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Article

Characterizing Behavior, Sex, and Subtype in Childhood ADHD via the Related Spectrum of Functional Network Connectivity at Rest

Emily G Lundstrum, Haylee Hudson, Caitlyn Busch, Parth R.K. Patel and Anastasia Kerr-German *

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Abstract: This study examines sex differences between children with and without ADHD. Specifically, functional near-infrared spectroscopy (fNIRS) resting-state functional connectivity measures were used to analyze neural profiles of female and male children based on both group and symptom severity score. Participants, aged 6-8, participated in this study by performing a *Passive Viewing Paradigm* resting-state task. The K-SADS interview was used to determine ADHD diagnosis and subtype, from which a continuous symptom severity score across group and subtype was calculated. It was found that female children with combined-type ADHD demonstrate different neural profiles than male children overall and based on symptom severity. Male children with ADHD, across subtypes, demonstrate less refined functional connectivity. Males with the combined type also show less significant connectivity. Most notably, within the combined-type group, connectivity increases as symptom severity increases in male children whereas connectivity decreases as symptom severity increases in female children, contrasting from their typically developing peers.

Keywords: resting state; ADHD; Sex; subtype; symptom severity

Introduction

Attention Deficit/Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder that affects 7–11% of school-age children, and 60–70% of these cases persist into adulthood (Burke et al., 2014; Danielson et al., 2018). ADHD is characterized by poor planning and memory with increased impulsivity, inattention, and hyperactivity (Brock et al., 2009). The average age of diagnosis for ADHD is 7 years old, though advances in assessment have allowed diagnosis to occur as early as preschool age. The spectrum of ADHD consists of three clusters of traits grouped into subtypes (e.g., inattentive, hyperactive, and combined) descriptive of different dominant behavioral dysregulation (Barnard et al., 2010; Rowland et al., 2015; Scahill & Schwab-Stone, 2000; Thomas et al., 2015).

Despite advances in treatment, there is much to learn about individual differences in the neural circuitry that underly the broader ADHD phenotype. Early diagnoses primarily occur in children with the most severe symptoms—typically males with the hyperactive subtype—neglecting female children, children with the inattentive or combined subtype, and children with less severe symptoms. Furthermore, males with ADHD are more likely to have comorbid learning disabilities, disruptive behavior, social dysfunction, and depression, whereas females have an increased rate of substance use disorders, anxiety, and depression, and are twice as likely to have the inattentive subtype of the disorder (Gilbert et. al., 2023; Yoshimasu et al., 2012). In addition, women with ADHD are more likely to be diagnosed in adulthood rather than in childhood, whereas men are more likely to be diagnosed in childhood and to present with the hyperactive subtype (Barnard et al., 2010). Moreover, males are twice (10%) as likely compared to females (5%) to be diagnosed with ADHD overall (Ayano et. al., 2023). These discrepancies lead to systemic long-term issues such as inequivalences in who receives treatment and who does not (Martin, 2024; Skoglund et. al., 2024).

Not only do these limitations exist in the clinic, but they are also present in research.

Specifically, idiosyncrasies in symptom severity, referral, sex specific prevalence rates, and subtype have also been largely neglected in research surrounding the neural ontogeny of this disorder (Arnett et al., 2015; Biederman et al., 2002). Despite this, few research studies consider subtypes and subtype trait characteristics spanning the ADHD phenotype in their analysis of intersections between cognitive processing and neural substrates underlying this process. Traditionally, neuroimaging work has been done with male children or adults who have the hyperactive subtype, even though this group represents just 50% of the clinical phenotype (Willcutt, 2012) with another source showing that the inattentive subtype is actually the most common subtype (Ayano et. al., 2023). Only recently has the field begun to explore sex and subtype, as well as symptom severity, at the neural level for ADHD (Park & Park, 2016; Rosch et. al., 2018). As a result, the role of sex differences in the emergence of ADHD in early childhood is muddled by underrepresentation in the samples, in part due to larger systemic issues already discussed, but also in part due to the research available on those children that might initially be missed in the clinic. These discrepancies are not isolated to clinical practice; the current parental identification and subsequent clinical referral problem for girls and women with ADHD, specifically, is also perpetuated by societal norms for appropriate behavior prior to school age (Cho et. al., 2024; Mowlem et al., 2019; Murray et al., 2019).

A review of recent literature demonstrates that the basis of this study is still present and necessary. More studies are advancing and promoting the idea of studying sex differences within ADHD, especially related to neural correlates of ADHD, but these results are lacking conclusive results. One study using diffusion tensor imaging and a battery of Go/No-Go tasks showed that females with ADHD had higher fractional anisotropy (white matter microstructure index) in the medial orbitofrontal cortex than males with ADHD as well as males with ADHD showing more impulsivity on the Go/No-Go tasks than females with ADHD (Peterson et. al., 2023). Another study also using diffusion tensor imaging showed that reduced fractional anisotropy in the orbitofrontal cortex-amygdala and ventral anterior cingulate cortex-amygdala tracts was specific to males with ADHD compared to females with ADHD (Rosch et. al., 2023). An fMRI study recently found that (unrelated to sex), different ADHD subtypes show different neural correlates of segregation, specifically with the inattentive subtype showed a negative correlation with segregation, and the inattentive and combined subtypes showed lower segregation components than TD children (Wang et. al., 2024). Outside of neuroimaging studies, recent work has shown sex-related differences in behavior as well as other aspects of ADHD in general. One study showed that there is a significant gap in auditory and visual attention behavioral outcomes between TD and ADHD-diagnosed children as well as a specific effect of sex in both groups (Lin et. al., 2023). Another study has demonstrated marked differences based on sex in emotional dysregulation, specifically that girls with ADHD levels remain high whereas boys with ADHD improve significantly during adolescence (De Ronda et. al., 2024). Lastly, another study showed that cortisol secretion is affected differentially based on a sex by subtype interaction in that inattentive boys showed lower hair cortisol concentration than TD boys and combined-type girls showed higher hair cortisol concentration than TD girls (Pauli-Pott et. al., 2024). Overall, this area of research is increasing in prevalence, but more is needed and necessary as outcomes of this research have major implications for clinical practice in the field of ADHD.

The notion that we need a better understanding of the neural mechanism(s) driving cognitive dysfunction associated with ADHD to fully address the needs of this group is not a new one. The NIH has been working to extend neural work to consider symptom severity and presentation as a spectrum, rather than grouping individuals as simply clinical or control. (Pacheco, et. al., 2022). Beyond separating groups based on ADHD diagnostic status, there is increasing support for analysis based on symptom severity. Recent studies have identified that reduced activation in the left prefrontal, left premotor, left frontal eye field, left primary motor cortex, and right supplementary motor cortex seen in ADHD populations is significantly correlated with symptom severity (Jacobson et al., 2018). The same correlation is seen in research with younger ADHD populations where a

dimensional approach allows for accurate evaluation of a wider range of functioning (Stephens et al., 2021). Including both males and females in the sample, as well as all three subtypes, is necessary to fully understand the spectrum of this neurocognitive delay as it emerges in early and middle childhood. One way to accomplish this would be to examine children prior to or at the beginning of treatment, along with better sampling to account for the lack of generalizability of neural findings related to ADHD.

Functional Connectivity in the ADHD Brain: A Potential Lifeline to Address Sample Disparities in Neuroscience

Even with a large body of existing behavioral research on ADHD, there is still limited information on the temporal dynamics underlying neural differences in this disorder. Specifically, the literature has largely neglected functional connectivity (FC) and profile work with younger populations at the precipice of typical diagnosis (5–6-year-olds). Known structural brain differences between individuals with and without ADHD partially account for behavioral performance differences in executive functioning. For example, research done on slightly older children with ADHD demonstrated reduced gray matter in bilateral frontal, parietal, and temporal lobes (Jacobson et al., 2018) as well as abnormalities in right inferior frontal gyrus and white matter volume in caudal portion of temporal cortex (Pironti et al., 2014). Despite these findings, the literature is inconsistent on whether structure and anatomy or functional activation drives these findings. Using functional magnetic resonance imagery (fMRI) data collected during the resting state, Hearne et al. (2019) found that structural connectivity did not significantly differ between ADHD and control groups, but the ADHD group showed reduction in structure function coupling, including linking frontoparietal systems with sensory networks. Additional research supports the conclusion that dysfunction is caused by differences in connectivity rather than regional abnormalities, and that the use of stimulant medications can normalize the dysfunctional connectivity in affected individuals (Konrad & Eickhoff, 2010). These studies had limited samples that underrepresented the larger phenotype of ADHD. Thus, either approach would be an appropriate starting point for broadening the application of these neural findings to this understudied clinical group.

Neuroimaging of very young children is difficult when utilizing common neuroimaging technology, like fMRI. The primary objective of this study is to address these issues more comprehensively. Functional near-infrared spectroscopy (fNIRS) is a valuable technique to use for successfully collecting FC data in young children with ADHD because it allows the participant to move and therefore does not require longer recording times due to sampling constraints (e.g., fMRI). Moreover, this method of using resting-state FC analyses to elucidate the neural underpinnings of group differences or behavioral outcomes is an important aspect of growing neuroimaging literature. Resting-state functional connectivity shows synchronized activation of spatially remote neural populations at rest and can be used as a baseline or intrinsic neural measure that can then correlate with or predict group differences or behaviors (Lu, et. al., 2010). This has many applications in research, but also in clinical practice, as these neural profiles that are being created allow for biological underpinnings to be understood without needing to use an extensive battery of tasks or assessments, and it can be used across neuroimaging techniques, fNIRS being a common choice.

Current Approach

The current study utilizes a measure of FC during rest (i.e., passive viewing) to further evaluate functional brain differences between children with and without ADHD. Specifically, steps were taken to include an even number of female and male participants, younger children prior to or who had recently begun treatment, and a variety of subtypes beyond hyperactive. Symptom severity and sex across results were also investigated.

Hypotheses

It is hypothesized that marked differences in functional connectivity will be seen at rest between male and female children with and without ADHD. First, global hypoconnectivity in children with ADHD as compared to TD children is expected across the frontal, parietal, and temporal cortices. Between male and female children, differences are expected in the nature of the functional connectivity profile, in that TD and ADHD females will have more fine-tuned resting state functional connectivity profiles. Within the ADHD group, it is predicted that the differences between male and female children will be exaggerated beyond the main effect of sex. These relationships will be looked at with a continuous symptom severity score, with the prediction that male children will show different patterns of hypoconnectivity with increasing symptom severity as compared to female children.

Methods

Participants

A total of 52 children between six and eight years of age were included in this study ($M=6.80$, Female=24). All participants were recruited from the community of Southeastern Nebraska based on voluntary entry into a database for research participation, parental consent and child assent (for children seven or eight years of age) was obtained prior to the start of the study. In the first part of the study, a licensed clinical psychologist with experience working with ADHD populations administered the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS) in combination with parental interviews and the Disruptive Behavior Disorder (DBD) Parent/Teacher rating scale. Based on these interviews, twenty-five children were assigned to the clinical group with a diagnosis of ADHD ($M=6.92$, Female=11), and twenty-seven children were assigned to the typically developing (TD) group ($M=6.70$, Female=13).

Exclusion criteria for this study included history of seizures, Tourette's syndrome, autism spectrum disorder, and a lack of evidence for impairment across multiple settings (despite a clinically relevant number of ADHD symptoms). Moreover, the Wechsler Abbreviated Scale of Intelligence-II (WASI-II) was administered, and children scoring below eighty were excluded to exclude children with confounding developmental delays. In total, seven children were excluded based on these criteria, mainly due to lack of impairment across multiple settings, and these children were separate from the total $n=52$ described above.

Survey Procedures

When possible, consent, demographics, KSADS, and WASI-II were obtained via virtual appointment prior to performing the tasks to minimize contact while recruiting during a pandemic. First, the parents filled out a demographics form. Then, the clinician gave the participant a shortened version of the WASI-II that included the vocabulary and matrix reasoning assessments. The WASI-II is a general intelligence test designed to assess overall cognitive capabilities in children and adults (6–89 years old). The K-SADS is a semi-structured interview designed to measure mood, anxiety, psychotic, and disruptive behavior disorders in children from 6–18 years old. A collaborating clinician at Boys Town National Research Hospital gave a K-SADS interview to one or both parents. If the parent had concerns about ADHD, the clinician offered to give the DBD Parent/Teacher rating scale to the teacher. This assessment was taken into consideration for the final grouping when available.

Demographics

Researchers administered a demographics questionnaire that was specifically designed to collect information concerning household income, parental education level, number of siblings, race, ethnicity, sex, primary spoken languages, special education, and adoption status. Demographics were used for descriptive statistics only.

The Affective Reactivity Index Parent Form (ARI-P)

The ARI-P was given to measure irritability in the participant. This parental report scale has been tested and found to be consistent for clinical and research use in multiple different samples (Stringaris et. al., 2012). The ARI-P is scored from "0 - Not true" to "2 - Certainly true."

Parental Stress Scale (PSS)

The PSS was given to the parent to measure the total stress that the role of parenting has put on the parent. Scores ranged from "1 - Strongly disagree" to "5 - Strongly agree." The questionnaire can be focused on an individual child, or all their children, and we requested that the parents report on the former. The PSS has been validated many times over for each psychometric property (Algarvio et al., 2018; Berry, 1995; Harding et al., 2020; Pontoppidan et al., 2018; Zelman & Ferro, 2018).

The Disruptive Behavior Disorder Parent/Teacher Rating Scale

The DBD Parent/Teacher rating scale was given to the parent and the participants teacher and used to determine group placement. This scale consists of 42 items with four subscales: conduct disorder, Oppositional Defiant Disorder (ODD), ADHD-inattention, and ADHD-hyperactive. It is rated on a 4-point scale, where 0 means "not at all" and 3 means "very much." The teacher can also withhold a response by indicating they do not know.

Parent IRS: The Narrative Description of a Child

The Parent IRS was given to the accompanying parent to scale how their child's behavioral problems affect different aspects of their life at home and at school and whether each area needs special treatment or services (Fabiano et al., 2006). This scale is rated from 0–7 and is on a sliding scale. The parents could also explain and expand on their answers in their own words.

fNIRS Procedures

The participants sat in front of a laptop computer on a table adjusted to the participants' height. First, the circumference of the child's head was measured, which we used to mark the central anatomical point on the head (Cz), halfway between the nasion and inion and both pre-aural areas. Caps were between 52 and 56 cm, which was based on two cm added to the circumference of the child's head. Once capped, the sources and detectors were adjusted to an appropriate signal-to-noise ratio as calculated by NIRStar 15.5 software. During the task, fNIRS was collected using NIRScout continuously at 3.4 Hz with light wavelengths of 760 and 850 nm. The probe used was comprised of 16 sources and 16 detectors arranged to cover bilateral frontal, parietal, and temporal cortices as seen in the sensitivity profile (Figure 1). All sources and detectors were placed 3 cm apart creating a 38-channel array for functional connectivity measures. Placement of sources was relative to the revised 10-10 system (see Figure 1; see supplemental Table S1 for corresponding MNI coordinates) over bilateral frontal cortex (FP 1-2, AF 5-6, F 3-8, FC 3-8), bilateral parietal cortex (CP 1-6, P 1-6), and bilateral temporal cortex/temporal-parietal junction (T 7-8, TP 7-8). We used timestamps at trial onsets to synchronize data. The fNIRS cap was on and recorded data throughout all tasks included in this study, and data collection was stopped briefly between each task.

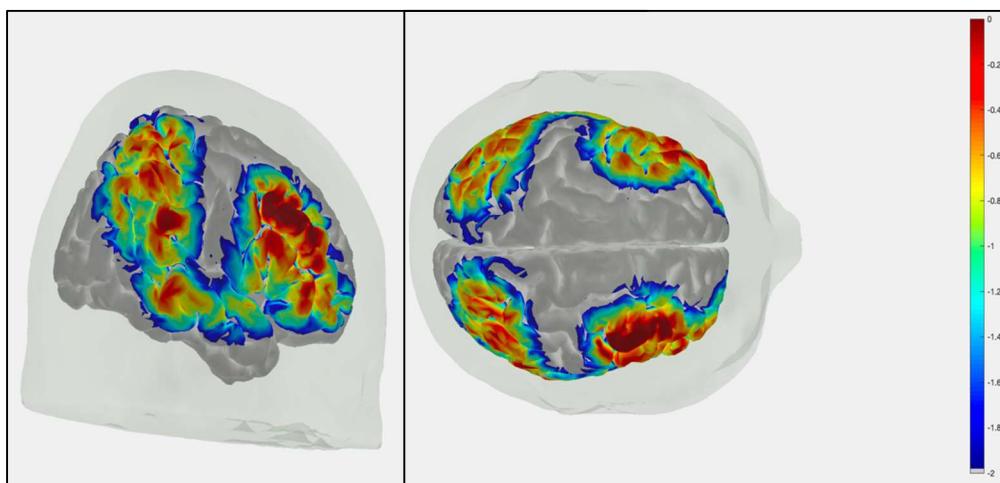


Figure 1. Probe sensitivity profile.

Passive-Viewing Paradigm

The task used to collect resting-state functional connectivity data was a *Passive Viewing Paradigm* as studies have shown that passively watching a video provides better compliance (Vanderwal et. al., 2015) and data collected is roughly analogous to other rest protocols, even in children (Zhang et. al., 2019). In this task, children watched a series of five short videos interrupted briefly by a black screen with a white fixation. Each video (see Figure 2) was soothing and low stimulation that was paired with calming, instrumental music. The music was slow-tempo and temporally synchronized with motion in the videos to avoid any brain activity related to perceptual asynchrony (Lo & Zeki, 2014). While watching the set of videos, children were given the following instructions: "For this game, you will need to be very still and calm before I start the videos. Remember to keep your eyes on the screen while watching and stay as still and quiet as you can." Each video lasted between 45 and 90 seconds, which gave a total of between four and five minutes of resting (video watching) time. Each child met the criterion of having at least four minutes of recorded data after motion corrections were run (Kerr-German et. al., 2022).

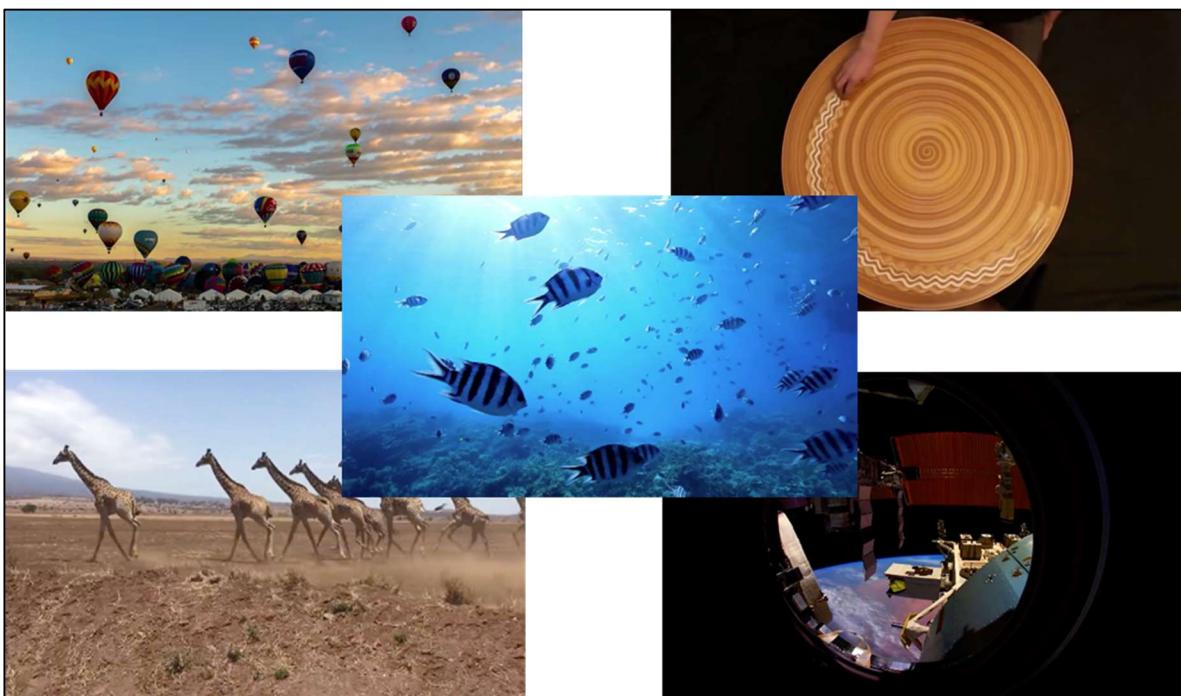


Figure 2. Screen captures from videos included in the Passive Viewing Paradigm task.

Analysis

Survey Data

Participants were given total scores for the PSS, ARI-P, and Parent IRS and specific sub scores for the Parent/Teacher DBD rating scale (ADHD, ODD, Conduct Disorder) and K-SADS (Symptom Severity and Vocabulary) based on conventional scoring criteria for each survey. T tests were performed to ensure that there were no differences in any scores between any age group or sex ($p > .05$). A partial correlation was run between each of the survey totals and sub-scored to determine if the scores between surveys were correlated. A Symptom Severity sub score was calculated using the K-SADS interviews and was used as a continuous variable for the entire sample during neural analysis. Results from the K-SADS interviews were also used to determine ADHD subtype (hyperactive, inattentive, or combined-type).

fNIRS Data

In the current study, the same analyses were employed as used with children at risk for ADHD in (Kerr-German et al., 2022) for this passive viewing task. At least thirty seconds of recording prior to the first video was obtained, and only data from the task—during passive viewing—was included in these analyses. For this analysis, the AnalyzIR toolbox within MATLAB (Santosa et. al., 2018) was used. After correcting for motion artifacts using the PCA method, raw fNIRS data was converted to changes in optical density. Then, the measured intensity data of the two wavelengths were converted to relative HbO and HbR concentration changes using the modified Beer-Lambert law (Cope et. al., 1988). To extract the individual FC measures, a robust correlation approach was taken, implementing an iterative autoregressive least-square technique (Santosa et al., 2017) to calculate the robust correlation coefficient of the temporally whitened signals to control the false-discovery rate. This approach yields more reliable estimates of serially correlated errors and statistical outliers due to motion artifacts in functional connectivity data (Temporal Derivative Distribution Repair [TDDR]; Fishburn et al., 2019). To be considered significant, q values had to be $\leq .05$. The analyses included are the main effect of sex within the combined-type group compared to the main effect of sex within the TD group. In addition, the interaction between symptom severity score and sex within the combined-type group and TD group are included. All analyses were done while controlling for any possible age effects to avoid confounds, as there are still outstanding questions surrounding the way the brain at rest changes with age (Camacho et. al., 2020).

Results

Demographics

Table 1 displays the number of total participants ($n=52$) in the study broken down by demographic information recorded using our demographics survey filled out by the participants' parents. The sample was not evenly distributed based on race, ethnicity, and SES. Most of the sample was English-speaking, white, non-Hispanic/Latino, and of high SES. Due to this, the results provided should not be generalized across all populations, and future work is needed to create more generalizability among these data.

Table 1. Breakdown of the number of participants in the study based on recorded demographics information.

		Age 6 (n=22)	Age 7 (n=18)	Age 8 (n=12)	Total (n=52)
Sex	Female	8	10	6	24
	Male	14	8	6	28
Race	White	18	16	9	43
	Multiracial	4	2	3	9
Ethnicity	Non-Hispanic/Latino	18	17	11	46
	Hispanic/Latino	4	0	1	5
	Unknown	0	1	0	1
Main Language in Household	English	20	16	12	48
	Spanish	1	0	0	1
	Other	1	2	0	3
Highest Level of Parental Education	Some High School	1	0	0	1
	High School Degree	1	0	0	1
	Some College/Technical School	3	3	0	6
	College Degree	10	5	4	19
	Graduate/Professional Degree	7	10	8	25
Household Income	\$5,000-\$9,999	1	1	0	2
	\$10,000-\$14,999	0	1	1	2
	\$15,000-\$24,999	2	1	0	3
	\$25,000-\$39,999	0	1	0	1
	\$40,000-\$59,000	2	1	0	3
	\$60,000-\$89,000	5	5	3	13
	\$90,000-\$179,000	7	5	7	19
	Greater than \$180,000	5	3	1	9
Number of Adults in Household	One	0	6	0	1
	Two	21	11	11	43
	Three or More	1	1	1	3
Number of Children in Household	One-Two	8	7	2	17
	Three-Four	11	10	8	29
	Five or More	3	1	2	6
Adoption	Child is Adopted	1	1	1	3
	Child is Not Adopted	21	17	11	49
Special Education	Child in Special Education	2	0	2	4
	Child Not in Special Education	20	18	10	48

Survey Analyses

As shown in Table 2, the hyperactive and inattentive groups both have very small sample sizes. Due to this, combined type or overall ADHD groups were considered in future analyses. However, samples of male and female children across age are relatively balanced.

Table 2. Breakdown of participants into clinical and TD groups (including subtype) by age and sex.

	Age 6		Age 7		Age 8		Total
	Male	Female	Male	Female	Male	Female	
ADHD Group	5	3	5	6	4	2	25
Subtype	Hyperactive	0	1	0	0	0	1
	Inattentive	0	0	1	0	0	3
	Combined	5	2	4	6	2	21
TD Group	9	5	3	4	2	4	27
Total	14	8	8	10	6	6	52

Table 3 shows the mean symptom severity scores by group (TD, clinical ADHD, and each subtype) also broken down by age and sex. The symptom mean severity scores are drastically higher in the ADHD sample versus the TD sample ($t(34.88) = 5.832 \times 10^{14}, p < 0.05$), validating this as a continuous measure of ADHD symptom level across groups. The combined-type group, which will be important for later analyses, also has a significantly higher mean symptom severity score ($t(29.4) = 7.928 \times 10^{14}, p < 0.05$) than the TD group.

The difference between symptom severity score based on sex between groups was also investigated. Males have a significantly higher mean symptom severity score ($M=26.91, 24.21, 2.64$) than females ($M=21.90, 20.91, 2.46$) in all three groups (combined-type, ADHD, and TD respectively according to three t-tests. For combined-type group, $t(19) = 0.0967, p < 0.05$, for the ADHD group, $t(23) = 0.287, p < 0.05$, and for the TD group, $t(25) = 0.905, p < 0.05$.

Table 3. Mean symptom severity for each group by age and sex.

		Age 6		Age 7		Age 8		Total
		Male	Female	Male	Female	Male	Female	
	ADHD Group	25.60	21.67	29.00	21.33	16.50	18.50	22.76
Subtype	Hyperactive	0.00	11.00	0.00	0.00	0.00	0.00	11.00
	Inattentive	0.00	0.00	14.00	0.00	14.50	0.00	14.33
	Combined	25.60	27.00	32.80	21.33	18.50	18.50	24.52
	TD Group	2.00	2.00	5.33	2.00	1.50	3.50	2.55

Survey Results

All participants completed all of the aforementioned surveys in full. There were no significant differences between any age group for the total scores for the Parent IRS, Parent/Teacher DBD rating scale, PSS, ARI-P, K-SADS Symptom Severity, or clinical grouping ($p > .05$). As expected, 6-year-olds did have a significantly lower K-SADS Vocabulary subscore than their 8-year-old counterparts [$F(2, 49) = 11.049, p < .001$]. The ADHD group and TD group showed differences in their ARI-P [$F(1, 50) = 10.376, p < .001$] and Symptom Severity scores [$F(1, 50) = 151.467, p = .002$], while the PSS and Vocabulary sub-score did not ($p > .05$).

Table 1. Partial Correlations for ADHD Survey Data (K-SADS, PSS, ARI-P, and Parent/Teacher DBD Rating Scale).

	1	2	3	4	5	6	7
1. K-SADS							
Vocabulary	--						
2. K-SADS							
Symptom							
Severity	-						
	.043	--					
3. PSS	-.04	.339	--				
4. ARI-P	-						
	.371	.557*	.349	--			
5. ADHD-							
Inattention	-						
	.025	.766*	.264	.351	--		
6. ADHD-							
Hyperactive	.084	.824*	.463*	.5*	.836*	--	
	-						
7. ODD	.101	.304	.246	.669*	.315	.458*	--

Note. *Bonferroni corrected $p < .007$, two-tailed test, controlling for age in years.

A partial correlation analysis was conducted to examine the main variables of the survey data (K-SADS Vocabulary and Symptom Severity, PSS, ARI-P, and Parent Teacher DBD rating scale) while controlling for age (see Table 1). **Neural Results**

Of the 52 participants that completed the final battery, 47 were included in the RS final analysis. Participants were excluded (TD = 2, ADHD = 2) for two reasons: (a) if 20% of channels were lost due to poor signal quality, or (b) less than 80% of data remained due to motion artifact (see Table 1). Though neither younger nor older children were excluded more often, those in the clinical group were generally excluded more than the TD population, displaying one challenge with recording neural data from this population.

Passive Video Watching/Resting State Task

The resting state task was analyzed for functional connectivity between regions during passive video watching. A difference between sexes was investigated because a difference in FC is generally observed (Tomasi & Volkow, 2012), and a large dichotomy between males and females exists in ADHD symptomology and connectivity (Park & Park, 2016). There were nine synchronous connections in the IFC within males at rest and one negative connection between the left frontal cortex and the right parietal. Within females, there were two connected channel pairings, one within the IFC and another within the IPC. Finally, there was a significant connection between channels in the left and right parietal cortex for participants high on the Symptom Severity score (see Table 2).

Table 2. ΔHbO_2 as It Relates to Symptom Severity, & Sex Effect During Resting State.

Channel Connectivity	MNI Region	Condition	R	z	t	q
1<-->2	lFC<-->lFC	Male	0.521209	0.577999	4.883782	0.002015
1<-->3	lFC<-->lFC	Male	0.334026	0.347353	4.618476	0.004508
2<-->4	lFC<-->lFC	Male	0.338104	0.35195	5.179304	0.000809
2<-->6	lFC<-->lFC	Male	0.350914	0.366486	5.378394	0.00044
3<-->2	lFC<-->lFC	Male	0.281118	0.288896	4.694692	0.003648
3<-->4	lFC<-->lFC	Male	0.403652	0.428005	4.431514	0.008137
3<-->5	lFC<-->lFC	Male	0.184477	0.186613	4.002845	0.02873
4<-->6	lFC<-->lFC	Male	0.32942	0.342178	5.33512	0.000501
4<-->35	lFC<-->lFC	Male	-0.19612	-0.19869	-3.98387	0.029831
5<-->6	lFC<-->rPC	Male	0.415942	0.442775	3.807233	0.046841
3<-->5	lFC<-->lFC	Female	0.205807	0.208789	3.94482	0.03296
13<-->14	lPC<-->IPC	Female	0.53267	0.593866	3.894906	0.037276
13<-->33	lPC<-->rPC	Symptom Severity	0.001943	0.001943	4.210226	0.015532

*q < .05.

Resting-State Functional Connectivity Analyses

As described above, there were four main analyses of resting-state functional connectivity ran from this study. Table 4 shows the main effect of sex within the combined-type group (n=21, Female=10), and Table 5 shows the main effect of sex within the TD group (n=27, Female=13). First, it is seen that there is generally more connectivity in the TD group than the combined-type group, especially in male children. This shows less connectivity in the combined-type group than TD. It can also be seen that connectivity in female children seems to be more fine-tuned than male children, as predicted. Females in the combined-type group show hypoconnectivity between the parietal cortices compared to their TD peers. Male children in the combined-type group specifically show increased

connectivity within the right frontal cortex compared to their TD peers, other than showing less connectivity overall.

Table 4. Resting-State Functional Connectivity HbO for Main Effect of Sex within the Combined Subtype Group.

Condition	R-value	q-value	Channel Conn.	Region Conn.
Male	0.20	<0.01	6 β à12	lFC β àlTC
Male	-0.18	0.02	6 β à38	lFC β àrPC
Male	0.47	0.03	23 β à24	rFC β àrFC
Female	-0.06	0.03	15 β à33	lPC β àrPC

Table 5. Resting-State Functional Connectivity HbO for Main Effect of Sex within the TD Group.

Condition	R-value	q-value	Channel Conn.	Region Conn.
Male	0.38	0.04	2 β à6	lFC β àlFC
Male	0.23	0.03	2 β à11	lFC β àlTC
Male	0.24	<0.01	2 β à15	lFC β àlPC
Male	0.42	0.01	4 β à6	lFC β àlFC
Male	-0.21	0.02	10 β à16	lTC β àlPC
Male	0.19	0.04	10 β à38	lTC β àrPC
Male	-0.20	<0.01	15 β à34	lPC β àrPC
Male	-0.21	0.02	18 β à37	lPC β àrPC
Female	0.47	0.04	3 β à4	lFC β àlFC
Female	0.49	0.03	35 β à36	rPC β àrPC

Table 6 shows the results within the combined-type group looking at the interaction between sex and symptom severity, and Table 7 shows this for the TD group. Again, less significant connectivity is seen within the combined-type group when compared to the TD group, especially for male children who show less refined functional connectivity overall. In the combined-type group, female children show decreased connectivity as symptom severity increases whereas male children show increasing connectivity as symptom severity increases. However, female children in the TD group have increased connectivity with increasing symptom severity between the left frontal and parietal cortices, which is lacking in the combined-type group. Male children in the TD group show a lot of functional connectivity patterns both increasing and decreasing with increases in symptom severity, but in the combined-type group, it is seen that connectivity solely increases with severity. These data show that there are different resting-state functional connectivity profiles correlating to symptom severity in male and female children depending on whether they have combined-type ADHD or are in the TD group.

Table 6. Resting-State Functional Connectivity HbO for Sex by Symptom Severity (SS) Interaction within the Combined Subtype Group.

Condition	R-value	q-value	Channel Conn.	Region Conn.
Male:SS	0.04	0.02	5 β à23	lFC β àrFC
Male:SS	0.03	0.05	6 β à21	lFC β àrFC
Male:SS	0.02	0.03	12 β à36	lTC β àrPC
Male:SS	0.03	<0.01	15 β à23	lPC β àrFC
Female:SS	-0.03	0.01	8 β à38	lFC β àrPC

Female:SS	-0.06	0.05	17βà18	lPCβàlPC
Female:SS	-0.03	0.01	19βà33	lPCβàrPC

Table 7. Resting-State Functional Connectivity HbO for Sex by Symptom Severity (SS) Interaction within the TD Group.

Condition	R-value	q-value	Channel Conn.	Region Conn.
Male:SS	-0.05	<0.01	1βà15	lFCβàlPC
Male:SS	-0.05	<0.01	1βà23	lFCβàrFC
Male:SS	-0.04	0.03	1βà31	lFCβàrTC
Male:SS	0.03	0.01	1βà32	lFCβàrPC
Male:SS	-0.10	<0.01	2βà4	lFCβàlFC
Male:SS	-0.15	<0.01	2βà5	lFCβàlFC
Male:SS	-0.06	0.03	2βà32	lFCβàrPC
Male:SS	-0.05	<0.01	2βà37	lFCβàrPC
Male:SS	-0.06	0.01	3βà32	lFCβàrPC
Male:SS	-0.17	<0.01	4βà6	lFCβàlFC
Male:SS	0.08	0.01	4βà25	lFCβàrFC
Male:SS	-0.04	0.01	5βà15	lFCβàlPC
Male:SS	0.03	0.02	5βà31	lFCβàrTC
Male:SS	0.06	0.05	6βà35	lFCβàrPC
Male:SS	-0.07	<0.01	6βà37	lFCβàrPC
Male:SS	-0.10	<0.01	8βà11	lFCβàlTC
Male:SS	-0.05	<0.01	9βà32	lFCβàrPC
Male:SS	-0.06	<0.01	11βà19	lTCβàlPC
Male:SS	-0.07	<0.01	12βà16	lTCβàlPC
Male:SS	0.08	<0.01	12βà17	lTCβàlPC
Male:SS	0.01	0.05	13βà16	lPCβàlPC
Male:SS	-0.07	0.01	14βà32	lPCβàrPC
Male:SS	0.04	0.04	15βà19	lPCβàlPC
Male:SS	0.10	<0.01	17βà25	lPCβàrFC
Male:SS	0.04	<0.01	17βà28	lPCβàrFC
Male:SS	-0.10	<0.01	18βà19	lPCβàlPC
Male:SS	0.05	<0.01	18βà31	lPCβàrTC
Male:SS	-0.06	<0.01	19βà28	lPCβàrFC
Male:SS	0.11	<0.01	20βà38	rFCβàrPC
Male:SS	0.08	<0.01	21βà34	rFCβàrPC
Male:SS	0.08	<0.01	21βà38	rFCβàrPC
Male:SS	0.05	0.02	22βà34	rFCβàrPC
Male:SS	0.04	0.03	22βà35	rFCβàrPC
Male:SS	0.06	<0.01	22βà38	rFCβàrPC
Male:SS	0.06	<0.01	23βà33	rFCβàrPC
Male:SS	0.09	<0.01	25βà37	rFCβàrPC

Male:SS	0.08	<0.01	25βà38	rFCβàrPC
Male:SS	0.05	0.03	27βà32	rFCβàrPC
Male:SS	0.11	<0.01	27βà34	rFCβàrPC
Female:SS	0.09	0.01	1βà18	lFCβàlPC
Female:SS	-0.08	0.03	16βà17	lPCβàlPC
Female:SS	-0.07	0.02	19βà23	lPCβàrFC

Discussion

This study investigated neural and behavioral differences in children with and without ADHD, with a focus on sex differences and subtype variation in resting-state functional connectivity (rsFC) using functional near-infrared spectroscopy (fNIRS). The findings provide novel insights into the distinct neural profiles of male and female children with ADHD, especially within the combined subtype, and their relationship with symptom severity at the time of diagnosis.

Sex Differences in Functional Connectivity

The results revealed significant differences in rsFC between male and female children with ADHD. Specifically, male children exhibited less refined functional connectivity overall compared to their female counterparts, aligning with previous research suggesting that ADHD manifests differently by sex at the neural level (citation). Within the combined-type group, male children showed increased connectivity with rising symptom severity, whereas female children showed decreased connectivity with increasing severity. This suggests that males and females may have distinct neural mechanisms underlying symptom expression in ADHD that is directly related to hypo or hyper-connections within and between critical attention and executive functioning cortical regions.

These findings align with prior research indicating that males with ADHD tend to present with more hyperactive and impulsive traits, whereas females are more likely to exhibit inattentive symptoms and emotional dysregulation (citation). The observed hypoconnectivity in males with ADHD further support the notion that males may have more widespread functional network disruptions, whereas females display more localized alterations.

Impact of Symptom Severity on Sub type-Specific Findings

A key strength of this study is the examination of ADHD symptom severity as a continuous variable rather than a binary classification of diagnosis. The results showed that increased symptom severity was linked to increased connectivity in males within the combined-type group, but the opposite trend was observed in females. This highlights the importance of considering symptom severity when investigating ADHD-related neural differences. It also suggests that symptom severity may have a sex-specific impact on functional connectivity patterns in ADHD.

The findings underscore the importance of considering ADHD subtypes in neuroimaging research. Most previous studies have focused primarily on the hyperactive subtype or male-dominant samples, which limits the generalizability of the findings. In this study, the combined-type group demonstrated distinct connectivity profiles compared to the typically developing (TD) group, with less refined connectivity in males and more consistent patterns in females. This supports the hypothesis that different ADHD subtypes may be driven by different underlying neural mechanisms.

Clinical and Research Implications

The observed sex and subtype differences have important implications for clinical practice and future research. Early diagnosis and intervention strategies should be tailored to account for these neural and behavioral differences. The findings suggest that male and female children with ADHD may benefit from different therapeutic approaches, particularly those targeting functional connectivity. Moreover, the study highlights the need for more inclusive sampling in ADHD research to better capture the full spectrum of symptom presentation across sexes and subtypes.

Despite its strengths, this study has several limitations. First, the sample size for the hyperactive and inattentive subtypes was small, which may have limited the power to detect subtype-specific

differences. Second, the study primarily included children from high socioeconomic backgrounds, which may reduce the generalizability of the findings to more diverse populations. Third, while fNIRS provides valuable insights into functional connectivity, it has limited spatial resolution compared to other imaging modalities like fMRI. Future studies should aim to replicate these findings in larger and more diverse samples and explore the longitudinal trajectories of rsFC patterns in ADHD.

Conclusions

This study contributes to a growing body of research demonstrating that ADHD is a heterogeneous disorder with distinct neural signatures based on sex, subtype, and symptom severity. The findings reinforce the importance of using a dimensional approach to better capture individual differences in ADHD and to develop more targeted and effective interventions. Understanding the neural basis of these differences is critical for improving diagnostic accuracy and treatment outcomes for children with ADHD.

Clinical research has neglected to investigate the neural and individual differences between sex and subtype in populations with ADHD. Utilizing fNIRS, the research presented uncovers differences in the neural functional pathways of early-age males and females with and without ADHD. Possible implications of the research presented include a deeper understanding of neural circuitry that paves way for clearer subtype understanding, symptom presentation between the sexes, and diagnosis and intervention at an earlier age for girls. Future research could explore the socialization of females and include broader demographic populations for richer generalizability.

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