REVIEW

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Systematic Review and Meta-analysis: Resting-State Functional Magnetic Resonance Imaging Studies of Attention-Deficit/Hyperactivity Disorder

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Objective: To conduct a meta-analysis of resting-state functional magnetic resonance imaging (R-fMRI) studies in children and adolescents with attention-deficit/hyperactivity disorder (ADHD) and in adults with ADHD to assess spatial convergence of findings from available studies.

Method: Based on a preregistered protocol in PROSPERO (CRD42019119553), a large set of databases were searched up to April 9, 2019, with no language or article type restrictions. Study authors were systematically contacted for additional unpublished information/data. Resting-state functional magnetic resonance imaging studies using seed-based connectivity (SBC) or any other method (non-SBC) reporting whole-brain results of group comparisons between participants with ADHD and typically developing controls were eligible. Voxelwise meta-analysis via activation likelihood estimation with cluster-level familywise error (voxel-level: $p < .001$; cluster-level: $p < .05$) was used.

Results: Thirty studies (18 SBC and 12 non-SBC), comprising 1,978 participants (1,094 with ADHD; 884 controls) were retained. The meta-analysis focused on SBC studies found no significant spatial convergence of ADHD-related hyperconnectivity or hypoconnectivity across studies. This nonsignificant finding remained after integrating 12 non-SBC studies into the main analysis and in sensitivity analyses limited to studies including only children or only non–medication-naïve patients.

Conclusion: The lack of significant spatial convergence may be accounted for by heterogeneity in study participants, experimental procedures, and analytic flexibility as well as in ADHD pathophysiology. Alongside other neuroimaging meta-analyses in other psychiatric conditions, the present results should inform the conduct and publication of future neuroimaging studies of psychiatric disorders.

Key words: ADHD, ALE, meta-analysis, neuroimaging, resting state

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Over the past 3 decades, a large number of magnetic resonance imaging (MRI) studies have been conducted to elucidate the pathophysiology of attention-deficit/hyperactivity disorder (ADHD). Whereas early studies focused on localized effects, recent work addresses localized network effects or diffuse network dysfunction. Indeed, a specific neuroimaging modality, referred to as resting-state functional MRI (R-fMRI), has gained traction in estimating brain function across neuropsychiatric disorders, including ADHD. Practical advantages of R-fMRI include its applicability to nearly the entire range of ages and levels of cognitive functioning.[1] R-fMRI quantifies brain activity during fMRI scans without an active, explicit task, as required in task-based fMRI. Even when at rest (ie, when the individual is not asked to complete any active task), brain regions show an intrinsic, spontaneous activity,[2] defined as "ongoing neural and metabolic activity which is not directly associated with subjects' performance of a task."[3] Brain regions characterized by significantly correlated spontaneous activity are considered functionally connected and are part of so-called resting-state networks.[1] The most common measure in R-fMRI is referred to as seed-based connectivity (SBC). It examines large-scale correlations of blood oxygen level–dependent signal between a region of interest (seed) and other gray matter voxels.[1] Another approach allowing estimation of large-scale connectivity is termed independent component analysis. Other R-fMRI metrics focus on local connectivity (eg, regional homogeneity) or, more generally, its variability (eg, fractional amplitude of low-frequency fluctuations).

Based on results of individual R-fMRI studies in ADHD, a number of pathophysiological hypotheses on ADHD have been proposed,[1,4,5] but results of individual studies testing

such hypotheses are inconsistent. Structural[6–8] and task-based functional[7–12] ADHD neuroimaging studies have been quantitatively synthesized in a number of meta-analyses, with overall mixed findings across meta-analyses, which possibly are due to different age range of participants (eg, children[7] or adultseg[12]), type of comparison (eg, ADHD subjects versus typically developing controls [TDCs][9] or ADHD subjects versus subjects with other neuropsychiatric disorderseg[8]), and meta-analytic methods (eg, signed differential mapping[6] or activation likelihood estimation [ALE][7]). Additionally, in a large sample from the ENIGMA-ADHD consortium, subtle differences in surface area emerged in frontal, cingulate, and temporal regions between children with ADHD and controls, but no significant differences were detected in adolescents or adults with ADHD compared with TDCs.[13]

Indeed, ADHD has been conceptualized as a dysconnectivity syndrome[14] rather than as a disorder characterized by alterations in isolated brain areas detected by structural or task-based MRI studies. A recent meta-analysis by Sutcubasi *et al.*[15] of 20 R-fMRI studies using an approach named multilevel kernel density analysis (MKDA) found that compared with TDCs, participants with ADHD presented with disrupted within–default mode network (DMN) connectivity—reduced in the core (ie, posterior cingulate cortex seed) but elevated in the dorsomedial prefrontal cortex subsystem (ie, temporal pole–inferior frontal gyrus). In this review, we aimed to provide a quantitative synthesis of R-fMRI studies in ADHD using an alternative meta-analytic approach, namely, ALE, and a different study selection process. Whereas Sutcubasi *et al.*[15] included only studies that focused on 4 predefined brain networks, we adopted a theory-free approach without restricting networks examined. Additionally, while Sutcubasi *et al.*[15] focused on SBC studies, we included studies based on SBC or R-fMRI methods other than SBC (non-SBC) in our meta-analysis to test convergence in patterns of abnormal functional connectivity across studies. Combining results of SBC with different seeds might seem problematic. However, resting-state functional connectivity analyses should be reciprocal: a region that is identified in the disconnectivity pattern of several different seeds may be inferred conversely as showing aberrant connectivity with a broad range of regions, ie, a pathophysiological hub. In our analysis, we aimed to identify such hubs. No measure was excluded a priori. Within the framework of the meta-analytic approach used in this study, the main question was to what extent findings from the studies retained in the analysis converge—ie, was there spatial overlap in the patterns of abnormal connectivity across studies. Given the exploratory nature of this approach, no a priori hypotheses were formulated.

METHOD

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[16] recommendations and the published best practice on the conduct of neuroimaging meta-analyses.[17] Here, the term systematic review is used in accordance to the Cochrane definition (https://uk.cochrane.org/news/what-are-systematic-reviews). The protocol was registered in the Prospective Register of Systematic Reviews (CRD42019119553). In the spirit of Open Science, the full dataset used for analyses will be freely available online in the open source platform ANIMA (http://anima.fz-juelich.de/)[18] on publication of this article.

Search

With the support of a librarian, we searched PubMed, Ovid MEDLINE, Biological Abstracts, EMBASE Classic+EMBASE, PsycINFO, BIOSIS Previews, and Web of Science (Science Citation Index Expanded, BIOSIS, Food Science and Technology Abstracts) databases, from inception to April 9, 2019, with no language or article type restrictions. Articles in languages other than English were translated by the authors or their collaborators. Also, references of retrieved pertinent papers and proceedings of relevant conferences were hand-searched to find additional potentially relevant studies. Details on the search strategy/syntax are reported in Appendix 1, Supplement 1, available online.

Selection Criteria

Study Type. We included empirical studies using R-fMRI contrasting subjects with ADHD versus TDCs, reporting results as coordinates in standard space at the whole-brain level. In addition to data from published reports, we systematically contacted the corresponding authors of studies retrieved as abstracts/conference proceedings to enquire about their eligibility and, if needed, gather unpublished information/data necessary for the meta-analysis.

Population. ADHD populations comprised children, adolescents, or adults with a formal categorical diagnosis of ADHD according to *DSM-III, DSM-III-R, DSM-IV, DSM-IV-TR*, or *DSM-5* or hyperkinetic disorder as per ICD-10 or previous versions. As per protocol, studies were deemed eligible regardless of the past or current treatment of participants with ADHD medications. However, in the prespecified protocol we stated a sensitivity analysis would be conducted including only studies with participants with ADHD who were medication-naive. Comparison populations comprised TDCs.

Outcome. The outcome for the main set of analyses was the difference in SBC between ADHD subjects and TDCs. In additional analyses, consistent with previous published meta-analyses of data across different imaging modalities,[19] we added data from studies with any other R-fMRI measure, which increased statistical power and tested more broadly ADHD-related abnormalities in brain activity.

Study Identification/Selection and Data Extraction

Details on study identification/selection and data extraction, conducted according to the PRISMA recommendations,[16] are reported in Appendix 2, Supplement 1, available online.

Statistical Analysis

Convergence of significant between-group differences, ie, significant foci of the original studies, was analyzed using GingerALE Version 3.0.2 (http://www.brainmap.org/ale/) for coordinate-based meta-analysis. ALE evaluates the brain locations in which the convergence of reported hypoconnectivity or hyperconnectivity across studies is higher than would be expected by chance. Therefore, the main question here is: where have hyperconnectivity or hypoconnectivity foci in a particular disorder consistently been reported across studies? In evaluating this question, it is important to consider that the spatial coordinates referring to significant findings in each study are associated with some degree of spatial convergence. The key aspect underlying ALE is thus to represent the foci reported in the individual studies not as exact points, but rather by treating them as centers of a tridimensional Gaussian probability distribution, with the center indicating the highest probability of activation. This procedure is performed for each focus of each study included in the meta-analysis and yields a probabilistic location of the effects reported in that particular study.[20] Following ALE, the spatial uncertainty associated with the reported foci was first modeled based on an established procedure,[21] yielding probabilistic maps of effect locations corrected to avoid within-experiment summation of effects.[22] Inference was then sought relative to a null distribution of random spatial association using cluster-level correction for multiple comparisons.[23] In our meta-analysis, we included studies showing ADHD-related hypoconnectivity and hyperconnectivity. We then conducted a post hoc meta-analysis across hypoconnectivity and hyperconnectivity to test convergence in aberrant connectivity (either hyperconnectivity or hypoconnectivity). Because of the reciprocal nature of R-fMRI, integrating hypoactivations and hyperactivations enabled us to identify hubs of heterogeneous patterns of disconnectivity.

We considered the analyses adequately powered when at least 17–20 experiments were available, which has been shown by simulation to achieve 80% power to detect an effect occurring in one third of the underlying population of experiments (in the ALE approach, the effect size is defined as the percentage of experiments that converge at a specific location).[24] As per protocol, we planned separate analyses for studies in children and adolescents and studies in adults to assess possible developmental differences and analyses focused on studies including male participants only, as ADHD is more common in males, and sex differences in clinical presentations have been reported.[25] We also explored the possibility of grouping the seeds by canonical brain networks.[26]

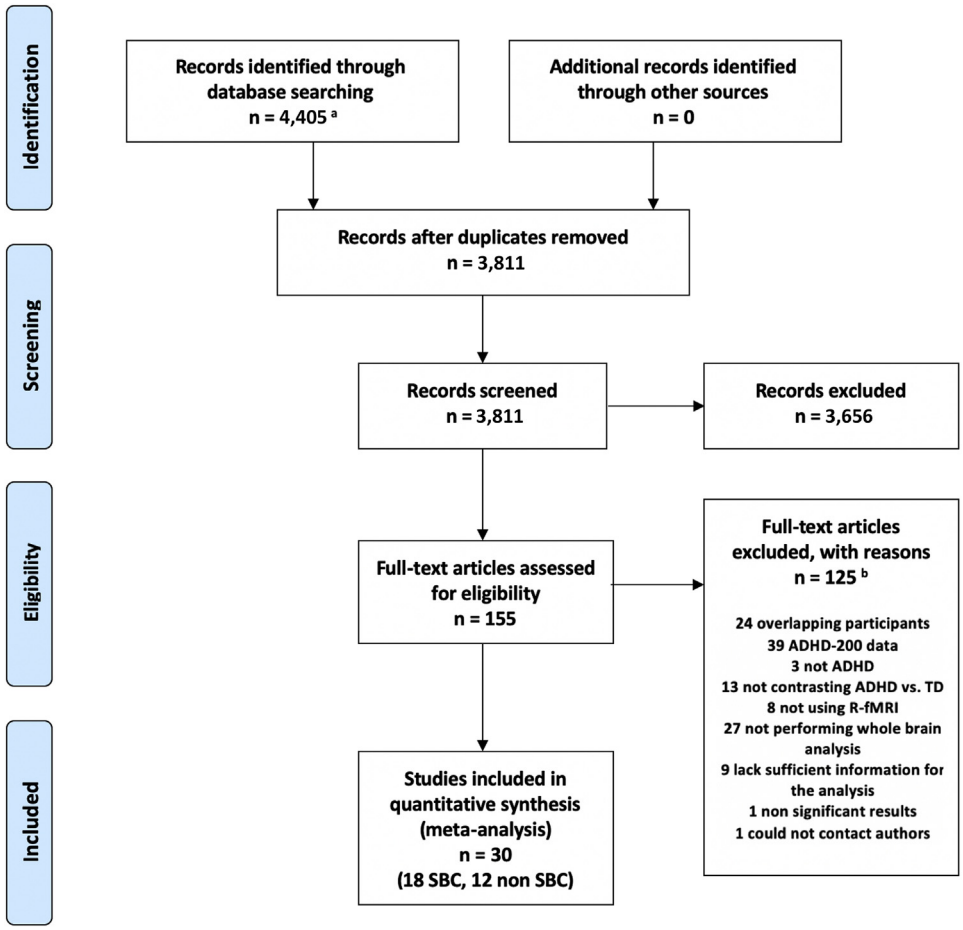
As recommended,[17] cluster-level familywise error was used (voxel-level: $p < .001$; cluster-level: $p < .05$). Talairach coordinates were converted into Montreal Neurological Institute space before using them in analyses. Changes in relation to the preregistered protocol are reported in Appendix 3, Supplement 1, available online.

RESULTS

The study selection process is shown in Figure 1 and reported in detail in Appendix 4, Supplement 1, available online (list of studies excluded after full-text screening, with reasons for exclusion). From 4,405 potentially eligible citations, 30 studies[27–56] (datasets) were retained for the meta-analysis (SBC: n = 18; non-SBC: n = 12). Table 1 shows the characteristics of included studies. Table 2 summarizes the key findings from each study. Four SBC studies and 2 non-SBC studies were conducted in adults. Retained studies comprised 1,978 participants (SBC = 953; non-SBC = 1,025): 1,094 with ADHD [SBC = 526 (children = 437); non-SBC = 568 (children = 452)] and 884 TDCs [SBC = 427 (children = 337); non-SBC = 457 (children = 331)].

The main ALE analysis (18 SBC studies, 13 experiments, 91 foci for ADHD subjects > TDCs and 17 experiments with 141 foci for TDCs > ADHD subjects, respectively) did not show any statistically significant clusters in both contrasts (ADHD-related hyperactivity or hypoactivity). Likewise, the additional ALE analysis integrating 12 studies with non-SBC measures (20 experiments, 127 foci for ADHD subjects > TDCs, and 26 experiments, 183 foci for TDCs > ADHD subjects) did not detect any statistically significant clusters in both contrasts. The extracted peak coordinates from each study are reported in Table S1, available online. Owing to the lack of significant spatial convergence, it is not possible to show the results of the thresholded analyses on a brain map; however, Figures 2 and 3 report unthresholded (positive) z-score maps considering SBC studies and SBC plus non-SBC studies, respectively.

FIGURE 1 PRISMA Flow Diagram



Note: ADHD = attention-deficit/hyperactivity disorder; R-fMRI = resting-state functional magnetic resonance imaging; SBC = seed-based connectivity; TD = typically developing (control).

[a]Results for each database are reported in Appendix 1, Supplement 1, available online.

[b]References of excluded studies are reported, with reasons for exclusion, in Appendix 4, Supplement 1, available online.

Significant results were also lacking in a sensitivity analysis limited to studies in children, although the ADHD > TDC contrast was not examined owing to insufficient statistical power, and in a sensitivity analysis of non–medication-naïve participants, which could be performed only by meta-analysis of SBC and non-SBC studies and only in relation to the TDC > ADHD contrast. Other planned sensitivity analyses (ie, analyses limited to studies of medication-naïve subjects, studies in adults, and studies in male or female participants only) were not possible owing to insufficient numbers of experiments. Likewise, it was not possible to perform analyses grouping seeds by canonical brain networks.

Post hoc meta-analysis of both contrasts (ADHD-related hypoactivity and hyperactivity, 30 studies, 46 experiments, 127 foci for ADHD subjects > TDCs and 183 foci for TDCs > ADHD subjects) found a statistically significant cluster in the left superior temporal gyrus (STG) (Montreal Neurological Institute coordinates [−34, −8, 0], cluster size = 105 voxels, familywise error $p = .03$). The sensitivity analyses focused on studies including children only or medicated patients only, and meta-analysis of both contrasts (ADHD-related hypoactivity and hyperactivity) did not find any significant result.

DISCUSSION

We conducted a systematic review and meta-analysis of R-fMRI studies contrasting participants with ADHD and TDCs following published best practices for the conduct of meta-analyses in neuroimaging[17] and including unpublished information/data that we gathered after systematically contacting study authors. The meta-analysis of SBC did not find any spatial convergence of ADHD-related hyperconnectivity or hypoconnectivity across the 18 retained

TABLE 1 Description of Studies Included in Meta-analysis

Reference	ADHD No.	ADHD Age, y, mean	TDC No.	TDC Age, y, mean	Medication -naïve	Scan duration	Eyes	Exclusion criteria for motion	Head motion correction (first level)	Seed(s) or name of R-fMRI measure	Source of data
Seed-based connectivity											
Cao *et al.*, 2009[27]	19	13	23	13	100%	8 min	Closed	>3 mm or >3°	WM, CSF, 6 MPs, GSR	Bil putamen	Published
Castellanos *et al.*, 2008[28]	20	35	20	31	NA	6.5 min	Open	NA	WM, CSF, 6 MPs, GSR	dACC, R IFG, R MFG	Published and unpublished information/ data
Hoekzema *et al.*, 2014[29]	22	33	23	29	100%	NA	Open	>3 mm	aCompCor	DLPFC	Published
Hong *et al.*, 2015[30]	83	10	22	10	88%	6 min 24 s	Closed	>2 mm or >2°	WM, CSF, GSR	[a]	Published
Icer *et al.*, 2018[31]	15	12	15	13	100%	9 min 44 s	Closed	>0.3 mm and/ or >0.3°	WM, CSF, 6 MPs (aCompCor)	[b]	Published
Karalunas *et al.*, 2014[32]	39	8.9	15	NA	NA	7–10 min	Open	>3 mm or >3°[c]	WM, CSF, 6 MPs and their temporal derivatives, GSR	Bil amygdala	Published and unpublished information/ data
Kim *et al.*, 2017[33]	13	11	13	10	NA	NA	Closed	>3 mm or >3°	NA	Vermis of the cerebellum	Published
Kucyi *et al.*, 2015[34]	23	24	23	24	30%	10 min 8 s	Open	NA	WM, CSF, 6 MPs (aCompCor)	Bil cerebellum	Published and unpublished information/ data
Li *et al.*, 2014[35]	33	10	32	11	100%	6 min 40 s	Closed	>2 mm or >2°	WM, CSF, MPs, GSR	[d]	Published
Lin and Gau, 2016[37]	24	30	24	30	100%	6 min	Closed	≥1.5 mm or ≥1.5°	WM, CSF, 6 MPs and their 1st-order temporal derivatives (aCompCor)	Bil subgenual ACC, Bil TPJ, Bil VFC, Bil IPS, Bil FEF, Bil DLPFC, Bil R PRE, PCC, mPFC	Published and unpublished information/ data

(*continued*)

TABLE 1 Continued

Reference	ADHD No.	ADHD Age, y, mean	TDC No.	TDC Age, y, mean	Medication -naïve	Scan duration	Eyes	Exclusion criteria for motion	Head motion correction (first level)	Seed(s) or name of R-fMRI measure	Source of data
Lin *et al.*, 2018[36]	46	8	31	9	100%	8 min	Closed	>3 mm or >3°	WM, CSF, 24 MPs	PRE, TPJ, VFC, IPS, FEF	Published
Lin *et al.*, 2015[38]	25	9.9	25	10	NA	6 min	Closed	>1 mm maximum FD	WM, CSF, Friston-24, GSR	aPFC	Published and unpublished information/ data
McLeod *et al.*, 2016[39]	21	13	23	11	NA	5 min	Open	NA	WM, CSF, 6 MPs	L M1	Published
Mennes *et al.*, 2011[40]	17	11	17	11	64%	6.5 min	Open	>4 mm[e]	WM, CSF, 6 MPs, GSR	[f]	Published
Mizuno *et al.*, 2017[41]	31	9.7	30	11	42%	7 min 42 s	Closed	>2.5 mm, 2.5°, and mean FD 0.5 mm	WM, CSF, Friston 24	Bil crus I/II in the cerebellum	Published
Posner *et al.*, 2014[42]	30	9.8	31	11	100%	10 min	Closed	NA	aCompCor	Bil anterior hippocampus	Published
Yang *et al.*, 2013[43]	30	9.2	30	9.4	100%	6 min	Closed	>1 mm or >1°	WM, CSF, 6 MPs, GSR	PCC	Published
Yu *et al.*, 2020[44]	35	10	30	10	100%	8 min	Closed	>2.5 mm or >2.5°	WM, CSF, 6 MPs, GSR	3 subamygdala	Published
Non–seed-based connectivity											
An *et al.*, 2013[45]	23	13	32	12	68%	8 min	Closed	>3 mm or >3°	NA	ReHo	Published
Cao *et al.*, 2007[46]	15	13	15	13	NA	8 min	Closed	>2 mm or >1°	Need help	ReHo	Published
Jiang *et al.*, 2014[47]	31	9.5	31	9.7	NA	6 min	Closed	>3 mm or >3°	NA	VMHC	Published
Kim *et al.*, 2018[48]	67	9.6	44	11	NA	NA	NA	NA	aCompCor	ReHo, sliding window ReHo	Published and unpublished information/ data

(*continued*)

TABLE 1 Continued

Reference	ADHD No.	ADHD Age, y, mean	TDC No.	TDC Age, y, mean	Medication -naïve	Scan duration	Eyes	Exclusion criteria for motion	Head motion correction (first level)	Seed(s) or name of R-fMRI measure	Source of data
Mostert *et al.*, 2016[49]	99	35	113	36	13%	9 min	Closed	Absolute >1.5 mm and/or RMS of relative >0.2 mm	ICA-AROMA	ICA	Published and unpublished information/ data
Pruim *et al.*, 2019[50]	179	18	90	17	NA	8 min 30 s	Open	RMS-FD >0.74 mm	ICA-AROMA	ICA	Published
Qian *et al.*, 2019[51]	41	9	16	10	95%	8 min 12 s	Open	FD >0.8 or DVARS >0.05	ICA	ICA	Published and unpublished information/ data
Shang *et al.*, 2018[52]	37	11	37	11	100%	6 min	Closed	FD >1 SD	ICA-AROMA, aCompCor	ReHo	Published
Shekarchi *et al.*, 2014[53]	21	8.5	21	NA	NA	6 min 24 s	Closed	NA	NA	ICA	Published
Sokunbi *et al.*, 2013[54]	17	30	13	30	NA	6 min	NA	NA	NA	SampEn	Published
Yang *et al.*, 2013[55]	18	8.8	18	9.9	50%	NA	Closed	>2 mm or >2°	NA	ALFF, ReHo	Published
Yoo *et al.*, 2018[56]	20	11	27	11	100%	7 min	Closed	NA	aCompCor	ICA, fALFF	Published

Note: ACC = anterior cingulate cortex; ADHD = attention-deficit/hyperactivity disorder; ALFF = amplitude of low-frequency fluctuations; aPFC = anterior prefrontal cortex; BA = Brodmann area; Bil = Bilateral; aCompCor = a component based noise correction method; CSF = cerebrospinal fluid; dACC = dorsal anterior cingulate cortex; DLPFC = dorsolateral prefrontal cortex; DMN = default mode network; fALFF = fractional amplitude of low-frequency fluctuations; FD = frame displacement; FEF = frontal eye field; GSR = global signal regression; ICA = independent component analysis; ICA-AROMA =ICA-based Automatic Removal Of Motion Artifacts; IFG = inferior frontal gyrus; IPS = inferior parietal sulcus; L = left; MFG = middle frontal gyrus; MP = motion parameter; mPFC = medial prefrontal cortex; NA = not available; OFC = orbitofrontal cortex; PCC = posterior cingulate cortex; PRE = precuneus; R = right; ReHo = regional homogeneity; R-fMRI = resting-state functional magnetic resonance imaging; RMS = root mean square; SampEn = sample entropy; SMA = supplementary motor area; TDC = typically developing control; TPJ = temporoparietal junction; VFC = ventral frontal cortex; VMHC = voxel-mirrored homotopic connectivity; WM = white matter.

[a]*Dorsal caudate, ventral caudate/nucleus accumbens, dorsal caudal putamen, ventrorostral putamen.*

[b]*95 seeds (42 BAs in each hemisphere and 11 DMN-related regions.*

[c]*Participants with >50% of their frames removed were not included in the analyses (n = 16 ADHD, n = 1 TDC).*

[d]*R frontal operculum, R and L insula, R pre-SMA, ACC, R supramarginal gyrus, L mid-occipital gyrus, L and R caudate, R and L thalamus.*

[e]*>4 mm maximum displacement between consecutive time points.*

[f]*R and L globus pallidus, dorsal superior frontal gyrus, OFC, ventral superior frontal gyrus.*

TABLE 2 Summary of Key Findings From Studies Included in the Meta-analysis

Reference	Summary of findings
Seed-based connectivity	
Cao *et al.*, 2009[27]	L putamen: ↑ iFC with globus pallidus/thalamus; ↓ subcallosal gyrus/nucleus accumbens, SFG, declive, and STG/MTG in ADHD R putamen: ↓ iFC with precuneus and declive in ADHD
Castellanos *et al.*, 2008[28]	Dorsal ACC: ↓ iFC with PCC and precuneus in ADHD PCC: ↓ iFC with MFG, STG, and cingulate gyrus in ADHD
Hoekzema *et al.*, 2014[29]	DLPFC: ↑ iFC with L postcentral gyrus, L precentral gyrus, R temporal pole, L SMG, L inferior parietal gyrus, R insula, L orbitofrontal gyrus, L cerebellar tonsil, R precentral gyrus, and R medial prefrontal gyrus
Hong *et al.*, 2015[30]	Dorsal caudate: ↓ iFC with L SFG and R MFG Dorsal putamen: ↓ iFC with L parahippocampal gyrus
Icer *et al.*, 2018[31]	L premotor cortex: ↓ iFC with L primary somatosensory cortex in ADHD R fusiform gyrus: ↓ iFC with cerebellum in ADHD R MTG: ↑ iFC with primary motor cortex in ADHD R STG: ↑ iFC with R SMG in ADHD R ventral PCC: ↑ iFC with L associative visual cortex, L secondary visual cortex, and R dorsal PCC in ADHD R temporopolar area: ↑ iFC with R angular gyrus in ADHD R angular gyrus: ↑ iFC with R somatosensory association cortex in ADHD L inferior frontal cortex pars opercularis: ↑ iFC with R dorsal frontal cortex in ADHD L DLPFC: ↑ iFC with R angular gyrus and L dorsal PCC in ADHD R DLPFC: ↑ iFC with L inferior prefrontal gyrus in ADHD PCC: ↑ iFC with R MTG and R STG in ADHD R IPL: ↑ iFC with L DLPFC in ADHD mPFC: ↑ iFC with R angular gyrus and R STG in ADHD
Karalunas *et al.*, 2014[32]	Amygdala: ↑ iFC with occipital lobe, precuneus/posterior cingulate, IPL, anterior insula, cerebellum, and caudate in mild subtype of ADHD; ↑ iFC with medial frontal in surgent subtype; ↓ iFC with occipital lobe, lateral frontal, and cerebellum in mild subtype of ADHD; ↓ iFC with cerebellum in surgent subtype of ADHD; ↓ iFC with anterior insula, precuneus, and medial frontal in irritable subtype of ADHD
Kim *et al.*, 2017[33]	Vermis of the cerebellum: ↓ iFC with R MFG in ADHD
Kucyi *et al.*, 2015[34]	Cerebellar DMN areas: ↑ iFC with Bil insula, Bil mid-cingulate cortex, Bil retrosplenial cortex, Bil putamen, Bil precentral and postcentral gyri, R STG, Bil lateral occipital cortex, Bil fusiform and lingual gyri, Bil cuneus, Bil FEF, Bil superior parietal lobule, and L cerebellum in ADHD
Li *et al.*, 2014[35]	R globus pallidus: ↑ iFC with Bil OFC in ADHD L globus pallidus: ↑ iFC with Bil OFC in ADHD R DLPFC: ↑ iFC with L VMPFC in ADHD L OFC: ↑ iFC with Bil SFG in ADHD L ventral SFG: ↑ iFC with Bil SFG and Bil OFC in ADHD R dorsal SFG: ↓ iFC with R STG, Bil precentral gyrus, Bil SMG, and Bil putamen in ADHD L OFC: ↓ iFC with L cerebellum is ADHD L ventral SFG: L SMG and R angular gyrus in ADHD

(continued)

TABLE 2 Continued

Reference	Summary of findings
Lin and Gau, 2016[37]	Dorsal attention network: ↓ iFC with Bil FEF and R MFG in ADHD Cognitive control network: ↓ iFC with Bil DLPFC in ADHD DMN: ↓ iFC with L precuneus in ADHD
Lin *et al.*, 2018[36]	R FEF: ↑ iFC with R postcentral gyrus in ADHD L FEF: ↑ iFC with R precentral gyrus in ADHD R precuneus: ↑ iFC with R postcentral gyrus, L lingual gyrus, and L STG in ADHD L precuneus: ↑ iFC with R precentral gyrus and L lingual gyrus in ADHD
Lin *et al.*, 2015[38]	L anterior PFC: ↓ iFC with R anterior IPL in ADHD R anterior PFC: ↓ iFC with R VLPFC and R putamen in ADHD
McLeod *et al.*, 2016[39]	M1: ↓ iFC with R parietal operculum, R SMG, R auditory cortex, FEF, L pallidum, R inferior frontal gyrus, L angular gyrus, L SMG, brainstem, L amygdala, L insular cortex, L IFG, R anterior cingulate gyrus, Bil putamen, L MFG, and L pallidum in ADHD
Mennes *et al.*, 2011[40]	R caudate: ↑ iFC with R frontal operculum, L planum temporale, L frontal pole, L frontal operculum, and R cingulate gyrus in ADHD R frontal operculum: ↑ iFC with R caudate and ↓ iFC with R precuneus in ADHD R supramarginal gyrus: ↑ iFC with R caudate and R cingulate gyrus in ADHD L thalamus: ↑ iFC with L SMG and L MFG,↓ iFC with R cerebellum in ADHD R thalamus: ↑ iFC with L frontal pole and L MTG in ADHD L caudate: ↓ iFC with R subcallosal cortex in ADHD
Mizuno *et al.*, 2017[41]	R crus I/II: ↓ iFC with L DLPFC in ADHD
Posner *et al.*, 2014[42]	L anterior hippocampus: ↑ iFC with L STG, Bil parietal lobe, and R SMG; ↓ iFC with temporal pole and R parietal lobe R anterior hippocampus: ↑ iFC with L rectus, R fusiform gyrus, L calcarine, R medial frontal, R middle temporal, and L precuneus; ↓ iFC with L amygdala, R subcallosal gyrus, R parahippocampal region, R middle temporal, L calcarine, R medial frontal gyrus, and L middle frontal in ADHD
Yang *et al.*, 2013[43]	PCC: ↓ iFC with Bil mPFC, R posterior cingulate gyrus, R ITG, cerebellar posterior lobe, L insula, R IPL, L postcentral gyrus, Bil STG, and L fusiform gyrus in ADHD
Yu *et al.*, 2020[44]	L basolateral amygdala: ↓ iFC with vermis and L postcentral gyrus in ADHD R basolateral amygdala: ↓ iFC with vermis and Bil thalamus in ADHD L centromedial amygdala: ↓ iFC with L cerebellum, R postcentral gyrus, and Bil superior temporal pole in ADHD R centromedial amygdala: ↓ iFC with R precuneus and Bil inferior occipital pole in ADHD L superficial amygdala: ↓ iFC with Bil mPFC and R SFG; ↑ iFC with L postcentral gyrus in ADHD R superficial amygdala: ↓ iFC with Bil lingual gyrus, Bil IPL, Bil SFG, and R MFG in ADHD
Non–seed-based connectivity	
An *et al.*, 2013[45]	↓ ReHo in Bil SFG in ADHD ↑ ReHo in L cuneus, Bil sensorimotor cortex, R premotor area, R calcarine gyrus, L postcentral gyrus, and R superior occipital gyrus in ADHD
Cao *et al.*, 2007[46]	↓ ReHo in L MFG, L SFG, and R ITG in ADHD-C ↓ ReHo in R IFG, L SFG, R pyramis, L STG, and R ITG in ADHD-I ↑ ReHo in R lingual gyrus, R cuneus, L lingual gyrus, R inferior parietal gyrus, L lingual gyrus, and L cuneus in ADHD-I

(continued)

TABLE 2 Continued

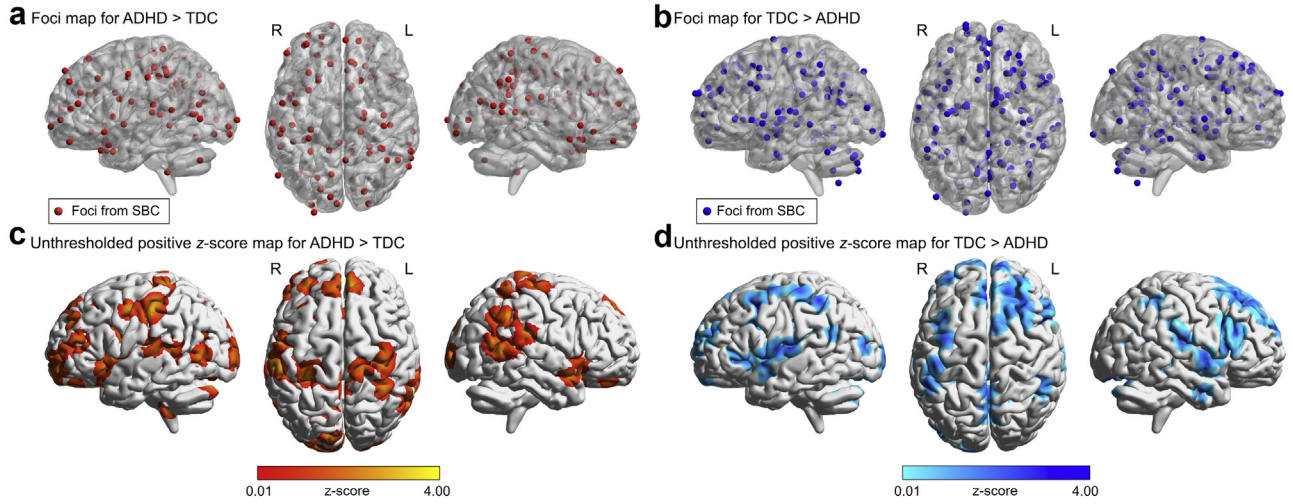
Reference	Summary of findings
Jiang *et al.*, 2014[47]	↑ VMHC in Bil frontal lobe, Bil occipital lobe, and cerebellar posterior lobe in ADHD
Kim *et al.*, 2018[48]	↓ Dynamic ReHo in L superior parietal surface in ADHD
Mostert *et al.*, 2016[49]	↑ FC in executive control network in ADHD
Pruim *et al.*, 2019[50]	Diagnostic effect of ADHD on FC in L dorsal ACC, R PCC, L dorsomedial prefrontal cortex, L caudate, L putamen, R precentral gyrus, and R cerebellum
Qian *et al.*, 2019[51]	Diagnostic effect of ADHD on FC in anterior DMN
Shang *et al.*, 2018[52]	↓ ReHo in Bil putamen, L posterior cingulate, R precentral gyrus, L supplementary motor area, and L precuneus in ADHD
Shekarchi *et al.*, 2014[53]	↓ FC in R frontal pole, R frontal medial cortex, R ITG, R occipital pole, and R temporal pole in ADHD
Sokunbi *et al.*, 2013[54]	↓ SampEn in L occipital lobe, L parietal lobe, L frontal lobe, and R limbic lobe in ADHD
Yang, *et al.* 2013[55]	↓ ALFF in Bil posterior lobes of cerebellum and L side of pons ↑ ALFF in R precentral gyrus in ADHD ↓ ReHo in L MFG, R SFG, and L precuneus ↑ ReHo in L anterior lobe of cerebellum, L caudate nucleus, R parahippocampal gyrus, L precentral gyrus, and R MFG in ADHD
Yoo *et al.*, 2018[56]	↓ FC in Bil precuneus and R DLPFC in ADHD

Note: ACC = anterior cingulate cortex; ADHD = attention-deficit/hyperactivity disorder; ADHD-C = attention-deficit/hyperactivity disorder combined presentation; ADHD-I = attention-deficit/hyperactivity disorder inattentive presentation; ALFF = amplitude of low-frequency fluctuations; Bil = bilateral; DLPFC = dorsolateral prefrontal cortex; DMN = default mode network; FC = functional connectivity; FEF = frontal eye field; iFC = intrinsic functional connectivity; IFG = inferior frontal gyrus; IPL = inferior parietal lobe; ITG = inferior temporal gyrus; L = left; MFG = middle frontal gyrus; mPFC = medial prefrontal cortex; MTG = middle temporal gyrus; OFC = orbitofrontal cortex; PCC = posterior cingulate cortex; R = right; ReHo = regional homogeneity; SampEn = sample entropy; SFG = superior frontal gyrus; SMG = supramarginal gyrus; STG = superior temporal gyrus; VLPFC = ventrolateral prefrontal cortex; VMPFC = ventromedial prefrontal cortex; VMHC = voxel-mirrored homotopic connectivity.

studies. Likewise, no significant convergence was detected with meta-analysis of the 18 SBC studies with 12 additional R-fMRI studies using measures other than SBC. Sensitivity analyses focused on studies including children only or medicated patients only were in line with the findings of the main analysis. The post hoc meta-analysis of hyperconnectivity and hypoconnectivity showed that the left STG had a consistently dysregulated connectivity, with evidence of both hypoconnection and hyperconnection to diverse seeds.

The lack of significant findings in the present study, in contrast to the significant results in a recent meta-analysis of R-fMRI by Sutcubasi *et al.*,[15] should not be surprising because we used a different approach to select studies, adopting a theory-free approach that led us to include studies regardless of the specific resting measure and the brain networks on which they focused, as opposed to a theory-driven selection of SBC studies focused on 4 predefined networks (default mode, cognitive control, salience, affective/motivational), and we used a different meta-analytic approach (and related software). Sutcubasi *et al.*[15] adopted MKDA, an alternative approach to ALE. Both MKDA and ALE create a study-specific contrast map using a set of foci reported by an empirical study. However, to create contrast maps, ALE accounts for the empirical estimates of the spatial uncertainty driven by the between-subject and between-template variability of the individual studies.[23] By contrast, MKDA uses a different kernel of user-defined size and treats a cluster of peaks as a blob during Monte Carlo simulation, which lowers the risk of false-positive findings when a cluster has subpeaks. Thus, the choice of approach is based on the scope of the study. As Sutcubasi *et al.*[15] focused on atypical connectivity within and between 4 large brain networks, MKDA was a reasonable choice. By contrast, the main scope of the current study was to detect spatial convergence in patients with ADHD, for which ALE is more suitable. Therefore, our meta-analysis provides an alternative synthesis of the R-fMRI literature in ADHD that complements the results by Sutcubasi *et al.*[15]

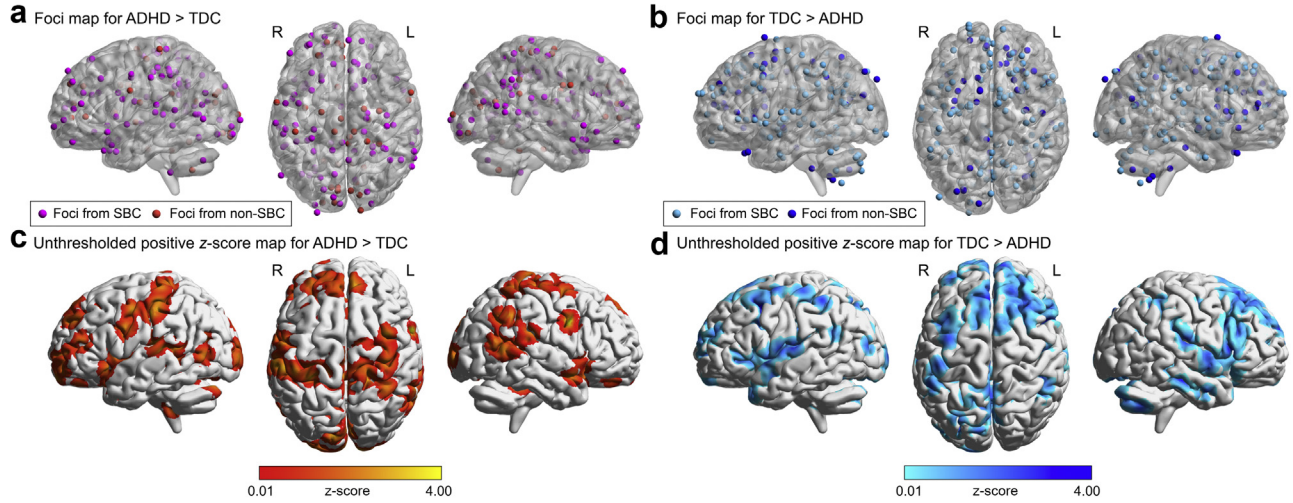
FIGURE 2 Anatomical Location of Foci Reported in Individual Seed-Based Connectivity Studies



Note: *Foci where studies showed hyperconnectivity in attention-deficit/hyperactivity disorder (ADHD) are shown in red (a), while foci where studies reported hypoconnectivity in ADHD are illustrated in blue (b). Unthresholded positive z-score maps are shown for hyperconnectivity (c) and hypoconnectivity in ADHD (d). L = left; R = right; SBC = seed-based connectivity; TDC = typically developing controls. Please note color figures are available online.*

The lack of significant spatial convergence is not in line with previous hypotheses in the field. Here, we mention 4 hypotheses. First, ADHD has been found to be characterized by alterations in the normal interplay between the DMN, a cluster of brain regions associated with self-referential cognitions, ruminations, and mind-wandering (typically less active during active tasks), and brain regions of cognitive control networks (usually active during explicit tasks). Whereas the functional activity of DMN and cognitive control networks is expected to be anticorrelated (ie, inversely correlated) over time in typically developing people, studies have reported significantly decreased anticorrelation between these 2 networks in people with ADHD.[1,4] This lends support to the DMN hypothesis of ADHD, postulating that the function of cognitive control networks is disrupted in ADHD by abnormal intrusion of the DMN during an active task, leading to attention lapses that would underpin attention difficulties in ADHD.[5]

FIGURE 3 Anatomical Location of Foci Reported in Individual Studies Regardless of Measure



Note: *Foci with hyperconnectivity in attention-deficit/hyperactivity disorder (ADHD) reported in seed-based connectivity (SBC) studies and non-SBC studies are shown in purple and red, respectively (a). Foci with hypoconnectivity in ADHD reported in SBC and non-SBC studies are shown in light blue and dark blue, respectively (b). Unthresholded positive z-score maps are shown for hyperconnectivity (c) and hypoconnectivity (d). L = left; R = right; TDC = typically developing controls. Please note color figures are available online.*

However, the location of the components of the DMN and cognitive control network found to interact abnormally has not been consistent across studies.[1] Second, significantly decreased synchrony within the DMN components themselves has been found in people with ADHD compared with TDCs, which would also disrupt the interplay between the DMN and the cognitive control network. However, findings across such studies have not been unanimous.[1,4] Third, some studies pointed to a disruption of connectivity in cognitive, reward, and affective cortico-striatothalamocortical loops, with both hyperconnectivity and hypoconnectivity reported.[1,4] Finally, more recently, a multinetwork model has been proposed, characterized by an inappropriate engagement of the salience network with the central executive network and DMN.[57] Overall, our results suggest that each of these hypotheses is supported by a limited set of studies, but none of them are specifically supported by evidence across available studies subjected to meta-analysis in an atheoretical and unbiased data-driven manner.

The lack of statistically significant spatial convergence in hypoconnectivity or hyperconnectivity across studies may reflect a number of factors. First, it could be argued that our meta-analysis of SBC was underpowered to detect significant effects. However, the total number of experiments from studies included in the main meta-analysis (n = 18) was equal to the lower bound of the recommended range of experiments (n = 17–20) that yield adequate statistical power in simulations.[24] We note that this is not a rigid threshold, as the required number of experiments for a meta-analysis to be sufficiently powered depends on the expected effect size. To detect small/medium effect sizes typical of neurobiology, a larger number of experiments is needed. Nevertheless, we still found no significant convergence in a more powered analysis quantitatively synthesizing all available SBC studies (30 experiments in total). Second, lack of significant spatial convergence could be due to study heterogeneity in terms of study participants' characteristics (sex, age, comorbidities, medication status), MRI and analytic procedures (statistical thresholding/correction and, more specific to R-fMRI, correction for head motion–related artifacts) (Table 1).

Third, the heterogeneity of ADHD per se, in terms of severity and type of core symptoms, contributing genetic factors and environmental stressors, and underlying pathophysiology, cannot be discounted.[58] To wit, the field has converged on the notion that brain alterations in ADHD are accounted for by multiple models, rather than a single one.[59,60] In this respect, case-control paradigms, commonly used in neuroimaging studies of ADHD (including the ones retained for the present meta-analysis), do not seem appropriate, as they basically disguise such sources of heterogeneity. Indeed, by means of normative modeling, a recent voxel-based morphometry study of adults with persistent ADHD showed that only a few individual brain foci showed extreme deviations in more than 2% of the participants with ADHD, providing quantitative support to the notion of interindividual differences at the level of brain structure in people with persistent ADHD.[61] If the same pattern were to apply to R-fMRI measures in ADHD, our findings of no significant convergence would not be surprising.

The lack of convergence would be compatible with 2 alternative models: First, ADHD is characterized by alterations in the interplay across brain networks, and the networks involved differ across individuals with the disorder, and, second, the same networks are involved for all individuals, but the precise locations of disrupted connectivity within networks vary across individuals. In fact, a number of studies detected abnormal interplay between the DMN and cognitive control networks, but the abnormally connected subcomponents of the DMN and cognitive control networks varied across studies.[4] More specifically, Castellanos *et al.*[28] found a significant inverse correlation between the resting-state activity in the frontal cognitive control regions and the precuneus/posterior cingulate cortex, which are central hubs of the DMN. Cao *et al.*[27] found decreased negative connectivity of regions of interest in the putamen to right cerebellum and right temporal lobe as well as of right putamen to left cerebellum and right precuneus. Sun *et al.*[62] showed a significantly decreased negative resting-state connectivity between the dorsal anterior cingulate cortex and specific regions in the DMN, including the dorsomedial prefrontal cortex and the posterior cingulate cortex. Similarly, Sato *et al.*[63] also found abnormal connectivity between the dorsal anterior cingulate cortex and the posterior cingulate cortex. Fourth, it is at least theoretically possible that ADHD is not characterized by abnormal intrinsic brain connectivity. However, before embracing this position, the previously discussed caveats should be rigorously addressed.

Consistent dysregulation in the left STG is in line with a report of abnormal graph spectral entropy in the STG in ADHD,[64] but we consider this finding provisional, as it was based on a post hoc analysis. However, it is worth noting that the STG is involved in auditory processing as well as social cognition,[65] and ADHD impairment in processes related to language semantics has also been found in another meta-analysis of studies in adults with ADHD using functional decoding.[12]

The results of this systematic review and meta-analysis should be considered in light of its strengths and

limitations. As for strengths, we performed a comprehensive search in a large number of databases and included unpublished information/data from studies published as conference proceedings after systematically contacting authors. Additionally, we carefully selected the studies that met inclusion criteria, thus ensuring that the methodological assumptions underpinning the validity of ALE were met. As such, despite the plethora of publications on R-fMRI studies in ADHD, we discarded a large number of publications relying on the same dataset (ADHD-200, n = 39), analyzing overlapping data from the same dataset (n = 24), or failing to report results from whole-brain analyses (n = 27), which would have violated the statistical null assumption underpinning the validity of ALE meta-analysis.

In addition to the limitations discussed above in relation to the individual studies included in the meta-analysis, possible limitations of the meta-analysis per se should also be considered. Although we endeavored to perform a comprehensive search, we may have missed pertinent studies. Even though we systematically contacted all study corresponding authors to seek clarification or additional data, we could not gather relevant information/data from some (Appendix 4, Supplement 1, available online). It should also be noted that ALE does not allow meta-analysis of studies with nonsignificant results, as it is designed to detect spatial convergence of significant results. However, we excluded only 1 study with nonsignificant results (Appendix 4, Supplement 1, available online). Finally, we did not carry out any formal appraisal of study quality, such as the Cochrane risk of bias tool (https://methods.cochrane.org/bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials), which is used to assess the risk of bias in randomized controlled trials. We are unaware of any similar tool to critically appraise R-fMRI study quality.

Despite these caveats, our findings are in line with findings from other recent meta-analyses of brain structural and task-based studies of ADHD[7] and neuroimaging studies of other psychiatric disorders (eg, depression[66]) that failed to find significant spatial convergence of results across studies. We believe that, alongside these other meta-analyses, the results of our study call for a paradigm shift in the conduct and publication process of neuroimaging studies, including R-fMRI studies of ADHD. Owing to their considerable costs, neuroimaging studies in psychiatric disorders typically have small samples, with a likely tendency to prioritize publishing positive results over replication and negative studies. As such, whereas individual studies have produced intriguing signals, R-fMRI studies in ADHD have not yielded coherent conclusions.

Homogeneous calibration across scanners, analysis protocol preregistration, standardization in technical procedures and analytic approaches, inclusion of medication-naïve participants, large samples based on data sharing of existing data and prospectively collected samples via consortia, discovery and validation datasets, and use of paradigms other than case-control studies (eg, normative modeling approaches) seem the way forward. The ADHD-200 initiative served as a proof-of-concept, but larger samples and more sophisticated, standardized approaches are needed to attain meaningful significant results.[67] The ABCD study could provide a model for prospective, methods-aligned multisite data collection.[68] Furthermore, a more precise non–imaging-based subphenotyping of ADHD, based on detailed questionnaires, actigraphy, or more precise neurocognitive tasks, may provide more homogeneous subgroups for inclusion in R-fMRI studies, such as the study by Karalunas *et al.*,[32] which showed that subtypes of ADHD identified based on temperamental traits were characterized by unique patterns of resting-state connectivity. The ENIGMA consortium,[69] which was set up to address small sample size and heterogeneity, provides an example of how the field is reacting and moving forward. Furthermore, given the challenges of selecting clinically homogeneous samples of ADHD defined categorically, we argue that a dimensional approach, sufficiently powered to allow multiple distinct dimensions to be examined, should be more consistently implemented.

Overall, our negative results (lack of spatial convergence across studies) should not lead to dismissing the possible utility of R-fMRI studies in ADHD. Rather, the present study will be informative for researchers planning future R-fMRI studies of ADHD and for clinicians when they interpret and appraise the literature in this still growing field.

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