHD symptoms, but only in the context of inconsistent parenting. Findings support the motivation dysfunction hypothesis (Mitchell, 2010), which proposes that ADHD develops due to high approach-related tendencies. However, results provide the important caveat that this pathway is only relevant for a subset of individuals with the disorder and add to the growing support for multiple-pathway models in ADHD (Nigg et al., 2004).

Prior theory, including the motivation dysfunction hypothesis (Mitchell, 2010) and work identifying an overactive behavioral activation system (Quay, 1988) in ADHD, suggests that the disorder should be characterized by high approach and a right frontal alpha asymmetry. However, in addition to an ADHD group characterized by high approach/positive affect, there is growing recognition that a subgroup of children shows high levels of negative affect and withdrawal (Karalunas et al., 2019, 2014), and there have been calls in the field to better integrate emotional findings in ADHD with neurobiological theories of the disorder (Shaw et al., 2014). Current findings confirm that emotional heterogeneity in ADHD is associated with unique neurobiological markers— rightward asymmetry characterized the disorder, but only when negative affect was low. Children with ADHD and high negative affect showed little asymmetry (i.e., similar alpha activation in right and left hemispheres). This may indicate that approach-withdrawal tendencies for children with ADHD and high negative affect are similar to those of typically-developing children. Alternatively, because negative affect is associated with an opposing pattern of left (rather than right) alpha asymmetry (Diego et al., 2001; Henriques and Davidson, 1991; Thibodeau et al., 2006; Tomarken et al., 1992a), competing patterns of activation may result in similar scalp-level patterns as typically-developing controls that in fact reflect unique underlying brain function. Task-based designs that examine changes in alpha asymmetry in response to emotional stimuli or events may provide additional information to disentangle these possibilities. In either case, resting asymmetry patterns do not appear to be a strong marker of diagnosis for those with ADHD and high negative affect.

Other studies investigating the effects of negative affect on alpha asymmetry in those with ADHD have found inconsistent results. Some have found that ADHD with high negative affect is associated with a leftward asymmetry (Jaworska et al., 2013) while others find a rightward asymmetry in ADHD even in the presence of high negative affect (Hale et al., 2010, 2009; Keune et al., 2011). Varying results may be due to the use of categorical (Hale et al., 2010, 2009; Jaworska et al., 2013) versus dimensional measures of negative affect (Keune et al., 2015, 2011). Within ADHD many individuals who do not meet full criteria for a comorbid disorder nonetheless experience chronic negative affect

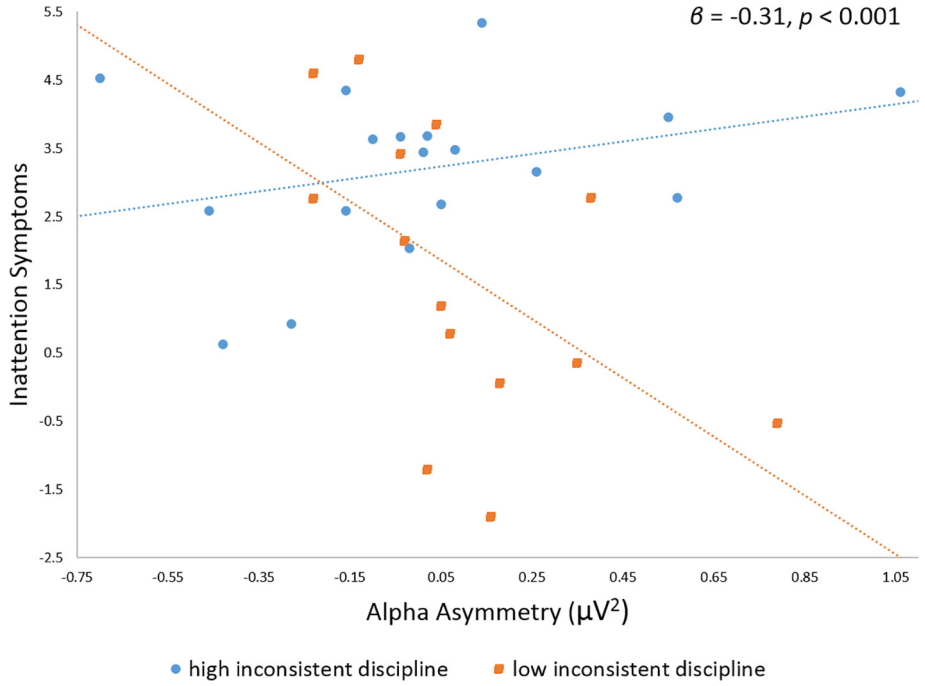

Fig. 3. Depiction of how inconsistent discipline moderates the relationship between alpha asymmetry and ADHD inattention symptoms. *Of note*: high and low inconsistent discipline groups were dichotomized (± 1SD from the mean) for depiction purposes.

(Eyre et al., 2017; Fernández de la Cruz et al., 2015; Karalunas et al., 2014), suggesting dimensional measures may be needed to capture these effects. Additionally, differences in statistical methods related to controlling for negative affect versus formally testing moderation could explain inconsistencies.

Frontal alpha asymmetry patterns during infancy predict later psychopathology (Smith and Bell, 2010) and alpha asymmetry has adequate stability over time (Tomarken et al., 1992b). Although we measured alpha asymmetry in adolescence, we would predict that the observed patterns are evident earlier in development and reflect emotional traits, in addition to influences by emotional state. If this is the case, right alpha asymmetry may serve as an important risk marker for ADHD and may be helpful in identifying at least some individuals with the disorder for early prevention efforts. We are undertaking studies designed to answer these questions now. In addition, although alpha asymmetry is relatively stable over time, the findings in the current study would be strengthened by repeated measurement of alpha asymmetry, which may be better indicators of trait effects (Hewig et al., 2004; Keune et al., 2015). Future work should consider taking multiple measures to differentiate state and trait effects.

The relationship between frontal alpha asymmetry and symptom severity within the ADHD group depended on parenting practices. Right asymmetry was associated with greater symptom severity in the context of inconsistent discipline, but with less symptom severity in the context of consistent discipline. Findings are in line with well-established relationships between inconsistent parenting and ADHD symptom severity (Bhide et al., 2016; Ellis and Nigg, 2009; Ullsperger et al., 2016), but demonstrate for the first time that the sensitivity to parenting effects may depend on neurobiological traits related to approach-withdrawal and affective tendencies. Consistent discipline may serve as a protective factor for children with right alpha asymmetry and behavioral parenting interventions may be particularly important for these children. Both a rightward alpha asymmetry (Harmon-Jones, 2007; Harmon-Jones and Allen, 1998; Keune et al., 2012; Peterson et al., 2008) and inconsistent discipline are also related to aggressive behavior (Jia et al., 2016; Miller and Tolan, 2019; Waller et al., 2018; Yoon et al., 2019). It is possible that a rightward asymmetry in ADHD drives aggression which then interacts with parenting behavior to predict symptom severity. However, future work investigating the relationship between inconsistent discipline, aggression, and alpha asymmetry in those with ADHD is needed.

The primary focus in the literature has been on frontal alpha asymmetry, which has a strong theoretical interpretation. However, several studies have also identified posterior effects (Hale et al., 2010, 2009). To contribute to the small number of publications in this area, we report exploratory analyses of posterior effects for which we did not have specific hypotheses. Posterior findings in the current study were marginal and should be considered with caution but were suggestive of a sex-dependent left alpha asymmetry. Females with ADHD had greater posterior left asymmetry than typically-developing females; this difference was not present in males. Prior studies have suggested that *right* posterior asymmetry in ADHD may reflect an adaptive mechanism to increase left hemisphere bottom-up processing to compensate for linguistic processing deficits common to the disorder. The results here show an opposite pattern (i.e., left asymmetry) and are not easily interpreted in a language processing deficit framework because females with ADHD do not have higher rates of language-based disorders than males with ADHD.

Other literature related to posterior alpha asymmetry has found a more leftward posterior alpha asymmetry in those with versus without depression (Mathersul et al., 2008; Metzger et al., 2004; Pössel et al., 2008), although inconsistencies exist (Blackhart et al., 2006; Deslandes et al., 2008; Kentgen et al., 2000; Miller et al., 2002). The sex-dependent effect occurring in our adolescent sample may be related to higher rates of depressive disorder onsets in females than males occurring at this age, in which case we would expect it to strengthen with age. Additional research across a wide developmental span is needed to clarify the interpretation of posterior asymmetry patterns in ADHD and whether they are related to higher susceptibility to developing depression and/or depressive symptoms in females with ADHD.

4.1. Limitations and future directions

The current analyses used an average reference when calculating alpha asymmetry. This is consistent with several prior studies (Gordon et al., 2010; Keune et al., 2015), but an array of other references have

also been used (Baving et al., 1999; Hale et al., 2010, 2009; Jaworska et al., 2013; Keune et al., 2011). Using a Cz reference is potentially problematic and may reduce reliability of results (Coan and Allen, 2003); however, other common references, such as mastoids and average, are generally accepted. Convergence across these reference schemes is not well-established (Hagemann et al., 2001), but at least some work suggests findings for frontal asymmetry are similar under these two approaches (Coan and Allen, 2003). Our findings are consistent with prior studies using both average and other references. Nonetheless, future work examining the effects of reference choice on alpha asymmetry measures may be important.

Issues related to sample generalizability are also important to consider. The ADHD and control groups' IQ scores were both above average, which may indicate a less impaired sample overall. The control group was restricted to individuals with 4 or fewer ADHD symptoms, which ensures exclusion of "borderline" or difficult to classify cases but leads to a less generalizable control sample. However, several factors reassure us of the generalizability of our findings. Both ADHD and control IQ scores remained within one standard deviation of the mean, and the group difference between those with and without ADHD was consistent with prior meta-analysis of ADHD-related differences in IQ scores (Frazier et al., 2004). In addition, groups were recruited using a community-based strategy that tends to increase generalizability as compared to clinic-based recruitment. Finally, our ADHD group shows a full range of symptom severity (6–18 symptoms) and normed rating scale scores are in the clinical range. Nonetheless, additional work using a fully dimensional approach or including subthreshold cases in the control group may be important for clarifying generalizability of findings.

The current study focused on alpha asymmetry due to the strong theoretical foundation for this measure as well as the growing emphasis on understanding emotional aspects of ADHD. However, there are a variety of other EEG metrics that have been investigated in ADHD and may serve as promising measures in future work, including excessive beta, increased slow wave/fast wave, and differences in coherence (Aldemir et al., 2018; Barry et al., 2009; Clarke et al., 2013, 2011; 2001; Robbie et al., 2016). Of note, one challenge with this literature is that many of these metrics lack a clear theoretical interpretation (Barry et al., 2009; Gloss et al., 2016; Loo et al., 2013; Saad et al., 2015) and studies often neglect to consider within group heterogeneity. Because of this it will be important for future work to continue to clarify the functional significance of these measures, as well as consider the effects of moderators.

Overall, the current results confirm that alpha asymmetry plays an important role as an indicator of ADHD liability and symptom severity but primarily for those with ADHD and low negative affect. Parsing emotional heterogeneity and considering how biological risk interacts with environmental context, such as parenting, will be critical for characterizing the role of this putative endophenotype in ADHD and elucidating targetable risk factors related to disease etiology or severity.

Conflicts of interest

The authors have no conflicts of interest to disclose.

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