Subcortico-Cortical Dysconnectivity in ADHD: A Voxel-Wise Mega-Analysis Across Multiple Cohorts

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Objective: A large body of functional MRI research has examined a potential role for subcortico-cortical loops in the pathogenesis of attention deficit hyperactivity disorder (ADHD), but has produced inconsistent findings. The authors performed a mega-analysis of six neuroimaging data sets to examine associations between ADHD diagnosis and traits and subcortico-cortical connectivity.

Methods: Group differences were examined in the functional connectivity of four subcortical seeds in 1,696 youths with ADHD diagnoses (66.39% males; mean age, 10.83 years [SD=2.17]) and 6,737 unaffected control subjects (47.05% males; mean age, 10.33 years [SD=1.30]). The authors examined associations between functional connectivity and ADHD traits (total N=9,890; 50.3% males; mean age, 10.77 years [SD=1.96]). Sensitivity analyses were used to examine specificity relative to commonly comorbid internalizing and non-ADHD externalizing problems. The authors further examined results within motion-matched subsamples, and after adjusting for estimated intelligence.

Results: In the group comparison, youths with ADHD showed greater connectivity between striatal seeds and temporal, fronto-insular, and supplementary motor regions, as well as between the amygdala and dorsal anterior cingulate cortex, compared with control subjects. Similar findings emerged when ADHD traits were considered and when alternative seed definitions were adopted. Dominant associations centered on the connectivity of the caudate bilaterally. Findings were not driven by in-scanner motion and were not shared with commonly comorbid internalizing and externalizing problems. Effect sizes were small (largest peak d, 0.15).

Conclusions: The findings from this large-scale mega-analysis support established links with subcortico-cortical circuits, which were robust to potential confounders. However, effect sizes were small, and it seems likely that resting-state subcortico-cortical connectivity can capture only a fraction of the complex pathophysiology of ADHD.

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Understanding the neural basis of complex behavioral phenotypes involves studying small effect sizes, requiring large sample sizes and validation across independent cohorts (1, 2). These considerations apply to efforts to parse the neural substrates of the core symptoms of attention deficit hyperactivity disorder (ADHD), a neurodevelopmental disorder that affects around 5%–10% of school-age children (3).

Decades of research point to altered interactions between subcortical regions and cortex in ADHD. Most implicated is a fronto-striato-thalamic circuit comprising reciprocal connections between the caudate, putamen, thalamus, supplementary motor area, lateral prefrontal cortex, and parietal lobe. This circuit is critical to executive functions, including working memory and inhibitory control, known to be impaired in ADHD (4, 5). Additionally, a second fronto-striatal circuit involving the nucleus accumbens and orbitofrontal cortex has been associated with ADHD (6–8). Dysfunction within this loop may underlie deficits in delay of gratification, reinforcement sensitivity, and effort-related decision making, which are characteristic of ADHD motivation styles (9). Finally, there is emerging evidence for involvement of circuits connecting the amygdala with the insula and dorsal and ventral medial prefrontal cortex, pivotal to affective processing, learning, and regulation, particularly in the context of negative emotions (10, 11). While the evidence for a role for the amygdala in ADHD is less compelling than for fronto-striatal loops, alterations within these amygdala-centered circuits have been observed in recent work in the disorder and have been proposed to underlie commonly co-occurring affective problems in youths with ADHD (10, 11).

Despite the large body of research implicating subcortico-cortical circuitry in ADHD, there has been a lack of convergence across studies examining the functioning of these circuits at rest, as the effects are likely to be small, and most individual studies are likely underpowered (12). Although typically including larger sample sizes, retrospective meta-analyses of published studies have also failed to detect robust group differences (12). However, these meta-analyses are severely limited by a lack of consistency in seed selection and

region-of-interest definitions across different studies. Moreover, given the limited availability of unthresholded statistical maps, neuroimaging meta-analyses are typically conducted using published coordinates (5). Consequently, only group differences meeting thresholds for statistical significance in published studies are includable, with subthreshold group differences not considered. This is especially problematic considering the known issues in the literature concerning low statistical power and publication bias, which lead to inflated type I and type II error rates among published neuroimaging findings (1, 2). Furthermore, the reliance on published group-level summary statistics means that published meta-analyses have not been able to consider potential confounders at the individual subject level, including in-scanner motion and comorbid emotional and behavioral problems.

Our aim in this study was to overcome these limitations by applying a mega-analytic approach to data from six data sets. We compared 1,696 youths with ADHD diagnoses against 6,737 unaffected control subjects. We followed up this analysis by examining associations with ADHD traits in 9,890 individuals, assessed using the attention problems subscale of the Child Behavior Checklist (CBCL) (13). All analyses controlled for key demographic variables, including age, sex, race/ethnicity, and socioeconomic status, as well as comorbid internalizing and non-ADHD externalizing problems and in-scanner motion. We examined the robustness of findings to considerations of estimated general intelligence and medication status, and examined associations in motion-matched subsamples. We also examined the specificity of findings relative to commonly comorbid internalizing and externalizing symptoms. Finally, we examined whether neuropsychological domains that are known to be subserved by subcortico-cortical circuits and commonly associated with ADHD were similarly associated with alterations in resting-state subcortico-cortical connectivity.

We hypothesized that the dominant patterns of associations between ADHD diagnosis and traits and subcortico-cortical dysfunction would center on the connectivity of striatal seeds, as the weight of the literature points to these striatal regions as pivotal in ADHD pathogenesis (4, 14). However, based on accumulating evidence for a role for the amygdala in the disorder (11, 14, 15), we also hypothesized ADHD-related abnormalities in amygdala connectivity, which may be tied to commonly comorbid affective problems (10, 11).

METHODS

Cohorts and Measures of ADHD

The methods section in the online supplement summarizes the recruitment methods, sampling strategies, protocols, and image acquisition parameters for each cohort. We contrasted individuals with ADHD against unaffected control subjects using data from the Adolescent Brain Cognitive Development Study (ABCD; N=7,268), the Healthy Brain Network (N=766), the Neurobehavioral Clinical Research cohort (N=226), and the enhanced Nathan Kline Institute–Rockland cohort (N=173) (16–19). Diagnoses were determined using DSM-5 criteria from semistructured interviews. Unaffected control subjects had minimal ADHD problems and were not taking psychostimulant medication (see the online supplement).

For the trait analyses, we used the attention problems subscale of the CBCL. We included data from the ABCD (N=7,703), Healthy Brain Network (N=846), Neurobehavioral Clinical Research (N=232), Nathan Kline Institute–Rockland (N=188), Human Connectome Project–Development (N=439), and National Consortium on Alcohol and Neurodevelopment in Adolescence (N=482) cohorts (16–21).

All studies had ethical approval and obtained informed assent or consent using institutional review board–approved procedures. The main inclusion criteria were availability of all covariate data, usable neuroimaging data, and ages ≥6 and ≤18 years. This age range was chosen because it corresponds to the age range for the CBCL (13).

Resting-State Connectivity

Details on image acquisition parameters for each cohort are provided in the online supplement. Preprocessing was performed using a well-validated and standardized 36-parameter plus despiking pipeline (22). Seeds for the caudate, putamen, nucleus accumbens, and amygdala were selected from the Harvard-Oxford probabilistic anatomical atlas (threshold ≥25% probability) (23). In the first instance, we examined seed regions bilaterally. However, supplementary analyses tested for potential hemisphere-specific associations. Mean time series were extracted for each region of interest. These time series were then correlated with the time series of each gray matter voxel in the brain, thereby creating subject-level voxel-wise connectivity maps for each seed, which were subsequently Fisher-z-transformed.

Subtle differences in seed placement can impact resting-state neuroimaging findings. We therefore performed supplementary analyses using alternative seed definitions (24). These supplementary analyses considered potential functional heterogeneity between dorsal and ventral subdivisions of subcortical structures. See the online supplement for details; Figures S1 and S2 depict the spatial location for the adopted seeds.

Modeling Approach

Voxel-wise linear mixed-effects modeling was performed using the lmerTest package (25) for R (http://www.r-project.org). We examined connectivity at each voxel as a function of ADHD diagnosis, while controlling for age, sex, socioeconomic status (household income), race/ethnicity, internalizing and non-ADHD externalizing problems assessed using the CBCL broadband subscales, and in-scanner motion (mean root-mean-squared [RMS] and mean RMS-squared). These covariates were included as fixed effects. Nested random effects were included for study, scanner ID, and nuclear family. The resultant statistical maps were thresholded using an initial cluster-forming threshold of $p<0.0001$ and a family-wise-error cluster-level-corrected threshold of $p<0.0125$

($p<0.05/4$ seed regions). We adopted a similar approach to examine associations with scores on the attention problems subscale. Sensitivity analyses and robustness checks included removing the associations between ADHD diagnosis or attention problems and in-scanner motion using a greedy matching algorithm (26), controlling for the potential confounder of estimated general intelligence and performing analyses in psychostimulant-free subgroups.

Owing to similar patterns of connectivity across subcortical seeds, partial correlation analyses were also performed to test for potentially more direct associations. Specifically, at the individual subject level, we assessed connectivity between the seed time series and the remaining voxels of the brain while controlling for the time series of the remaining three seed regions.

We next assessed disorder specificity of associations relative to commonly comorbid internalizing and externalizing problems assessed using the CBCL.

To examine the possibility that subcortico-cortical connectivity may be linked to ADHD via altered neuropsychological performance, within the large ABCD cohort we tested for associations between resting-state subcortico-cortical connectivity and performance on neuropsychological tests of cognitive domains commonly linked with ADHD (4, 5, 27), including working memory, inhibitory control, processing speed, and impulsive decision making (28, 29).

Finally, we examined whether associations between subcortico-cortical connectivity and ADHD diagnoses and traits changed or remained stable with age. As in previous work, to limit confounding between age range and cohort, we explored this question in the five data sets with suitably wide age ranges, excluding the ABCD cohort because subjects in that cohort were largely 9–10 years of age at the time of scanning (30).

See the online supplement for further details, including model syntax.

RESULTS

The participants' demographic and clinical characteristics are summarized in Table 1. Groups differed on key demographic variables, including age, sex, and race/ethnicity. Consequently, we controlled for these variables as covariates in all models.

Within-Group Brain Findings

Group-average seed-based maps for 9,890 youths are provided in Figures S3 and S4 in the online supplement.

Group Comparison

The caudate, putamen, and nucleus accumbens seeds showed heightened connectivity with left and right middle and superior temporal gyri/insula/inferior parietal lobe, extending into inferior frontal gyri for the caudate and putamen seeds, for 1,696 children/adolescents with ADHD relative to 6,737 unaffected control subjects. Those with ADHD also showed heightened connectivity between the caudate and putamen seeds and clusters including supplementary motor area/precentral gyrus/postcentral gyrus/inferior parietal lobe regions. The amygdala seed was associated with heightened connectivity with the dorsal anterior cingulate cortex in youths with ADHD relative to control subjects. Peak effect sizes were small, with d values ranging from 0.11 to 0.15 (Table 2 and Figure 1; see also Figures S5–S9 in the online supplement).

Associations Between ADHD Traits and Functional Connectivity

The diagnostic findings were partially echoed by findings for ADHD traits (N=9,890). Specifically, connectivity between the caudate seed and left and right middle and superior temporal gyri/insula/inferior parietal lobe and the supplementary motor area/precentral gyrus/postcentral gyrus/inferior parietal lobe was positively associated with scores on the attention problems subscale, as was connectivity between the nucleus accumbens and left and right superior temporal lobe/insula and right inferior parietal lobe. Scores on the attention problems subscale were also positively associated with connectivity between the amygdala seed and right middle frontal gyrus and supramarginal gyrus/superior temporal lobe/inferior parietal lobe. Peak effect sizes were again small, with partial r values ranging from 0.05 to 0.07. These are provided in Table S1 in the online supplement; see also Figures S10–S14 in the online supplement.

Sensitivity Analyses and Robustness Checks

Matching on motion. The primary findings remained significant after matching groups on in-scanner motion (ADHD group, N=1,642; control group, N=6,737). After removing significant associations between in-scanner motion and scores on the attention problems subscale (N=9,867), findings for the caudate seed remained significant, as did associations between scores on the attention problems subscale and connectivity between the amygdala and right middle frontal gyrus. Effect sizes were also largely unchanged. (See Tables S2 and S3 and Figures S15 and S16 in the online supplement.)

Controlling for estimated general intelligence. The primary findings remained significant after controlling for estimated general intelligence. Effect sizes were also largely unchanged. (See Tables S4 and S5 and Figures S16 and S17 in the online supplement.)

Psychostimulant-free subgroup analysis. When comparing 1,114 psychostimulant-free youths with ADHD against unaffected control subjects, widespread group differences (ADHD group > control group) in connectivity between striatal seeds and left and right middle and superior temporal gyri/inferior and superior parietal lobe/insula/inferior frontal gyri and left and right parietal lobe/precentral gyrus/postcentral gyrus regions were observed, albeit only at

TABLE 1. Characteristics of youths with ADHD and unaffected control subjects included in the case-control analysis, as well as subjects included in the analyses of ADHD traits (CBCL analyses)[a]

Variable	ADHD Group (N=1,696)		Control Group (N=6,737)		Statistic	p	Effect Size	CBCL Analyses (N=9,890)	
	Mean	SD	Mean	SD				Mean	SD
Age (years)	10.83	2.17	10.33	1.30	t=9.53	<0.001	d=0.29	10.77	1.96
Minutes of useable data	12.73	4.96	15.48	4.35	t=−21.09	<0.001	d=−0.59	15.05	4.93
In-scanner motion (mean RMS)	0.181	0.054	0.176	0.051	t=3.38	<0.001	d=0.09	0.174	0.05
IQ	100.41	16.54	105.57	16.47	t=−5.24	<0.001	d=−0.31	105.93	16.83
Scaled matrix	9.66	2.91	10.32	2.85	t=−6.63	<0.001	d=−0.23	10.24	2.92
NIH Toolbox									
Working memory	94.59	15.44	97.17	16.22	t=−4.92	<0.001	d=−0.16	96.63	16.12
Processing speed	85.39	16.94	88.57	17.41	t=−5.55	<0.001	d=−0.19	88.03	17.38
Inhibitory control	92.39	11.71	94.08	13.26	t=−4.20	<0.001	d=−0.14	93.76	13.08
	Median	IQR	Median	IQR				Median	IQR
CBCL									
Attention problems (raw)	8	6	1	3	W=10,735,550	<0.001	δ=0.88	2	5
Internalizing (raw)	7	10	3	5	W=8,297,186	<0.001	δ=0.45	3	6
Externalizing (raw)	7.5	12	1	4	W=9,047,786	<0.001	δ=0.58	2	6
	N	%	N	%				N	%
Sex					χ^2=201.97	<0.001	OR=2.22		
Male	1126	66.39	3,170	47.05				4,975	50.30
Female	570	33.61	3,567	52.95				4,915	49.70
Cash choice task					χ^2=0.46	0.50	OR=1.05		
3 days	393	39.18	2,484	40.37				3,039	40.09
3 months	610	60.82	3,669	59.63				4,542	59.91
Race/ethnicity					χ^2=18.40	0.001	V=0.02		
Asian	23	1.35	159	2.36				236	2.39
Black/African American	215	12.61	708	10.51				1,110	11.22
Hispanic/Latino	333	19.65	1,265	18.78				1,822	18.42
Mixed/other	191	11.26	660	9.80				1,001	10.12
White	934	55.13	3,945	58.56				5,721	57.85
Household income					z=−0.51	0.61	OR=0.98		
<$50,000	446	26.3	1,609	23.88				2,409	24.36
$50,000–100,000	487	28.71	1,937	28.75				2,779	28.10
$100,001–$200,000	444	26.18	2,205	32.73				3,128	31.63
>$200,000	319	18.81	986	14.64				1,574	15.92

[a] ADHD=attention deficit hyperactivity disorder; CBCL=Child Behavior Checklist; OR=odds ratio; RMS=root-mean-square; V=Cramér's V; W=Wilcoxon signed rank test; δ=Cliff's delta.

a relaxed cluster-forming threshold of $p<0.005$. This may reflect the reduction in sample size for the ADHD group and resultant loss of statistical power. At the same threshold, heightened connectivity between the amygdala seed and dorsal anterior cingulate cortex in youths with ADHD relative to control subjects was retained from the primary analyses. (See Figure S19 and Table S6 in the online supplement for details.)

Partial correlation analyses. After controlling for the time series of the other seeds, greater connectivity between the caudate and supplementary motor area/precentral gyrus/postcentral gyrus, right inferior parietal lobe, and right middle and superior temporal gyri was found in patients with ADHD relative to unaffected control subjects. At a relaxed cluster-forming threshold of $p<0.005$, the findings for the caudate seed closely resembled those observed in the primary analyses (i.e., heightened connectivity with left and right temporal lobe/insula/inferior parietal lobe/inferior frontal gyri and supplementary motor area/precentral gyrus/postcentral gyrus/parietal lobe in patients with ADHD relative to unaffected control subjects). Findings from the primary group comparison were not retained for the other seeds at either threshold.

Furthermore, after controlling for the time series of the other seeds, positive associations were observed between scores on the attention problems subscale and connectivity between the caudate and left and right superior temporal lobe (extending into inferior parietal lobe on the right side). At a liberal cluster-forming threshold of $p<0.005$, the findings for the caudate seed closely resembled those observed in the primary analyses. (See Figures S20 and S21 and Tables S7 and S8 in the online supplement.)

TABLE 2. Results of case-control comparison[a]

Cluster	x	y	z	Peak d	Mean d	Size (voxels)	Overlap (%)	Talairach Label
Left and right caudate								
1	64	−7	−3	0.15	0.10	17,555	9.2	Left superior temporal gyrus
							9.1	Right superior temporal gyrus
							7.7	Right postcentral gyrus
							5.9	Right insula
							5.8	Left postcentral gyrus
							5.3	Right precentral gyrus
							4.1	Left insula
							3.8	Left precentral gyrus
							3.0	Right inferior parietal lobule
							2.9	Right medial frontal gyrus
							2.8	Left middle temporal gyrus
							2.5	Left medial frontal gyrus
							2.4	Right inferior frontal gyrus
							2.3	Left inferior parietal lobule
							1.8	Right paracentral lobule
							1.7	Left paracentral lobule
							1.6	Right middle temporal gyrus
Left and right putamen								
1	−51	−3	−1	0.13	0.09	2,193	37.4	Left superior temporal gyrus
							34.1	Left middle temporal gyrus
							10.6	Left insula
							2.9	Left postcentral gyrus
							1.4	Left inferior temporal gyrus
							1.1	Left fusiform gyrus
							1.1	Left precentral gyrus
							1.0	Left inferior parietal lobule
2	44	−25	8	0.12	0.09	982	37.9	Right superior temporal gyrus
							37.4	Right middle temporal gyrus
							7.5	Right transverse temporal gyrus
							5.3	Right insula
							1.8	Right postcentral gyrus
							1.5	Right inferior temporal gyrus
3	−31	−39	44	0.12	0.09	564	28.3	Left inferior parietal lobule
							21.3	Left postcentral gyrus
							13.0	Left precentral gyrus
							1.2	Left superior parietal lobule
4	52	−29	36	0.12	0.09	517	54.9	Right postcentral gyrus
							14.2	Right precentral gyrus
							9.0	Right inferior parietal lobule
5	30	20	−21	0.12	0.09	472	41.5	Right inferior frontal gyrus
							29.5	Right insula
							10.7	Right superior temporal gyrus
							8.4	Right uncus
							1.1	Right middle frontal gyrus
6	58	24	12	0.11	0.09	367	95.6	Right inferior frontal gyrus
							1.0	Right precentral gyrus
Left and right nucleus accumbens								
1	6	−23	68	0.12	0.09	1,179	29.6	Right medial frontal gyrus
							10.9	Left medial frontal gyrus
							9.1	Right paracentral lobule
							6.2	Left precentral gyrus
							5.5	Right cingulate gyrus
							3.5	Right postcentral gyrus
							2.1	Left postcentral gyrus
							2.1	Left paracentral lobule
2	34	−5	12	0.13	0.09	1,141	27.0	Right precentral gyrus
							17.7	Right insula
							17.3	Right postcentral gyrus
							14.8	Right superior temporal gyrus
							3.5	Right inferior parietal lobule
							2.8	Right middle temporal gyrus

continued

TABLE 2, *continued*

Cluster	x	y	z	Peak d	Mean d	Size (voxels)	Overlap (%)	Talairach Label
							2.5	Right inferior frontal gyrus
							1.7	Right claustrum
							1.0	Right transverse temporal gyrus
3	−63	−19	2	0.12	0.09	796	42.6	Left superior temporal gyrus
							21.6	Left insula
							11.7	Left lentiform nucleus
							10.2	Left precentral gyrus
							3.7	Left inferior parietal lobule
							2.4	Left middle temporal gyrus
							1.7	Left claustrum
4	−39	−15	50	0.13	0.09	579	42.4	Left precentral gyrus
							42.2	Left postcentral gyrus
							7.7	Left inferior parietal lobule
Left and right amygdala								
1	−9	−1	42	0.11	0.09	244	44.0	Left cingulate gyrus
							22.4	Right cingulate gyrus
							12.6	Right medial frontal gyrus
							12.6	Left superior frontal gyrus
							8.5	Left medial frontal gyrus

[a] Youths with attention deficit hyperactivity disorder (ADHD), N=1,696; unaffected control subjects, N=6,737. For all clusters, ADHD group > control group.

Alternative seed definitions. Findings for the Harvard-Oxford seeds broken down by hemisphere are presented in Figures S22–S25 and Tables S9–S12 in the online supplement.

When the primary analyses were rerun using alternative seed definitions, associations similar to those in the primary analyses based on the Harvard-Oxford seeds emerged for the dorsal/ventral caudate and nucleus accumbens seeds. Specifically, ADHD was associated with greater connectivity relative to unaffected control subjects between striatal seeds and left and right middle and superior temporal gyri/insula/inferior parietal lobe (extending into the inferior frontal gyri bilaterally for the caudate seeds) and supplementary motor area/precentral gyrus/postcentral gyrus/parietal lobe regions. For the putamen seed, similar patterns of greater connectivity in youths with ADHD relative to unaffected control subjects were found for the ventral subdivision only. Similarly, greater connectivity between the amygdala and dorsal anterior cingulate cortex was found for the ventral, but not the dorsal, amygdala seed. (See Figure S26 and Table S13 in the online supplement.)

As in the primary analyses using the Harvard-Oxford seeds, connectivity between the caudate seeds and left and right middle/superior temporal lobe/insula/inferior parietal lobe regions was positively associated with scores on the attention problems subscale. However, associations between attention problems scores and connectivity between the caudate and supplementary motor area/precentral gyrus/postcentral gyrus/parietal lobe were significant only for the dorsal caudate seed. Further associations for the remaining seeds are reported in Figure S27 and Table S14 in the online supplement.

Effect sizes were similar across seed definitions (range for peak voxel effect sizes for alternative seed definitions: d, 0.11–0.14; partial r, 0.05–0.07).

Disorder specificity. No significant associations were observed for scores on the internalizing problems subscale. Scores on the externalizing problems subscale had negative associations with connectivity between subcortical seeds and predominantly middle and superior temporal and parietal regions. (See Figures S28 and S29 and Table S15 in the online supplement.) All clusters from the primary analysis examining associations with attention problems scores emerged as differentially associated with scores on this subscale compared with the externalizing problems subscale. Furthermore, for the caudate seed, connectivity with left and right temporal lobe/insula/inferior parietal lobe/inferior frontal gyri regions also emerged in our direct comparisons with the internalizing problems subscale. (See Figures S30 and S31 and Tables S16 and S17 in the online supplement.)

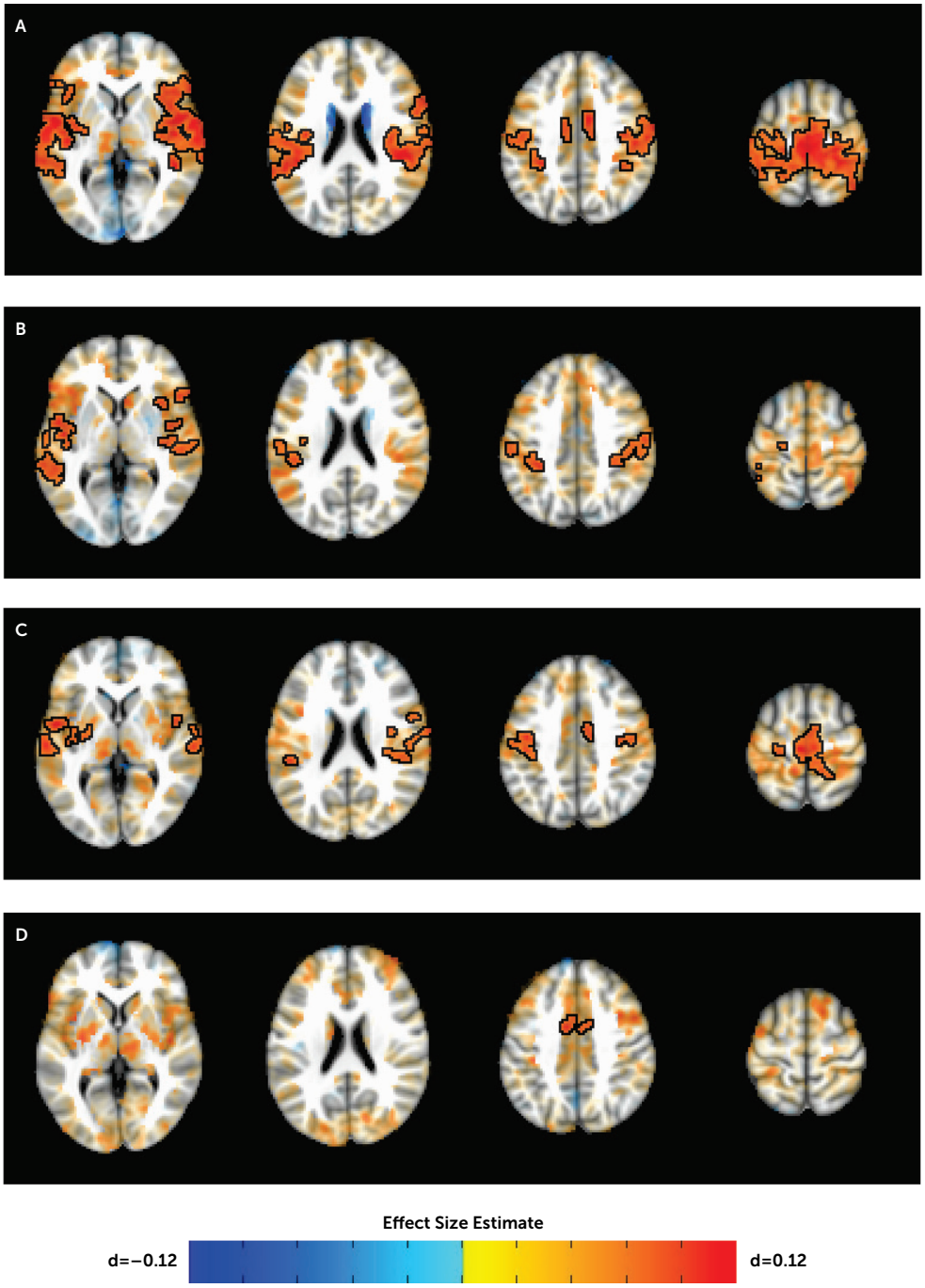
Associations with neuropsychological measures. There were minimal associations between scores on the neuropsychological tests or decision-making task and subcortico-cortical resting-state connectivity. Subthreshold associations also point to a lack of overlap with brain regions showing greater connectivity in youths with ADHD relative to unaffected control subjects. (See Figures S32–S36 and Table S18 in the online supplement.)

Interactions with age. There were minimal significant interaction effects with age on subcortico-cortical resting-state connectivity. None overlapped with primary findings. (See Figures S37–S40 and Table S19 in the online supplement.)

DISCUSSION

In this study, we applied voxel-wise mega-analytic methods to examine patterns of resting-state subcortico-cortical

FIGURE 1. Findings from a mega-analysis of differences in seed-based subcortico-cortical connectivity in youths with attention deficit hyperactivity disorder (ADHD) and unaffected control subjects[a]



[a] Panels A–D show, respectively, results from the caudate, putamen, nucleus accumbens, and amygdala seeds. Positive effect sizes indicate ADHD group > control group. Voxels in significant clusters are opaque and boxed. Subthreshold voxels are presented translucently.

connectivity associated with ADHD diagnosis (1,696 youths with ADHD and 6,737 unaffected control subjects) and ADHD traits (in 9,890 participants). In line with fronto-striatal models of the disorder, ADHD diagnosis and traits were associated with abnormal connectivity between striatal seeds and inferior frontal, insular, supplementary motor, and inferior parietal regions, with the dominant and most widespread associations centered on the connectivity of the caudate bilaterally (4, 5). Greater connectivity was also observed between the amygdala and dorsal anterior cingulate cortex in youths with ADHD relative to control subjects. The overall pattern of results was robust across two sets of region-of-interest definitions, after adjustments for estimates of general intelligence, and after matching subjects on in-scanner motion. Furthermore, this pattern of findings was not shared with commonly comorbid internalizing or externalizing problems.

Associations with ADHD diagnosis and traits were most widespread for connectivity of the caudate seed, and after including the time series for all subcortical seeds in first-level partial-correlation models, group differences were observed only for this region of interest. These associations were not shared with scores on the internalizing and externalizing problems subscales. Such findings align with well-established neurobiological models of ADHD, which emphasize alterations in caudate functioning (4, 5, 31). Moreover, they are supported by decades of research that have linked caudate alterations to the disorder through techniques such as in vivo receptor imaging, structural MRI, and task-based fMRI (5, 14, 31). The specificity of these findings in relation to internalizing and externalizing problems is consistent with previous studies. These studies have demonstrated the disorder-specific nature of task-based connectivity and activation within the same set of regions, including the caudate, inferior frontal, and supplementary motor regions, when compared with various psychiatric conditions

commonly observed in childhood (5, 32). Furthermore, the present findings suggest that these brain alterations are specifically associated with ADHD and are not indicative of general features of childhood psychopathology or influenced by comorbid symptoms (5, 30, 32).

Contemporary accounts often link alterations in resting-state connectivity to ADHD symptoms via neuropsychological functions such as working memory, inhibitory control, and impulsive decision making (32–34). These functions are closely relevant to the symptom profile of ADHD and have been linked to subcortico-cortical functioning (4, 5, 32). However, in our study, no significant associations were found between neuropsychological performance and subcortico-cortical connectivity. Furthermore, while the regions implicated by our connectivity findings resemble those from previous imaging meta-analyses of task-based fMRI studies of inhibitory control in ADHD (5, 32), a recent literature review of task-based functional connectivity studies pointed to hypo-connectivity, not hyperconnectivity as we found, in similar regions during inhibitory control tasks in ADHD (32, 35). Thus, while our findings are broadly consistent with models centered on roles for fronto-striatal circuits in ADHD (4, 5), they also indicate the need for models that can explain the absence of associations with neuropsychological task performance and the contradictory direction of effects observed under task-based and resting-state conditions.

The small effect sizes observed in the present mega-analysis (largest peak Cohen's d, 0.15; largest peak partial r, 0.07) align with the emerging consensus that reproducible associations between individual differences in brain functioning and complex psychological phenotypes such as ADHD will almost certainly involve small univariate effect sizes, and further indicate that most previous neuroimaging studies of ADHD have been significantly underpowered. Consequently, small-scale, cross-sectional, mass-univariate observational studies are expected to offer limited utility in advancing the field. However, the neuroimaging research of ADHD is entering an exciting phase, with the ever-expanding availability of large-scale longitudinal data sets that encompass genetic, neuroimaging, clinical, and family data (19, 21, 36, 37). These data sets hold promise for investigating important clinically relevant questions and ensuring the reproducibility of brain-behavior associations (2, 38). For instance, contrary to the traditional understanding of ADHD as an early-onset disorder with symptoms gradually diminishing over time, recent longitudinal clinical investigations have revealed greater variability in ADHD symptom course. This includes late adolescent/adult onset, idiosyncratic fluctuations in symptom trajectories and diagnostic status, and shifts in dominant symptom domains over time (19, 39). With the advent of multiple large-scale independent discovery and test longitudinal data sets, the field will soon be empowered to meaningfully apply longitudinal multivariate prediction methods. This can aid in exploring questions such as whether brain imaging data can predict later ADHD symptom trajectories (2, 19). Furthermore, future research may leverage sophisticated imaging genetics and within-subject, repeated-measures designs to enable quasi-causal inferences (2). Such studies can help differentiate features of brain structure and functioning that play mechanistic roles in the etiology of ADHD from those that are secondary to ADHD symptoms or otherwise linked to the disorder in a non-causal manner (2).

Some important limitations of our study must be kept in mind. First, analyses were performed in volume space, and previous work has indicated improvements in both statistical sensitivity and spatial accuracy with surface-based relative to volume-based fMRI (40). Second, subjects were instructed to keep their eyes open during scanning, and eye-tracking data were not available to ensure compliance with these instructions or for use in models controlling for eyes-open/eyes-closed status at the level of individual subjects. Third, we integrated data from several diverse data sets characterized by distinct imaging protocols, recruitment procedures, and diagnostic tools. Research conducted on more homogeneous samples might exhibit larger effect sizes, although this approach might compromise the generalizability of the findings. Fourth, it is important to acknowledge that the mega-analytic study sample did not accurately reflect the demographics of the U.S. population. Notably, over 15% of the children and adolescents included in the study came from households with incomes exceeding $200,000. This skewed representation likely rendered the sample unrepresentative of the entire ADHD population, which is a well-known concern in neuroimaging studies focusing on neurodevelopmental disorders (30). Therefore, it is inappropriate to consider our effect size estimates as representative of the entire U.S. child population. Fifth, because of our reliance on cross-sectional data, we were limited in our ability to investigate whether the connections between resting-state connectivity and ADHD diagnoses and traits varied with age. Although we addressed this matter using a cross-sectional approach, such methods are susceptible to cohort effects and fail to capture individual-level fluctuations in brain functioning and ADHD traits. Moreover, our utilization of cross-sectional data prevented us from making definitive statements regarding the direction of effects (2).

In summary, we conducted the largest study to date on changes in subcortico-cortical connectivity in ADHD. The brain regions showing altered connectivity align with fronto-striatal models of the disorder, but the effects observed were small. Resting-state subcortico-cortical connectivity can only capture a small fraction of the complex pathophysiology of ADHD.

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