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Functional Connectivity of Frontoparietal and Salience/Ventral Attention Networks Have Independent Associations With Co-occurring Attention-Deficit/Hyperactivity Disorder Symptoms in Children With Autism

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ABSTRACT

BACKGROUND: Children with autism spectrum disorder (ASD) and co-occurring attention-deficit/hyperactivity disorder (ADHD) symptoms have worse functional outcomes and treatment response than those without ADHD symptoms. There is limited knowledge of the neurobiology of ADHD symptoms in ASD. Here, we test the hypothesis that aberrant functional connectivity of two large-scale executive brain networks implicated in ADHD—the frontoparietal and salience/ventral attention networks—also play a role in ADHD symptoms in ASD.

METHODS: We compared resting-state functional connectivity of the two executive brain networks in children with ASD (n = 77) and typically developing control children (n = 82). These two executive brain networks comprise five subnetworks (three frontoparietal, two salience/ventral attention). After identifying aberrant functional connections among subnetworks, we examined dimensional associations with parent-reported ADHD symptoms.

RESULTS: Weaker functional connectivity in ASD was present within and between the frontoparietal and salience/ventral attention subnetworks. Decreased functional connectivity within a single salience/ventral attention subnetwork, as well as between two frontoparietal subnetworks, significantly correlated with ADHD symptoms. Furthermore, follow-up linear regressions demonstrated that the salience/ventral attention and frontoparietal subnetworks explain unique variance in ADHD symptoms. These executive brain network–ADHD symptom relationships remained significant after controlling for ASD symptoms. Finally, specificity was also demonstrated through the use of a control brain network (visual) and a control co-occurring symptom domain (anxiety).

CONCLUSIONS: The present findings provide novel evidence that both frontoparietal and salience/ventral attention networks' weaker connectivities are linked to ADHD symptoms in ASD. Moreover, co-occurring ADHD in the context of ASD is a source of meaningful neural heterogeneity in ASD.

Keywords: ADHD, Anterior cingulate, ASD, Comorbidity, Insula, Resting state, Selective attention

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For children with autism spectrum disorder (ASD), the presence of co-occurring attention-deficit/hyperactivity disorder (ADHD) is associated with worse functional outcomes and treatment response (1–5). Children with ASD and co-occurring ADHD struggle to a greater degree with skills needed for adaptive behavior (self-care, communicating and interacting effectively with others) and experience diminished quality of life (1–3). Compared with the nonautistic ADHD population, autistic children who seek treatment for ADHD symptoms have lower response and remission rates to ADHD medications, such as stimulants or α_2 agonists (4,5). Defining the brain networks contributing to ADHD symptoms in ASD may provide insight into the poor treatment response of children with co-occurring ADHD and ASD. Poor treatment response likely contributes to the poor functional outcomes for children with ASD and co-occurring ADHD symptoms. Despite these highly detrimental effects, few neuroimaging studies have directly evaluated multiple brain networks that may drive co-occurring ADHD symptoms in children with ASD.

ADHD is characterized by poor cognitive control, the ability to constrain thought and action to achieve goals (6–8). The triple-network model of psychopathology posits that complex cognition like cognitive control is subserved by two of the three large-scale brain networks: the frontoparietal and salience/ventral attention networks (9,10). The frontoparietal network includes portions of dorsolateral and medial prefrontal cortex (Brodmann area [BA] 6/9/10/44/46), intraparietal sulcus (BA 7/39/40), precuneus (BA 7), and cingulate cortex

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(BA 24/31). This network is linked to cognitive control processes including behavioral response inhibition, working memory, and set shifting. Impairments in this network in ADHD populations have long been observed in neuropsychological studies (6). Task-based functional magnetic resonance imaging (fMRI) studies have demonstrated decreased frontoparietal activation in children with ADHD (11,12). Recovery of frontoparietal activation is observed in stimulant medication responders with ADHD during cognitive control tasks (13,14), alongside changes in resting-state functional connectivity in the dorsolateral prefrontal cortex—a key hub of the frontoparietal network (15). Furthermore, decreased activation in the frontoparietal network during a cognitive-control fMRI task has been reported in children with ASD relative to typically developing control (TDC) children, and ADHD symptoms correlated with lower functional connectivity within the frontoparietal network during this task (16).

The salience/ventral attention network includes the anterior cingulate cortex (BA 24/32), insula (BA 13), lateral prefrontal cortex (BA 8/9/10/44/46), precuneus/posterior cingulate cortex (BA 7/31), supramarginal gyrus (BA 2/40), and parietal operculum (BA 40). The salience and ventral attention networks were originally studied independently (17,18), but recent functional connectivity research on large-scale brain networks shows the two to be highly associated (19,20). The salience/ventral attention network is linked to multiple components of attention including error monitoring, selective attention, and task switching (10,17). Task-based fMRI studies of selective attention have shown increased activation of the salience/ventral attention network in children with ADHD compared with TDC children (21,22). Functional connectivity within the salience/ventral attention network shows atypical development in children with ASD (23). The salience/ventral attention network also has atypical functional connectivity to other networks in children with ASD compared with TDC children (24). However, to our knowledge, no study has directly assessed whether ADHD symptoms in ASD are associated with abnormalities of functional connectivity of the salience/ventral attention network.

The primary objective of the present study is to examine whether aberrant functional connectivity within and between the frontoparietal and salience/ventral attention networks relates to co-occurring ADHD symptoms in children with ASD. Prior research has implicated these networks as atypical in ASD (23–28), but those studies did not test whether the functional connectivity differences were related to co-occurring ADHD symptoms. Therefore, it is not known whether differences in the frontoparietal and salience networks are strictly related to ASD, or whether they may be related to co-occurring ADHD symptoms. We used resting-state fMRI to measure functional connectivity in children with ASD without an intellectual disability, as well as TDC children. A dimensional index of ADHD symptoms was provided by the parent-reported ADHD rating scale (29). Based on prior literature (16), we hypothesized that a measure of the overall strength of functional connectivity within both the frontoparietal and salience/ventral attention networks would be reduced in ASD and that greater reductions in functional connectivity would be associated with more ADHD symptoms. To assess the specificity of our hypothesis, we also tested for group differences and correlations with a control brain network (visual subnetworks) and a control co-occurring symptom domain (anxiety). We hypothesized that ADHD symptoms would be associated with the salience/ventral attention and frontoparietal but not visual networks and that the salience/ventral attention and frontoparietal networks would not be associated with anxiety symptoms (30).

METHODS AND MATERIALS

Participants

A total of 214 children (111 children with ASD and 103 TDC children) between 6 and 17 years of age completed a resting-state scan across multiple studies at the Center for Autism Research from 2010 to 2014. Children in the ASD group met the DSM-IV-TR criteria for autism, Asperger's syndrome, or pervasive developmental disorder not otherwise specified (31), which was informed by the Autism Diagnostic Interview, Revised (32) and the Autism Diagnostic Observation Schedule (ADOS). We used the revised ADOS algorithm (33) that aligns with the second edition's algorithm (34). DSM-IV-TR criteria were used because data collection started prior to the release of the DSM-5 and we wanted to maintain diagnostic consistency in our sample across this group of studies. Children with ASD were excluded if parents reported that their child had any known genetic, active mood, or psychotic symptoms or neurological disorder; extreme premature birth (gestational age $<$32 weeks); or other significant medical condition that affected functioning or completion of research procedures. TDC participants were excluded if parents reported that their child had any known genetic, language, learning, neurological, or psychiatric disorder; premature birth; any first- or second-degree relative with ASD; or if the child was receiving any psychoactive medication. TDC children were also excluded if they presented scores in the clinical range on the parent-reported Child and Adolescent Symptom Inventory (35). We excluded 4 children with scores below 75 on General Conceptual Ability (analogous to full-scale IQ) as measured by the Differential Ability Scales–Second Edition (36) and 48 children (ASD group n = 28; TDC group n = 20) with a mean framewise displacement $>$0.2 mm during fMRI scanning (37). Three more children (ASD n = 2) were excluded because their global functional connectivity was $>$4 SDs from their own group's mean. Thus, our final sample included 159 children (ASD group n = 77; TDC group n = 82; 7–17 years of age (see Table 1 for group characteristics). Thirty-seven children with ASD were not prescribed medications at the time of the scan (48%), and 7 of the 40 children prescribed medications were prescribed more than one medication. Prescribed medications included stimulants (n = 20), selective serotonin reuptake inhibitors (n = 18), selective norepinephrine reuptake inhibitors (n = 5), α_{2A} agonists (n = 5), an atypical antipsychotic (n = 2), and an aminoketone antidepressant (n = 1). A subset of children prescribed stimulant medication were asked to withhold their medication on the day of scanning to minimize the effects of these medications on brain function (n = 6).

Of note, 20 children in the ASD group did not have an ADHD Rating Scale–Fourth Edition for correlation analyses. The 57 children with ADHD symptom scores did not differ from the 20 missing ADHD symptom scores in age, IQ, gender ratio, ASD or anxiety symptoms, or functional connectivity of any brain

Table 1. Participant Characteristics

	ASD Group (n = 77)	TDC Group (n = 82)	p Value	Hedges' g
Age, Months	149 ± 31	149 ± 33	.94	0.01
General Conceptual Ability Score	108 ± 18	112 ± 17	.16	0.24
Male/Female	60/17	67/15	.69	–
ADOS Social Affect	8.65 ± 3.59	–	–	–
ADOS Repetitive Behaviors	2.30 ± 1.64	–	–	–
ADOS Total Score	10.95 ± 3.72	–	–	–
ADOS Calibrated Severity Score	6.39 ± 2.05	–	–	–
ADHD-IV Rating Scale Total Score	23.84 ± 11.56	4.28 ± 4.53	<.001	2.24
CASI-IV Anxiety Score (20 Items)	12.49 ± 8.18	1.84 ± 2.33	<.001	1.79
In-Scanner Motion (Relative Mean Displacement)	0.10 ± 0.05	0.11 ± 0.04	.29	0.17

Values are mean ± SD or n.

ADOS, Autism Diagnostic Observation Schedule (Revised Algorithm); ASD, autism spectrum disorder; CASI-IV, Child and Adolescent Symptom Inventory–Fourth Edition; TDC, typically developing control.

network, but did have lower in-scanner head motion (mean relative displacement: 0.09 vs. 0.13) (see Supplemental Table S1 for detailed comparison).

Image Acquisition

Functional images were acquired on a 3T Siemens Verio scanner (Siemens Healthineers, Erlangen, Germany) using a T2*-weighted gradient-echo pulse sequence: 160 whole-brain volumes, 40 slices, repetition time = 2340 ms, echo time = 25 ms, flip angle = 60°, voxel size = 3.55-mm isotropic. Thirty-seven children (20 with ASD) received a slightly modified sequence: 172 whole-brain volumes, 36 slices, repetition time = 2110 ms, echo time = 25 ms, flip angle = 60°, voxel size = 3.5-mm isotropic (with a 0.35-mm gap between slices). A high-resolution T1-weighted image for coregistration of the functional images was acquired with an magnetization prepared rapid acquisition gradient-echo sequence: repetition time = 300 ms, echo time = 2.46 ms, voxel size = 1-mm isotropic, flip angle = 60°. Participants were instructed to keep their eyes open and lie still while the monitor displayed a black screen with a gray cross at the center.

Subject-Level Time Series Processing

All functional time series data were preprocessed using a procedure that has been validated in multiple large-scale developmental datasets and has been shown to be highly effective at reducing the influence of motion artifact on functional connectivity data (38–40). Preprocessing included removal of the first four volumes to allow for signal stabilization, slice-time correction, realignment to the median volume, brain extraction, spatial smoothing (7-mm full width at half maximum), and grand mean scaling. Mean white matter and cerebrospinal fluid signals were extracted from the filtered time series data using tissue segments generated for each subject. Confound regression included nine standard confound signals (six motion parameters + global/white matter/cerebrospinal fluid) as well as the temporal derivative, quadratic term, and the temporal derivative of the quadratic term (36 parameters total). We bandpass filtered the functional time series and the confound regressors simultaneously to retain frequencies between 0.01 and 0.08 Hz; identical temporal filtering prevented frequency mismatch between the confound parameters and the time series data (41). A recent benchmarking article comparing more than a dozen preprocessing pipelines for resting-state fMRI data demonstrated that the 36-parameter model is a good choice for pediatric group comparisons compared with other commonly used approaches (37). We also measured in-scanner motion as mean framewise displacement of brain slices. Framewise displacement was calculated by FSL's MCFLIRT software, defined as the relative mean displacement across all rotations and translations (42).

The T1 image was skull-stripped using FSL's BET (43), bias corrected and segmented using FSL's FAST algorithm (44), and registered to the Montreal Neurological Institute template using DRAMMS, a highly accurate deformable registration with attribute matching and mutual salience weighting (45). Processed subject-level echo-planar images were coregistered to the T1 image using boundary-based registration with integrated distortion correction as implemented in FSL5. All registrations were visually inspected.

Brain Networks and Functional Connectivity Analysis

We extracted time series data from a 200-area parcellation scheme of the cortex, which maps to 17 functional networks (19). The functional networks were derived from an independent sample (20), which included three frontoparietal subnetworks and two salience/ventral attention subnetworks. Per Schaefer *et al.* (19), the frontoparietal A subnetwork includes parcels located in the intraparietal sulcus, dorsal and lateral portions of prefrontal cortex, and anterior cingulate cortex (see Figure 1 and Supplemental Table S2 for comprehensive list of parcels for all subnetworks). The frontoparietal B subnetwork includes parcels in the lateral and ventrolateral portions of prefrontal cortex, lateral temporal cortex, and intraparietal lobule. The frontoparietal C network includes the precuneus and posterior cingulate cortex. The salience/ventral attention A subnetwork includes parcels located in the insula, medial parietal (operculum), and supplementary motor area (also referred to as the juxtapositional cortex and medial prefrontal cortex in the Harvard-Oxford cortical atlas). The salience/ventral attention B subnetwork includes parcels in the intraparietal lobule,

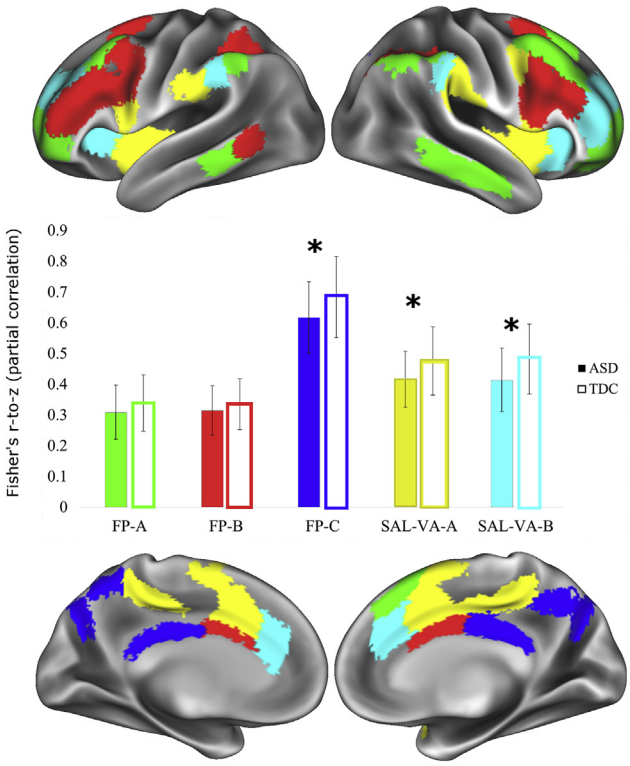

Figure 1. The three frontoparietal and two salience/ventral attention subnetworks are shown here on an inflated brain on the 32,000-vertex Conte atlas available with Workbench. Green indicates frontoparietal A (FP-A), red indicates frontoparietal B (FP-B), dark blue indicates frontoparietal C (FP-C), yellow indicates salience/ventral attention A (SAL-VA-A), and light blue indicates salience/ventral attention B (SAL-VA-B). The bar graph in the middle shows the means of group differences for within-subnetwork functional connectivity and the error bars represent the standard deviations. Significant group differences with Welch's two-group *t* test, Bayesian analysis, and analysis of covariance surviving false discovery rate (FDR) correction are denoted with an asterisk. The autism spectrum disorder (ASD) group had significantly weaker functional connectivity within three subnetworks: FP-C ($t_{156.35}$ = 3.39, FDR-corrected p = .004, Hedges' g = 0.53 [95% confidence interval, 0.028–0.106]), SAL-VA-A ($t_{154.24}$ = 3.65, FDR-corrected p = .003, Hedges' g = 0.573 [95% confidence interval, 0.027–0.091]), and SAL-VA-B ($t_{156.9}$ = 3.98, FDR-corrected p = .002, Hedges' g = 0.627 [95% confidence interval, 0.034–0.102]). TDC, typically developing control.

lateral prefrontal cortex, and supplementary motor area (or medial prefrontal cortex). The visual peripheral network includes parcels in the superior extrastriate cortex (BA 18/19). The visual central network includes parcels in the extrastriate cortex (BA 18/19/30/31). All parcels by definition are nonoverlapping even if they lie within similarly labeled regions of cortex. We estimated functional connectivity between all parcels of interest to create an 87 × 87 functional connectivity matrix, which represents pairwise Pearson's correlations between all pairs of parcels.

We calculated the mean overall functional connectivity within and between the five a priori subnetworks after transforming the entire matrix into z-scores using Fisher's *r*-to-*z* transformation, yielding a total of 15 variables (mean within- and between-subnetwork functional connectivity). We compared each of those 15 variables between the ASD and TDC groups with a Welch's two-group *t* test; the false discovery rate (FDR) was used to correct for multiple comparisons for an overall $p < .05$ (46). We report Hedges' g for effect size and 95% confidence interval (CI) of the difference in group means in brackets.

As a means of increasing scientific rigor, we conducted two additional analyses owing to growing concerns regarding reproducibility of findings in psychology and related fields (47). We estimated the difference in group means using the Bayesian Estimation Supersedes the *t* test (48) algorithm implemented in the Bayesian First Aid package (49); we report group means, difference of the means, and standard deviations with their 95% credibility intervals, as well as an associated p value. We also conducted analyses of covariance to control for confounds that may covary with ADHD symptoms (age [linear, quadratic, and cubic effects], gender, IQ, echo-planar sequence, and relative mean displacement to capture residual effects of head motion). Initial models included all covariates, and nonsignificant covariates were dropped from the final models. We report η_p^2 as the effect size for these models. These additional analyses are reported in Supplemental Tables S3 and S4.

Symptom Analysis

We tested associations between ADHD symptoms and subnetworks that differed among the ASD and TDC groups. For rigor, we then conducted follow-up analyses to control for potential confounds (ASD symptoms and residual motion), as well as using an alternative statistical approach (Bayesian). Finally, we had two control analyses, one using a different brain network (vision) and another using a different symptom domain (anxiety), to demonstrate the specificity of our findings. We used the Pearson correlation coefficient for initial analysis and partial correlations to account for variance related to ASD symptoms or for variance related to residual motion (relative mean displacement). We utilized the raw scores from the ADHD Rating Scale–Fourth Edition (0–54) and the 20 anxiety items in ASD from the Child and Adolescent Symptom Inventory (0–60) as dimensional measures of ADHD and anxiety symptoms because both have been validated in pediatric ASD samples (50,51). We included the ADOS calibrated severity score (52,53) in partial correlations because this study required the use of more than one ADOS module. Bayesian estimation was used again for the Pearson correlation to demonstrate robustness of findings across statistical approaches.

A secondary analysis explored whether the relationships between ADHD symptoms and frontoparietal and salience/ventral attention subnetworks were independent or overlapping. The first step was a Pearson correlation between the functional connectivity strength of the salience/ventral attention B subnetwork and the functional connectivity strength between the frontoparietal A and frontoparietal C subnetworks. The second step included a series of linear regressions to determine if the salience/ventral attention B subnetwork and frontoparietal A to frontoparietal C subnetwork explained unique variance in ADHD symptoms. All analyses were calculated using the R statistical package version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria) and the

following packages: nlme, lmSupport, psych, stats, effsize, ggplot2, BayesianFirstAid.

RESULTS

As seen in Table 1, groups were matched on chronological age, male/female ratio, General Conceptual Ability score, and in-scanner head motion.

Group Analyses Reveal Weaker Functional Connectivity in the ASD Group Compared With the TDC Group for the Frontoparietal and Salience/Ventral Attention Networks

The ASD group had significantly weaker functional connectivity than the TDC group within the frontoparietal and within salience ventral-attention subnetworks (see Figure 1). Relative to the TDC group, functional connectivity was weaker for the ASD group for regions within frontoparietal C subnetwork ($t_{156.35}$ = 3.39, FDR-corrected p = .004, Hedges' g = 0.53 [95% CI, 0.028–0.106]). The ASD group had weaker functional connectivity between frontoparietal A and frontoparietal C subnetworks compared with the TDC group ($t_{137.7}$ = 2.78, FDR-corrected p = .023, Hedges' g = 0.43 [95% CI, 0.009–0.057]). The ASD group had weaker functional connectivity than the TDC group within the salience/ventral attention subnetworks: salience/ventral attention A ($t_{154.24}$ = 3.65, FDR-corrected p = .003, Hedges' g = 0.573 [95% CI, 0.027–0.091]), salience/ventral attention B ($t_{156.9}$ = 3.98, FDR-corrected p = .002, Hedges' g = 0.627 [95% CI, 0.034–0.102]). All other subnetworks within the frontoparietal network had FDR-corrected $p > .05$ (see Supplemental Table S5).

Compared with the TDC group, the ASD group had weaker functional connectivity between the frontoparietal A and salience/ventral attention B subnetworks ($t_{156.59}$ = 2.43, FDR-corrected p = .049, Hedges' g = 0.382 [95% CI, 0.006–0.066]). All other group comparisons of functional connectivity among the frontoparietal and salience/ventral attention subnetworks had weak effects and were nonsignificant (FDR-corrected $p > .05$) (see Supplemental Table S5).

Our two additional analyses to enhance scientific rigor largely supported the primary analyses reported above. The Bayesian analyses replicated all group differences reported above (Supplemental Table S3). The analysis of covariance replicated all group differences except the finding that the ASD group had weaker functional connectivity between the frontoparietal A and frontoparietal C subnetworks compared with the TDC group; this effect was weaker and marginally significant after applying FDR correction (Supplemental Table S4 contains results and covariates that were retained in final models).

Symptom Analyses in ASD Reveal That Frontoparietal and Salience/Ventral Attention Differences Are Related to ADHD Symptoms but Not to Each Other

For the ASD group, increased symptoms of ADHD were associated with decreased functional connectivity strength within the salience/ventral attention B subnetwork ($r_{55} = -.29$, $p < .05$) and with the functional connectivity between the frontoparietal A and frontoparietal C subnetworks ($r_{55} = -.27$, $p < .05$) (Figure 2A, B). The results were largely unaffected when ASD symptoms or residual head motion were entered as covariates in partial correlations or when a Bayesian correlational approach was used (see Supplemental Table S6). Correlations of ADHD symptoms with the other three subnetworks were not significant (all $r < .15$, $p > .33$).

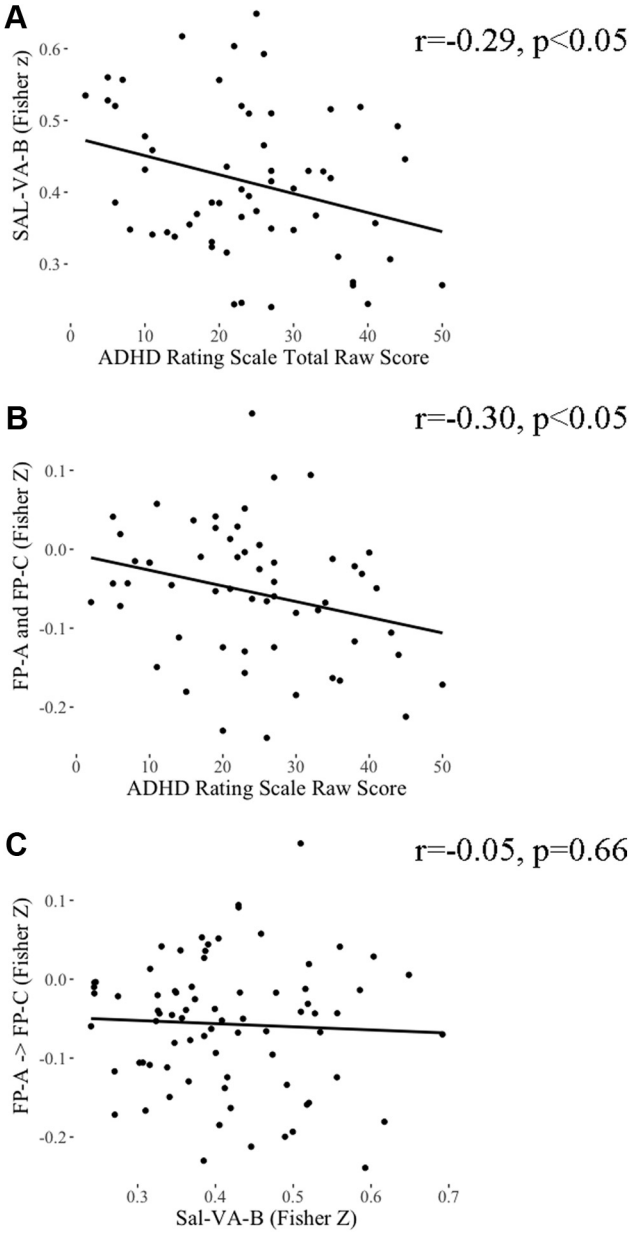

Figure 2. Scatterplots of the autism spectrum disorder group showing **(A)** the relationship between attention-deficit/hyperactivity disorder (ADHD) symptoms and functional connectivity within the salience/ventral attention network B (SAL-VA-B) subnetwork, **(B)** the relationship between ADHD symptoms and functional connectivity between the frontoparietal A (FP-A) and frontoparietal C (FP-C) subnetworks, and **(C)** the lack of a relationship between functional connectivity strength within the SAL-VA-B subnetwork and the functional connectivity strength between the FP-A and FP-C subnetworks.

Our secondary analysis within the ASD group revealed weak and nonsignificant relationships between functional connectivity strength within the salience/ventral attention B subnetwork and functional connectivity strength between the frontoparietal A and frontoparietal C subnetworks ($r_{75} = -.05$, $p = .66$; Bayesian: $r_{77} = -.05$, $p = .665$ [95% CI, −0.28 to 0.18]). Furthermore, linear regressions showed that both of these functional connectivity differences in children with ASD explained significant, independent variance in ADHD symptoms (multiple $R^2 = .156$, $F_{2,54} = 5.00$, $p < .05$) (see Table 2 for details).

Control Analyses Reveal That Visual Networks Do Not Differ in Functional Connectivity Between Groups or Associate With ADHD Symptoms in ASD and That Anxiety Symptoms Are Not Associated With Functional Connectivity Strength in the Frontoparietal and Salience/Ventral Attention Networks

Follow-up control analyses revealed no group differences in the visual networks (FDR-corrected p values $> .05$) (see Supplemental Table S5). Furthermore, functional connectivity within visual subnetworks were not correlated with ADHD symptoms. Finally, anxiety symptoms were not correlated with functional connectivity within the two salience/ventral attention subnetworks or the functional connectivity between the frontoparietal A and frontoparietal C subnetworks (all $r < .19$, $p > .11$).

Table 2. Linear Regressions of the Frontoparietal and Salience/Ventral Attention Subsystems Explaining ADHD Symptoms

	ADHD Symptoms			
Predictor	*B*	SE *B*	*t (df)*	R^2
Frontoparietal Subsystem				
Model 1				
FP-A to FP-C	−36.61	17.63	−2.08[a] (1,55)	.073
Model 2				
FP-A to FP-C	−35.83	16.98	−2.11[a] (2,54)	
SAL-VA-B	−32.19	13.92	−2.31[a] (2,54)	.156
Salience/Ventral Attention Subsystem				
Model 1				
SAL-VA-B	−32.78	14.35	−2.29[a] (1,55)	.087
Model 2				
SAL-VA-B	−32.19	13.92	−2.31[a] (2,54)	
FP-A to FP-C	−35.83	16.98	−2.11[a] (2,54)	.156

Owing to rounding, R^2 is slightly less than the summing the individual effect of each predictor.

ADHD, attention-deficit/hyperactivity disorder; FP-A, frontoparietal A; FP-C, frontoparietal C; SAL-VA-B, salience/ventral attention B.

[a]$p < .05$.

DISCUSSION

To our knowledge, this study is the first to associate ADHD symptoms in ASD with changes in large-scale, executive brain networks. In a large, single-site sample of children with ASD that have a range of ADHD symptoms, results indicate that both frontoparietal and salience/ventral attention subnetworks have weaker functional connectivity in children with ASD compared with children with typical development. Even after controlling for core ASD symptoms, functional connectivity in frontoparietal and salience/ventral attention subnetworks was significantly associated with co-occurring ADHD symptoms, but not with anxiety symptoms. Using visual subnetworks as control subnetworks, no group differences were observed in functional connectivity, and visual subnetworks were not significantly correlated with ADHD symptoms. Additional Bayesian analyses for statistical rigor supported the primary findings.

Our findings that the frontoparietal and salience/ventral attention networks differ in the strength of their functional connectivity in children with ASD relative to typical development are consistent with an accumulating literature on atypical functional connectivity of large-scale executive networks during rest (23,25,26,54) and task conditions (16,24,27,28,55).

The current study extends these findings in a number of important ways. First, it extends the relationship of ADHD symptoms and the salience/ventral attention network into the ASD population. In particular, our study showed that both of the salience/ventral attention subnetworks had weaker functional connectivity strength in the ASD group compared with the TDC group. This finding converges with evidence that the salience/ventral attention network plays a role in ADHD symptoms for those children without ASD (22). It also converges with a critical review of animal literature implicating the network in complex forms of attention (56). Prior research on the salience/ventral attention network in ASD ranged from social and sociocognitive processes (26,57–59) to behavioral flexibility (24). However, the present study also expands the scope into the co-occurrence with ADHD symptoms, which was specifically related to the ventral attention subnetwork. This finding is also consistent with the Research Domain Criteria initiative from the National Institute of Mental Health that ascribes all of psychopathology to five major dimensions of neurobiology and behavior that cut across diagnostic boundaries (60,61). Findings from the present study fall in the Cognitive Systems research domain and support the idea that differences in cognitive control associate with ADHD symptoms regardless of whether a child has a formal diagnosis of ADHD or not.

Second, this study demonstrates both reduced functional connectivity of the frontoparietal network in resting-state data and a relationship with ADHD symptoms. Our findings converged with prior task-based functional connectivity data showing weaker frontoparietal network functional connectivity in children with ASD compared with TDC children. Furthermore, this diminished functional connectivity was associated with ADHD symptoms (16).

Third, our finding that the salience/ventral attention and frontoparietal networks explained unique variance in ADHD symptoms suggests that that these two networks may not be affected in the same children. An alternative possibility is that these two networks are correlated, but these relationships may be suppressed by a subset of children with ASD whose co-occurring ADHD symptoms are adding “noise” and suppressing the relationship between the networks. Finally, our use of visual subnetworks and anxiety symptoms as negative control subnetworks for nonexecutive networks and co-occurring symptoms is innovative because it demonstrates that the relationship between executive brain networks and ADHD

symptoms is not the result of some general feature about functional connectivity or co-occurring symptoms in ASD.

The present study has some limitations. Our sample's IQ range had a lower bound of 75, a common problem among resting-state functional connectivity studies (62); however, the IQ score threshold was scientifically motivated in the present study because the ADHD Rating Scale–Fourth Edition has not yet been validated in those with ASD and an intellectual disability (51). At first glance, this study might appear to be inconsistent with our prior publication in which we demonstrated an atypical topography of the ventral attention network in ASD (54). However, our prior investigation demonstrated globally weaker connectivity overall before examining topography. Thus, our current findings of weaker functional connectivity in the salience/ventral attention and frontoparietal networks align with our prior finding that absolute functional connectivity is weaker in ASD. The present study had a wide age range; however, the ages of participants were not equally distributed across the range, which limited our ability to look at age-by-group interactions in functional connectivity. Future longitudinal investigations would be best placed to examine this question. There may be some concern that using the calibration severity score from the ADOS may not be an ideal symptom measure for correlations owing to its ordinal, noncontinuous nature; however, recent efforts have shown that other dimensional measures like the Social Responsiveness Scale are sensitive to ADHD symptoms in both ADHD samples (63) and ASD samples (2,64). Thus, we elected to not use a measure that would have knowingly removed variance of interest. Finally, the present study implicates both the frontoparietal and salience/ventral attention networks at the group level; future work should seek to identify how one or both networks are associated with ADHD symptoms at the individual level.

The present findings open an avenue of research to further define the neural networks underlying co-occurring ADHD symptoms in ASD. Future research will need to define brain and behavioral profiles related to cognitive control and other processes affected in ADHD (e.g., working memory). Developing neurobiologically and cognitively homogeneous subgroups of children with ASD will allow us to optimize treatments—both pharmacological and behavioral—for specific subgroups of children. Doing so will reduce co-occurring ADHD symptoms and improve long-term outcomes for people with ASD.

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REFERENCES

1. Sikora DM, Vora P, Coury DL, Rosenberg D (2012): Attention-deficit/hyperactivity disorder symptoms, adaptive functioning, and quality of life in children with autism spectrum disorder. Pediatrics 130(suppl 2): S91–S97.
2. Yerys BE, Wallace GL, Sokoloff JL, Shook DA, James JD, Kenworthy L (2009): Attention deficit/hyperactivity disorder symptoms moderate cognition and behavior in children with autism spectrum disorders. Autism Res 2:322–333.
3. Yerys BE, Bertollo JR, Pandey J, Guy L, Schultz RT (in press): ADHD symptoms associates with lower adaptive behavior skills in youth with autism. J Am Acad Child Adolesc Psychiatry.
4. Research Units on Pediatric Psychopharmacology Autism Network (2005): Randomized, controlled, crossover trial of methylphenidate in pervasive developmental disorders with hyperactivity. Arch Gen Psychiatry 62:1266–1274.
5. Scahill L, McCracken JT, Rockhill C, Shah B, Politte L, Sanders R, *et al.* (2015): Extended-release guanfacine for hyperactivity in children with autism spectrum disorder. Am J Psychiatry 172:1197–1206.
6. Willcutt EG, Doyle AE, Nigg JT, Faraone SV, Pennington BF (2005): Validity of the executive function theory of attention-deficit/hyperactivity disorder: A meta-analytic review. Biol Psychiatry 57:1336–1346.

7. Pennington BF, Ozonoff S (1996): Executive functions and developmental psychopathology. J Child Psychol Psychiatry 37:51–87.
8. Fair DA, Bathula D, Nikolas MA, Nigg JT (2012): Distinct neuropsychological subgroups in typically developing youth inform heterogeneity in children with ADHD. Proc Natl Acad Sci U S A 109:6769–6774.
9. Menon V (2011): Large-scale brain networks and psychopathology: A unifying triple network model. Trends Cogn Sci 15:483–506.
10. Menon V, Uddin LQ (2010): Saliency, switching, attention and control: A network model of insula function. Brain Struct Funct 214:655–667.
11. Rubia K, Overmeyer S, Taylor E, Brammer M, Williams SCR, Simmons A, Bullmore ET (1999): Hypofrontality in attention deficit hyperactivity disorder during higher-order motor control: A study with functional MRI. Am J Psychiatry 156:891–896.
12. Vaidya CJ, Bunge SA, Dudukovic NM, Zalecki CA, Elliott GR, Gabrieli JDE (2005): Altered neural substrates of cognitive control in childhood ADHD: Evidence from functional magnetic resonance imaging. Am J Psychiatry 162:1605–1613.
13. Scheres A, Oosterlaan J, Swanson J (2003): The effect of methylphenidate on three forms of response inhibition in boys with AD/HD. J Abnorm Child Psychol 31:105–120.
14. Vaidya CJ, Austin G, Kirkorian G, Ridlehuber HW, Desmond JE, Glover GH, Gabrieli JD (1998): Selective effects of methylphenidate in attention deficit hyperactivity disorder: A functional magnetic resonance study. Proc Natl Acad Sci U S A 95:14494–14499.
15. Yang Z, Kelly C, Castellanos FX, Leon T, Milham MP, Adler LA (2016): Neural correlates of symptom improvement following stimulant treatment in adults with attention-deficit/hyperactivity disorder. J Child Adolesc Psychopharmacol 26:527–536.
16. Solomon M, Ozonoff S, Ursu S, Ravizza S, Cummings N, Ly S, Carter CS (2009): The neural substrates of cognitive control deficits in autism spectrum disorders. Neuropsychologia 47:2515–2526.
17. Fox MD, Corbetta M, Snyder AZ, Vincent JL, Raichle ME (2006): Spontaneous neuronal activity distinguishes human dorsal and ventral attention systems. Proc Natl Acad Sci U S A 103:10046–10051.
18. Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, *et al.* (2007): Dissociable intrinsic connectivity networks for salience processing and executive control. J Neurosci 27:2349–2356.
19. Schaefer A, Kong R, Gordon EM, Laumann TO, Zuo X-N, Holmes AJ, *et al.* (2018): Local-global parcellation of the human cerebral cortex from intrinsic functional connectivity MRI. Cereb Cortex 28:3095–3114.
20. Yeo BTT, Krienen FM, Sepulcre J, Sabuncu MR, Lashkari D, Hollinshead M, *et al.* (2011): The organization of the human cerebral cortex estimated by intrinsic functional connectivity. J Neurophysiol 106:1125–1165.
21. Carter CS, Krener P, Chaderjian M, Northcutt C, Wolfe V (1995): Abnormal processing of irrelevant information in attention deficit hyperactivity disorder. Psychiatry Res 56:59–70.
22. Tegelbeckers J, Bunzeck N, Duzel E, Bonath B, Flechtner H-H, Krauel K (2015): Altered salience processing in attention deficit hyperactivity disorder: Novelty processing in ADHD. Hum Brain Mapp 36:2049–2060.
23. Farrant K, Uddin LQ (2016): Atypical developmental of dorsal and ventral attention networks in autism. Dev Sci 19:550–563.
24. Uddin LQ, Supekar K, Lynch CJ, Cheng KM, Odriozola P, Barth ME, *et al.* (2015): Brain state differentiation and behavioral inflexibility in autism. Cereb Cortex 25:4740–4747.
25. Elton A, Di Martino A, Hazlett HC, Gao W (2016): Neural connectivity evidence for a categorical-dimensional hybrid model of autism spectrum disorder. Biol Psychiatry 80:120–128.
26. Uddin LQ, Supekar K, Lynch CJ, Khouzam A, Phillips J, Feinstein C, *et al.* (2013): Salience network-based classification and prediction of symptom severity in children with autism. JAMA Psychiatry 70:869–879.
27. Lee PS, Yerys BE, Della Rosa A, Foss-Feig J, Barnes KA, James JD, *et al.* (2009): Functional connectivity of the inferior frontal cortex changes with age in children with autism spectrum disorders: A fcMRI study of response inhibition. Cereb Cortex 19:1787–1794.
28. Odriozola P, Uddin LQ, Lynch CJ, Kochalka J, Chen T, Menon V (2016): Insula response and connectivity during social and non-social attention in children with autism. Soc Cogn Affect Neurosci 11:433–444.
29. DuPaul GJ, Power TJ, Anastopoulos AD, Reid R (1998): ADHD Rating Scale-IV: Checklists, Norms, and Clinical Interpretation. New York: Guilford Press.
30. Kerns CM, Maddox BB, Kendall PC, Rump K, Berry L, Schultz RT, *et al.* (2015): Brief measures of anxiety in non-treatment-seeking youth with autism spectrum disorder. Autism 19:969–979.
31. American Psychiatric Association (2000): Diagnostic and Statistical Manual of Mental Disorders, 4th ed rev. Washington, DC: American Psychiatric Press.
32. Lord C, Rutter M, Le Couteur A (1994): Autism Diagnostic Interview-Revised: A revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. J Autism Dev Disord 24:659–685.
33. Gotham K, Risi S, Pickles A, Lord C (2007): The Autism Diagnostic Observation Schedule: Revised algorithms for improved diagnostic validity. J Autism Dev Disord 37:613–627.
34. Lord C, Rutter M, DiLavore PC, Risi S, Gotham K, Bishop S (2012): Autism Diagnostic Observation Schedule, second edition (ADOS-2) manual (Part I): Modules 1-4. Torrance, CA: Western Psychological Services.
35. Gadow KD, Sprafkin J (2010): Child & Adolescent Symptom Inventory - Fourth Edition Revised. Stony Brook, NY: Checkmate Plus.
36. Elliott CD (2007): Differential Ability Scales-II (DAS-II). San Antonio, TX: Pearson Assessments.
37. Ciric R, Wolf DH, Power JD, Roalf DR, Baum GL, Ruparel K, *et al.* (2017): Benchmarking of participant-level confound regression strategies for the control of motion artifact in studies of functional connectivity. Neuroimage 154:174–187.
38. Satterthwaite TD, Wolf DH, Loughead J, Ruparel K, Elliott MA, Hakonarson H, *et al.* (2012): Impact of in-scanner head motion on multiple measures of functional connectivity: Relevance for studies of neurodevelopment in youth. Neuroimage 60:623–632.
39. Satterthwaite TD, Elliott MA, Gerraty RT, Ruparel K, Loughead J, Calkins ME, *et al.* (2013): An improved framework for confound regression and filtering for control of motion artifact in the preprocessing of resting-state functional connectivity data. Neuroimage 64:240–256.
40. Satterthwaite TD, Wolf DH, Ruparel K, Erus G, Elliott MA, Eickhoff SB, *et al.* (2013): Heterogeneous impact of motion on fundamental patterns of developmental changes in functional connectivity during youth. Neuroimage 83:45–57.
41. Hallquist MN, Hwang K, Luna B (2013): The nuisance of nuisance regression: Spectral misspecification in a common approach to resting-state fMRI preprocessing reintroduces noise and obscures functional connectivity. Neuroimage 82C:208–225.
42. Jenkinson M, Bannister P, Brady M, Smith S (2002): Improved optimization for the robust and accurate linear registration and motion correction of brain images. Neuroimage 17:825–841.
43. Popescu V, Battaglini M, Hoogstrate WS, Verfaillie SCJ, Sluimer IC, van Schijndel RA, *et al.* (2012): Optimizing parameter choice for FSL-Brain Extraction Tool (BET) on 3D T1 images in multiple sclerosis. Neuroimage 61:1484–1494.
44. Zhang Y, Brady M, Smith S (2001): Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm. IEEE Trans Med Imaging 20:45–57.
45. Ou Y, Sotiras A, Paragios N, Davatzikos C (2011): DRAMMS: Deformable registration via attribute matching and mutual-saliency weighting. Med Image Anal 15:622–639.
46. Benjamini Y, Hochberg Y (1995): Controlling the false discovery rate: A practical and powerful approach to multiple testing. J R Stat Soc Series B Stat Methodol 57:289–300.
47. Open Science Collaboration (2015): PSYCHOLOGY. Estimating the reproducibility of psychological science. Science 349:aac4716.
48. Kruschke JK (2013): Bayesian estimation supersedes the t test. J Exp Psychol Gen 142:573–603.
49. Bååth R (2014): Bayesian first aid. Available at: http://www.sumsar.net/blog/2014/01/bayesian-first-aid/. Accessed June 7, 2018.

50. Sukhodolsky DG, Scahill L, Gadow KD, Arnold LE, Aman MG, McDougle CJ, *et al.* (2008): Parent-rated anxiety symptoms in children with pervasive developmental disorders: Frequency and association with core autism symptoms and cognitive functioning. J Abnorm Child Psychol 36:117–128.
51. Yerys BE, Nissley-Tsiopinis J, de Marchena A, Watkins MW, Antezana L, Power TJ, Schultz RT (2017): Evaluation of the ADHD Rating Scale in youth with autism. J Autism Dev Disord 47:90–100.
52. Gotham K, Pickles A, Lord C (2009): Standardizing ADOS scores for a measure of severity in autism spectrum disorders. J Autism Dev Disord 39:693–705.
53. Hus V, Lord C (2014): The Autism Diagnostic Observation Schedule, Module 4: Revised algorithm and standardized severity scores. J Autism Dev Disord 44:1996–2012.
54. Yerys BE, Herrington JD, Satterthwaite TD, Guy L, Schultz RT, Bassett DS (2017): Globally weaker and topologically different: Resting-state connectivity in youth with autism. Mol Autism 8:39.
55. von dem Hagen EAH, Stoyanova RS, Baron-Cohen S, Calder AJ (2013): Reduced functional connectivity within and between "social" resting state networks in autism spectrum conditions. Soc Cogn Affect Neurosci 8:694–701.
56. Mueller A, Hong DS, Shepard S, Moore T (2017): Linking ADHD to the neural circuitry of attention. Trends Cogn Sci 21:474–488.
57. Burrows CA, Timpano KR, Uddin LQ (2017): Putative brain networks underlying repetitive negative thinking and comorbid internalizing problems in autism. Clin Psychol Sci 5:522–536.
58. Uddin LQ, Menon V (2009): The anterior insula in autism: under-connected and under-examined. Neurosci Biobehav Rev 33:1198–1203.
59. Hogeveen J, Krug MK, Elliott MV, Solomon M (2018): Insula-retrosplenial cortex overconnectivity increases internalizing via reduced insight in autism. Biol Psychiatry 84:287–294.
60. National Advisory Mental Health Council Workgroup on Tasks and Measures for Research Domain Criteria (2016): Behavioral Assessment Methods for RDoC Constructs: A report by the National Advisory Mental Health Council Workgroup on Tasks and Measures for Research Domain Criteria. Bethesda, MD: National Institute of Mental Health.
61. Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, *et al.* (2010): Research domain criteria (RDoC): Toward a new classification framework for research on mental disorders. Am J Psychiatry 167:748–751.
62. Uddin LQ, Dajani DR, Voorhies W, Bednarz H, Kana RK (2017): Progress and roadblocks in the search for brain-based biomarkers of autism and attention-deficit/hyperactivity disorder. Transl Psychiatry 7:e1218.
63. Reiersen AM, Constantino JN, Volk HE, Todd RD (2007): Autistic traits in a population-based ADHD twin sample. J Child Psychol Psychiatry 48:464–472.
64. Factor RS, Ryan SM, Farley JP, Ollendick TH, Scarpa A (2017): Does the presence of anxiety and ADHD symptoms add to social impairment in children with autism spectrum disorder? J Autism Dev Disord 47:1122–1134.