Cingulate-Precuneus Interactions: A New Locus of Dysfunction in Adult Attention-Deficit/ Hyperactivity Disorder

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Background: Pathophysiologic models of attention-deficit/hyperactivity disorder (ADHD) have focused on frontal-striatal circuitry with alternative hypotheses relatively unexplored. On the basis of evidence that negative interactions between frontal foci involved in cognitive control and the non-goal-directed "default-mode" network prevent attentional lapses, we hypothesized abnormalities in functional connectivity of these circuits in ADHD.

Methods: Resting-state blood oxygen level– dependent functional magnetic resonance imaging (fMRI) scans were obtained at 3.0-Tesla in 20 adults with ADHD and 20 age- and sex-matched healthy volunteers.

Results: Examination of healthy control subjects verified presence of an antiphasic or negative relationship between activity in dorsal anterior cingulate cortex (centered at x = 8, y = 7, z = 38) and in default-mode network components. Group analyses revealed ADHD-related compromises in this relationship, with decreases in the functional connectivity between the anterior cingulate and precuneus/posterior cingulate cortex regions ($p < .0004$, corrected). Secondary analyses revealed an extensive pattern of ADHD-related decreases in connectivity between precuneus and other default-mode network components, including ventromedial prefrontal cortex ($p < 3 \times 10^{-11}$, corrected) and portions of posterior cingulate ($p < .02$, corrected).

Conclusions: Together with prior unbiased anatomic evidence of posterior volumetric abnormalities, our findings suggest that the long-range connections linking dorsal anterior cingulate to posterior cingulate and precuneus should be considered as a candidate locus of dysfunction in ADHD.

Key Words: ADHD, anterior cingulate cortex, default-mode network, functional magnetic resonance imaging, precuneus, posterior cingulate cortex

Pathophysiologic models of attention-deficit/hyperactivity disorder (ADHD) have focused on prefrontal-striatal and mesolimbic circuits (1) on the basis of findings of executive and motivational dysfunction (2,3). However, as pointed out in a recent quantitative meta-analysis of functional imaging studies of ADHD (4), the focus on executive dysfunction and the frontal lobes has left alternative hypotheses unexplored. Additionally, standard task-based functional imaging studies depend on the precise specification of underlying neuropsychological deficits. Although the hypothesis that ADHD results from a primary inhibitory deficit was proposed a decade ago (5), the accumulated evidence has been equivocal at best (1).

A complementary approach is to examine the neural substrates of ADHD-relevant behaviors, such as attentional lapses (6,7), and assess whether the underlying circuits are implicated in ADHD through analysis of the temporal correlations among distributed brain regions. This method of functional connectivity (8), first applied to mapping the motor cortical system (9), provides remarkably detailed spatial maps of putatively functionally related regions (10).

Momentary lapses in attention have been associated with failure to suppress activity in the default-mode network (11). First identified by Raichle *et al.* (12), the default-mode network is a large and robustly replicable network (13–15) that comprises ventral medial prefrontal cortex (VMPFC) and posterior cingulate cortex (PCC) and precuneus in the midline and that has been linked to non-goal-directed processes (16). By definition, default-mode network activity can be detected during resting state scans, and abnormalities in this network have been reported in ADHD (17,18), Alzheimer's disease (19,20), autism (21), schizophrenia (22), and depression (23).

The starting point for this study was the finding that decreased cue-related activation in three prefrontal regions predicted slower response times and decreased default-mode network suppression in healthy adult volunteers (11), suggesting potential control loci for default-mode regulation. We hypothesized that these fronto-default mode interactions may represent loci of dysfunction in ADHD. Given reports that fronto-default-mode interactions are intrinsically represented in spontaneous activity at rest (14,24), we tested for the presence of ADHD-related

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Table 1. Demographics

	ADHD Subjects	Healthy Comparison Subjects
Total Subjects	20	20
Mean ± SD Age (years)	34.9 ± 9.9	31.2 ± 9.0
Number (%) Male	16 (80%)	14 (70%)
Years of Education Completed	17.2 ± 1.9	17.6 ± 1.6
Inattentive Symptoms[a]	7.4 ± 1.6	1.2 ± 0.4
Hyperactive/Impulsive Symptoms[a]	5.9 ± 2.6	1.5 ± 0.6
Number (%) Treated	9 (45%)	0

ADHD, attention-deficit/hyperactivity disorder.

[a]Current DSM-IV inattention and hyperactivity/impulsivity symptoms (lifetime symptoms for healthy comparisons) were assessed using the Adult ADHD Clinical Diagnostic Scale 2.1. Symptom data on this scale were unavailable for two subjects diagnosed with combined-type ADHD by clinical interview. Age, sex distributions, and educational attainment did not differ significantly ($p > .20$).

differences in functional connectivity between each of the three previously identified frontal foci (dorsal anterior cingulate cortex [dACC]; right inferior frontal gyrus [rIFG]; right middle frontal gyrus [rMFG]) and the default-mode network.

Methods and Materials

Participants

Twenty adult participants with ADHD were recruited from the New York University (NYU) School of Medicine Adult ADHD Program (directed by author LA). Twenty age-matched comparisons were recruited through local media advertisements. All prospective participants were screened with the Symptom Checklist-90-Revised (SCL-90-R) to exclude a broad range of psychiatric psychopathology (25). Exclusion criteria for both groups included the following:1) lifetime history of psychotic, bipolar, or substance use disorders; 2) current history of mood, psychotic, anxiety, or substance use disorders; 3) lifetime history of treatment with psychotropics other than stimulants (for ADHD group only); or 4) history of neurological or chronic medical illness. All participants were evaluated with the Adult ADHD Clinical Diagnostic Scale (ACDS) Version1.2 (26), a semistructured interview that probes for the presence, severity, and impairment associated with ADHD symptoms in childhood and adulthood and which has been validated with informant-only reports (27). All participants with ADHD met lifetime criteria for Combined Type ADHD; they were also administered the Structured Clinical Interview for DSM-IV (SCID) to rule out other Axis I comorbid diagnoses. Best estimate diagnoses for probands were established by LA. A psychiatrist (AK or MG) administered a semistructured clinical interview to healthy comparison subjects to rule out all Axis I psychiatric disorders, including presence of ADHD or learning disorders in childhood or adulthood. Educational attainment (level attained, e.g., high school graduate = 12; college graduate = 16) and strong right-handedness were obtained from self-report. Demographic characteristics are shown in Table 1. All participants reported graduating from high school and attending at least 1 year of college. Nine patients were currently being treated with stimulants, which were discontinued for at least 1 day before scanning. All participants provided signed informed consent as approved by the institutional review boards of NYU and the NYU School of Medicine. Participants were compensated.

Scanning

Each participant underwent one resting state scan consisting of 197 contiguous whole-brain functional volumes using echo planar imaging on a Siemens 3.0-Tesla Allegra (repetition time = 2000 msec; echo time = 25 msec; flip angle = 90, 39 slices, matrix = 64 × 64; field of view = 192 mm; acquisition voxel size = 3 × 3 × 3 mm; 6.5 min). Participants were verbally instructed to relax and remain still with eyes open while the word "Relax" was centrally displayed. A high-resolution T1-weighted magnetization prepared gradient echo sequence was also obtained.

Preprocessing

Initial image preprocessing, including motion correction, despiking, and slice time correction, was done using AFNI software (http://www.afni.nimh.nih.gov/afni). Subsequent preprocessing, including spatial filtering (full width at half maximum [FWHM] = 6 mm), temporal bandpass filtering, and spatial normalization, was performed using FSL software (http://www.fmrib.ox.ac.uk/fsl).

Study Specific Template Generation

To optimize automated spatial normalization and avoid possible group differences related to registration errors (28), we created a study-specific template based on the approach employed in optimized voxel-based morphometry protocols (28). To create the template, all participants' brain images were 1) spatially normalized to Montréal Neurological Institute (MNI) space using a 12-parameter affine transformation in the FLIRT program (http://www.fmrib.ox.ac.uk/fsl), 2) spatially filtered (FWHM = 8 mm), and 3) averaged. Using this template, we recalculated the spatial transformation for each participant using a 12-parameter affine implemented in FLIRT. Repeating our analyses using the standard adult 152 brain MNI template rather than the study specific template yielded nearly identical results.

Functional Connectivity Analyses

To obtain time series for each seed in each participant, we 1) transform the subject's time series into MNI space using a 12 degrees of freedom linear affine implemented in FLIRT (voxel size = 1 × 1 × 1 mm) and 2) calculate the mean time series for each of the three mask spheres centered around the three spherical regions of interest (ROIs; 123 voxels, radius = 3.5 mm) centered at the coordinates reported by Weissman *et al.* (2006) converted to MNI space (dACC: x = 8, y = 7, z = 38; rIFG: x = 34, y = 45, z = 23; rMFG: x = 49, y = 19, z = 0). For each ROI, individual participant analyses were carried out using the GLM implemented in FEAT, using a seed-based regression approach employed in our prior work (10), with the time series for the ROI, as well as for the nuisance covariates (time series regressors for global signal intensity, white matter, cerebrospinal fluid, and six motion parameters) as predictors. (See Figure 1 for schematic outline). We produced individual subject-level maps of all positively and negatively predicted voxels for each regressor, correcting for multiple comparisons at the cluster level using Gaussian random field theory (min $Z > 2.3$; cluster significance: $p < .05$, corrected). Group-level analyses (within and between) were conducted using a mixed-effects model (FLAME) implemented in FSL, which produced thresholded Z score maps of activity associated with each ROI. On the basis of the assumption that cortical connectivity should be reciprocal (29), we used the time series corresponding to the region that differed significantly between groups in our primary analyses and derived the corre-

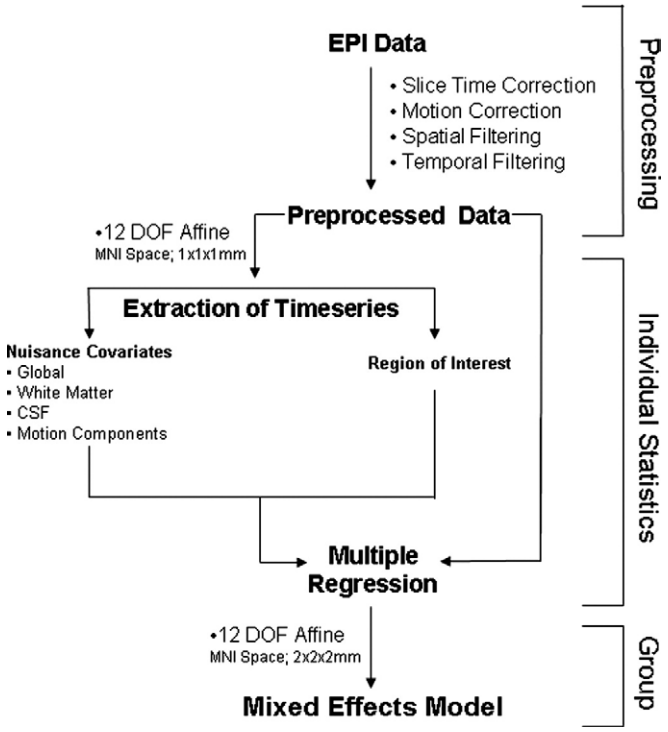

Figure 1. Data analytical path for preprocessing, extraction of region of interest and nuisance covariate time series, individual subject multiple regression analyses, and mixed effects analyses of group results.

sponding positively and negatively predicted networks and their significant group differences.

Exploratory correlations between inattention and hyperactivity/impulsivity symptom severity reports were performed with the regression parameter estimates for the significant between group difference at a two-sided alpha of .05.

Table 2. ADHD-Related Decreases in Functional Connectivity with ACC (MNI coordinates x = 8, y = 7, z = 38)

Region[a]	BA	x	y	z	*Z* Score
Posterior Cingulate Gyrus	31	15	−56	28	4.42
Precuneus	7	−8	−63	38	4.14
Precuneus	7	22	−59	28	4.05
Precuneus	7	1	−80	41	3.83
Precuneus	7	4	−66	37	3.5
Precuneus	7	22	−60	37	3.37

ACC, anterior cingulate cortex; ADHD, attention-deficit/hyperactivity disorder; BA, Brodmann's area.

[a]Peak activations reported for cluster identified in precuneus (x = 4, y = −65, z = 34; $p = 3.7 \times 10^{-4}$, corrected; cluster size = 3661). All table coordinates in Talairach space.

Results

Although both rIFG and rMFG ROIs were significantly negatively related to precuneus and PCC in both groups (see Supplement 1), these relationships did not differentiate the groups significantly. By contrast, functional connectivity analyses of the dACC ROI demonstrated significantly less negatively correlated activity ($p < .0004$, corrected; 3989 cubic voxels 1.5 mm per side = 13,436 mm^3) in precuneus/PCC in subjects with ADHD (see Figure 2 and Table 2).

As shown in Figure 3, the precuneus/PCC mask obtained from the dACC ROI-based group difference robustly predicted positively and negatively correlated activity in healthy volunteers. The positively correlated regions coincided with the default-mode network in control subjects, but the ADHD group lacked the anterior component of that network. As the right panel of Figure 3 shows, the groups differed significantly in medial prefrontal cortex and

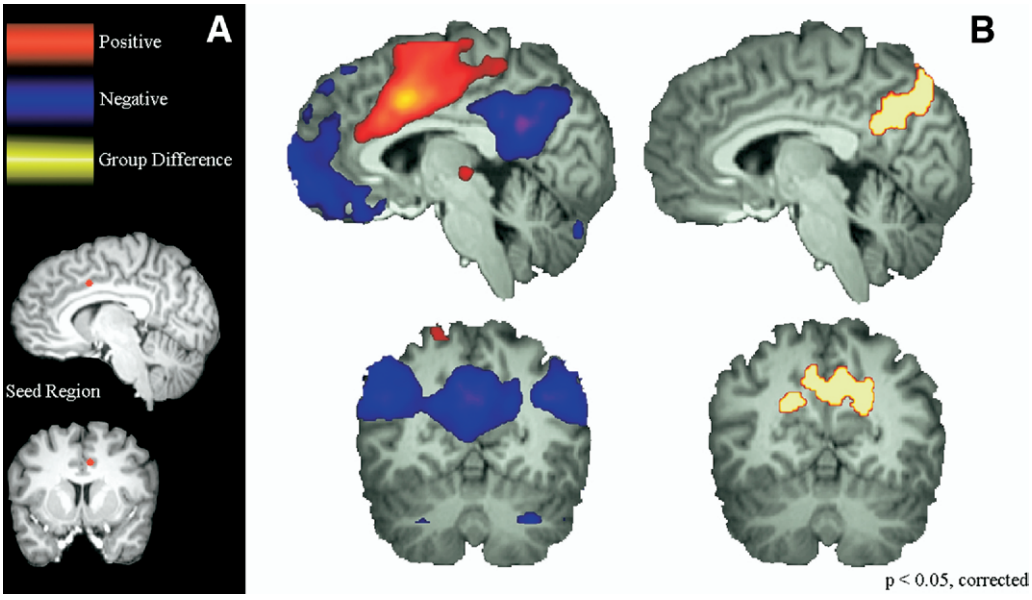

Figure 2. (A) Functional connectivity analyses were carried out using a spherical region of interest (ROI) located in anterior cingulate cortex (ACC; diameter = 7 mm, number of voxels = 123; MNI coordinates x = 8, y = 7, z = 38), based on the findings of Weissman *et al.* (2006). **(B)** Voxels positively (red) and negatively (blue) predicted by the time series for the ACC ROI (sagittal slice: x = 6; coronal slice: y = −62). A robust negative or antiphasic relationship was noted between the ACC seed region and default-mode network components (i.e., an increase in ACC activity predicts a decrease in default-mode activity). Attention-deficit/hyperactivity disorder–related decreases in functional connectivity were noted between the ACC and precuneus.

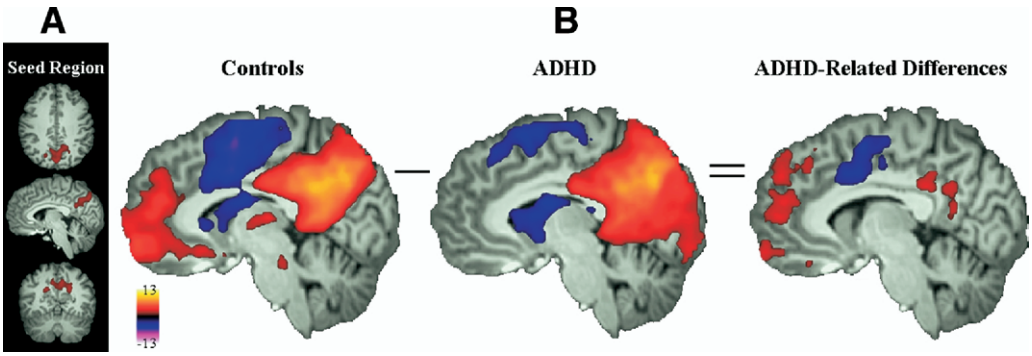

Figure 3. (A) Secondary functional connectivity analyses were carried out using the posterior cingulate/precuneus cluster identified in our primary analyses as the seed region. **(B)** For each group (attention-deficit/hyperactivity disorder [ADHD] and control subjects), voxels positively (red) and negatively (blue) predicted by the time series for the seed region are indicated. These analyses provided further support for ADHD-related decreases in precuneus/anterior cingulate cortex (ACC) connectivity. Furthermore, they identified areas of ADHD-related decreases in connectivity among precuneus and other default-mode network components, including ventromedial prefrontal cortex and anterior portions of posterior cingulate cortex.

superior frontal gyrus ($p < 3 \times 10^{-11}$, corrected) and also in PCC/precuneus ($p < .02$, corrected; see Table 3). The ADHD group also showed significantly less negatively correlated functional activity in ACC (Brodmann's area [BA] 24, 31, 32) and medial frontal gyrus (BA 6) ($p < .00002$, corrected) and in superior temporal gyrus (BA 22, 41; $p < .04$, corrected), including claustrum and precentral gyrus (BA 43, 44). Figure 4 shows the distribution of regression parameter estimates for the negatively correlated relationship between dACC ROI and PCC/precuneus in the two groups (means ± SD −.23 ± 0.12 and −.01 ± .15 for healthy control and ADHD groups, respectively; $t(38) = 5.10$, $p = 9.6 \times 10^{-6}$; $d = 1.61$, 95% confidence interval .79–2.43). The regression parameter estimates were significantly negatively correlated with ADHD symptoms across the entire sample (Pearson Correlation Coefficients ranged between −.61 and −.54 ($n = 38$, $p < .001$) for the childhood or adulthood symptoms of hyperactivity/impulsivity or inattention. However, despite our prediction, we did not detect significant relationships between the parameter estimates and severity of

Table 3. ADHD-Related Decreases in Negatively and Positively Correlated Functional Connectivity with Precuneus/Posterior Cingulate Regions

Region	BA	x	y	z	Cluster Size (No. Voxels)	Cluster Significance	Peak *Z* Scores
			Negatively Correlated Functional Connectivity				
Middle Frontal Gyrus[a]	6	14	−6	49	5201	$p = 1.5 \times 10^{-5}$, corrected	—
Cingulate Gyrus	24	9	3	37	—	—	4.41
Cingulate Gyrus	24/32	9	6	37	—	—	4.17
Middle Frontal Gyrus	6	6	0	55	—	—	4.09
Cingulate Gyrus	32	9	10	37	—	—	4.08
Cingulate Gyrus	24	13	4	44	—	—	4.02
Cingulate Gyrus	31	19	−36	43	—	—	3.82
Superior Temporal Gyrus[a]	22	−47	−10	5	1704	$p = .038$, corrected	—
Superior Temporal Gyrus	41	−47	−23	10	—	—	4.17
Claustrum	—	−32	−12	11	—	—	4.08
Claustrum	—	−38	−12	5	—	—	3.66
Superior Temporal Gyrus	22	−53	3	1	—	—	3.44
Precentral Gyrus	43	−59	−8	10	—	—	3.38
Precentral Gyrus	44	−49	3	7	—	—	3.36
			Positively Correlated Functional Connectivity				
Middle Frontal Gyrus[a]	9	−4	45	25	13,479	$p = 3 \times 10^{-11}$, corrected	—
Superior Frontal Gyrus	9	−7	55	26	—	—	4.47
Superior Frontal Gyrus	10	−19	63	22	—	—	4.36
Superior Frontal Gyrus	10	−19	66	22	—	—	4.24
Middle Frontal Gyrus	9	−2	48	22	—	—	4.1
Middle Frontal Gyrus	9	−2	51	20	—	—	4.05
Middle Frontal Gyrus	6	31	18	53	—	—	4
Cingulate Gyrus[a]	31	0	−49	28	1971	$p = .018$, corrected	—
Posterior Cingulate	31	−4	−54	26	—	—	3.66
Precuneus	31	−7	−60	26	—	—	3.59
Cingulate Gyrus	31	6	−39	29	—	—	3.48
Posterior Cingulate	23	−5	−59	19	—	—	3.34
Cuneus	7	3	−63	31	—	—	3.33
Cingulate Gyrus	31	1	−29	37	—	—	3.18

ADHD, attention-deficit/hyperactivity disorder; BA, Brodmann's area.
[a]Peak activations reported for cluster.

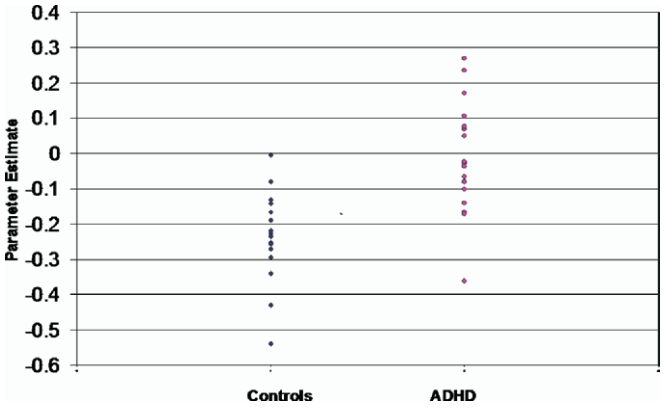

Figure 4. Decreased anterior cingulate cortex (ACC)/precuneus connectivity in attention-deficit/hyperactivity disorder (ADHD). The scatterplot depicts the mean parameter estimates for dorsal ACC connectivity (seed region: x = 8, y = 7, z = 38) in the precuneus/posterior cingulate cortex (PCC) region found to exhibit ADHD-related decrease in antirelationship to the ACC. As depicted in the plot, spontaneous activity in ACC negatively predicted activity in precuneus/PCC for control subjects, but no such relationship was found in ADHD ($p < 9 \times 10^{-6}$).

inattentive symptoms in the ADHD group (or the control group), presumably reflecting the highly restricted ranges of symptom counts within each group.

Discussion

By analyzing the intrinsic functional connectivity of putative frontal control loci in unbiased whole brain comparisons, we confirmed that the negative relationship posited by Weissman *et al.* (11) between control regions and the default-mode network is intrinsically represented in brain. Consistent with our hypothesis that ADHD is associated with abnormalities in fronto-default-mode interactions implicated in preventing attentional lapses, we found ADHD-related decreases in functional connectivity between a dorsal ACC seed and posterior components of the default-mode network (i.e., precuneus and PCC). Iteratively using the precuneus/PCC region as a "seed" for an additional regression analysis revealed ADHD-related decreases in connectivity among components of the default-mode network, notably between precuneus/PCC and ventromedial prefrontal cortex. We did not find a specific relationship between functional connectivity measures and inattention symptoms within the ADHD group, perhaps because inattentive and hyperactive symptoms, both of which were significantly negatively correlated with the regression parameter estimates, were highly correlated in our combined-type ADHD sample ($r = .68$). Of note, these novel results fit with the three unbiased voxel-based morphometric findings of diminished volume (30,31) or decreased cortical thickness (32) in precuneus and PCC in ADHD.

Although not the primary focus of this study, our finding of ADHD-related decreases in connectivity between anterior and posterior default mode components may suggest a novel locus of dysfunction for working-memory deficits commonly observed in ADHD (33). Better performance on a working-memory task has been reported to be positively related to the strength of functional connectivity between anterior and posterior default-mode components (VMPFC and PCC) (34). In this light, our findings of ADHD-related decreases in functional connectivity among default-mode components and abnormal connectivity with control regions suggest a potential neural basis for a linkage between working memory deficits and attentional fluctuations that will be addressed in future studies. Similarly, future studies combining pharmacologic manipulations and electrophysiologic methods or magnetoencephalography are required to move beyond functional connectivity to effective connectivity, the influence exerted by one neural system on another (8).

Our results do not confirm a prior report of greater functional connectivity in adolescents with ADHD between dACC and widespread regions including thalamus, cerebellum, insula, and pons (17). There are several possible explanations for our divergent findings. First, the ACC is functionally and structurally complex (35,10); we "seeded" an ACC subregion empirically linked to default-mode interactions, while the seed ROI used by Tian *et al.* (17) comprised the entire dorsal ACC. Second, Tian *et al.* did not differentiate the antiphase relationships ("anticorrelations") (14,24) that accounted for our findings. It is possible that undiagnosed learning disorders in the ADHD participants may have contributed to our finding, although the reasonably high level of educational attainment in all participants tends to diminish this concern. Finally, the studies differed with respect to age group (child, adult). In future studies, we plan to examine age effects and directly assess cognitive measures such as attentional lapses (6,7), working memory (33), response variability (36), and medication response.

In summary, we found strong evidence of disconnection between an anterior cingulate control region implicated in ADHD (32,37) and posterior components of the default-mode network (i.e., precuneus and PCC). In the context of increasing awareness of the complex role of precuneus and PCC in "high-level integration between posterior association processes and anterior executive functions" (38, p. 578), our findings suggest that structural and functional circuits linking the dACC to precuneus and PCC may represent "small-world network" long-range connections (39) that should be considered as a candidate locus of dysfunction in ADHD.

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Dr. Sonuga-Barke has potential conflicts of interest in relation to UCB Pharmaceuticals (consultancy, advisory board, and speaker honoraria), Janssen Cilag (consultancy, research grant, speaker honoraria), Shire Pharmaceuticals (advisory board), and Medice (speaker honoraria).

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Supplementary material cited in this article is available online.

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