

Original Investigation

Attention Network Hypoconnectivity With Default and Affective Network Hyperconnectivity in Adults Diagnosed With Attention-Deficit/Hyperactivity Disorder in Childhood

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IMPORTANCE The neurobiological underpinnings of attention-deficit/hyperactivity disorder (ADHD) and particularly those associated with the persistence of ADHD into adulthood are not yet well understood. The correlation patterns in spontaneous neural fluctuations at rest are known as resting-state functional connectivity (RSFC) and could characterize ADHD-specific connectivity changes.

OBJECTIVE To determine the specific location of possible ADHD-related differences in RSFC between adults diagnosed as having ADHD in childhood and control subjects.

DESIGN Using resting-state functional magnetic resonance imaging, we calculated and compared functional connectivity from attention, affective, default, and cognitive control networks involved in the psychopathology of ADHD between the ADHD and control groups.

SETTING University psychiatric service and magnetic resonance imaging research center.

PARTICIPANTS Sixteen drug-free adults (5 women and 11 men; mean age, 24.5 years) diagnosed with combined-type ADHD in childhood and 16 healthy controls matched for age (mean age, 24.4 years), sex, handedness, and educational level recruited from the community.

INTERVENTION Functional magnetic resonance imaging.

MAIN OUTCOMES AND MEASURES Connectivity data from ventral and dorsal attention, affective, default, and cognitive control networks and ADHD symptoms derived from ADHD-specific rating instruments.

RESULTS Adults with ADHD showed significantly decreased RSFC within the attention networks and increased RSFC within the affective and default mode and the right lateralized cognitive control networks compared with healthy controls ($P < .01$, familywise error for whole-brain cluster correction). Lower RSFC in the ventral and dorsal attention network was significantly correlated with higher levels of ADHD symptoms ($P < .001$).

CONCLUSIONS AND RELEVANCE These RSFC findings might underpin a biological basis for adult ADHD and are functionally related to persistent inattention, disturbance in cognitive control, and emotional dysregulation in adults with ADHD. These findings need to be understood in the context of all aspects of brain function in ADHD.

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Attention deficit-hyperactivity/disorder (ADHD) is characterized by the onset of developmentally inappropriate levels of impaired inattention, hyperactivity, and impulsivity before the age of 7 years.¹ Attention deficit-hyperactivity/disorder is one of the most common mental disorders, with a worldwide prevalence estimate of 5.29% and a heritability estimate of about 76%.² Attention deficit-hyperactivity/disorder is no longer considered a disorder exclusive to childhood; Faraone et al³ estimate that 15% of adults with a previous diagnosis of childhood ADHD meet the full criteria for ADHD, 65% show partial remission, and only 20% show complete remission in adulthood.

Accurately diagnosing ADHD in adults is difficult, because the diagnostic criteria for ADHD are founded on research conducted among individuals aged 4 to 17 years.⁴ The clinical presentation of ADHD changes with increasing age³; the hyperactive and impulsive symptoms of childhood ADHD become less pronounced, whereas inattentive symptoms persist.⁵ Emotional dysregulation and disorganization characteristically accompany persistent inattentive symptoms in adult ADHD.⁶ Attention-deficit/hyperactivity disorder in adulthood is socially and occupationally debilitating and is significantly associated with comorbid depression, anxiety, and substance abuse.⁴

Neuroimaging may provide some insights into the neurobiological underpinnings of the persistence and remission of ADHD symptoms during the disease course from childhood to adulthood. Most ADHD-related functional magnetic resonance imaging (fMRI) differences have been found in task-based studies.⁷ Researchers have proposed that ADHD-related deficiencies in functional circuits, identified through task-based fMRI studies, may sculpt the topography of resting-state networks.^{8,9} Thus, a growing interest in the use of resting-state fMRI, which does not require the use of a task, has become a popular means of complementing the results of task-based fMRI studies while providing a new perspective on the psychopathology of ADHD.¹⁰

Resting-state fMRI allows for the examination of large-scale neural systems that exhibit spontaneous synchronous fluctuations during goal-directed behavior and non-goal-directed behaviors such as wakeful rest, sleep, and anesthesia.⁹ These low-frequency (<0.1 Hz) spontaneous fluctuations in blood oxygen level-dependent (BOLD) signal correlate with interactions between adjacent and nonadjacent brain areas that form spatially distributed networks of brain function.¹¹ Functional connectivity is the observed correlation in spontaneous neural activity between brain areas at rest.⁸

To improve our understanding of resting-state functional connectivity (RSFC) in adults with a childhood diagnosis of ADHD, we extracted the coordinates for regions of interest involved in the psychopathological features of ADHD¹² from 5 neural networks.^{13,14} These coordinates were used as correlates with all other time series in the brain to determine temporally coherent networks of RSFC.¹⁴

The first network included was the affective network. This network contains integrated regions of the affective subdivision of the anterior cingulate cortex (ACC), amygdala, nucleus accumbens, hypothalamus, anterior insula, hippocampus, and

orbitofrontal cortex, with reciprocal connections to autonomic, visceromotor, and endocrine systems.¹⁴ This network is involved in emotional regulation and monitoring of the salience of motivational stimuli.¹⁴ Affective disorders are highly comorbid with adult ADHD,⁴ and previous resting-state studies examining affective disorders and children with ADHD have found increased connectivity compared with controls within affective network regions, which were attributed to emotional control deficits.¹⁴⁻¹⁶ These findings suggest increased sensitivity to affective stimuli in ADHD.¹⁷ Heightened functional connectivity for participants with ADHD compared with control subjects within this network was anticipated.

The second network, the ventral attention network, uses the temporoparietal junction (TPJ) and ventral frontal cortex (VFC) to reorient attention to salient behaviorally relevant stimuli.¹³ A recent meta-analysis of task-based fMRI studies found that an ADHD group had consistently hypoactivated ventral attention network regions compared with a control group in tasks requiring manipulation of attention in response to target stimuli.¹² Because the neural deficits apparent during task-based studies in ADHD may indicate an RSFC deficit,⁸ hypoconnectivity throughout this network was expected.

The third network, the bilateral dorsal attention network, uses regions such as the intraparietal sulcus (IPS) and the frontal eye field (FEF) to enable the control of spatial attention through the selection of sensory stimuli based on internal goals or expectations and links them to appropriate motor responses.¹³ A meta-analysis of fMRI task studies¹² showed that for participants with ADHD, intraparietal regions of the dorsal attention network were routinely hypoactivated. In addition, reduced functional connectivity of the dorsal attention network has been found in resting-state fMRI studies of child and adult samples with ADHD.^{18,19} Thus, we assumed that the ADHD group would elicit hypoconnectivity compared with the control group within this network.

The fourth network, the cognitive control network, uses regions such as the bilateral dorsolateral prefrontal cortex (DLPFC), presupplementary motor area, inferior frontal junction, anterior insular cortex, dorsal premotor cortex, and posterior parietal cortices.²⁰ This network is involved in inhibition and goal-directed decision making, which is impaired in ADHD.²¹ A recent meta-analysis²² of inhibition and attentional tasks found DLPFC activity to be reduced in participants with ADHD compared with controls. At rest, the ADHD group previously displayed decreased functional connectivity involving this network compared with controls.²³ These results suggest that use of this network is diminished in the participants with ADHD compared with controls.²³

The fifth network is the default mode network, which contains the precuneus/posterior cingulate cortex, medial prefrontal cortex, and dorsal ACC and acts as a form of functional connectivity baseline thought to reflect intrinsic brain activity.⁸ Typically, the spontaneous fluctuations emitted by the default mode network are routinely heightened at rest and are then reduced during goal-directed tasks that activate frontal attentional networks.⁹ Resting-state studies^{21,24,25} investigating the default mode network in ADHD found heterogeneous results in the form of reduced functional connectivity

between the medial prefrontal cortex and the posterior cingulate/precuneus cortices within the default mode network in participants with ADHD compared with controls. Also, connectivity was increased between the default mode network and sensory brain regions in participants with ADHD compared with controls.¹⁵ Therefore, we aimed to confirm reduced functional connectivity within default mode regions and increased connectivity between the default mode network and the sensory regions.

The aim of this study was to explore RSFC in ADHD and to determine the localization and specificity of ADHD-related connectivity differences between adults diagnosed with ADHD in childhood and controls by examining these 5 predefined neural networks. We sought to confirm our hypothesis that participants with ADHD would show increased connectivity in the affective network and less connectivity within the attention and cognitive control networks compared with the control group. Moreover, we aimed to confirm increased connectivity between the default mode network and sensory brain regions and reduced connectivity within the default mode network itself in ADHD.

Methods

Participants

Sixteen adults with combined-type ADHD who underwent careful clinical assessment as children (mean [SD] age at diagnosis, 8.9 [2.1] years) when taking part in genetic and neuropsychological studies^{26,27} were compared with 16 healthy controls matched for age, sex, handedness, and educational level. Full-scale IQ also did not differ between groups significantly (Supplement [eTable]). Handedness was determined using the Edinburgh Inventory.²⁸ Educational and occupational attainments were based on the Hollingshead Four Factor Index of Social Status.²⁹ Full-scale IQ was measured using the Wechsler Adult Intelligence Scale, Fourth Edition³⁰; the subscales of Verbal Comprehension, Perceptual Reasoning, Working Memory, and Processing Speed were used to compute full-scale composite IQ scores.

Two participants with ADHD were medication naive. Ten participants with ADHD were drug-free for a mean of 11.6 (SD, 4.2) years but had a history of methylphenidate hydrochloride treatment (mean [SD] months of medication, 20.6 [32.8]). Four participants were still being treated with methylphenidate and were required to undergo a washout period 48 hours before investigation. Exclusion criteria consisted of previous head injury with loss of consciousness, comorbid psychiatric disorder or disease, a history of hydrocortisone use, and current alcohol or substance abuse and/or dependency. All participants were interviewed and underwent diagnosis and screening for any potential comorbidity according to exclusion criteria using the Structured Clinical Interview for *DSM-IV* Axis I Disorders³¹ by a psychiatrist (D.M., J.K., or T.F.).

Rating Instruments

Self-administered and observer-rated scales were completed by all participants for diagnostic and correlational purposes.

The rating scales used were the Structured Clinical Interview for *DSM-IV* Axis II Disorders Personality Questionnaire³²; the Wender Utah Rating Scale (WURS)³³ with a control cutoff score of 46; the Conners Adult ADHD Observer and Self-report rating scales in which T scores of greater than 65 across all 4 scales are indicative of clinically elevated symptoms³⁴; the Hamilton Rating Scale for Depression³⁵; and the Beck Depression Inventory.³⁶ Ethical approval for the study was granted by the ethics committees of The Adelaide and Meath Hospital, Dublin, and St James' Hospital. Each participant was given detailed oral and written information and had to sign an informed consent form before participation. Participants received €30 (\$40).

MRI Methods

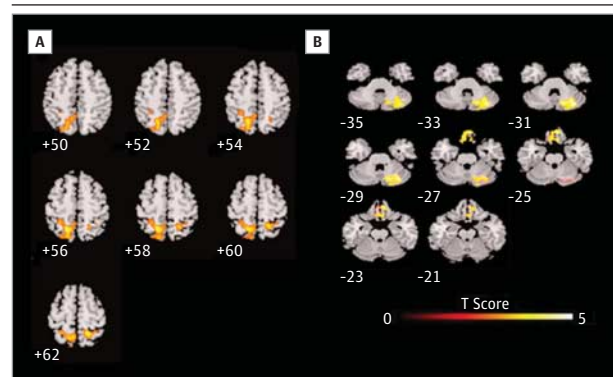
Functional and structural images from each participant were obtained with an MRI scanner (Philips Achieva; Philips Medical Systems Netherlands BV) operating at 3 T. The functional images were collected in single runs using gradient echoplanar imaging (echo time, 28 milliseconds; repetition time, 2000 milliseconds; field of view, 131 mm; flip angle, 90°) sensitive to BOLD contrast (T2* weighting). A total of 37 contiguous sections with 3.2-mm thickness were acquired parallel to the anterior-posterior commissure plane (3 mm approximately isotropic resolution), providing complete brain coverage. The fMRI run included 220 volumes acquired continuously lasting 7.2 minutes in total. Structural data (for definitive atlas transformation) included a high-resolution sagittal, 3-dimensional, T1-weighted, turbo gradient-echo sequence scan (echo time, 3.9 milliseconds; repetition time, 8.5 milliseconds; inversion time, 1060 milliseconds; flip angle, 8°; 256 × 240 acquisition matrix, 1 × 1 × 1-mm voxels).

Preprocessing of Functional Data

We used SPM software (SPM8; Wellcome Trust Centre for Neuroimaging [www.fil.ion.ucl.ac.uk/spm/software/spm8]) to preprocess fMRI data in the following steps: first, the compensation of systematic, section-dependent time shifts; second, the elimination of systematic odd- and even-section intensity differences due to interleaved acquisition; and third, rigid body correction for interframe head motion within and across runs. Data were excluded if motion parameters exceeded 3 mm in any direction or 3.0° of any angular motion during the scan. Next, we coregistered the structural T1 image to the functional scans. Spatial normalization to standard 3 × 3 × 3-mm Montreal Neurological Institute space was then applied to the functional images and to the structural image to allow for intersubject analysis. Functional resting-state data were then spatially smoothed (smoothing full width at half maximum, 8 mm).

Using resting-state software (CONN; National Institutes of Health Blueprint for Neuroscience Research [www.nitrc.org/projects/conn/]), the data were temporally band-pass filtered (filter range, 0.009-0.08). Several sources of spurious variance along with their temporal derivatives then were removed from the data by linear regression, such as signal from regions centered in the white matter, cerebrospinal fluid, and movement. CONN implements the component-

Figure 1. Functional Magnetic Resonance Imaging of Bilateral Affective Regions



Participants with attention-deficit/hyperactivity disorder displayed greater resting-state functional connectivity between the anterior cingulate cortex (ACC) and superior parietal and cerebellar areas than did control subjects. A, Left ACC ($x = 18$, $y = -50$, $z = 64$). B, Right ACC ($x = 34$, $y = -76$, $z = -30$). Values next to the images indicate the sections in axial view.

based noise-correction method strategy for physiological and other noise source reduction.³⁷ This method has the advantage of not requiring external monitoring of physiological fluctuations. Compared with methods that rely on global signal regression, the component-based noise-reduction method allows for interpretation of anticorrelations because there is no regression of the global signal within this method. This approach may enhance the sensitivity and specificity of positive correlations and produce comparable negative correlations.³⁸ This regression procedure removes fluctuations unlikely to be involved in specific regional correlations.

Functional Connectivity Analysis of Resting-State Activity

To compute functional connectivity maps corresponding to a selected seed region of interest, we correlated the regional time course against all other voxels within the brain. Based on data from 2 previous resting-state studies,^{13,14} we explored connectivity within the affective network, ventral attention system, dorsal attention system, cognitive control network, and default mode network. Correlation maps were produced by extracting the BOLD time course from a seed region and then by computing the correlation coefficient between that time course and the time course from all other brain voxels. The following seed regions of interest with a 5-mm radius were extracted for these 5 specific neural networks: the ACC ($x = \pm 10$, $y = -35$, $z = 2$) in the affective network, the TPJ ($x = \pm 53$, $y = -48$, $z = 20$) and VFC ($x = \pm 37$, $y = -18$, $z = 1$) in the ventral attention system, the IPS ($x = \pm 27$, $y = -58$, $z = 49$) and FEF ($x = \pm 24$, $y = -13$, $z = 51$) in the dorsal attention system, the DLPFC ($x = \pm 36$, $y = 27$, $z = 29$) in the cognitive control network, and the precuneus ($x = \pm 7$, $y = -60$, $z = 21$) in the default mode network. For the ventral (TPJ and VFC) and dorsal (IPS and FEF) attention network, we extracted 2 connectivity maps. The principal technique used was computation of whole-brain, voxel-wise intrinsic functional connectivity maps.

Statistical Analysis

We analyzed resting-state fMRI data in SPM8 using 2-sample t tests to determine significant differences in functional connectivity between ADHD participants and controls using a familywise error whole-brain-corrected threshold of $P < .01$. The threshold was reduced to $P < .01$ from $P < .05$ because we analyzed connectivity within the 5 different networks. Mean connectivity data were extracted from areas that showed significant differences between ADHD participants and controls. We used commercially available software (SPSS, version 16; SPSS Inc) to calculate Spearman rank correlation coefficients between ADHD symptoms from the Conners Adult ADHD Self-report rating scale and the WURS using a Bonferroni-corrected P threshold of .004 based on 12 extracted areas. Because the Beck Depression Inventory and Hamilton Rating Scale for Depression scores were different between ADHD participants and controls (although the values and variance were still below the threshold for depression), these were added as covariates in additional analysis of covariance in SPM8 to observe the difference between the ADHD and control groups.

Results

Compared with the control group, participants with ADHD displayed significantly greater functional connectivity bilaterally throughout the affective network (Figure 1) and the dorsal attention, in the right hemisphere of the cognitive control network (Supplement [eFigure 1]), and in the right hemisphere of the default mode network (Table 1).

For ADHD participants compared with controls, significantly less functional connectivity was found between the following regions in the ventral attention network: the left TPJ and the left temporal gyrus, the left VFC and the left frontal inferior operculum, and the right VFC and the left precentral gyrus (Table 2 and Figure 2). In the dorsal attention network, participants with ADHD showed significantly reduced functional connectivity between the right IPS and the right fusiform gyrus compared with the control group (Table 2). The cognitive control network showed significantly reduced functional connectivity between the left DLPFC and the right inferior occipital lobe for the ADHD group compared with the control group (Table 2). All group comparison results held true when the Beck Depression Inventory and Hamilton Rating Scale for Depression scores were included as covariates.

Control Correlation Results

To correct for multiple correlations, $P \leq .004$ was used as the significance threshold. Higher WURS scores were significantly negatively correlated with reduced functional connectivity in the ventral attention network between the left TPJ and left middle temporal gyrus ($r = -0.81$; $P < .001$) (Supplement [eFigure 2]). A reduction in functional connectivity between the left TPJ and left middle temporal gyrus was also significantly negatively correlated with higher *DSM-IV* inattentive symptoms ($r = -0.72$; $P = .001$), higher *DSM-IV* hyperactive/impulsive symptoms ($r = -0.54$; $P = .02$), and higher total *DSM-IV* symptom scores ($r = -0.59$; $P = .01$).

Table 1. Resting-State Functional Connectivity Increased in Participants With ADHD Compared With Controls^a

Network and Regions	FWE-Corrected <i>P</i> Value	K Value ^b	Talairach Coordinates ^c		
			x	y	z
Affective network					
Left ACC, left superior parietal lobule	<.001	1619	−16	−60	58
Left ACC, right superior parietal lobule	.02	528	18	−50	64
Right ACC, right cerebellum	<.001	967	34	−76	−30
Ventral attention network					
Left TPJ	...				
Right TPJ	...				
Left VFC	...				
Right VFC	...				
Dorsal attention network					
Right IPS	...				
Left IPS	...				
Left FEF, inferior occipital lobe	.01	693	−30	−74	−4
Right FEF, left middle occipital gyrus	<.001	4242	−38	−74	10
Cognitive control network					
Left DLPFC	...				
Right DLPFC, posterior cingulate cortex	.006	769	18	−52	28
Default mode network					
Left PREC	...				
Right PREC, right precentral gyrus	.02	637	20	−22	62

Abbreviations: ACC, anterior cingulate cortex; ADHD, attention-deficit/hyperactivity disorder; DLPFC, dorsolateral prefrontal cortex; FEF, frontal eye field; FWE, familywise error; IPS, intraparietal sulcus; PREC, precuneus; TPJ, temporoparietal junction; VFC, ventral frontal cortex.

^a Includes regions where patients had higher resting-state functional connectivity than controls. Nonsignificant regions are marked with an ellipsis.

^b Indicates voxel size.

^c Indicates for each significant region.

Table 2. Resting-State Functional Connectivity Increased in Controls Compared With Patients^a

Network and Regions	FWE-Corrected P Value	K Value ^b	Talairach Coordinates ^c		
			x	y	z
Affective network					
Right ACC	...				
Left ACC	...				
Ventral attention network					
Right TPJ	...				
Left TPJ, left middle temporal gyrus	.047	551	−62	−4	−8
Left VFC, left frontal inferior operculum	.006	769	−30	6	30
Right VFC, left precentral gyrus	.005	776	−50	2	28
Dorsal attention network					
Right IPS, right fusiform gyrus	.03	593	40	−32	−26
Left IPS	...				
Left FEF	...				
Right FEF	...				
Cognitive control network					
Left DLPFC, right inferior occipital lobe	.04	483	48	−80	−6
Right DLPFC	...				
Default mode network					
Left PREC	...				
Right PREC	...				

Abbreviations: See Table 1.

^a Includes regions where controls had higher functional connectivity than patients with attention-deficit/hyperactivity disorder. Nonsignificant regions are marked with an ellipsis.

^b Indicates voxel size.

^c Indicates for each significant region.

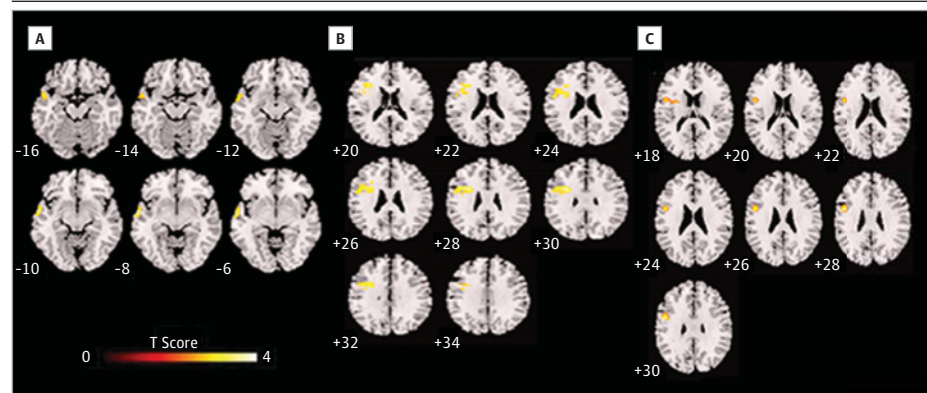
Correlations that did not reach significance after considering multiple testing but were $P < .05$ uncorrected included higher levels of ADHD symptoms during childhood. These symptoms were measured with the WURS and negatively correlated with a reduction in functional connectivity in the dorsal attention network between the left FEF and the inferior occipital lobe ($r = -0.53$; $P = .03$) and between the right FEF and the left middle occipital gyrus ($r = -0.66$; $P = .005$). Reduced

functional connectivity in the ventral attention network between the left TPJ and left middle temporal gyrus also correlated significantly with higher Hamilton Rating Scale for Depression scores in controls ($r = -0.52$; $P = .04$).

ADHD Correlation Results

No significant correlations were found when considering multiple correlations for the ADHD group. With the less conser-

Figure 2. Functional Magnetic Resonance Imaging of the Ventral Attention Network



In control subjects, the ventral attention network showed more significant resting-state functional connectivity bilaterally than did participants with attention-deficit/hyperactivity disorder. A, Left temporoparietal junction and left middle temporal gyrus ($x = -62$, $y = -4$, $z = -8$). B, Left ventral frontal cortex (VFC) and left inferior operculum ($x = -30$, $y = 6$, $z = 30$). C, Right VFC and left precentral gyrus ($x = -50$, $y = 2$, $z = 28$). Values next to the images indicate the sections in axial view.

vative threshold of $P < .05$, uncorrected findings can be reported that need further replication: higher WURS scores significantly negatively correlated with reduced functional connectivity in the ventral attention network between the right TPJ and right fusiform gyrus ($r = -0.51$; $P = .046$). Reduced functional connectivity in the dorsal attention network between the left FEF and the inferior occipital lobe was negatively correlated with higher total *DSM-IV-TR* symptom scores ($r = -0.58$; $P = .02$). Reduced functional connectivity between the right IPS and right fusiform gyrus was significantly negatively correlated with higher *DSM-IV-TR* inattentive symptoms ($r = -0.56$; $P = .02$) and with higher total *DSM-IV-TR* symptom scores ($r = -0.52$; $P = .04$) in the ADHD group.

Discussion

To our knowledge, this study represents the first time the affective, ventral, and dorsal attention networks have been explored in tandem with the cognitive control and default mode networks to determine the localization and specificity of ADHD-related RSFC differences in adults diagnosed with ADHD in childhood. A main finding within our study was the pronounced lack of significant RSFC within the ventral attention network for ADHD participants compared with controls. The ventral attention network directs attention toward salient stimuli, and an activation increase within the dorsal attention network occurs with the ventral attention network when reorientation of attention is required.¹³ Disrupted information exchange between the ventral attention network and the dorsal attention network has been linked to adult ADHD symptoms, such as intensified distractibility and perseverance.³⁹ Because hypofunction of the ventral attention network has been found during task-based fMRI studies,¹² our RSFC finding bolsters the dysregulation apparent within this network for participants with ADHD.⁴⁰ The link between ADHD and hypofunction of the ventral attention network is supported by our correlational analysis finding. We found that even for controls, and less significantly for ADHD participants, higher WURS and overall *DSM-IV* symptom scores were significantly associated with reduced functional connectivity between the left TPJ of the ventral attention network and the left middle tem-

poral gyrus. The latter region mediates attentional processing of auditory information, which is necessary for rehearsing verbally mediated task strategies in ADHD.⁴¹ Participants with ADHD have been found to display slower reaction times and hypoactivation of this region compared with controls during aural and visual attention tasks.^{41,42} This finding suggests that elevated ADHD symptoms in controls and participants with ADHD could indicate a reduced capacity for control of auditory and visuospatial attention.

Compared with the control group, we found significantly increased RSFC for ADHD participants between the bilateral FEF and occipital areas within the dorsal attention network. Heightened occipital region RSFC in ADHD has been linked to poor inhibition of sensory perception.⁴³ First, inhibitory control may require a greater effort for ADHD participants compared with controls owing to the lack of ventral attention network RSFC for which they may compensate.⁴⁴ Second, this finding may result from the dysfunctional interplay between the IPS and bilateral FEF and their afferent connections outside the dorsal attention network.⁴⁵ Moreover, we found reduced RSFC—although not significantly reduced after correction for multiple comparisons—for ADHD participants compared with controls between the right IPS and the right fusiform gyrus, which is involved in semantic retrieval.⁴⁰ Hypoactivity of the fusiform gyrus in ADHD has been linked to poor inhibition of emotional memory.⁴⁰

We found more RSFC for the ADHD participants than for the control group throughout the affective network. Participants with ADHD displayed significantly more RSFC between the right ACC of the affective network and the right cerebellum than did controls. The cerebellum is bidirectionally linked with regions modulating motor and affective output, including the parietal cortices and prefrontal regions.⁴⁶ Similar changes in the cerebellum have also been found in adults with major depressive disorder and children and adolescents with ADHD.^{15,16,47} We found significantly higher RSFC between the left ACC and the bilateral superior parietal lobules in the ADHD compared with the control groups ($P < .001$ and $P = .02$, respectively), which to date has been found solely in children with ADHD.^{18,23}

However, our affective network results are dissimilar to those of reduced affective network RSFC commonly found in

adults with ADHD.^{19,48} Different exposure to methylphenidate across studies, which has been linked to the normalization of ACC dysregulation in ADHD,⁴⁹ may account for these differences. The heterogeneity of these results warrant further research in longitudinal and treatment studies to clarify the effect of heightened affective network RSFC on emotional control in ADHD.

Participants with ADHD exhibited significantly less connectivity between the left DLPFC and the inferior occipital lobe than did the controls but displayed more RSFC in the cognitive control network between the right DLPFC and the posterior cingulate cortex. The DLPFC has been linked to adaptive control,²⁰ and the posterior cingulate is associated with introspection.⁴⁸ In more than 50% of cases, ADHD in adulthood is associated with a comorbid affective disorder.⁴ This finding is relevant to our cognitive control network finding because greater right DLPFC RSFC has been linked to heightened negative affect in those with and without major depressive disorder.⁵⁰

The RSFC within the default mode network was not significantly changed with regard to a $P < .01$ whole-brain correction. However, we found a trend for heightened RSFC within the default mode network between the right precuneus and the right precentral gyrus in ADHD participants compared with controls. The overactivation of the precuneus during task engagement in ADHD has been linked to instances of error and attention lapses.⁴⁸ The right precentral gyrus of the posterior frontal lobe is involved in the execution of sensorimotor demands, hyperfunction of which has been linked to impaired motor inhibition in ADHD.¹² Our finding supports that of Tian et al,⁵¹ who found heightened RSFC between the precuneus and sensory motor regions in ADHD participants; this result was linked to the processing of somatosensory information at rest more than in controls. In addition, our finding may also reflect compensation within the ADHD group for the dysregulated attention network connectivity that typically coordinates sensorimotor attention.⁴⁴

Our findings are contrary to previous findings of reduced functional connectivity among the superior precuneus, medial prefrontal cortex, and posterior cingulate cortices in ADHD participants.^{21,24,25} One study seeded their default mode network RSFC study of adults with ADHD within the posterior cingulate cortex²⁵ and another examined RSFC in this network using the frontal control region as a seed region.⁴⁸ Our findings may differ from these studies because we examined default mode network connectivity according to published methods^{13,14} and, unlike Uddin et al,²⁵ we did not examine RSFC within the default mode network exclusively.

Our findings must be considered in light of limiting factors. First, the size and heterogeneous treatment history of the

ADHD group limited a comparison between medication-naïve vs treated subgroups. Within the ADHD group, 2 participants (13%) were treatment naïve, 10 (63%) were drug free but had a previous history of methylphenidate drug treatment spanning a mean of 20.6 months, and 4 (25%) withheld their stimulant medication for 48 hours. A history of treatment with stimulant medication may be relevant because improved suppression of the default mode network during task engagement⁵² and cognitive-enhancement effects in adults with ADHD⁵³ have been linked to a history of stimulant medication therapy. At present, few longitudinal studies have explored the effect of stimulant medication from childhood to adulthood. Thus, more prospective, longitudinal, long-term studies are needed to investigate the effect of long-term stimulant treatment on brain structure and function.

Second, those still being treated within our investigation may have been susceptible to rebound effects caused by abrupt discontinuation of stimulant medication therapy that has been linked to heightened motor and ACC activity for ADHD participants.⁵⁴ To account for a rebound effect, we applied a washout period of 48 hours for participants using medication. The examination of a medication-naïve sample is considered optimal and could alleviate concerns about the effect of medication on RSFC in adult ADHD.

The inclusion of ADHD participants who underwent careful diagnosis in childhood and again in adulthood by the Structured Clinical Interview for *DSM-IV* Axis I Disorders, all of whom still fulfilled diagnostic criteria for combined-type ADHD, allowed us to examine the developmental progress of ADHD from childhood into adulthood.¹⁹ Potential recall bias associated with retrospective diagnoses of ADHD in childhood was also avoided by studying this specific group.³ Our results are valuable because they were corrected for multiple comparisons and were strong enough to survive conservative Bonferroni testing, which reduced type I errors.

Our findings shed light on ADHD-related RSFC and its role in symptoms presented by adults in whom childhood ADHD does not remit. Affective network hyperconnectivity might be related to emotional problems seen in adults with ADHD. In addition, ventral attention network hypoconnectivity may underlie attentional impairment in ADHD and seems to be closely related in particular to persistent inattention. Finally, the tentative compensation with hyperconnectivity of regions within the dorsal attention, cognitive control, and default mode networks requires future examination. These ADHD-related functional connectivity findings need to be understood in the context of a complex picture with social, environmental, physiological, biological, and genetic factors influencing brain function in ADHD.

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REFERENCES

- American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Washington, DC: American Psychiatric Association; 2000.
- Faraone SV, Sergeant J, Gillberg C, Biederman J. The worldwide prevalence of ADHD: is it an American condition? *World Psychiatry*. 2003;2(2):104-113.
- Faraone SV, Biederman J, Mick E. The age-dependent decline of attention deficit hyperactivity disorder: a meta-analysis of follow-up studies. *Psychol Med*. 2006;36(2):159-165.
- Frodl T. Comorbidity of ADHD and substance use disorder (SUD): a neuroimaging perspective. *J Atten Disord*. 2010;14(2):109-120.
- Biederman J, Mick E, Faraone SV. Age-dependent decline of symptoms of attention deficit hyperactivity disorder: impact of remission definition and symptom type. *Am J Psychiatry*. 2000;157(5):816-818.
- Greydanus DE, Pratt HD, Patel DR. Attention deficit hyperactivity disorder across the lifespan: the child, adolescent, and adult. *Dis Mon*. 2007;53(2):70-131.
- Mannuzza S, Castellanos FX, Roizen ER, Hutchison JA, Lashua EC, Klein RG. Impact of the impairment criterion in the diagnosis of adult ADHD: 33-year follow-up study of boys with ADHD. *J Atten Disord*. 2011;15(2):122-129.
- Deco G, Corbetta M. The dynamical balance of the brain at rest. *Neuroscientist*. 2011;17(1):107-123.
- Castellanos FX, Proal E. Large-scale brain systems in ADHD: beyond the prefrontal-striatal model. *Trends Cogn Sci*. 2012;16(1):17-26.
- Yang H, Wu Q-Z, Guo L-T, et al. Abnormal spontaneous brain activity in medication-naïve ADHD children: a resting state fMRI study. *Neurosci Lett*. 2011;502(2):89-93.
- Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. A default mode of brain function. *Proc Natl Acad Sci U S A*. 2001;98(2):676-682.
- Cortese S, Kelly C, Chabernaud C, et al. Toward systems neuroscience of ADHD: a meta-analysis of 55 fMRI studies. *Am J Psychiatry*. 2012;169(10):1038-1055.
- Fox MD, Corbetta M, Snyder AZ, Vincent JL, Raichle ME. Spontaneous neuronal activity distinguishes human dorsal and ventral attention systems. *Proc Natl Acad Sci U S A*. 2006;103(26):10046-10051.
- Sheline YI, Price JL, Yan Z, Mintun MA. Resting-state functional MRI in depression unmasks increased connectivity between networks via the dorsal nexus. *Proc Natl Acad Sci U S A*. 2010;107(24):11020-11025.
- Tian L, Jiang T, Wang Y, et al. Altered resting-state functional connectivity patterns of anterior cingulate cortex in adolescents with attention deficit hyperactivity disorder. *Neurosci Lett*. 2006;400(1-2):39-43.
- Zang YF, He Y, Zhu CZ, et al. Altered baseline brain activity in children with ADHD revealed by resting-state functional MRI. *Brain Dev*. 2007;29(2):83-91.
- Pliszka SR, Glahn DC, Semrud-Clikeman M, et al. Neuroimaging of inhibitory control areas in children with attention deficit hyperactivity disorder who were treatment naïve or in long-term treatment. *Am J Psychiatry*. 2006;163(6):1052-1060.
- Zhu C-Z, Zang Y-F, Cao Q-J, et al. Fisher discriminative analysis of resting-state brain function for attention-deficit/hyperactivity disorder. *Neuroimage*. 2008;40(1):110-120.
- Cubillo A, Halari R, Ecker C, Giampietro V, Taylor E, Rubia K. Reduced activation and inter-regional functional connectivity of fronto-striatal networks in adults with childhood attention-deficit hyperactivity disorder (ADHD) and persisting symptoms during tasks of motor inhibition and cognitive switching. *J Psychiatr Res*. 2010;44(10):629-639.
- Cole MW, Schneider W. The cognitive control network: integrated cortical regions with dissociable functions. *Neuroimage*. 2007;37(1):343-360.
- Castellanos FXK, Kelly C, Milham MP. The restless brain: attention-deficit hyperactivity disorder, resting-state functional connectivity, and intrasubject variability. *Can J Psychiatry*. 2009;54(10):665-672.
- Hart HRJ, Nakao T, Mataix-Cols D, Rubia K. Meta-analysis of functional magnetic resonance imaging studies of inhibition and attention in attention-deficit/hyperactivity disorder: exploring task-specific, stimulant medication, and age effects. *JAMA Psychiatry*. 2012;70(2):185-198.
- Wang L, Zhu C, He Y, et al. Altered small-world brain functional networks in children with attention-deficit/hyperactivity disorder. *Hum Brain Mapp*. 2009;30(2):638-649.
- Fair DA, Posner J, Nagel BJ, et al. Atypical default network connectivity in youth with attention-deficit/hyperactivity disorder. *Biol Psychiatry*. 2010;68(12):1084-1091.
- Uddin LQ, Kelly AMC, Biswal BB, et al. Network homogeneity reveals decreased integrity of default-mode network in ADHD. *J Neurosci Methods*. 2008;169(1):249-254.
- Brookes K, Xu X, Chen W, et al. The analysis of 51 genes in DSM-IV combined type attention deficit hyperactivity disorder: association signals in DRD4, DAT1 and 16 other genes [published correction appears in *Mol Psychiatry*. 2006;11(12):1139]. *Mol Psychiatry*. 2006;11(10):934-953.
- Johnson KA, Kelly SP, Robertson IH, et al. Absence of the 7-repeat variant of the DRD4 VNTR is associated with drifting sustained attention in children with ADHD but not in controls. *Am J Med Genet B Neuropsychiatr Genet*. 2008;147(6):927-937.
- Oldfield RC. The assessment and analysis of handedness: the Edinburgh Inventory. *Neuropsychologia*. 1971;9(1):97-113.
- Hollingshead AB. *Four Factor Index of Social Status*. New Haven, CT: Yale University Dept of Sociology; 1975.
- Wechsler D. *Wechsler Adult Intelligence Scale*. 4th ed. San Antonio, TX: Pearson; 2008.
- First MB SR, Williams JB. Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I): Clinician Version, Administration Booklet. Washington, DC: American Psychiatric Press; 1997.
- First MB, Gibbon M, Spitzer RL, Williams JBW, Smith Benjamin L. Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II): Interview and Questionnaire. Washington, DC: American Psychiatric Press; 1997.
- Ward MFWP, Wender PH, Reimherr FW. The Wender Utah Rating Scale: an aid in the retrospective diagnosis of childhood attention deficit hyperactivity disorder. *Am J Psychiatry*. 1993;150(6):885-890.
- Conners CK. Clinical use of rating scales in diagnosis and treatment of attention-deficit/hyperactivity disorder. *Pediatr Clin North Am*. 1999;46(5):857-870; vi.
- Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23(1):56-62.
- Beck AT, Steer RA, Carbin MG. Psychometric properties of the Beck Depression Inventory: twenty-five years of evaluation. *Clin Psychol Rev*. 1988;8(1):77-100.
- Behzadi Y, Restom K, Liu J, Liu TT. A component based noise correction method (CompCor) for BOLD and perfusion based fMRI. *Neuroimage*. 2007;37(1):90-101.
- Chai XJ, Castañón AN, Ongür D, Whitfield-Gabrieli S. Anticorrelations in resting state networks without global signal regression. *Neuroimage*. 2012;59(2):1420-1428.
- Cubillo A, Halari R, Smith A, Taylor E, Rubia K. A review of fronto-striatal and fronto-cortical brain abnormalities in children and adults with attention deficit hyperactivity disorder (ADHD) and new evidence for dysfunction in adults with ADHD

during motivation and attention. *Cortex*. 2012;48(2):194-215.

40. Depue BE, Burgess GC, Willcutt EG, Ruzic L, Banich MT. Inhibitory control of memory retrieval and motor processing associated with the right lateral prefrontal cortex: evidence from deficits in individuals with ADHD. *Neuropsychologia*. 2010;48(13):3909-3917.
41. Tamm L, Menon V, Ringel J, Reiss AL. Event-related fMRI evidence of frontotemporal involvement in aberrant response inhibition and task switching in attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*. 2004;43(11):1430-1440.
42. Stevens MC, Pearson GD, Kiehl KA. An fMRI auditory oddball study of combined-subtype attention deficit hyperactivity disorder. *Am J Psychiatry*. 2007;164(11):1737-1749.
43. Cao X, Cao Q, Long X, et al. Abnormal resting-state functional connectivity patterns of the putamen in medication-naïve children with attention deficit hyperactivity disorder. *Brain Res*. December 2009;1303:195-206.
44. Fassbender C, Schweitzer JB. Is there evidence for neural compensation in attention deficit hyperactivity disorder? a review of the functional neuroimaging literature. *Clin Psychol Rev*. 2006;26(4):445-465.
45. Shulman GL, Astafiev SV, Franke D, et al. Interaction of stimulus-driven reorienting and expectation in ventral and dorsal frontoparietal and basal ganglia-cortical networks. *J Neurosci*. 2009;29(14):4392-4407.
46. Turner BM, Paradiso S, Marvel CL, et al. The cerebellum and emotional experience. *Neuropsychologia*. 2007;45(6):1331-1341.
47. Guo WB, Sun XL, Liu L, et al. Disrupted regional homogeneity in treatment-resistant depression: a resting-state fMRI study. *Prog Neuropsychopharmacol Biol Psychiatry*. 2011;35(5):1297-1302.
48. Castellanos FX, Margulies DS, Kelly C, et al. Cingulate-precuneus interactions: a new locus of dysfunction in adult attention-deficit/hyperactivity disorder. *Biol Psychiatry*. 2008;63(3):332-337.
49. Lee JS, Kim BN, Kang E, et al. Regional cerebral blood flow in children with attention deficit hyperactivity disorder: comparison before and after methylphenidate treatment. *Hum Brain Mapp*. 2005;24(3):157-164.
50. Davidson RJ, Irwin W. The functional neuroanatomy of emotion and affective style. *Trends Cogn Sci*. 1999;3(1):11-21.
51. Tian L, Jiang T, Liang M, et al. Enhanced resting-state brain activities in ADHD patients: a fMRI study. *Brain Dev*. 2008;30(5):342-348.
52. Peterson BS, Potenza MN, Wang Z, et al. An fMRI study of the effects of psychostimulants on default-mode processing during Stroop task performance in youths with ADHD. *Am J Psychiatry*. 2009;166(11):1286-1294.
53. Stoy M, Schlagenhauf F, Schlottermeier L, et al. Reward processing in male adults with childhood ADHD: a comparison between drug-naïve and methylphenidate-treated subjects. *Psychopharmacology (Berl)*. 2011;215(3):467-481.
54. Langleben DD, Acton PD, Austin G, et al. Effects of methylphenidate discontinuation on cerebral blood flow in prepubescent boys with attention deficit hyperactivity disorder. *J Nucl Med*. 2002;43(12):1624-1629.