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Review

Task-Based Functional Connectivity in Attention-Deficit/Hyperactivity Disorder: A Systematic Review

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ABSTRACT

Altered neurocognitive functioning is a key feature of attention-deficit/hyperactivity disorder (ADHD), and increasing numbers of studies assess task-based functional connectivity in the disorder. We systematically reviewed and critically appraised functional magnetic resonance imaging (fMRI) task-based functional connectivity studies in ADHD. A systematic search conducted up to September 2020 found 34 studies, including 51 comparisons. Comparisons were divided into investigations of ADHD neuropathology (37 comparing ADHD and typical development, 2 comparing individuals with ADHD and their nonsymptomatic siblings, 2 comparing remitted and persistent ADHD, and 1 exploring ADHD symptom severity) and the effects of interventions (8 investigations of stimulant effects and 1 study of fMRI neurofeedback). Large heterogeneity in study methodologies prevented a meta-analysis; thus, the data were summarized as a narrative synthesis. Across cognitive domains, functional connectivity in the cingulo-opercular, sensorimotor, visual, subcortical, and executive control networks in ADHD consistently differed from neurotypical populations. Furthermore, literature comparing individuals with ADHD and their nonsymptomatic siblings as well as adults with ADHD and their remitted peers showed ADHD-related abnormalities in similar sensorimotor and subcortical (primarily striatal) networks. Interventions modulated those dysfunctional networks, with the most consistent action on functional connections with the striatum, anterior cingulate cortex, occipital regions, and midline default mode network structures. Although methodological issues limited many of the reviewed studies, the use of task-based functional connectivity approaches has the potential to broaden the understanding of the neural underpinnings of ADHD and the mechanisms of action of ADHD treatments.

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Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder defined by age-inappropriate levels of hyperactivity, impulsivity, and/or inattention (1). ADHD is associated with impairments in various "hot" and "cool" executive functions (2–5). The neural underpinnings of these behavioral problems include hypoactivation in frontostriatal and temporoparietal domain-relevant regions (6–12), which have been associated with disorder severity (13–15), cognitive performance (13,16), and symptomatic improvement with treatment (17,18) and can be modulated with pharmacotherapy (19). However, a recent meta-analysis highlighted the lack of convergence of brain activation alterations in ADHD (20), perhaps reflecting a failure to consider the interconnected nature of neural processing.

As most complex cognitive functions depend on information processing in multiple regions, studying regional interactions is crucial in characterizing brain function. Furthermore, given the large-scale neural reorganization in youth, investigations of functional connectivity may provide a better understanding of neurodevelopmental disorders (21–23). Consequently, many studies in ADHD focused on network-wide alterations in resting-state connectivity to characterize domain-independent neural function (24–26). Assessments of task-based functional connectivity, however, allow these findings to be extended by investigating functional connections specific to distinct cognitive processes (27). Given the presence of discrete cognitive deficits in ADHD, studies of task-based connectivity in ADHD are becoming increasingly common.

Several systematic reviews and meta-analyses examined differences in cognition-related activation (6–12,20,28,29) and connectivity during resting-state paradigms in ADHD (24–26). Although reviews of functional connectivity have been published (30–34), there have been no systematic evaluations of task-based functional connectivity literature of ADHD or its quality. Consequently, this review focused on functional networks in ADHD aiming to provide a framework for considering the neural correlates of the disorder accommodating context-dependent, correlated activity across brain regions and its modulation with interventions. Furthermore, given the recent advances in understanding the limitations of functional magnetic resonance imaging (fMRI), this review aimed to appraise the quality of studies and reporting practices in the field.

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METHODS AND MATERIALS

This preregistered review (https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=205500) was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (35).

Information Sources and Search Strategy

A systematic search was conducted using the Cochrane Library, Embase, PubMed/MEDLINE, PsycINFO, and Web of Science Core Collection identifying fMRI studies of task-based functional connectivity in ADHD. The search was undertaken by one investigator (OSK) with keywords approved by the study team. The search string included (*functional connectivity* or *connecti**) and (*ADHD* or *attention deficit hyperactivity disorder* or *attention deficit disorder* or *hyperkinetic*) and (*functional magnetic resonance imaging* or *fMRI* or *BOLD* or *blood oxygen level dependent*). The search was limited to articles published in English between January 1990 and September 2020. Additionally, reference lists of past reviews focusing on functional connectivity in ADHD (30–34) were screened for relevant publications.

Study Selection Criteria

The identified citations were uploaded onto CADIMA (36). Duplicates were removed semiautomatically using CADIMA's inbuilt function and reviewed manually by one investigator (OSK). Titles and abstracts and subsequently full texts of surviving records were screened for eligibility in parallel by two investigators (OSK and MC). A screening exercise was conducted on 20 randomly selected records ensuring good reliability between investigators [κ = 0.63, calculated according to measuring agreement of Cochrane Version 5.1 (37)]. Only peer-reviewed fMRI studies of task-based functional connectivity in patients of all ages, sexes, and races/ethnicities where ADHD (per DSM or ICD) was the primary diagnosis were retained. Discrepancies were resolved by consensus.

Exclusion Criteria

Studies were excluded if they did not assess fMRI task-based functional connectivity, did not present primary data, or were not published in a peer-reviewed journal. Studies comparing ADHD solely with other psychiatric/neurodevelopmental disorders, including participants without a formal ADHD diagnosis, recruiting only ADHD remitters, or including participants for whom ADHD was not the primary diagnosis were excluded.

Data Extraction and Critical Appraisal

Data were extracted by two investigators (OSK and MC). Records were divided into two equal-sized batches, one for each investigator. The investigators independently extracted data from their allocated studies and cross-checked the accuracy of the other investigator's extraction. Data pertaining to 1) the study sample (sample size, age, sex, medication history, ADHD presentation, comorbidities); 2) study methods (connectivity estimation method, motion correction [method and exclusion criteria], drug washout period, task, case-control matching criteria); and 3) functional connectivity findings (changes of connectivity [increases/decreases] and their manuscript-defined location in the brain and justification of method used [e.g., choice of seed region]) were extracted and critically appraised. We defined decreased or increased functional connectivity if a hub/network was found in the group contrast in at least two comparisons. Findings were defined as mixed when the hub/network was observed in increased and decreased connectivity.

Additionally, risk of bias in intervention studies was examined using the Cochrane Collaboration risk of bias tool (37) across selection, performance, detection, attrition, and reporting biases. Two investigators (OSK and MC) independently conducted critical appraisal. Records were divided into two equal-sized batches, each assigned to one investigator.

RESULTS

Study Selection

The search yielded 946 unique records, of which 802 were excluded during title and abstract screening. A further 110 were excluded after full-text screening for one or more of the following reasons: 1) not measuring fMRI task-based connectivity (n = 87), 2) no peer review (n = 39), 3) not assessing individuals with current primary ADHD diagnosis (n = 25), 4) not presenting an empirical investigation (n = 20), and 5) no available full text (n = 1). Following the selection process, 34 studies remained (Figure 1; Supplement lists included studies).

These 34 studies included 51 comparisons. Of these, 37 investigated differences between ADHD and neurotypical groups, 9 tested effects of interventions in patients, 2 compared individuals with ADHD and their nonsymptomatic siblings, 2 compared remitted and persistent ADHD, and 1 explored ADHD symptom severity (investigations of siblings, remitters, and disorder severity are described in the Supplement and Table 2). Across all studies, this review included 981 individuals with ADHD, 38 ADHD remitters, 134 nonsymptomatic siblings of individuals with ADHD, and 774 neurotypical controls.

The heterogeneity of methodologies of this literature prevented a meta-analysis. Consequently, the comparisons were summarized as a narrative synthesis.

Functional Connectivity in ADHD

The differences in connectivity between ADHD and neurotypical groups were investigated in 37 comparisons (youths = 23, adults = 14) (Table 1). Based on the collective descriptions in the literature (38), the following cognitive domains emerged: attention (n = 4) (39–42), cognitive control (n = 6) (15,43–47), response inhibition (n = 5) (15,48–51), reward processing (n = 5) (52–56), working memory (n = 5) (55,57–60), and emotion processing (n = 6) (43,55,61–64). Additionally, 6 comparisons that could not be classified into the above domains included error monitoring (65), response preparation (66), motor response (55), social cognition/relational processing (55), and time discrimination (46).

Differences Between Individuals With ADHD and Neurotypical Populations by Cognitive Domain. There was an overall decrease of connectivity in ADHD compared

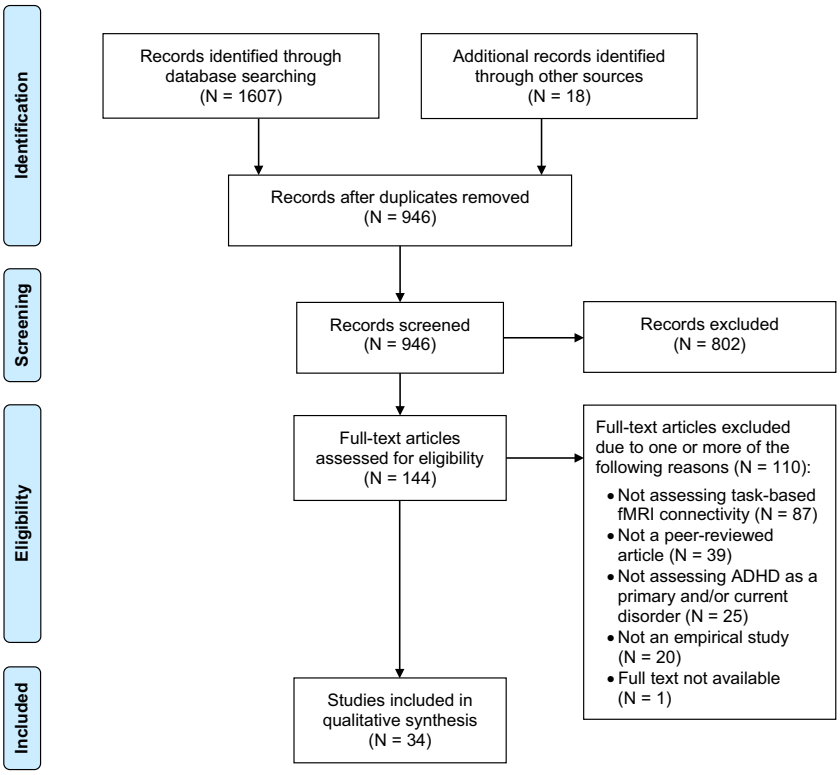

Figure 1. Study selection flow chart. ADHD, attention-deficit/hyperactivity disorder; fMRI, functional magnetic resonance imaging.

with neurotypical control subjects during attention tasks (74 patients and 90 control subjects across 4 comparisons). The right inferior frontal cortex (IFC) and bilateral inferior parietal lobules (IPLs) were indicated as hubs of connectivity decreases in ADHD, whereas the anterior cingulate cortex (ACC), left middle frontal gyrus (MFG), precentral gyrus, and bilateral occipital lobes showed both increases and decreases of connectivity, all with a 1:1 ratio indicating equal number of increases and decreases.

The cognitive control results were heterogeneous, not yielding many common case-control differences (104 patients and 119 control subjects across 6 comparisons). Only the right IFC consistently showed abnormalities, with both increases and decreases (1:1 ratio) of functional connectivity.

ADHD was related to predominantly decreased functional connectivity compared with neurotypical control subjects during response inhibition (263 patients and 211 control subjects across 5 comparisons). The right IFC, supplementary motor complex, and parieto-occipital regions showed decreased connectivity in ADHD, while the left precentral gyrus exhibited increased connectivity. Conversely, the right striatum (2:1 ratio, decreases-to-increases ratio), left IFC (3:1), MFG (2:1), superior frontal gyrus (SFG) (1:1) middle temporal gyrus (1:1), ACC (1:1), and cerebellum (1:1) were hubs of increased and decreased connectivity in patients.

ADHD was associated with an overall increase in connectivity compared with control subjects during working memory (111 patients and 111 control subjects across 5 comparisons). The right insula, superior temporal gyrus, striatum, and left MFG and IPL showed increased connectivity in patients. Bilateral IFCs, SFG, left insula, cingulate, precuneus, cuneus, and cerebellum showed both increases and decreases of connectivity in ADHD, all with a 1:1 ratio except for the cerebellum, which showed more increases (3:1).

During reward processing, the medial frontal cortex showed decreased functional connectivity, while the precentral gyrus was a hub of increased connectivity in ADHD (254 patients and 167 control subjects across 5 comparisons). The right insula, middle temporal gyrus, left thalamus, striatum, bilateral ACC, and cerebellum exhibited increases and decreases of connectivity in patients, all with a 1:1 ratio.

During emotion processing, the left postcentral gyrus showed decreased connectivity in ADHD compared with control subjects (143 patients and 146 control subjects across 6 comparisons). Additionally, the right amygdala, left insula, and ACC formed hubs of increased and decreased connectivity in ADHD, all with a 1:1 ratio.

Differences Between Individuals With ADHD and Neurotypical Populations by Functional Network. We also aimed to identify hubs and networks exhibiting common connectivity differences in ADHD across cognitive functions. Regions that formed hubs of connectivity differences between patients and control subjects included the ACC (6:7, decreases-to-increases ratio), IFC (4:3), MFG (3:4), SFG (5:3),

Table 1. Studies Investigating fMRI Functional Connectivity Differences Between ADHD and Typical Development Grouped by Cognitive Domain

Study	Analysis Method	Task (Contrast)	N_{ADHD} (% Male)	Age_{ADHD}, Years, Mean (SD)	Medication History	Medication Washout	ADHD Comorbidities	$N_{Control}$ (% Male)	$Age_{Control}$, Years, Mean (SD)	Control > ADHD	ADHD > Control
Attention											
Li *et al.*, 2012 (39)	SBC	CPT (unspecified)	22 (55%)	11.6 (2.86)	Current MPH use (41%); medication-free (59%)	48 hours	None	22 (45%)	12.1 (2.23)	L pulvinar nuclei ↔ R IFC, MFG; R pulvinar nuclei ↔ R PFC	R pulvinar nuclei ↔ BIL occipital lobe
Luo *et al.*, 2018 (40)	GTTs	Cued attention task (cues)	17 (77%)	24.69 (2.1)	Current stimulant use (12%); past stimulant use (unspecified)	48 hours	None	33 (85%)	24.27 (2.2)	Acting network hubs in BIL IPL; L IPL ↔ L SFG; degree in R MFG; betweenness centrality in L SFG, MFG, precentral, R IFC	Acting network hubs in L MFG and precentral
Rubia *et al.*, 2009 (41)	SBC	CPT (targets > nontargets)	13 (100%)	12.5 (1.3)	Medication-naïve (100%)	–	ODD/CD (8%)	13 (100%)	13 (1.7)	L IFC ↔ striatum, cerebellum; R IFC ↔ striatum, BIL cerebellum; BIL thalamus/striatum ↔ striatum, R cerebellum; L striatum ↔ BIL cerebellum, R striatum; ACC ↔ cerebellum, cerebellar vermis; R IPL ↔ cerebellum, L IPL; cerebellar vermis ↔ PCC; R cerebellum ↔ PCC, L IPL; L cerebellum ↔ L IPL	None
Xia *et al.*, 2014 (42)	GTTs	CPT (unspecified)	22 (55%)	11.6 (2.86)	Current MPH use (41%); medication-free (59%)	48 hours	None	22 (45%)	12.1 (2.23)	Nodal efficiency in L superior OFG and R SOG; degree and betweenness centrality in BIL occipital lobes, R temporal lobe, L paracentral, SMG	Nodal efficiency in L cuneus; degree and betweenness centrality in ACC
Cognitive Control											
Cubillo *et al.*, 2010 (15)	SBC	Switch task (unspecified)	11 (100%)	29 (1)	Medication-naïve (100%)	–	Anxiety disorder (9%), mood disorder (27%), CD (9%), substance use disorder (18%)	13 (100%)	28 (1)	None	None
Hwang *et al.*, 2015 (43)	$gPPI_{AFNI}$	Affective Stroop task (incongruent > congruent stimuli)	26 (65%)	14.53 (unspecified)	Current stimulant use (42%); medication-free (58%)	>24 hours	ODD (4%), substance use disorder (8%)	35 (51%)	13.91 (unspecified)	L DMFG ↔ R lateral frontal, claustrum[a]	L DMFG ↔ L posterior insula
Querne *et al.*, 2017 (44)	ICA	Flanker task (unspecified)	11 (unspecified)	9.8 (1.7)	Medication-naïve (100%)	–	None	11 (unspecified)	10.8 (1.7)	Anticorrelation between DMN and frontotemporoparietal regions (direct group comparison not reported)	None
Plessen *et al.*, 2016 (45)	ICA	Flanker task (post-error > post-correct trials)	25 (68%)	10.75 (1.09)	Medication-naïve (100%)	–	ODD (40%), ODD+CD (8%), phobia (16%), tics (4%), separation anxiety disorder (4%), elimination disorder (4%)	29 (52%)	10.15 (1.04)	None	Cingulo-opercular network ↔ VAN[a]

Table 1. Continued

Study	Analysis Method	Task (Contrast)	N_{ADHD} (% Male)	Age_{ADHD}, Years, Mean (SD)	Medication History	Medication Washout	ADHD Comorbidities	$N_{Control}$ (% Male)	$Age_{Control}$, Years, Mean (SD)	Control > ADHD	ADHD > Control
Vloet *et al.*, 2010 (46)	PPI_{SPM}	Time discrimination + stimulus-response compatibility task (stimulus-response compatibility)	14 (100%)	11.3 (2)	Past or current stimulant use (100%)	>48 hours	None	14 (100%)	11.9 (1.4)	L IFC ↔ L SPG; R IFC ↔ R SPG	None
Zamorano *et al.*, 2017 (47)	PPI_{FSL}	MSIT (incongruent > congruent conditions)	17 (100%)	11.6 (0.86)	Current MPH use (100%)	Medication not taken on study day	None	17 (100%)	11.7 (0.67)	Not reported	R MFG + R IFC ↔ BIL OFC, striatum
Emotion Processing											
Hafeman *et al.*, 2017 (61)	$gPPI_{SPM}$	Emotional dynamic faces task (emotional faces > shapes)	30 (67%)	14.1 (1.8)	Current use of stimulants (43%), antipsychotics (10%), antidepressants (10%)	Unspecified	ODD (53%), CD (3%), depressive disorder (53%), anxiety disorder (3%)	26 (46%)	13.2 (2.2)	None	BIL amygdala ↔ subgenual cingulate; BIL amygdala ↔ R SFG
Hwang *et al.*, 2015 (43)	$gPPI_{SPM}$	Affective Stroop task: 1) positive > neutral stimuli; 2) positive > neutral incongruent stimuli; 3) negative > neutral stimuli)	26 (65%)	14.53 (unspecified)	Current stimulant use (42%); medication-free (58%)	>24 hours	ODD (4%), substance use disorder (8%)	35 (51%)	13.91 (unspecified)	1) R amygdala ↔ R MOG, L lentiform nucleus; 2) R amygdala ↔ BIL postcentral[a]; 3) none	None
Park *et al.*, 2016 (55)	GTTs[b]	Emotive faces task (unspecified)	34 (59%)	27.88 (3.37)	Unspecified	Unspecified	Unspecified	34 (62%)	29.44 (3.57)	Degree in BIL medial frontal, L ACC, L postcentral, R caudate, L insula	Degree in L MFG, R SMG, R IPL, L MOG, L IOG, R cerebellum
Posner *et al.*, 2011 (62)	DCM	Fearful faces task with priming (fearful faces)	15 (87%)	13.5 (1.2)	Current stimulant use (100%)	>48 hours	ODD/CD (% unspecified)	15 (87%)	13.4 (1.2)	None	R amygdala ↔ R lateral PFC
Schulz *et al.*, 2014 (63)	PPI_{SPM}	Face emotion GNG (correct no-go > go)	14 (100%)	23.3 (2.3)	Medication-naïve (29%); past stimulant use but medication-free at time of study (71%)	–	Mood disorder (14%), anxiety disorder (14%), substance use disorder (36%)	14 (100%)	22.8 (2.7)	R DLPFC ↔ L IFC, putamen, BIL subgenual cingulate	None
Stoddard *et al.*, 2017 (64)	$gPPI_{AFNI}$	Implicit face emotion processing task (150% intensity across emotions)	24 (75%)	13.5 (2.9)	Unspecified	Unspecified	Unspecified	22 (41%)	14.2 (2.1)	None	L amygdala ↔ L insula
Response Inhibition											
Cai *et al.*, 2021 (48)	$gPPI_{SPM}$	GNG (correct no-go)	27 (78%)	13.95 (2.62)	Medication-free during testing (100%)	>5 half-lives of drug	Unspecified	30 (73%)	13.65 (2.47)	R DLPFC ↔ R posterior parietal	None
Cubillo *et al.*, 2010 (15)	SBC	SST (unspecified)	10 (100%)	28 (1)	Medication-naïve (100%)	–	Anxiety disorder (10%), mood disorder (30%), CD (10%), substance use disorder (20%)	14 (100%)	28 (2)	R IFC ↔ L IFC, R MFG, ACC, PCC, SMA, thalamus, striatum, BIL parietal/temporal/occipital; R ACC/PCC/SMA ↔ R thalamus, striatum	None
Massat *et al.*, 2018 (49)	PPI_{SPM}	SST (successful > failed stop)	18 (44%)	10.6 (1.13)	Medication-naïve (100%)	–	None	19 (47%)	10 (1.35)	R IFC ↔ R OFC, L MFG, IFC	R dorsal caudate ↔ R IPL, SPG, L MFG, middle cingulate, precentral, postcentral

Table 1. Continued

Study	Analysis Method	Task (Contrast)	N_{ADHD} (% Male)	Age_{ADHD}, Years, Mean (SD)	Medication History	Medication Washout	ADHD Comorbidities	$N_{Control}$ (% Male)	$Age_{Control}$, Years, Mean (SD)	Control > ADHD	ADHD > Control
Mulder *et al.*, 2011 (50)	SBC	GNG (unspecified)	Sample 1: 11 (100%) Sample 2: 12 (100%)	Sample 1: 13.97 (3.14) Sample 2: 14.9 (2.3)	Sample 1: current stimulant use (55%); medication-free (45%) Sample 2: current stimulant use (58%); medication-free (42%)	>24 hours	Sample 1: ODD (27%) Sample 2: ODD (33%)	Sample 1: 11 (100%) Sample 2: 12 (100%)	Sample 1: 15.27 (1.92) Sample 2: 15 (2.1)	Samples 1 and 2: ACC ↔ cerebellum Sample 1: motor cortex ↔ striatum[a] Sample 2: not reported	None
van Rooij *et al.*, 2015 (51)	PPI^{FSL}[b,c]	SST: 1) successful stop > go; 2) failed stop > go)	185 (70%)	17.3 (3.2)	Current medication use, class unspecified (77%); medication-free (23%)	Unspecified	ODD (30%), CD (7%), reading disability (18%)	125 (44%)	16.5 (3.3)	1) L IFC ↔ R putamen; L SFG ↔ L thalamus, operculum; 2) L IFC ↔ R IFC, BIL SFG/preSMA, L occipital cortex, MTG; L SFG ↔ L IFC	1) L IFC ↔ L MTG, cerebellum; L SFG ↔ R ACC, frontal pole, BIL precuneus, L precentral, R cerebellum; 2) L IFC ↔ BIL temporal pole, L cerebellum, R SMG; L SFG ↔ L MTG
Reward Processing											
Ceceli *et al.*, 2020 (52)	PPI_{FSL}	Free operant task with food rewards (late > early phase)	25 (56%)	22.31 (4.69)	Current or previous stimulant use (72%); past stimulant use but medication-free at time of study (16%); medication-naïve (12%)	36 hours	None	25 (56%)	21.48 (2.92)	L posterior putamen ↔ dorsal ACC, medial frontal	None
Ma *et al.*, 2016 (53)	$gPPI_{SPM}$	Rewarded Stroop task (rewarded > neutral Stroop)	25 (76%)	15.36 (1.08)	Current MPH use (60%); medication-free (40%)	24 hours	ODD and CD (% unspecified)	33 (67%)	15.3 (1.05)	None	L ventral striatum ↔ R precentral
Mowinckel *et al.*, 2017 (54)	Bayesian hierarchical mixed model	Value-based decision-making task (unspecified)	20 (35%)	29.9 (1.41)	Current stimulant use (100%)	>20 hours	None	27 (30%)	27.42 (1.23)	Within VIS, FPN, ECN, subcortical network, L VAN; ECN ↔ FPN ↔ sensorimotor network; DAN ↔ sensorimotor network; DAN ↔ VIS	VAN ↔ DMN; VAN ↔ ECN; DMN ↔ ECN
Park *et al.*, 2016 (55)	GTTs[b]	Gambling task: 1) gambling reward; 2) gambling punishment	34 (59%)	27.88 (3.37)	Unspecified	Unspecified	Unspecified	34 (62%)	29.44 (3.57)	1) Degree in BIL SFG, MTG; 2) degree in R medial frontal, MFG, insula, BIL SFG, L IPL, thalamus, parahippocampal	1) Degree in R ACC, L PCC, lingual, thalamus, BIL insula, cerebellum; 2) R precentral, MTG, L postcentral, STG, BIL cerebellum
von Rhein *et al.*, 2017 (56)	ICA	MID task (unspecified)	150 (70%)	17.7 (3)	Unspecified	>48 hours	ODD (23%), CD (5%)	48 (69%)	16.9 (3.2)	Within SAL (R ITG), ECN (R IFC, L cerebellum)	Within SAL (R cerebellum)
Working Memory											
Bédard *et al.*, 2014 (57)	PPI_{SPM}	Visuospatial n-back task: 1) 1-back > 0-back; 2) 2-back > 0-back	24 (88%)	13.07 (1.93)	Current stimulant use (4%); current nonstimulant use (4%); past stimulant/nonstimulant use but medication-free at time of study (29%); medication-naïve (63%)	2 weeks	ODD (8%), CD (4%), anxiety disorder (17%)	21 (76%)	12.44 (1.95)	1) L DLPFC ↔ L PCC; 2) L DLPFC ↔ L midcingulate, PCC	1) L DLPFC ↔ BIL posterior insula, R temporal cortex; 2) L DLPFC ↔ L intraparietal sulcus, cerebellum

Table 1. Continued

Study	Analysis Method	Task (Contrast)	N_{ADHD} (% Male)	Age_{ADHD}, Years, Mean (SD)	Medication History	Medication Washout	ADHD Comorbidities	$N_{Control}$ (% Male)	$Age_{Control}$, Years, Mean (SD)	Control > ADHD	ADHD > Control
Massat *et al.*, 2012 (58)	$gPPI_{SPM}$	Verbal n-back task (2-back > 0-back)	19 (47%)	10.75 (1.31)	Medication-naïve (100%)	–	None	14 (57%)	10.05 (1.28)	None	R cerebellum ↔ red nucleus, R amygdala[a], hippocampus[a], lingual[a], precuneus[a], L IFC[a], MFG[a], postcentral[a], cerebellum[a]; L occipital ↔ BIL MFG[a], R MTG[a], STG[a], fusiform[a], putamen[a], L cerebellum[a]; L IPL ↔ BIL IFC[a], MFG[a], STG[a], L ACC[a], SMA[a]; R caudate ↔ BIL MFG[a], R SFG[a], putamen[a], insula[a]
Park *et al.*, 2016 (55)	GTTs[b]	Visuospatial n-back task (unspecified)	34 (59%)	27.88 (3.37)	Unspecified	Unspecified	Unspecified	34 (62%)	29.44 (3.57)	Degree in L precuneus, MTG, cuneus, insula	Degree in L precentral, IPL, cerebellum, R MFG, IFC, STG, BIL SFG, caudate
Wolf *et al.*, 2009 (59)	ICA	Verbal working memory task (unspecified)	12 (100%)	22.2 (4.4)	Current MPH use (50%); past MPH use but medication-free at time of study (50%)	72 hours	None	12 (100%)	21.6 (4.7)	Within BIL IFC, SFG, SPG, cerebellum, L ACC, medial frontal	Within L dorsal cingulate, cuneus, R IFC, SFG
Wu *et al.*, 2017 (60)	ICA	Verbal n-back task (2-back > 0-back)	22 (100%)	12.71 (1.55)	Past stimulant use but medication-free at time of study (23%); medication-naïve (77%)	>4 weeks	ODD (18%)	30 (100%)	11.96 (1.72)	Within ECN (L SMG, insula)	Within FPN (L postcentral, SPG), auditory network (R cuneus, occipital pole, supracalcarine, intracalcarine, lateral SOG, precuneus)
Other Cognitive Functions											
Chevrier *et al.*, 2019 (65)	SBC	SST: 1) error detection; 2) post-error slowing	14 (50%)	13.7 (2.1)	Current stimulant use (43%); medication-free (57%)	24 hours	ODD (14%)	14 (64%)	15.4 (1.6)	1) SN ↔ medial septal; 2) LC ↔ L amygdala, L hypothalamus; medial septal nuclei ↔ R amygdala, LC, R hypothalamus; raphe nucleus ↔ R SN/parahippocampal	1) Dorsal striatum ↔ R IPL; SN ↔ R hypothalamus; SN ↔ L amygdala, LC, raphe nucleus; 2) ventral pallidum ↔ SN/parahippocampal, R dorsal pallidum, L amygdala; SN ↔ L hypothalamus; LC ↔ R IFC; medial septal nuclei ↔ BIL amygdala, L SN, BIL basal forebrain; raphe nucleus ↔ BIL amygdala, R SN, BIL hypothalamus
Clerkin *et al.*, 2013 (66)	PPI_{SPM}	Cued reaction time task (cues > noncues)	35 (83%)	24.6 (2.04)	Current stimulant use (6%); past stimulant use but medication-free at time of study (71%)	>48 hours	Mood disorder (23%), anxiety disorder (23%), substance use disorder (43%)	32 (84%)	24.38 (2.4)	R thalamus ↔ pons	None
Park *et al.*, 2016 (55)	GTTs[b]	Motor task (unspecified)	34 (59%)	27.88 (3.37)	Unspecified	Unspecified	Unspecified	34 (62%)	29.44 (3.57)	Degree in R precentral, medial frontal, SMG, L MFG, precuneus, cuneus, parahippocampal, cerebellum, BIL MTG, MOG	Degree in BIL SFG, PCC, R MFG, ACC, L postcentral
	GTTs[b]	Relational processing task (unspecified)	34 (59%)	27.88 (3.37)	Unspecified	Unspecified	Unspecified	34 (62%)	29.44 (3.57)	Degree in R medial frontal, SFG, BIL ACC, L lingual, cerebellum	Degree in R PCC, cuneus, BIL IPL, STG, L MTG
	GTTs[b]	Social cognition task (unspecified)	35 (59%)	27.88 (3.37)	Unspecified	Unspecified	Unspecified	34 (62%)	29.44 (3.57)	Degree in BIL SFG, R PCC, L cuneus	Degree in L precentral, postcentral, cerebellum, BIL precuneus, R MTG

Table 1. Continued

Study	Analysis Method	Task (Contrast)	N_{ADHD} (% Male)	Age_{ADHD}, Years, Mean (SD)	Medication History	Medication Washout	ADHD Comorbidities	$N_{Control}$ (% Male)	$Age_{Control}$, Years, Mean (SD)	Control > ADHD	ADHD > Control
Vloet *et al.*, 2010 (46)	PPI_{SPM}	Time discrimination + stimulus-response compatibility task (time discrimination)	14 (100%)	11.3 (2)	Past or current stimulant use (100%)	>48 hours	None	14 (100%)	11.9 (1.4)	R IFC ↔ R cerebellum	None

ACC, anterior cingulate cortex; ADHD, attention-deficit/hyperactivity disorder; BIL, bilateral; CD, conduct disorder; CPT, continuous performance task; DAN, dorsal attention network; DCM, dynamic causal modeling; DLPFC, dorsolateral prefrontal cortex; DMFG, dorsomedial frontal gyrus; DMN, default mode network; ECN, executive control network; fMRI, functional magnetic resonance imaging; FPN, frontoparietal network; GNG, go/no-go; gPPI, generalized psychophysiological interaction; GTT, graph theoretic technique; ICA, independent component analysis; IFC, inferior frontal cortex; IOG, inferior occipital gyrus; IPL, inferior parietal lobule; ITG, inferior temporal gyrus; L, left; LC, locus coeruleus; MFG, middle frontal gyrus; MID, monetary incentive delay; MOG, middle occipital gyrus; MPH, methylphenidate; MSIT, multi-source interference task; MTG, middle temporal gyrus; ODD, oppositional defiant disorder; OFG, orbitofrontal gyrus; PCC, posterior cingulate cortex; PFC, prefrontal cortex; PPI, psychophysiological interaction; preSMA, pre–supplementary motor area; R, right; SAL, salience network; SBC, seed-based correlation; SFG, superior frontal gyrus; SMA, supplementary motor area; SMG, supramarginal gyrus; SN, substantia nigra; SOG, superior occipital gyrus; SPG, superior parietal gyrus; SST, stop signal task; STG, superior temporal gyrus; VAN, ventral attention network; VIS, visual network.

[a]Correction for multiple comparisons not specified.

[b]White matter and cerebrospinal fluid signal regressors included in the model in addition to standard motion parameters.

[c]Scrubbing regressors included in the model for volumes with excessive motion in addition to standard motion parameters.

insula (3:4), sensorimotor cortex (1:1 ratio), IPL (1:2), striatum (3:1), and cerebellum (3:4). These regions exhibited increases and decreases of connectivity across tasks (Figure 2).

Several studies performed formal analyses of established functional networks, often described in resting-state literature (67,68), finding both within- and between-network differences. Relative to control subjects, patients showed reduced connectivity in visual (VIS), frontoparietal (FPN), executive control (ECN), ventral attention (VAN), subcortical, and salience networks during reward processing as well as in the ECN during working memory. Individuals with ADHD also showed increased connectivity within the salience network during reward processing and within the FPN and auditory networks during working memory compared with control subjects. Furthermore, ADHD was associated with decreased functional connectivity between the default mode (DMN) and frontotemporoparietal networks during cognitive control as well as between the ECN and both the FPN and the sensorimotor network (SMN), between the dorsal attention network (DAN) and SMN, and between the DAN and VIS during reward processing. Increased functional connectivity in ADHD was observed between the cingulo-opercular network (CON) and VAN in cognitive control and between the VAN and DMN, between the VAN and ECN, and between the DMN and ECN across cognitive domains.

These studies suggest that the functional network architecture differs in ADHD. Alterations of functional connectivity were observed primarily in SMN, VIS, ECN, DMN, CON, and subcortical networks across cognitive domains. Nonetheless, both increases and decreases of connectivity were observed in ADHD across all implicated networks.

Effects of Interventions on Functional Connectivity in ADHD

Nine studies tested the effects of interventions on functional connectivity, with 8 studies investigating stimulants (youths = 6, adults = 2) (41,44,54,60,62,69–71) and 1 study evaluating fMRI neurofeedback of the right IFC (73). The intervention studies investigated various cognitive domains, and thus findings were synthesized across cognitive functions and within treatment type (Table 3).

Stimulants increased connectivity of the striatum (although decreases were seen in one study), ACC, and cerebellum across tasks and decreased connectivity of the amygdala in emotion paradigms compared with no intervention/placebo. MFG, IFC, medial frontal cortex, posterior cingulate cortex (PCC), occipital cortex, and precuneus showed both increased and decreased connectivity with stimulants, all with 1:1 ratio. Additionally, network analyses showed decreased connectivity within DMN and VIS with stimulants relative to no treatment/placebo. Stimulants enhanced connections within the ECN and between the ECN and auditory networks.

The neurofeedback study showed increased functional connectivity between the right IFC and the right striatum and ACC relative to both baseline and control subjects. Additionally, neurofeedback was associated with decreased connectivity between the right IFC and various PCC-occipital, striatothalamic, and hippocampal regions. Overall, interventions

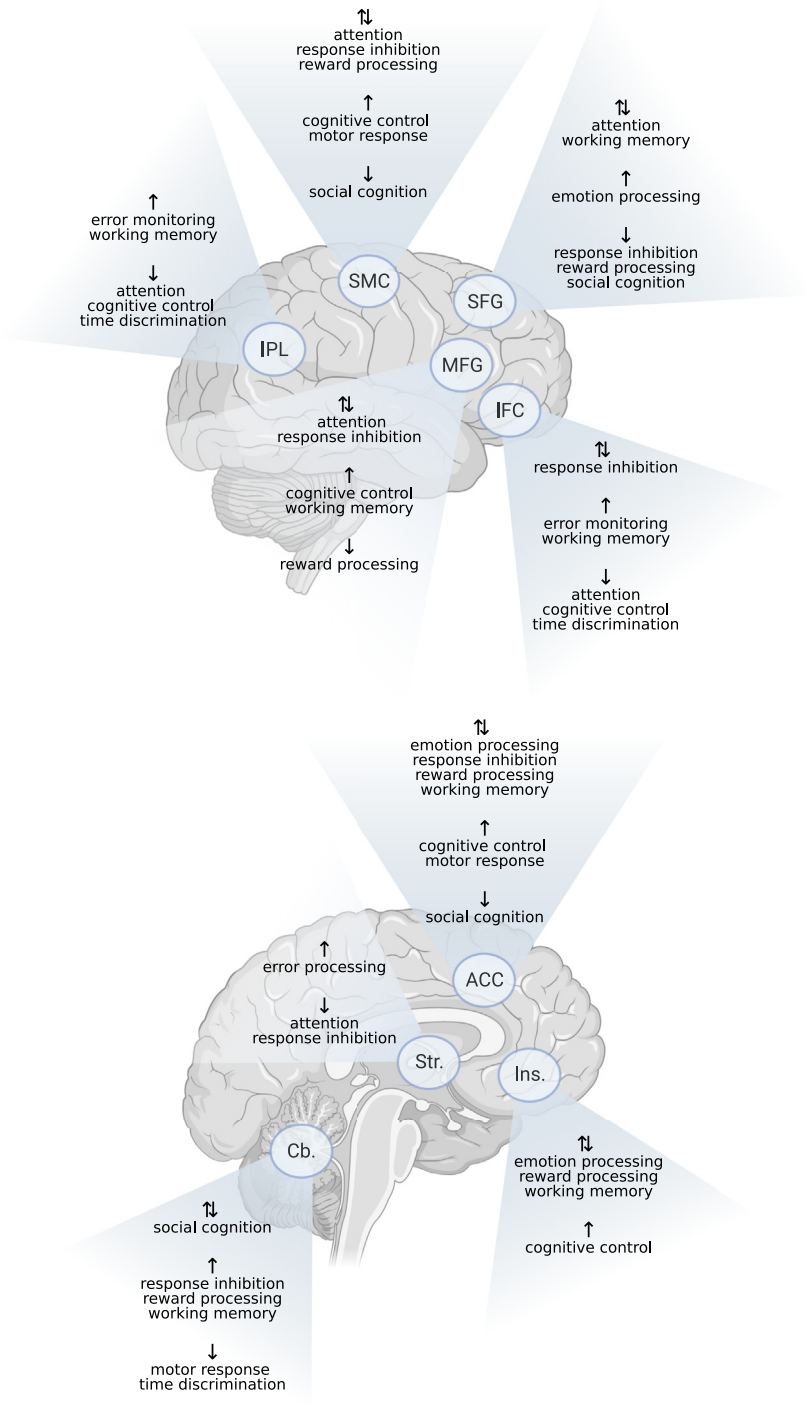

Figure 2. Regions that formed core hubs of functional connectivity differences between individuals with ADHD and neurotypical control subjects across cognitive domains. ACC, anterior cingulate cortex; Cb., cerebellum; IFC, inferior frontal cortex; Ins., insula; IPL, inferior parietal lobule; MFG, middle frontal gyrus; SFG, superior frontal gyrus; SMC, sensorimotor cortex; Str., striatum. (Figure created with BioRender; https://biorender.com/.)

Table 2. Studies Investigating fMRI Functional Connectivity Differences Between Individuals With ADHD and Nonsymptomatic Siblings and Persisters and Remitters and Exploring the Impact of Symptom Severity

Study	Analysis Method	Task (Contrast)	N_{ADHD} (% Male)	Age_{ADHD}, Years, Mean (SD)	Medication History	Medication Washout	ADHD Comorbidities	Comparison Group	$N_{Comparison}$ (% Male)	$Age_{Comparison}$, Years, Mean (SD)	Comparison > ADHD	ADHD > Comparison
Clerkin *et al.*, 2013 (66)	PPI_{SPM}	Cued reaction time task (cues > noncues)	16 (75%)	24.44 (2.02)	Current stimulant use (6%); past stimulant use but medication-free at time of study (71%)	>48 hours	Mood disorder (23%), anxiety disorder (23%), substance use disorder (43%)	Remitters	19 (90%)	24.74 (2.1)	R thalamus ↔ BIL frontal pole, L DLPFC	None
Kolodny *et al.*, 2020 (114)	$gPPI_{FSL}$[a]	GNG (rare no-go > prevalent no-go)	37 (41%)	26.6 (4)	Current stimulant use (84%); medication-free (16%)	>24 hours	None	–	–	–	L IPS ↔ R IFC, postcentral/SPG (negatively related to symptom severity)	
Luo *et al.*, 2018 (40)	GTTs	Cued attention task (cues)	17 (77%)	24.55 (2.2)	Current stimulant use (12%); past stimulant use (unspecified)	48 hours	None	Remitters	19 (84%)	24.79 (2.2)	Acting network hubs in R MFG, globus pallidus, putamen; nodal efficiency in BIL MFG	Acting network hubs in L MFG and precentral
Mulder *et al.*, 2011 (50)	SBC	GNG (unspecified)	Sample 1: 11 (100%) Sample 2: 12 (100%)	Sample 1: 13.97 (3.14) Sample 2: 14.9 (2.3)	Sample 1: current stimulant use (55%); medication-free (45%) Sample 2: current stimulant use (58%); medication-free (42%)	>24 hours	Sample 1: ODD (27%) Sample 2: ODD (33%)	Nonsymptomatic siblings	Sample 1: 11 (100%) Sample 2: 12 (100%)	Sample 1: 14.45 (2.58) Sample 2: 14.1 (2.7)	Motor cortex ↔ striatum	None

Table 2. Continued

Study	Analysis Method	Task (Contrast)	N_{ADHD} (% Male)	Age_{ADHD}, Years, Mean (SD)	Medication History	Medication Washout	ADHD Comorbidities	Comparison Group	$N_{Comparison}$ (% Male)	$Age_{Comparison}$, Years, Mean (SD)	Comparison > ADHD	ADHD > Comparison
van Rooij *et al.*, 2015 (51)	PPI_{FSL}[a,b]	SST: 1) successful stop > go; 2) failed stop > go	185 (70%)	17.3 (3.2)	Current medication use, class unspecified (77%); medication-free (23%)	Unspecified	ODD (30%), CD (7%), reading disability (18%)	Nonsymptomatic siblings	111 (43%)	17.3 (4)	1) L IFC ↔ R putamen; L SFG ↔ L thalamus, operculum; 2) L IFC ↔ L occipital cortex, MTG, R IFC, MFG	1) L IFC ↔ L cerebellum, precuneus, MTG; L SFG ↔ BIL precentral, precuneus, R frontal pole, ACC, cerebellum; 2) L IFC ↔ R medial frontal, ACC; L SFG ↔ L MTG

ACC, anterior cingulate cortex; ADHD, attention-deficit/hyperactivity disorder; BIL, bilateral; CD, conduct disorder; DLPFC, dorsolateral prefrontal cortex; fMRI, functional magnetic resonance imaging; GNG, go/no-go; gPPI, generalized psychophysiological interaction; GTT, graph theoretic technique; IFC, inferior frontal cortex; IPS, intraparietal sulcus; L, left; MFG, middle frontal gyrus; MTG, middle temporal gyrus; ODD, oppositional defiant disorder; PPI, psychophysiological interaction; R, right; SBC, seed-based correlation; SFG, superior frontal gyrus; SPG, superior parietal gyrus; SST, stop signal task.

[a]Scrubbing regressors included in the model for volumes with excessive motion in addition to standard motion parameters.

[b]White matter and cerebrospinal fluid signal regressors included in the model in addition to standard motion parameters.

modulated functional connectivity of the striatum, ACC, occipital regions, and midline DMN areas.

Critical Appraisal

Across all 51 included comparisons, 28 specified a motion cutoff. All comparisons included motion correction, with 36 comparisons applying standard methods (e.g., default software options) and 15 comparisons using more advanced approaches.

Average sample size of patient groups across all comparisons was 28, with larger samples in case-control than intervention comparisons (31 relative to 16, respectively). Independent samples were tested in 42 comparisons. Within those, studies reported matching groups on age in 40 comparisons, sex in 35 comparisons, handedness in 26 comparisons, motion in 21 comparisons, IQ in 21 comparisons, race/ethnicity in 9 comparisons, socioeconomic status in 7 comparisons, presence of unrelated symptoms in 7 comparisons, education level in 6 comparisons, working memory capacity in 1 comparison, and pubertal status in 1 comparison. Additionally, of all 51 comparisons, 42 reported information about ADHD presentation. On average, 72% of patients had combined ADHD, 22% had inattentive presentation, 3% had hyperactive-impulsive presentation, and 0.5% were classified as ADHD not otherwise specified.

The reviewed studies used heterogeneous methods to assess connectivity. Of all 51 comparisons, 20 used psychophysiological interaction (psychophysiological interaction = 12, generalized psychophysiological interaction = 8), 9 used seed-based correlations, 9 used graph theoretic techniques, 8 used independent component analysis, 2 used dynamic causal modeling, 2 used Bayesian hierarchical mixed models, and 1 used beta series correlation. Of all comparisons, 41 were seed-based and required definition of seed regions used in analysis. Within those, 21 used seeds defined independently of the dataset studied (based on past research or anatomical atlases), while 20 used seeds based on the same dataset (e.g., regions of peak activation in the same cohort). Furthermore, while most comparisons reported multiple comparisons correction, 6 of all 51 comparisons did not (indicated by a footnote symbol in Tables 1 and 3).

Of 51 comparisons, 34 recruited samples currently receiving pharmacotherapy, 9 recruited medication-naïve participants, 1 recruited participants who were medication-naïve or had a history of pharmacotherapy, and 7 did not specify medication history. Within the 34 comparisons recruiting currently medicated participants, 31 specified a washout period. Washout periods ranged from 20 hours to 4 weeks (20 hours = 2; 24 hours = 8; 36 hours = 1; 48 hours = 12; 72 hours = 1; 1 week = 1; 2 weeks = 2; 4 weeks = 2). Additionally, 2 comparisons used washout periods without specifying their exact duration (Tables 1 and 2).

The effects of interventions were tested in 9 comparisons. Selection bias (random sequence generation and allocation concealment) was deemed low in 6 comparisons, unclear in 2 comparisons, and high in 1 comparison. Performance (blinding of participants/personnel) and detection (blinding of outcome assessment) biases were rated low in 3 comparisons, unclear in 3 comparisons, and high in 3 comparisons.

Table 3. Studies Investigating the Impact of Interventions on fMRI Functional Connectivity in ADHD

Study	Analysis Method	Task (Contrast)	N_{ADHD} (% Male)	Age_{ADHD}, Years, Mean (SD)	Medication History	Medication Washout	ADHD Comorbidities	Intervention/ Comparison	Design	On Intervention > Off Intervention	Off Intervention > On Intervention
Mowinckel *et al.*, 2017 (54)	Bayesian hierarchical mixed model	Value-based decision making task (unspecified)	20 (35%)	29.9 (1.41)	Current stimulant use (100%)	>20 hours	None	Acute MPH (10–40 mg of regularly prescribed formulation)/placebo	Randomized, double-blind, crossover	Auditory network ↔ ECN	Within DMN and VIS
Posner *et al.*, 2011 (62)	DCM	Fearful faces task with priming (fearful faces)	15 (87%)	13.5 (1.2)	Current stimulant use (100%)	>48 hours	ODD/CD (% unspecified)	Acute stimulant (regularly prescribed formulation and dose)/off medication	Cross-over	None	None (main group comparison); BIL amygdala ↔ BIL lateral PFC (secondary nonparametric analysis)
Querne *et al.*, 2017 (44)	ICA	Flanker task (unspecified)	11 (unspecified)	9.8 (1.7)	Medication-naïve (100%)	–	None	4 weeks MPH (20–30 mg extended release)/off medication	Crossover (off medication → MPH)	DMN composed of anterior and posterior regions; anticorrelation between DMN and BIL anterior frontal, striatum, dorsal ACC, R occipitoparietal cortex, L cerebellum (direct group comparison not reported)	DMN composed posterior regions only (direct group comparison not reported)
Rubia *et al.*, 2009 (41)	SBC	CPT (targets > nontargets)	13 (100%)	12.5 (1.3)	Medication-naïve (100%)	–	ODD/CD (8%)	Acute MPH (0.3 mg/kg)/ placebo	Randomized, double-blind, crossover	L caudate/putamen ↔ R caudate/putamen	None
Rubia *et al.*, 2019 (72)	SBC	Neurofeedback	Active group: 18 (100%); control group: 13 (100%)	Active group: 14 (2); control group: 14 (2)	Active group: current use of stimulants (83%), withdrew from medication for duration of study (17%); control group: current stimulant use (69%), withdrew from medication for duration of study (23%), medication-naïve (8%)	>7 days for those willing to withdraw from medication	ODD/CD (% unspecified)	fMRI neurofeedback of R IFC/fMRI neurofeedback of L parahippocampal gyrus	11-run parallel groups active control (randomized single-blind control trial)	Relative to first run and control: R IFC (BA 45) ↔ R caudate, ACC; R IFC (BA 44) ↔ R ACC	Relative to first run: R IFC (BA 45) ↔ L parahippocampal, hippocampus, lingual, BIL PCC, precuneus, calcarine, thalamus, caudate, putamen, pallidum; R IFC (BA 44) ↔ BIL precuneus, PCC, hippocampus, parahippocampal, lingual, thalamus; relative to control: R IFC (BA 45) ↔ BIL PCC, precuneus, calcarine; R IFC (BA 44) ↔ BIL PCC, precuneus, hippocampus, parahippocampal, lingual, thalamus
Schulz *et al.*, 2018 (69)	PPI_{SPM}	Emotional GNG (correct go trials cued by sad faces)	25 (56%)	34.8 (9.8)	Current use of medication, class unspecified (8%); past stimulant and/or nonstimulant use but medication-free at time of study (36%); medication-naïve (56%)	2 weeks	None	5 weeks LDX (30–70 mg)/ placebo	Randomized, single-blind, crossover	None	L amygdala ↔ R SPG, L STG; R amygdala ↔ L IFC, STG, R SPG
Sheridan *et al.*, 2010 (70)	BSC	Delayed match to sample task (encoding)	5 (0%)	14.8 (2.4)	Current stimulant use (60%); current stimulant and nonstimulant use (20%); current stimulant and SSRI use (20%)	24 hours (for stimulants only)	Unspecified	Acute stimulant (regularly prescribed formulation and dose)/off medication	Crossover	BIL MFG ↔ cerebellar vermis[a]	BIL MFG ↔ striatum[a], L MFG[a], medial PFC[a], hippocampus[a], ITG[a], R TPJ[a], insula[a], lingual[a]
Wong and Stevens, 2012 (71)	ICA	Sternberg item recognition task (unspecified)	18 (83%)	14.6 (2)	Current stimulant use (100%)	48 hours	ODD (6%)	Acute stimulant (regularly prescribed formulation and dose)/placebo	Randomized, double-blind, crossover	Within ACC, medial frontal, PCC, precuneus, cuneus, lingual, SFG, cingulate, R postcentral, precentral, L IFC, SMG, MTG, angular regions	Within PCC, precuneus

Table 3. Continued

Study	Analysis Method	Task (Contrast)	N_{ADHD} (% Male)	Age_{ADHD}, Years, Mean (SD)	Medication History	Medication Washout	ADHD Comorbidities	Intervention/ Comparison	Design	On Intervention > Off Intervention	Off Intervention > On Intervention
Wu *et al.*, 2017 (60)	ICA	Verbal n-back task (2-back > 0-back)	22 (100%)	12.71 (1.55)	Past stimulant use but medication-free at time of study (23%); medication-naïve (77%)	>4 weeks	ODD (18%)	Acute MPH (10 mg/) placebo	Randomized, double-blind, crossover	Within ECN (R precuneus, L PCC)	None

ACC, anterior cingulate cortex; ADHD, attention-deficit/hyperactivity disorder; BIL, bilateral; BA, Brodmann area; BSC, beta series correlation; CD, conduct disorder; CPT, continuous performance task; DCM, dynamic causal modeling; DMN, default mode network; ECN, executive control network; fMRI, functional magnetic resonance imaging; GNG, go/no-go; gPPI, generalized psychophysiologic interaction; ICA, independent component analysis; IFC, inferior frontal cortex; ITG, inferior temporal gyrus; L, left; LDX, lisdexamfetamine; MFG, middle frontal gyrus; MPH, methylphenidate; MTG, middle temporal gyrus; ODD, oppositional defiant disorder; PCC, posterior cingulate cortex; PFC, prefrontal cortex; PPI, psychophysiological interaction; R, right; SBC, seed-based correlation; SFG, superior frontal gyrus; SMG, supramarginal gyrus; SPG, superior parietal gyrus; SSRI, selective serotonin reuptake inhibitor; STG, superior temporal gyrus; TPJ, temporoparietal junction; VIS, visual network.

[a]Correction for multiple comparisons not specified.

Attrition (incomplete outcome data) and reporting (selective reporting) biases were deemed low in all 9 comparisons (Supplement).

DISCUSSION

Task-Based Connectivity in ADHD

Across cognitive domains, changes of functional connectivity were observed in ADHD relative to neurotypical populations, with core hubs of connectivity differences in the ACC, IFC, MFG, SFG, sensorimotor cortex, insula, IPL, striatum, and cerebellum. Although changes of connectivity were observed when cognitive domains were considered individually, inhibition and attention were associated primarily with reductions in connectivity, whereas working memory was related to enhanced connectivity in ADHD relative to typical development.

Additional differences were observed in between-network connectivity. Across cognitive domains, individuals with ADHD showed stronger connections between VAN and both DMN and ECN as well as between ECN and DMN. During cognitive control, decreased connectivity was observed between DMN and frontotemporoparietal networks, while increased connectivity was seen between CON and VAN. During reward processing, only decreases of connectivity were observed between ECN and both FPN and SMN as well as between DAN and both SMN and VIS. Furthermore, for individuals with ADHD and their nonsymptomatic siblings and adults with ADHD and ADHD remitters, a limited literature showed connectivity differences similar to those seen between ADHD and neurotypical populations, specifically in striatal and sensorimotor regions (Table 2).

This review compiled findings estimated with several methods. Although these methods have fundamental differences and their outcomes may not represent the same aspects of connectivity, they reflect abnormal functioning of discrete networks in ADHD. This heterogeneity of methods prevents a synthesis yielding mechanistic insight into network-level pathophysiology of ADHD, although there is value in highlighting the cumulative evidence implicating certain neural systems.

The observations of abnormalities in task-relevant functional networks in ADHD bolster evidence of largely decreased local activation in core executive function–relevant areas, including ventrolateral, dorsolateral, and medial prefrontal, temporoparietal, and striatal regions in meta-analyses of fMRI studies in ADHD (6–12,28). Consequently, these findings support the presence of abnormalities in core task-positive networks and DMN in ADHD, and the high prevalence of abnormal sensorimotor connectivity resonates with similar observations in resting-state studies (24,73–75), which may reflect the previously proposed hypothesis of deviant maturational trajectories within these networks in ADHD (73). Nonetheless, the current literature largely focused on pediatric samples, and more exploration of adults and longitudinal cohorts is needed to better characterize the developmental trajectories of ADHD.

Our review also extends the knowledge base of resting-state connectivity alterations in ADHD in DMN, ECN, DAN, VAN, and salience networks (24,26,30,76,77) in two

important ways. First, during different tasks, both increases and decreases of connectivity in ADHD were observed. Relative to connectivity under unconstrained context (resting state), which may reflect underlying anatomical or long-term functional plasticity differences, task-based literature indicates that connectivity alterations in ADHD may reflect differences in adaptability of functional circuits to changing demands. These context-dependent changes may be related to arousal systems that respond differently under distinct tasks (78). Such explanations of ADHD pathophysiology move beyond seeing the brain as a static system and suggest a conceptualization of ADHD as a disorder of dynamic neurocognitive processes.

Second, the review emphasizes that even within tasks results to date are mixed. With small numbers of studies in some areas, it was not possible to assess whether these mixed findings were due to low power or specific task or patient factors. Although ADHD heterogeneity can contribute to the mixed findings (79), the association between neurocognitive phenotypes and individual differences is still poorly understood (Supplement). Task factors, however, are supported by a recent study that found that youths with ADHD engage more task-specific than generic networks, showing hypoconnectivity in executive and reward circuits relative to neurotypical control subjects and nonsymptomatic siblings of individuals with ADHD (80). These findings suggest that the inconsistencies in the literature may reflect inefficient task-specific networks in ADHD, with greater variability in functional connections.

This review summarizes impairments of functional connectivity in ADHD across several cognitive domains. The included studies used different tasks to elicit specific cognitive processes. However, there is a risk of nonspecificity in tasks. While this review indicates context-specific alterations, efforts have been made to understand the underlying processes key in explaining ADHD pathophysiology, with some investigators proposing executive dysfunction (3,81), while others argue for poor deployment of resources (78,82). As yet, the precise neurofunctional manifestation of these explanations is poorly understood in patients. While cross-sectional imaging studies cannot clearly address questions of multifinality or equifinality in ADHD, they demonstrate the context-dependent nature of the dysfunction. How this relates to symptoms, clinical presentation, and treatment effects can help determine the degree to which ADHD is associated with one set of dysfunctions that differentially manifest across patients or whether true biological subtypes exist. Such efforts show promise (83,84) but have not yet been applied to context-dependent connectivity.

Effects of Interventions on Task-Based Connectivity in ADHD

Most intervention studies investigated stimulant medications, while one addressed the effects of fMRI neurofeedback. All interventions modulated connections of the striatum, ACC, occipital regions, and midline DMN structures. Furthermore, stimulants increased connectivity of cerebellar hubs across task paradigms and decreased amygdala connectivity during emotion processing. Additionally, stimulants led to increases and decreases of connectivity with IFC, MFG, medial frontal cortex, PCC, precuneus, and occipital regions across cognitive functions. Network-wide modulation with stimulants was also observed, with decreased connectivity within DMN and auditory networks and increased connectivity within ECN as well as between ECN and auditory networks.

Our findings align with individual resting-state studies showing that stimulants modulate spontaneous brain activity in similar ventrolateral frontal, occipital, and cerebellar regions, along with connectivity within ECN, VIS, and DMN (85–88). Our findings also complement evidence of stimulant-related modulation of activation in areas dysfunctional in ADHD (7,9–11,19). These results highlight that stimulants also act on context-dependent network reorganization, potentially facilitating task performance.

One study explored the effects of fMRI neurofeedback. The modulation of connectivity of striatal, ventrolateral frontal, cingulate, and occipital regions observed with the intervention mirrored the changes seen with stimulant use, suggesting that neurofeedback of the right IFC may offer similar benefits as stimulants; however, more research is needed.

Limitations and Recommendations

Although this review supports the presence of network-wide dysfunction in ADHD and its modulation with treatment, a meta-analysis was not possible owing to the methodological heterogeneity of the literature. Consequently, it is difficult to quantify the degree of convergence across studies. A similar problem was noted in a recent systematic review of pharmacological effects on resting-state connectivity in ADHD (89). This is particularly relevant as recent task-based activation (20) and resting-state (25) meta-analyses of ADHD fMRI literature showed no spatial convergence across studies. Within the current review, eight different methods of estimating functional connectivity were used. Although most studies used seed-based methods, these comprised seven distinct approaches and different ways of defining seed regions. Furthermore, only approximately half of the studies used seeds defined independently of the dataset studied, thus avoiding the potential biases of circular analyses (90). Overall, while diverse methods provide different ways of characterizing the data and avoid potential issues stemming from one specific method, these benefits come at the cost of limiting the quantitative synthesis of findings across studies.

Past and current medication history represented another source of heterogeneity. Most studies included previously medicated participants. As stimulant use has been associated with structural (9,91,92), functional (7–9,11,93), and neurochemical changes (94), studying neural networks in currently or previously medicated individuals may confound pathophysiology of the disorder with the long-term impact of treatment. Another issue is the variability in the drug washout periods used (20 hours to 1 month). A minimum washout of 5 half-lives of the drug is recommended (95); however, discontinuing treatment can lead to withdrawal or rebound effects (96), and the length of the washout period may influence the level of neural differences between ADHD and neurotypical populations (10). Therefore, aside from the confounding effects of medication, some of the variability within the observed findings may be attributed to variable washout periods.

Small sample sizes, particularly in the intervention literature, which are linked to lower replicability of findings (97–101), are a limitation of this literature. Such issues have prompted recommendations such as a minimum sample size of 20 (100) and development of software allowing power calculations for fMRI studies (102). Consequently, these findings need to be interpreted with caution given that many were likely underpowered.

Some limitations of the reviewed studies involve the transparency of reporting, data quality assurance, and processing pipelines. For instance, only approximately half of the comparisons specified a motion cutoff. Given that ADHD is characterized by increased movement (103,104) and lower tolerability of the scanner environment (105) and that functional connectivity methods are particularly sensitive to motion artifacts (106–108), appropriate checks of data quality are essential. Issues with transparent reporting and data processing were also evident in studies not specifying multiple comparisons correction. False-positive rates in fMRI analyses are notorious without adjustment for multiple comparisons (98,109,110), and thus publications not reporting application of multiple comparisons correction should be interpreted with caution.

Further, the reviewed studies differed in general methodology, including study design, acquisition parameters, and data processing. Such heterogeneity further complicates cross-study synthesis of findings. Although these factors are not specific to this field and assessment of their impact was beyond the scope of this review, future studies should carefully consider and outline justification of their methodological choices.

This literature was also limited by other patient-specific factors frequently present in ADHD research, including male predominance, presence of comorbidities, variability of clinical presentation, and age-related differences (Supplement). Finally, ADHD is an inherently heterogeneous disorder with variable severity and class of symptoms, genetic and environmental risk factors, and profiles of associated pathophysiology (3,111–113). Consequently, it is likely that the heterogeneity of findings can be partly explained by the interindividual differences of ADHD groups. The impact of these factors should thus be explored further.

Overall, the limitations of the current literature illustrate the need for improved standards of study methodology and reporting. We propose that researchers prioritize recruiting larger, more diverse, and medication-naïve samples; implement greater control of in-scan motion and motion-related artifacts; use state-of-the-art data processing pipelines; and promote reporting transparency and openness [see Pereira-Sanchez *et al.* (89) for an in-depth discussion].

CONCLUSIONS

This is the first systematic review appraising the task-based functional connectivity literature of ADHD. We reviewed studies describing ADHD and the impact of interventions on task-relevant functional networks involved in the pathophysiology of the disorder. Our review supports the presence of CON, SMN, VIS, subcortical, ECN, and DMN network abnormalities in ADHD and shows that interventions can modulate the functional reorganization of those circuits. Overall, this review highlights the utility of task-based connectivity studies in broadening the understanding of the neural underpinnings of ADHD and in studying the mechanisms of action of ADHD treatments, but advocates for improvements to methodological quality of this line of research.

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