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.
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; Farace et al. \(^3\) 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 age; the hyperactive and impulsive symptoms of childhood ADHD become less pronounced, whereas inattentive symptoms the hyperactive and impulsive symptomsofchildhoodADHD

The 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; Faracce et al. \(^3\) 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.

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. \(^5\) 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. \(^6\) Functional connectivity is the observed correlation in spontaneous neural activity between brain areas at rest. \(^7\)

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 ADHD \(^8\) from 5 neural networks. \(^9\) These networks include the affective network, the default mode network, the cognitive control network, the lateral attention network, and the ventral attention network. \(^10\) The affective network is involved in the modulation of affective stimuli and has been associated with heightened functional connectivity in ADHD. \(^11\) The default mode network is involved in the intrinsic brain activity and has been associated with decreased functional connectivity in ADHD. \(^12\)

The cognitive control network is involved in the regulation of attention and goal-directed decision making, which is impaired in ADHD. \(^13\) The lateral attention network is involved in the allocation of attention to salient stimuli, and the ventral attention network is involved in the allocation of attention to affective stimuli. \(^14\) These networks are involved in the regulation of attention in ADHD and have been associated with increased functional connectivity. \(^15\) The default mode network is involved in the intrinsic brain activity and has been associated with decreased functional connectivity in ADHD. \(^16\)

The affective network is involved in the modulation of affective stimuli and has been associated with heightened functional connectivity in ADHD. \(^17\) The default mode network is involved in the intrinsic brain activity and has been associated with decreased functional connectivity in ADHD. \(^18\) The cognitive control network is involved in the regulation of attention and goal-directed decision making, which is impaired in ADHD. \(^19\) The lateral attention network is involved in the allocation of attention to salient stimuli, and the ventral attention network is involved in the allocation of attention to affective stimuli. \(^20\) These networks are involved in the regulation of attention in ADHD and have been associated with increased functional connectivity. \(^21\)

The default mode network is involved in the intrinsic brain activity and has been associated with decreased functional connectivity in ADHD. \(^22\) The affective network is involved in the modulation of affective stimuli and has been associated with heightened functional connectivity in ADHD. \(^23\) The cognitive control network is involved in the regulation of attention and goal-directed decision making, which is impaired in ADHD. \(^24\) The lateral attention network is involved in the allocation of attention to salient stimuli, and the ventral attention network is involved in the allocation of attention to affective stimuli. \(^25\) These networks are involved in the regulation of attention in ADHD and have been associated with increased functional connectivity. \(^26\)
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. 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 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 studies26,27 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 ratings 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 Netherland 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-
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.

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 = ±10, y = −35, z = 2) in the affective network, the TPJ (x = ±53, y = −48, z = 20) and VFC (x = ±37, y = −18, z = 1) in the ventral attention system, the IPS (x = ±27, y = −58, z = 49) and FEF (x = ±24, y = −13, z = 51) in the dorsal attention system, the DLPFC (x = ±36, y = 27, z = 29) in the cognitive control network, and the precuneus (x = ±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.

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 (\( r = −0.59; P = .01 \)).
Correlations that did not reach significance after considering multiple testing but were \( P < .05 \) uncorrected included higher levels of ADHD symptoms during childhood. These symptomswere 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 \( (r = -0.53; P = .02) \) 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 conservative approach, we did find increased functional connectivity in participants with ADHD compared with controls in the affective network for the left ACC, left superior parietal lobule \( (P < .001) \), and right superior parietal lobule \( (P = .02) \), and for the right ACC, right cerebellum \( (P < .001) \). In the ventral attention network, reduced functional connectivity was observed in the left FEF, inferior occipital lobe \( (r = -0.53; P = .03) \), and right FEF, 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 \( (r = -0.52; P = .04) \).

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

<table>
<thead>
<tr>
<th>Network and Regions</th>
<th>FWE-Corrected P Value</th>
<th>K Value*</th>
<th>Talairach Coordinates*</th>
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</thead>
<tbody>
<tr>
<td><strong>Affective network</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ACC, left superior parietal lobule</td>
<td>&lt;.001</td>
<td>1619</td>
<td>-16 -60 58</td>
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<tr>
<td>Left ACC, right superior parietal lobule</td>
<td>.02</td>
<td>528</td>
<td>18 -50 64</td>
</tr>
<tr>
<td>Right ACC, right cerebellum</td>
<td>&lt;.001</td>
<td>967</td>
<td>34 -76 -30</td>
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<tr>
<td><strong>Ventral attention network</strong></td>
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<tr>
<td>Left TPJ</td>
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<tr>
<td>Right TPJ</td>
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<td></td>
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<td>Left VFC</td>
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<td>Right VFC</td>
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<tr>
<td><strong>Dorsal attention network</strong></td>
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<td>Right IPS</td>
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<tr>
<td>Left IPS</td>
<td>...</td>
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<td>Left FEF, inferior occipital lobe</td>
<td>.01</td>
<td>693</td>
<td>-30 -74 -4</td>
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<td>Right FEF, left middle occipital gyrus</td>
<td>&lt;.001</td>
<td>4242</td>
<td>-38 -74 10</td>
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<td><strong>Cognitive control network</strong></td>
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<tr>
<td>Left DLPCF</td>
<td>...</td>
<td></td>
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<tr>
<td>Right DLPCF, posterior cingulate cortex</td>
<td>.006</td>
<td>769</td>
<td>18 -52 28</td>
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<tr>
<td><strong>Default mode network</strong></td>
<td></td>
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<tr>
<td>Left PREC</td>
<td>...</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right PREC, right precentral gyrus</td>
<td>.02</td>
<td>617</td>
<td>20 -22 62</td>
</tr>
</tbody>
</table>

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

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

** Indicates voxel size.

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

<table>
<thead>
<tr>
<th>Network and Regions</th>
<th>FWE-Corrected P Value</th>
<th>K Value*</th>
<th>Talairach Coordinates*</th>
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</thead>
<tbody>
<tr>
<td><strong>Affective network</strong></td>
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<tr>
<td>Right ACC</td>
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<td>Left ACC</td>
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<td><strong>Ventral attention network</strong></td>
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<tr>
<td>Right TPJ</td>
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<tr>
<td>Left TPJ, left middle temporal gyrus</td>
<td>.047</td>
<td>551</td>
<td>-62 -4 -8</td>
</tr>
<tr>
<td>Left VFC, left frontal inferior operculum</td>
<td>.006</td>
<td>769</td>
<td>-30 6 30</td>
</tr>
<tr>
<td>Right VFC, left precentral gyrus</td>
<td>.005</td>
<td>776</td>
<td>-50 2 28</td>
</tr>
<tr>
<td><strong>Dorsal attention network</strong></td>
<td></td>
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<tr>
<td>Right IPS, right fusiform gyrus</td>
<td>.03</td>
<td>593</td>
<td>40 -12 -26</td>
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<tr>
<td>Left IPS</td>
<td>...</td>
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<td>Left FEF</td>
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<td>Right FEF</td>
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<tr>
<td><strong>Cognitive control network</strong></td>
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</tr>
<tr>
<td>Left DLPCF, right inferior occipital lobe</td>
<td>.04</td>
<td>483</td>
<td>48 -80 -6</td>
</tr>
<tr>
<td>Right DLPCF</td>
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<tr>
<td><strong>Default mode network</strong></td>
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<tr>
<td>Left PREC</td>
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<td>Right PREC</td>
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</table>

Abbreviations: See Table 1.

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

** Indicates voxel size.

*** Indicates for each significant region.
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. 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 perseveration. Because hypofunction of the ventral attention network has been found during task-based fMRI studies, our RSFC finding bolsters the dysregulation apparent within this network for participants with ADHD. 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 temporal gyrus. The latter region mediates attentional processing of auditory information, which is necessary for rehearsing verbally mediated task strategies in ADHD. 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. 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. 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. Second, this finding may result from the dysfunctional interplay between the IPS and bilateral FEF and their afferent connections outside the dorsal attention network. 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. Hypoactivity of the fusiform gyrus in ADHD has been linked to poor inhibition of emotional memory.

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. Similar changes in the cerebellum have also been found in adults with major depressive disorder and children and adolescents with ADHD. 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. However, our affective network results are dissimilar to those of reduced affective network RSFC commonly found in ADHD.
Attention and Affective Changes in Adult ADHD

Original Investigation Research

Different exposure to methylphenidate across studies, which has been linked to the normalization of ACC dysregulation in ADHD, 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, and the posterior cingulate is associated with introspection. In more than 50% of cases, ADHD in adulthood is associated with a comorbid affective disorder. 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.

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. The right precuneus 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. Our finding supports that of Tian et al, 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.

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. One study seeded their default mode network RSFC study of adults with ADHD within the posterior cingulate cortex and another examined RSFC in this network using the frontal control region as a seed region. Our findings may differ from these studies because we examined default mode network connectivity according to published methods and, unlike Uddin et al, 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-naive vs treated subgroups. Within the ADHD group, 2 participants (13%) were treatment naive, 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 engagement and cognitive-enhancement effects in adults with ADHD 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. To account for a rebound effect, we applied a washout period of 48 hours for participants using medication. The examination of a medication-naive 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. Potential recall bias associated with retrospective diagnoses of ADHD in childhood was also avoided by studying this specific group. 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 hyperconnectivity 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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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.


