Journal Pre-proof

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PII: S2667-1743(21)00123-3

DOI: https://doi.org/10.1016/j.bpsgos.2021.10.006

Reference: BPSGOS 73

To appear in: *Biological Psychiatry Global Open Science*

Received Date: 2 August 2021

Revised Date: 7 October 2021

Accepted Date: 11 October 2021

Please cite this article as: Kowalczyk O.S., Mehta M.A., O'Daly O.G. & Criaud M., Task-based functional connectivity in attention-deficit/hyperactivity disorder: A systematic review, *Biological Psychiatry Global Open Science* (2021), doi: https://doi.org/10.1016/j.bpsgos.2021.10.006.

Task-based functional connectivity in attention-deficit/hyperactivity disorder: A systematic review

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Short title:

Task-based connectivity in ADHD: A systematic review

Keywords:

Attention-deficit/hyperactivity disorder; ADHD; functional magnetic resonance imaging; fMRI; Connectivity; Task-based functional connectivity

Abstract

Altered neurocognitive functioning is a key feature of attention-deficit/hyperactivity disorder (ADHD) and increasing number 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 non-symptomatic 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 summarised 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 non-symptomatic 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.

1. Introduction

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 behavioural problems include hypoactivation in fronto-striatal and temporo-parietal domain-relevant regions(6–12), which have been associated with disorder severity(13-15), cognitive performance(13,16), 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 characterising brain function. Furthermore, given the large-scale neural reorganisation 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 characterise domain-independent neural function(24-26). Assessments of task-based functional connectivity, however, allow to extend these findings 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 focuses 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 fMRI, this review aims to appraise the quality of studies and reporting practices in the field.

2. Methods and materials

This preregistered review (https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=205500) was conducted according to the PRISMA guidelines(35).

2.1. 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.

2.2. Study selection criteria

The identified citations were uploaded onto CADIMA(36,37). Duplicates were removed semi-automatically using CADIMA's in-built 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 (Kappa=0.63, calculated according to measuring agreement of Cochrane v5.1(38)). Only peer-reviewed fMRI studies of task-based functional connectivity in patients of all ages, sexes, and races/ethnicities

where ADHD (DSM or ICD) was the primary diagnosis were retained. Discrepancies were resolved by consensus.

2.3. 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 those for whom ADHD was not the primary diagnosis were excluded.

2.4. 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. Investigators independently extracted data from their allocated studies and cross-checked the accuracy of the other investigator's extraction. Data pertaining to (i) the study sample: sample size, age, sex, medication history, ADHD presentation, comorbidities; (ii) study methods: connectivity estimation method, motion correction (method and exclusion criteria), drug washout period, task, case-control matching criteria; and (iii) functional connectivity findings: changes of connectivity (increases/decreases) and their manuscript-defined location in the brain, and justification of used method (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's risk of bias tool(38) 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.

3. Results

3.1. 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 due to one or more of the following reasons: (i) not measuring fMRI task-based connectivity (N=87), (ii) no peer-review (N=39), (iii) not assessing individuals with current primary ADHD diagnosis (N=25), (iv) not presenting an empirical investigation (N=20), (v) no available full text (N=1). A total of 34 studies survived the selection process (Figure 1; Supplementary Materials list 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 non-symptomatic siblings, 2 compared remitted and persistent ADHD, and 1 explored ADHD symptom severity (investigations of siblings, remitters, and disorder severity are described in Supplementary Materials). Across all studies, this review included 981 individuals with ADHD, 38 ADHD remitters, 134 non-symptomatic siblings of individuals with ADHD, and 774 neurotypical controls.

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

~ Insert Figure 1 ~

3.2. Functional connectivity in ADHD

Thirty-seven comparisons (youth=23, adults=14) investigated the differences in connectivity between ADHD and neurotypical groups (Table 1). Based on the collective descriptions in the literature(39), the following cognitive domains emerged – attention (N=4)(40-43), cognitive control (N=6)(15,44-48), response inhibition (N=5)(15,49-52), reward processing (N=5)(53-57), working memory (N=5)(56,58-61), and emotion processing (N=6)(44,56,62-65). Additionally, six

comparisons could not be classified into the above domains and included error monitoring(66), response preparation(67), motor response(56), social cognition/relational processing(56), and time discrimination(47).

3.2.1. Differences between individuals with ADHD and neurotypical populations by cognitive domain

3.2.1.1. Attention

There was an overall decrease of connectivity in ADHD compared to neurotypical controls during attention tasks (total of 74 patients and 90 controls across four comparisons). The right inferior frontal cortex (IFC) and bilateral inferior parietal lobules (IPL) were indicated as hubs of connectivity decreases in ADHD, whereas the anterior cingulate cortex (ACC), left middle frontal (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.

3.2.1.2. Cognitive control

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

3.2.1.3. Response inhibition

ADHD was related to predominantly decreased functional connectivity compared to neurotypical controls during inhibition (total of 263 patients and 211 controls across five 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:increases), along with left IFC (3:1), MFG (2:1), superior frontal (SFG; 1:1) and middle temporal gyri (MTG; 1:1), ACC (1:1), and cerebellum (1:1) were hubs of increased and decreased connectivity in patients.

3.2.1.4. Working memory

ADHD was associated with an overall increase in connectivity compared to controls during working memory (total of 111 patients and 111 controls across five comparisons). The right insula, superior temporal gyrus (STG), striatum, and left MFG and IPL showed increased connectivity in patients. Bilateral IFC and 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).

3.2.1.5. Reward processing

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

3.2.1.6. Emotion processing

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

~ Insert Table 1 ~

~ Insert Figure 2 ~

3.2.2. 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 controls included the ACC (6:7, decreases:increases), IFC (4:3), MFG (3:4), SFG (5:3), 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(68,69), finding both within and between network differences. Relative to controls, patients showed reduced connectivity in visual (VIS), fronto-parietal (FPN), executive control (ECN), ventral attention (VAN), subcortical, and salience (SAL) networks during reward processing, as well as in the ECN during working memory. Individuals with ADHD also showed increased connectivity within the SAL during reward processing, within the FPN and auditory networks during working memory compared to controls. Furthermore, ADHD was associated with decreased functional connectivity between the default mode (DMN) and fronto-temporo-parietal networks during cognitive control, as well as between the ECN and both the FPN and the sensorimotor (SMN) networks, between DAN and SMN, and between DAN and the VIS during reward processing. Increased functional connectivity in ADHD was observed between the cingulo-opercular network (CON) and VAN in cognitive control, and between VAN and DMN, between VAN and ECN, and between 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.

~ Insert Table 2 ~

3.3. Effects of interventions on functional connectivity in ADHD

Nine studies tested the effects of interventions on functional connectivity, eight investigating stimulants (youth=6, adults=2)(42,45,55,61,63,70-72) and one evaluating fMRI neurofeedback of the right IFC(73). The intervention studies investigated various cognitive domains, thus findings were synthesised across cognitive functions and within treatment type (Table 3).

Stimulants increased connectivity of the striatum (although decreases were seen in one study), ACC, and the cerebellum across tasks, and decreased connectivity of the amygdala in emotion paradigms compared to no intervention/placebo. MFG, IFC, medial frontal, 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 ECN and between ECN and auditory networks.

The neurofeedback study showed increased functional connectivity between the right IFC and the right striatum and ACC relative to baseline and controls. Additionally, neurofeedback was associated with decreased connectivity between the right IFC and various PCC-occipital, striato-thalamic, and hippocampal regions.

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

~ Insert Table 3 ~

3.4. Critical appraisal

Across all 51 included comparisons, 28 specified a motion cut-off. 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, handedness in 26, motion in 21, IQ in 21, race/ethnicity in 9, socioeconomic status in 7, presence of unrelated symptoms in 7, education level in 6, working memory capacity in 1, and pubertal status in 1 comparison. Additionally, out of all 51 comparisons, 42 reported information about ADHD presentation. On average 72% of patients had combined ADHD, 22% had inattentive, 3% had hyperactive-impulsive presentation, and 0.5% were classified as ADHD not otherwise specified.

The reviewed studies used heterogeneous methods to assess connectivity. Out of all 51 comparisons, 20 used psychophysiological interaction (psychophysiological interaction=12, generalised psychophysiological interaction=8), 9 used seed-based correlations, 9 used graph theoretic techniques, 8 used independent component analysis, 2 used dynamic causal modelling, 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 (marked with an asterisk in Tables 1 and 3).

Of 51 comparisons, 34 recruited samples currently receiving pharmacotherapy, 9 recruited medication-naive participants, 1 recruited participants who were medication-naive or had 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, two 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, and high in 1. Performance (blinding of participants/personnel) and detection biases (blinding of outcome assessment) were rated low in 3, unclear in 3, and high in 3 comparisons. Attrition (incomplete outcome data) and reporting biases (selective reporting) were deemed low in all 9 comparisons (Supplementary Materials).

4. Discussion

4.1. 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 fronto-temporo-parietal 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 non-symptomatic 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.

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, temporo-parietal, 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(24,74-76), which may reflect the previously proposed hypothesis of deviant maturational trajectories within these networks in ADHD(74). Nonetheless, the current literature largely focused on paediatric samples and more exploration of adults and longitudinal cohorts is needed to better characterise 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 SAL(24,26,30,77,78) 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 which respond differently under distinct tasks(79). Such explanations of ADHD pathophysiology move beyond seeing the brain as a static system and suggest a conceptualisation of ADHD as a disorder of dynamic neurocognitive processes.

Second, the review emphasises 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(80), the association between neurocognitive phenotypes and individual differences is still poorly understood (Supplementary Materials). Task factors, however, are supported by a recent study, which found that youth with ADHD engage more task-specific than generic networks, showing hypoconnectivity in executive and reward circuits relative to neurotypical controls and non-symptomatic siblings of individuals with ADHD(81). This suggests that the inconsistencies in the literature may reflect inefficient task-specific networks in ADHD, with greater variability in functional connections.

This review summarises 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 non-specificity 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 proposing executive dysfunction(3,82), while others arguing for poor deployment of resources(79,83). 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 manifests across patients or whether true biological subtypes exist. Such efforts show promise(84,85) but have not yet been applied to context-dependent connectivity.

4.2. 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 stimulants modulate spontaneous brain activity in similar ventrolateral frontal, occipital, and cerebellar regions, along with connectivity within ECN, VIS, and DMN(86-89). 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 reorganisation, 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 neurofeedback of the right IFC may offer similar benefits as stimulants, however, more research is needed.

4.3. 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 due 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(90). 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, approximately half of the studies used seeds defined independently of the dataset studied, thus avoiding the potential biases of circular analyses(91). Overall, while diverse methods provide different ways of characterising 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. Since stimulant use has been associated with structural(9,92,93), functional(7-9,11,94), and neurochemical changes(95), 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 one month). A minimum washout of five half-lives of the drug is recommended(96), however, discontinuing treatment can lead to withdrawal or rebound effects(97) 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(98-102), are a limitation of this literature. Such issues have prompted recommendations, such as a minimum sample size of 20(101) and development of software allowing power calculations for fMRI studies(103). Consequently, these findings need to be interpreted with caution given that many were likely underpowered.

Some limitations of the reviewed studies surround the transparency of reporting, data quality assurance, and processing pipelines. For instance, only approximately half of the comparisons specified a motion cut-off. Given that ADHD is characterised by increased movement(104,105), lower tolerability of the scanner environment(106), and that functional connectivity methods are particularly sensitive to motion artefacts(107-109), 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(99,110,111) and thus publications not reporting applying multiple comparisons correction should be interpreted with caution.

Further, the reviewed studies differed in general methodology, including study design, acquisition parameters, 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 (Supplementary Materials). Finally, ADHD is an inherently heterogeneous disorder with variable severity and class of symptoms, genetic and environmental risk factors, and profiles of associated pathophysiology(3,112-114). Consequently, it is likely that the heterogeneity of findings can be partly explained by the inter-individual 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 future research prioritise recruiting larger, more diverse, and medication-naive samples, implement greater control of in-scan motion and motion-related artefacts, use state-of-the-art data processing pipelines, and promote reporting transparency and openness (see Pereira-Sanchez et al.(90) for an in-depth discussion).

4.4. Conclusion

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 abnormalities in ADHD, and shows that interventions can modulate the functional reorganisation 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.

Acknowledgements

This article represents independent research funded by the National Institute for Health Research (NIHR) Maudsley Biomedical Research Centre at South London and Maudsley National Health Service (NHS) Foundation Trust and King's College London. MC was supported by the Medical Research Council (MRC) through a postdoctoral appointment. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR, the MRC, or the Department of Health and Social Care.

Disclosures

The authors report no biomedical financial interests or potential conflict of interests.

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Legends for tables and figures

Table 1. Summary table of studies investigating fMRI functional connectivity differences between ADHD and typical development grouped by cognitive domain.

ACC = Anterior Cingulate Cortex; ADHD = Attention Deficit/Hyperactivity Disorder; B = Bilateral; CD = Conduct Disorder; CPT = Continuous Performance Task; DAN = Dorsal Attention Network; DCM = Dynamic Causal Modelling; DLPFC = Dorsolateral Prefrontal Cortex; DMFG = Dorsomedial Frontal Gyrus; DMN = Default Mode Network; ECN = Executive Control Network; FPN = Fronto-parietal Network; GNG = Go/No-go; gPPI = Generalised Psychophysiological Interaction; GTT = Graph Theoretic Techniques; 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; SD = Standard Deviation; 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.

Age is given in years.

*Correction for multiple comparisons not specified.

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

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

800

801 **Table 2.** Summary table of studies investigating fMRI functional connectivity differences between
802 ADHD and non-symptomatic siblings, persisters and remitters, and exploring the impact of
803 symptom severity.

804 ACC = Anterior Cingulate Cortex; ADHD = Attention Deficit/Hyperactivity Disorder; B = Bilateral;
805 CD = Conduct Disorder; DLPFC = Dorsolateral Prefrontal Cortex; GNG = Go/No-go;
806 gPPI = Generalised Psychophysiological Interaction; GTT = Graph Theoretic Techniques;
807 IFC = Inferior Frontal Cortex; IPS = Intraparietal Sulcus; L = Left; MFG = Middle Frontal Gyrus;
808 MTG = Middle Temporal Gyrus; ODD = Oppositional Defiant Disorder;
809 PPI = Psychophysiological Interaction; R = Right; SBC = Seed-based Correlation;
810 SD = Standard Deviation; SFG = Superior Frontal Gyrus; SPG = Superior Parietal Gyrus;
811 SST = Stop-signal Task.

812 Age is given in years.

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

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

817

818 **Table 3.** Summary table of studies investigating the impact of interventions on fMRI functional
819 connectivity in ADHD.

ACC = Anterior Cingulate Cortex; ADHD = Attention Deficit/Hyperactivity Disorder; B = Bilateral; BA = Brodmann Area; BSC = Beta Series Correlation; CD = Conduct Disorder; CPT = Continuous Performance Task; DCM = Dynamic Causal Modelling; DMN = Default Mode Network, ECN = Executive Control Network; GNG = Go/No-go; gPPI = Generalised 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 = Temporo-parietal Junction; VIS = Visual Network.

Age is given in years.

*Correction for multiple comparisons not specified.

Figure 1. Study selection flow chart.

Figure 2. Regions that formed core hubs of functional connectivity differences between individuals with ADHD and neurotypical controls across cognitive domains. Figure created with BioRender.com.

⇅ = Increases and Decreases of Functional Connectivity; ↑ = Increases of Functional Connectivity; ↓ = Decreases of Functional Connectivity; ACC = Anterior Cingulate Cortex;

842 Cb. = Cerebellum; Ins. = Insula; IPL = Inferior Parietal Lobule; MFG = Middle Frontal Gyrus;
843 SFG = Superior Frontal Gyrus; SMC = Sensorimotor Cortex; Str. = Striatum.

844 **Tables**

Table 1. Summary table of 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} Mean (SD)	Medication History	Medication Washout	ADHD Comorbidities	$N_{Control}$ (% male)	$Age_{Control}$ Mean (SD)	Control > ADHD	ADHD > Control
Attention											
Li et al. (40)	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 ↔ B occipital lobe
Luo et al. (41)	GTT	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 B 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. (42)	SBC	CPT (targets > non-targets)	13 (100%)	12.5 (1.3)	Medication-naive (100%)	-	ODD/CD (8%)	13 (100%)	13 (1.7)	L IFC ↔ striatum, cerebellum; R IFC ↔ striatum, B cerebellum; B thalamus/striatum ↔ striatum, R cerebellum; L striatum ↔ B 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.	GTT	CPT	22 (55%)	11.6 (2.86)	Current MPH	48 hours	None	22 (45%)	12.1 (2.23)	Nodal efficiency in L	Nodal efficiency in L

(43)		(unspecified)			use (41%), Medication-free (59%)					superior OFG and R SOG; Degree and betweenness centrality in B occipital lobes, R temporal lobe, L paracentral, SMG	cuneus; Degree and betweenness centrality in ACC
Cognitive Control											
Cubillo et al. (15)	SBC	Switch task (unspecified)	11 (100%)	29 (1)	Medication-naive (100%)	-	Anxiety disorder (9%), mood disorder (27%), CD (9%), substance use disorder (18%)	13 (100%)	28 (1)	None	None
Hwang et al. (44)	$gPPI_{AFNI}$	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*	L DMFG ↔ L posterior insula
Querne et al. (45)	ICA	Flanker task (unspecified)	11 (unspecified)	9.8 (1.7)	Medication-naive (100%)	-	None	11 (unspecified)	10.8 (1.7)	Anti-correlation between the DMN and fronto-temporo-parietal regions (direct group comparison not reported)	None
Plessen et al. (46)	ICA	Flanker task (post-error > post-correct trials)	25 (68%)	10.75 (1.09)	Medication-naive (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*
Vloet et al. (47)	PPI_{SPM}	Time discrimination + stimulus-response	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

		compatibility task (stimulus-response compatibility)									
Zamorano et al. (48)	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 ↔ B OFC, striatum
Emotion Processing											
Hafeman et al. (62)	$gPPI_{SPM}$	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	B amygdala ↔ subgenual cingulate; B amygdala ↔ R SFG
Hwang et al. (44)	$gPPI_{SPM}$	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 ↔ B postcentral*; 3. None	None
Park et al. (56)	GTT[a]	Emotive faces task (unspecified)	34 (59%)	27.88 (3.37)	Unspecified	Unspecified	Unspecified	34 (62%)	29.44 (3.57)	Degree in B 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 (63)	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. (64)	PPI_{SPM}	Face emotion GNG (correct no-go > go)	14 (100%)	23.3 (2.3)	Medication-naive (29%); Past stimulant use	-	Mood disorder (14%), anxiety disorder (14%),	14 (100%)	22.8 (2.7)	R DLPFC ↔ L IFC, putamen, B subgenual cingulate	None

					but medication-free at the time of the study (71%)		substance use disorder (36%)				
Stoddard et al. (65)	$gPPI_{AFNI}$	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. (49)	$gPPI_{SPM}$	GNG (correct no-go)	27 (78%)	19.95 (2.62)	Medication-free during testing (100%)	>5 half-lives of the drug	Unspecified	30 (73%)	13.65 (2.47)	R DLPFC ↔ R posterior parietal	None
Cubillo et al. (15)	SBC	SST (unspecified)	10 (100%)	28 (1)	Medication-naive (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, B parietal/temporal/occipital; R ACC/PCC/SMA ↔ R thalamus, striatum	None
Massat et al. (50)	PPI_{SPM}	SST (successful > failed stop)	18 (44%)	10.6 (1.13)	Medication-naive (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
Mulder et al. (51)	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)	Sample 1 and 2: ACC ↔ cerebellum*; Sample 1: Motor cortex ↔ striatum*; Sample 2: Not reported	None

Van Rooij et al. (52)	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%)	125 (44%)	16.5 (3.3)	1. L IFC ↔ R putamen; L SFG ↔ L thalamus, operculum; 2. L IFC ↔ R IFC, B SFG/preSMA, L occipital cortex, MTG; L SFG ↔ L IFC	1. L IFC ↔ L MTG, cerebellum; L SFG ↔ R ACC, frontal pole, B precuneus, L precentral, R cerebellum; 2. L IFC ↔ B temporal pole, L cerebellum, R SMG; L SFG ↔ L MTG
Reward Processing											
Ceceli et al. (53)	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 the time of the study (16%); Medication-naive (12%)	36 hours	None	25 (56%)	21.48 (2.92)	L posterior putamen ↔ dorsal ACC, medial frontal	None
Ma et al. (54)	$gPPI_{SPM}$	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. (55)	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. (56)	GTT[a]	Gambling task (1.	34 (59%)	27.88 (3.37)	Unspecified	Unspecified	Unspecified	34 (62%)	29.44 (3.57)	1. Degree in B SFG, MTG;	1. Degree in R ACC, L PCC, lingual,

		gambling reward; 2. gambling punishment)								2. Degree in R medial frontal, MFG, insula, B SFG, L IPL, thalamus, parahippocampal	thalamus, B insula, cerebellum; 2. R precentral, MTG, L postcentral, STG, B cerebellum
von Rhein et al. (57)	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. (58)	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 non-stimulant use (4%); Past stimulant/non-stimulant use but medication-free at the time of the study (29%); Medication-naive (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 ↔ B posterior insula, R temporal cortex; 2. L DLPFC ↔ L intraparietal sulcus, cerebellum
Massat et al. (59)	$gPPI_{SPM}$	Verbal n-back task (2-back > 0-back)	19 (47%)	10.75 (1.31)	Medication-naive (100%)	-	None	14 (57%)	10.05 (1.28)	None	R cerebellum ↔ red nucleus, R amygdala*, hippocampus*, lingual*, precuneus*, L IFC*, MFG*, postcentral*, cerebellum*; L occipital ↔ B MFG*, R MTG*, STG*, fusiform*, putamen*, L cerebellum*;

											L IPL ↔ B IFC*, MFG*, STG*, L ACC*, SMA*; R caudate ↔ B MFG*, R SFG*, putamen*, insula*
Park et al. (56)	GTT[a]	Visuospatial n-back task (unspecfiied)	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, B SFG, caudate
Wolf et al. (60)	ICA	Verbal working memory task (unspecified)	12 (100%)	22.2 (4.4)	Current MPH use (50%); Past MPH use but medication-free at the time of the study (50%)	72 hours	None	12 (100%)	21.6 (4.7)	Within B IFC, SFG, SPG, cerebellum, L ACC, medial frontal	Within L dorsal cingulate, cuneus, R IFC, SFG
Wu et al. (61)	ICA	Verbal n-back task (2-back > 0-back)	22 (100%)	12.71 (1.55)	Past stimulant use but medication-free at the time of the study (23%); Medication-naive (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. (66)	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 ↔ B amygdala, L SN, B basal forebrain; Raphe nucleus ↔ B amygdala, R SN, B hypothalamus
Clerkin et al. (67)	PPI_{SPM}	Cued reaction time task (cues > non-cues)	35 (83%)	24.6 (2.04)	Current stimulant use (6%); Past stimulant use but medication-free at the time of the 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. (56)	GTT[a]	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, B MTG, MOG	Degree in B SFG, PCC, R MFG, ACC, L Postcentral
Park et al. (56)	GTT[a]	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, B ACC, L lingual, cerebellum	Degree in R PCC, cuneus, B IPL, STG, L MTG
Park et al. (56)	GTT[a]	Social cognition task (unspecified)	35 (59%)	27.88 (3.37)	Unspecified	Unspecified	Unspecified	34 (62%)	29.44 (3.57)	Degree in B SFG, R PCC, L cuneus	Degree in L precentral, postcentral, cerebellum, B precuneus, R MTG
Vloet et al. (47)	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

Table 2. Summary table of studies investigating fMRI functional connectivity differences between ADHD and non-symptomatic siblings, persisters and remitters, and exploring the impact of symptom severity.

Study	Analysis Method	Task (Contrast)	N_{ADHD} (% male)	Age_{ADHD} Mean (SD)	Medication History	Medication Washout	ADHD Comorbidities	Comparison Group	$N_{Comparison}$ (% male)	$Age_{Comparison}$ Mean (SD)	Comparison > ADHD	ADHD > Comparison
Clerkin et al. (67)	PPI_{SPM}	Cued reaction time task (cues > non-cues)	16 (75%)	24.44 (2.02)	Current stimulant use (6%); Past stimulant use but medication-free at the time of the study (71%)	>48 hours	Mood disorder (23%), anxiety disorder (23%), substance use disorder (43%)	Remitters	19 (90%)	24.74 (2.1)	R thalamus ↔ B frontal pole, L DLPFC	None
Kolodny et al. (115)	$gPPI_{FSL}$[b]	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. (41)	GTT	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 B MFG	Acting network hubs in L MFG and precentral
Mulder et al. (51)	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%),	>24 hours	Sample 1: ODD (27%); Sample 2: ODD (33%)	Non-symptomatic 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

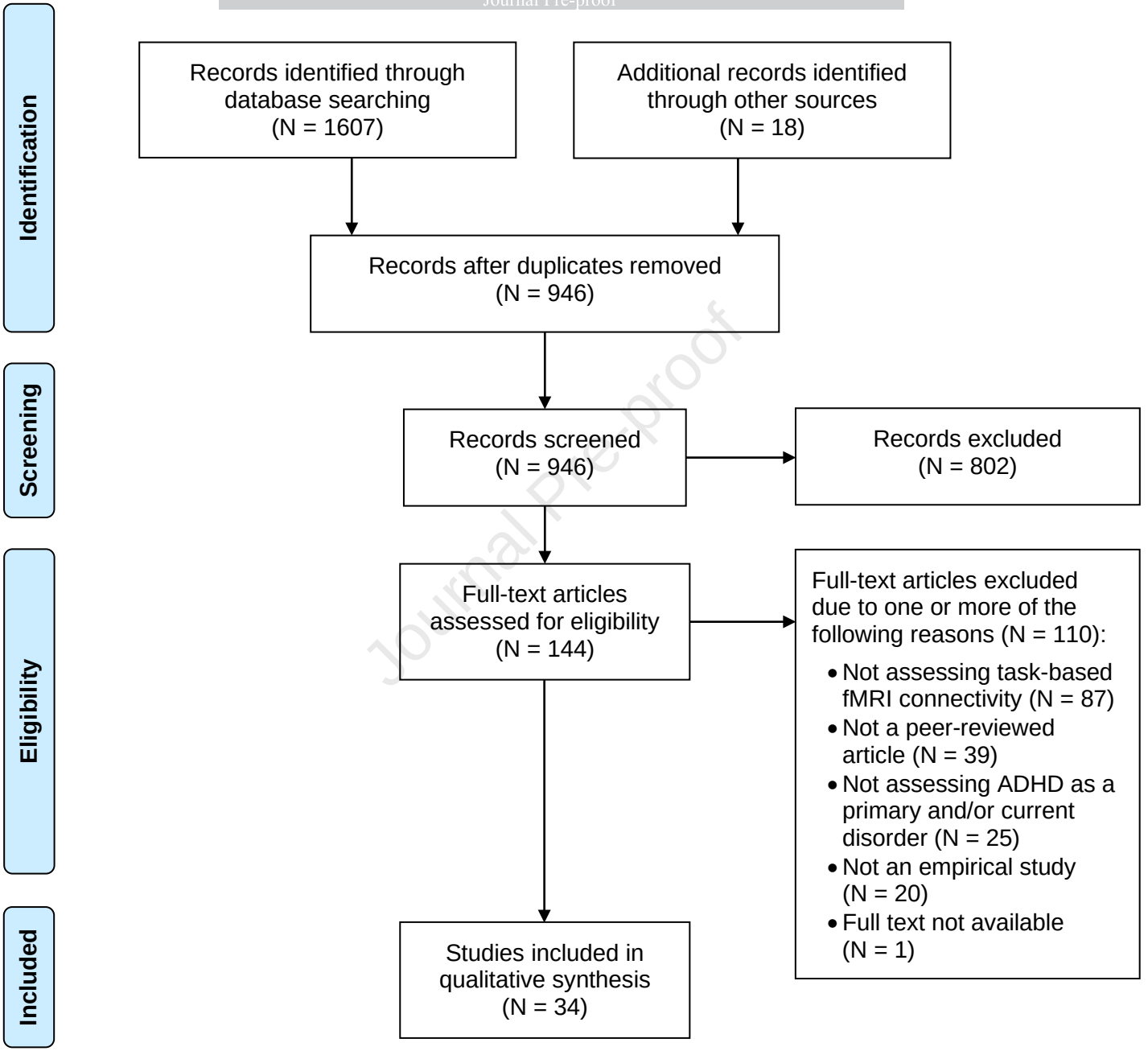
					Medication-free (42%)							
Van Rooij et al. (52)	PPI_{FSL}[a, b]	SST (1. successful stop > go; 2. failed stop > go)	185 (70%)	17.3 (3.2)	Current medication use, class unspecified (77%); Medication-free (23%)	Unspecified	ODD (30%), CD (7%), reading disability (18%)	Non-symptomatic siblings	111 (43%)	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 ↔ B precentral, precuneus, R frontal pole, ACC, cerebellum 2. L IFC ↔ R medial frontal, ACC; L SFG ↔ L MTG

Table 3. Summary table of studies investigating the impact of interventions on fMRI functional connectivity in ADHD.

Study	Analysis Method	Task (Contrast)	N_{ADHD} (% male)	Age_{ADHD} Mean (SD)	Medication History	Medication Washout	ADHD Comorbidities	Intervention / Comparison	Design	On Intervention > Off Intervention	Off intervention > On Intervention
Mowinckel et al. (55)	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 (10-40mg of regularly prescribed formulation) / Placebo	Randomised, double-blind, cross-over	Auditory network ↔ ECN	Within DMN and VIS
Posner et al. (63)	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); B amygdala ↔ B lateral PFC (secondary non-parametric analysis)
Querne et al. (45)	ICA	Flanker task (unspecified)	11 (unspecified)	9.8 (1.7)	Medication-naive (100%)	-	None	4 weeks MPH (20-30mg extended release) / Off medication	Cross-over (off medication → MPH)	DMN composed of anterior and posterior regions; Anti-correlation between DMN and B anterior frontal, striatum, dorsal ACC, R occipito-parietal cortex, L cerebellum (direct group comparison not reported)	DMN composed posterior regions only (direct group comparison not reported)
Rubia et al. (42)	SBC	CPT (targets > non-targets)	13 (100%)	12.5 (1.3)	Medication-naive (100%)	-	ODD/CD (8%)	Acute MPH (0.3mg/kg) / Placebo	Randomised, double-blind, cross-over	L caudate/putamen ↔ R caudate/ putamen	None
Rubia et al. (73)	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 the duration of the study (17%); Control group: Current	>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 (randomised 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, B PCC, precuneus, calcarine, thalamus, caudate, putamen, pallidum; R IFC (BA 44) ↔ B precuneus, PCC,

					stimulant use (69%), withdrew from medication for the duration of the study (23%), medication-naive (8%)							hippocampus, parahippocampal, lingual, thalamus; <u>Relative to control:</u> R IFC (BA 45) ↔ B PCC, precuneus, calcarine; R IFC (BA 44) ↔ B PCC, precuneus, hippocampus, parahippocampal, lingual, thalamu
Schulz et al. (70)	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 non-stimulant use but medication-free at the time of the study (36%); Medication-naive (56%)	2 weeks	None	5 weeks LDX (30-70mg) / Placebo	Randomised, single-blind, cross-over	None	L amygdala ↔ R SPG, L STG; R amygdala ↔ L IFC, STG, R SPG
Sheridan et al. (71)	BSC	Delayed match to sample task (encoding)	5 (0%)	14.8 (2.4)	Current stimulant use (60%); Current stimulant and non-stimulant use (20%); Current stimulant and SSRI use (20%)	24 hours (for stimulants only)	Unspecified	Acute stimulant (regularly prescribed formulation and dose) / Off medication	Cross-over	B MFG ↔ cerebellar vermis*	B MFG ↔ striatum*, L MFG*, medial PFC*, hippocampus*, ITG*, R TPJ*, insula*, lingual*
Wong & Stevens (72)	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	Randomised, double-blind, cross-over	Within ACC, medial frontal, PCC, precuneus, cuneus, lingual, SFG, cingulate, R postcentral, precentral, L IFC, SMG, MTG, angular regions	Within PCC, precuneus

Wu et al. (61)	ICA	Verbal n-back task (2-back > 0-back)	22 (100%)	12.71 (1.55)	Past stimulant use but medication-free at the time of the study (23%); Medication-naive (77%)	>4 weeks	ODD (18%)	Acute MPH (10mg) / Placebo	Randomised, double-blind, cross-over	Within ECN (R precuneus, L PCC)	None



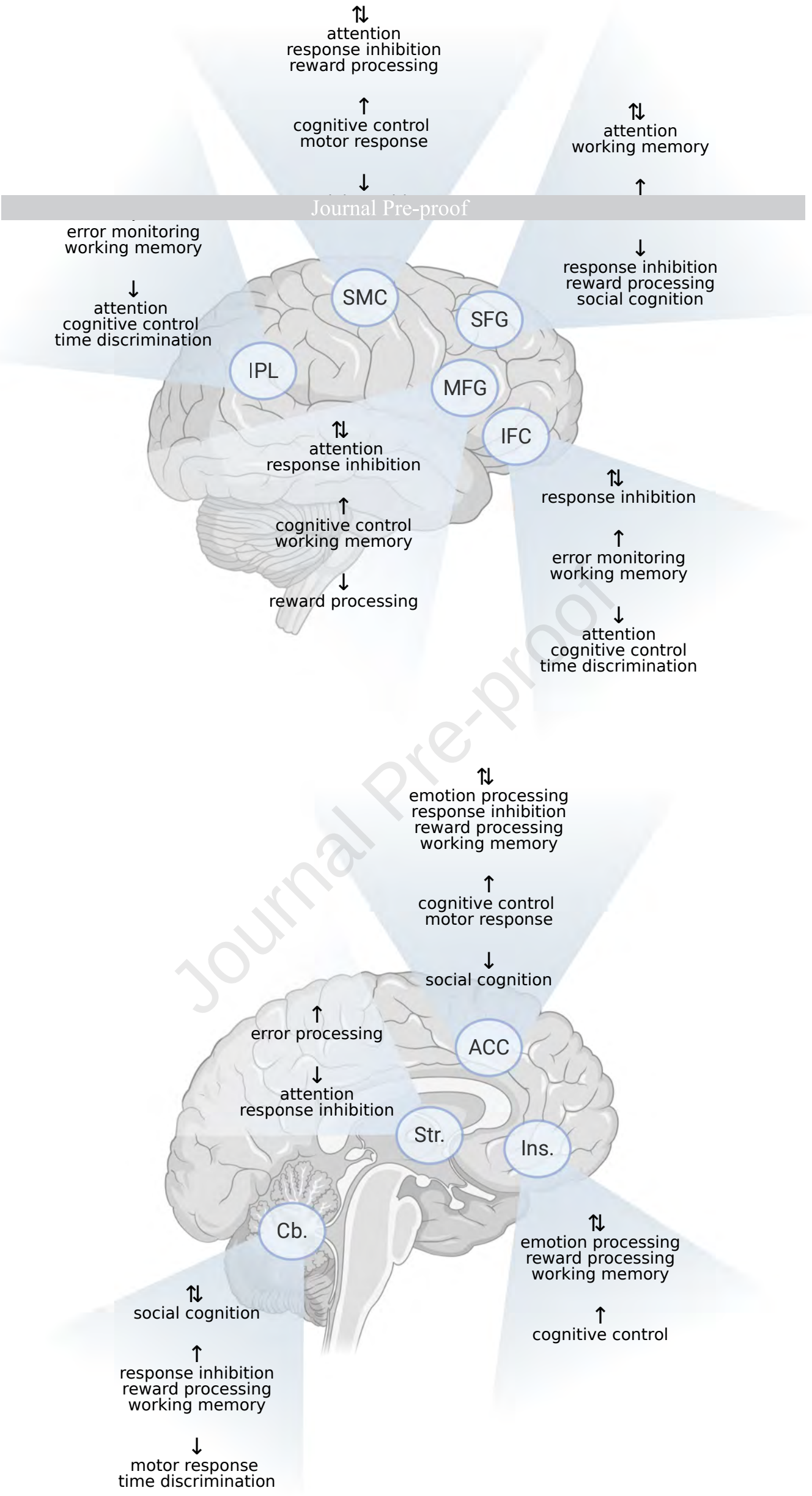


Figure legend:

Brain region forming a hub of functional connectivity

⇅ Increases and decreases of functional connectivity

↑ Increases of functional connectivity

↓ Decreases of functional connectivity