

Review Article

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Impairments of large-scale functional networks in attention-deficit/hyperactivity disorder: a meta-analysis of resting-state functional connectivity

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Abstract

Altered resting-state functional connectivity (rsFC) has been noted in large-scale functional networks in attention-deficit/hyperactivity disorder (ADHD). However, identifying consistent abnormalities of functional networks is difficult due to varied methods and results across studies. To integrate rsFC alterations and search for coherent patterns of intrinsic functional network impairments in ADHD, this research conducts a coordinate-based meta-analysis of voxel-wise seed-based rsFC studies comparing rsFC between ADHD patients and healthy controls. A total of 25 datasets from 21 studies including 700 ADHD patients and 580 controls were analyzed. We extracted the coordinates of seeds and between-group effects. Each seed was then categorized into a seed-network by its location within priori 7-network parcellations. Then, pooled meta-analyses were conducted for the default mode network (DMN), frontoparietal network (FPN) and affective network (AN) separately, but not for the ventral attention network (VAN), dorsal attention network (DAN), somatosensory network (SSN) and visual network due to a lack of primary studies. The results showed that ADHD was characterized by hyperconnectivity between the FPN and regions of the DMN and AN as well as hypoconnectivity between the FPN and regions of the VAN and SSN. These findings not only support the triple-network model of pathophysiology associated with ADHD but also extend this model by highlighting the involvement of the SSN and AN in the mechanisms of network interactions that may account for motor hyperactivity and impulsive symptoms.

Introduction

Attention-deficit/hyperactivity disorder (ADHD), the most common childhood-onset neuro-behavioral disorder (Wolraich *et al.*, 2011), is characterized by age-inappropriate inattention, hyperactivity and impulsivity (American Psychiatric Association, 2013). According to a latest meta-analysis of 175 studies, the worldwide-pooled prevalence of ADHD is 7.2% in children and adolescents (Thomas *et al.*, 2015), and approximately 60% of cases demonstrate symptom persistence in adulthood (Sibley *et al.*, 2017). Although numerous studies have been conducted on ADHD, the psychopathology of the disorder remains incompletely understood. In recent years, ADHD has been increasingly viewed as impairments among distributed functional networks or circuits. The functional network, which consists of brain regions that are correlated during a resting state or specific tasks, can be defined as a synchronized network of brain function (Fox *et al.*, 2005) and is believed to reflect distinct mental states or processes (Shirer *et al.*, 2012; Buckner and Krienen, 2013). Aberrant communication between or within functional networks may underlie deficits in cognitive and affective functioning (Zang *et al.*, 2007; Kessler *et al.*, 2014).

Resting-state functional connectivity (rsFC) techniques, which measure the correlations of brain activity across anatomically separated brain areas at rest, have been extensively applied to reveal abnormalities of large-scale intrinsic functional networks and the interaction between them in ADHD. Two recent narrative reviews of rsFC suggest that altered connectivity in ADHD is noted not only in the default mode network (DMN), frontoparietal network (FPN) and attention networks but also in reward-related and affective circuits (Castellanos and Aoki, 2016; Posner *et al.*, 2014a). However, these findings remain inconsistent across different studies. For instance, although weaker functional connectivity within the DMN has been widely observed in individuals with ADHD (Castellanos *et al.*, 2008; Fair *et al.*, 2010; Choi *et al.*, 2013; Sripada *et al.*, 2014), some studies have also reported stronger within-DMN functional connectivity in ADHD patients (McCarthy *et al.*, 2013; Barber *et al.*, 2015). Moreover, altered connectivity in the FPN and attention networks has been more divergent as both

increased and decreased functional connectivity (Lin and Gau, 2016; Mostert *et al.*, 2016; Sidlauskaite *et al.*, 2016) have been found in ADHD. Comparing these results can be problematic because of the different analytic methods used and variations in the nomenclature and boundaries of functional networks.

At the analysis stage, seed-based analysis is the most basic analytic approach for rsFC, which measures correlations of time series between a seed region-of-interest (ROI) and the rest voxels of the brain (Biswal *et al.*, 1995; Fox and Raichle, 2007). This analytic approach has become the most commonly used method in rsFC studies of ADHD due to its simplicity in terms of calculation and interpretation and can directly locate the effect regions that show functional connectivity with the seed regions. However, the locations and sizes of seed ROIs vary considerably across studies (Fox and Greicius, 2010; Power *et al.*, 2012), which make it a challenge to organize functional connectivity alterations. In addition, small sample sizes, non-uniform recruitment criteria and heterogenous results in current connectivity studies hamper our understanding of the neurobiological dysfunction in ADHD. A novel meta-analytic strategy proposed by Kaiser *et al.*, can help overcome these challenges (Kaiser *et al.*, 2015). This method allows unification of diverse findings in seed-based rsFC studies by categorizing seeds and corresponding effect regions into a priori functional network parcellations based on their locations. Based on this categorization, a meta-analysis is then performed for each seed-network to statistically synthesize the results and leverage large sample sizes to identify reliable and homogeneous patterns of functional connectivity alterations across existing studies. This strategy has been applied to major depressive disorder, schizophrenia and obsessive-compulsive disorder (Kaiser *et al.*, 2015; Dong *et al.*, 2018; Gursel *et al.*, 2018). The three studies investigating the above disorders with this strategy all used the multilevel kernel density analysis (MKDA) methodology, which allows the inclusion of only positive findings in a meta-analysis. As negative findings (i.e. null findings) may cause a decrease of meta-analytic estimates (Radua *et al.*, 2012), inclusion of only positive findings may increase the bias in the results.

Therefore, in this study, we conduct a meta-analysis using the anisotropic effect-size version of seed-based d mapping (AES-SDM), which considers both positive and negative findings (Radua and Mataix-Cols, 2012) to unify seed-based rsFC findings into consistent patterns of impairments among intrinsic functional networks in ADHD. We analyzed all networks from Yeo's 7 parcellations (Yeo *et al.*, 2011), including the DMN, FPN, ventral attention network (VAN), dorsal attention network (DAN), affective network (AN), somatosensory network (SSN) and visual network, since all these networks have been reported to be altered in individuals with ADHD (Castellanos and Aoki, 2016).

Methods

Search strategy

The online search was conducted in the PubMed, Web of Science and EMBASE databases to retrieve studies published before 29 November 2018, using the keywords 'attention deficit hyperactivity disorder' or 'attention-deficit/hyperactivity disorder' or 'ADHD' or 'hyperkinetic' plus 'rest*' plus 'connect*' or 'fMRI'. In addition, the references of retrieved studies and pertinent review articles were manually searched.

Study eligibility criteria

Original fMRI studies were included if they (1) had a current ADHD patient group diagnosed according to the DSM-IV, DSM-5, or ICD-10 criteria; (2) had a typically developing (TD) comparison group; (3) directly compared whole-brain seed-based rsFC between ADHD and TD subjects; and (4) reported results as coordinates in stereotactic space. Authors were contacted if the coordinates of seeds or between-group effects were not provided in the study. Moreover, studies with negative findings were also included.

The exclusion criteria for the studies were as follows: (1) not seed-based rsFC approach; (2) no whole-brain analyses (restricted to predefined ROIs); (3) coordinates of seed ROIs or between-group effects could not be retrieved; or (4) overlapping samples with the same seeds reported elsewhere. Studies on the same samples but with selection of different seeds were considered separate datasets; studies in which distinct ADHD groups were compared with a single TD group were coded as distinct datasets.

Data extraction

Data were extracted as follows. First, the coordinates of the center of mass of each seed ROI and the peaks of each between-group effect exhibiting significance at the whole-brain level were extracted. For seed ROIs that were anatomical regions from atlases or prior results, representative coordinates were obtained by calculating the center of mass of seed ROIs using 'fslstats' commands from the FMRIB Software Library (FSL; <http://www.fmrib.ox.ac.uk/fsl>). Then, we categorized seed ROIs based on their coordinates for the location of the center of mass into previously defined functional networks. These functional networks were defined by a previous whole-brain rsFC network parcellation from 1000 healthy participants and included the DMN, FPN, VAN, DAN, AN, SSN and visual network (Buckner *et al.*, 2011; Yeo *et al.*, 2011; Choi *et al.*, 2012). Finally, effects were categorized according to the direction of the actual values of the effects into hyperconnectivity (increased positive or decreased negative rsFC in ADHD patients compared with TD controls; that is, ADHD > TDC) or hypoconnectivity (increased negative or decreased positive rsFC in ADHD patients compared with TD controls; that is, ADHD < TDC).

In addition, negative results (i.e. those that did not survive statistical correction or showed no group differences in rsFC) were also included as another category of effect direction.

Meta-analysis

The voxel-wise meta-analysis was performed using the AES-SDM software package (version 5.15, <http://www.sdmproject.com/software>), which is a statistical technique for meta-analyzing studies on differences in brain activity (Radua and Mataix-Cols, 2012). First, we selected coordinates of cluster peaks (the voxels where the rsFC differences between ADHD and TD subjects were highest) and statistics (*T*-scores, *Z*-scores or *p* values, if available) according to AES-SDM inclusion criteria. Second, the effect-size maps of differences in rsFC between ADHD and TD subjects were recreated separately for each study using an anisotropic unnormalized Gaussian kernel, which assigned a higher value to the voxels closer to the peak coordinates (Radua *et al.*, 2014). Both positive and negative coordinates were reconstructed in

the same map, which is important for preventing a particular voxel erroneously appearing to be indicating opposite directions at the same time (Radua and Mataix-Cols, 2009). Finally, individual maps were combined using meta-analytic calculations, which were weighted by the intrastudy variance and interstudy heterogeneity. Statistical significance was determined using standard permutation tests with an uncorrected $p < 0.005$ and $|Z| > 1$ as the main threshold. This threshold is thought to be approximately equivalent to a corrected $p < 0.05$ in AES-SDM based on empirical comparisons (Radua *et al.*, 2012). To further reduce false positive errors, we reported only clusters with 100 or more voxels as recommended in a recent published meta-analysis (Tang *et al.*, 2018).

Complementary analysis

Five kinds of complementary analyses were performed for each seed-network as follows. (1) To control for age differences between studies, a subgroup analysis of nonadult studies was conducted. Therefore, the mean analysis was repeated including only samples of children and adolescents. Subgroup analyses of medication-naïve samples or medicated samples were not possible because of insufficient studies; (2) Interstudy heterogeneity was examined using the heterogeneity Q statistic. Clusters were considered heterogeneous among studies if they showed significant heterogeneity and overlapped with the main results. The sources of heterogeneity were further explored through meta-regression analyses; (3) The potential effects of several relevant demographic and clinical variables were examined using simple linear regression. Independent variables explored by meta-regression were sex, the mean age and the percentage of medication-naïve patients. The percentage of comorbidity-free patients could not be analyzed due to insufficient data; (4) A jackknife sensitivity analysis was conducted for both the main and subgroup analyses to evaluate the robustness and reliability of the results. The statistical analysis was repeated several times, excluding one different study each time. If a previously significant finding remained significant in all combinations of studies or with one or two exceptions, then it can be regarded as highly replicable; (5) Funnel plots and Egger's test in AES-SDM were used to visualize and quantitatively test the possibility of publication bias for each cluster, respectively (Egger *et al.*, 1997; Ioannidis *et al.*, 2014). The results showing $p < 0.05$ in Egger's test were considered to reflect a significant publication bias.

Results

Included studies

A total of 700 ADHD patients, including 497 children and adolescents (<18 years) and 203 adults (>18 years), 580 TD controls (464 children and adolescents, 116 adults), 49 seed ROIs, 235 peak coordinates and 8 negative results extracted from 25 datasets of 21 studies were analyzed. The demographic and clinical characteristics of the included studies are summarized in Table 1, and methodological information is also available (online Supplementary Table S1). Figure 1 shows the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) flow diagram (Liberati *et al.*, 2009) of the search strategy and selected studies. After categorizing seed ROIs into seven seed-networks, 10 studies for the DMN, 11 studies for the FPN and 8 studies for the AN were included in the meta-analysis

(online Supplementary Table S2). Given that the number of studies for the DAN, VAN, SSN and visual network separately was too small to draw reliable conclusions, pooled meta-analyses of those seed-networks were not conducted.

Within-network dysfunction

ADHD was associated with hypoconnectivity within the DMN. We found hypoconnectivity between the DMN seeds and the left middle frontal gyrus (MFG) (Table 2, Fig. 2a). This altered connectivity was also observed between the DMN seeds and areas of the medial prefrontal cortex (MPFC) in nonadult samples (online Supplementary Fig. S1A).

In addition, hyperconnectivity was found within the FPN in the nonadult samples, which peaked in the dorsal anterior cingulate cortex (dACC) (online Supplementary Fig. S1B).

Between-network dysfunction

Hyperconnectivity between the DMN and the FPN

ADHD was characterized by hyperconnectivity between the DMN seeds and the right supramarginal gyrus extending to the right angular gyrus that spread across the FPN and the DMN (Fig. 2a). Meanwhile, hyperconnectivity was also found between the FPN seeds and areas of the caudate in the DMN (Fig. 2b).

Hyperconnectivity and hypoconnectivity between the DMN and regions of the AN

ADHD showed hyperconnectivity between the DMN seeds and the left superior temporal gyrus (STG) as well as hypoconnectivity between the DMN seeds and portions of the subcallosal cingulate cortex (SCC) (Fig. 2a). Both of these clusters were located in the AN but were related to diverse functions.

Hypoconnectivity between the FPN and regions of the VAN or SSN

Hypoconnectivity was found between the FPN seeds and regions of the VAN, including the right putamen and the left insula (Fig. 2b). Moreover, hypoconnectivity was also observed between the FPN seeds and the bilateral precentral gyrus, regions belonging to the SSN (Fig. 2b).

Hyperconnectivity between the FPN and regions of the AN

Hyperconnectivity was observed between the FPN seeds and areas of the left orbital frontal cortex (OFC), which is in the AN (Fig. 2b).

Hyperconnectivity between the AN and regions of the DMN or FPN

ADHD was linked to hyperconnectivity between the AN seeds and regions of the left MFG, which is located in the DMN (Fig. 1c). Hyperconnectivity was also found between the AN seeds and parts of the left dorsolateral prefrontal cortex (DLPFC), which has been implicated as a key region of the FPN (Fig. 1c).

Complementary analyses

Subgroup analyses

Subgroup analyses of 13 nonadult studies (7 for the DMN and 8 for the FPN) revealed that the above results remained largely unchanged or were even more significant in some clusters (online Supplementary Table S5 and Fig. S1). Moreover, five additional significant clusters emerged in this subanalysis of studies. We

Table 1. Summary of the demographic and clinical characteristics of the studies included in the meta-analysis

Study	Subjects (females), <i>n</i>		Mean age ± SD (range), y		ADHD subtypes	Comorbidities, % (Type)	Medicated, %
	ADHD	TD	ADHD	TD			
Tian <i>et al.</i> (2006)	8 (0)	8 (0)	13.9 ± 0.4 (11–15)	13.4 ± 0.5 (12–15)	C = 1; I = 7	NA	100
Cao <i>et al.</i> (2009)	19 (0)	23 (0)	13.3 ± 1.4 (11–16)	13.2 ± 1.0 (11–16)	C = 7; I = 12	78 (ODD, CD)	0
Mennes <i>et al.</i> (2011)	17 (3)	17 (8)	11.0 ± 1.3 (8–13)	10.8 ± 1.9 (8–13)	C = 11; I = 6	29 (ODD, AD)	34
Mills <i>et al.</i> (2012)	70 (14)	89 (24)	9.9 ± 1.3 (7–11)	9.9 ± 1.2 (7–11)	All C	NA	NA
Sun <i>et al.</i> (2012)	19 (0)	23 (0)	13.3 ± 1.4 (11–16)	13.2 ± 1.0 (11–16)	C = 7; I = 12	58 (ODD, CD)	0
Costa Dias <i>et al.</i> (2013)	35 (8)	64 (25)	9.6 ± 1.5 (7–12)	9.2 ± 1.2 (7–12)	All C	NA	NA
McCarthy <i>et al.</i> (2013)	16 (5)	16 (5)	24.5 ± 8.3 (>18)	24.4 ± 8.0 (>18)	All C	NA	88
Posner <i>et al.</i> (2013)	22 (5)	20 (5)	10.0 ± 1.6 (7–12)	10.5 ± 1.4 (7–12)	C = 19; I = 3	32 (ODD, SAD)	0
Hoekzema <i>et al.</i> (2014)	22 (0)	23 (0)	32.8 ± 10.8 (>18)	29.2 ± 8.9 (>18)	All C	NA	0
Karalunas <i>et al.</i> (2014)	18 (NA)	15 (NA)	NA (7–11)	NA (7–11)	NA	NA	NA
Karalunas <i>et al.</i> (2014)	11 (NA)	15 (NA)	NA (7–11)	NA (7–11)	NA	NA	NA
Karalunas <i>et al.</i> (2014)	10 (NA)	15 (NA)	NA (7–11)	NA (7–11)	NA	NA	NA
Li <i>et al.</i> (2014)	33 (0)	32 (0)	10.1 ± 2.6 (6–16)	10.9 ± 2.6 (8–16)	C = 22; I = 11	NA	0
McLeod <i>et al.</i> (2014)	21 (1)	23 (12)	12.5 ± 2.9 (8–17)	11.3 ± 2.8 (8–17)	NA	0	52
McLeod <i>et al.</i> (2014)	18 (4)	23 (12)	11.5 ± 3.0 (8–17)	11.3 ± 2.8 (8–17)	NA	100 (DCD)	50
Posner <i>et al.</i> (2014b)	30 (6)	31 (10)	9.8 ± 2.1 (6–13)	10.8 ± 2.0 (6–13)	C = 24; I = 5; H = 1	58 (ODD/CD, MDD, etc.)	0
Hong <i>et al.</i> (2015)	83 (18)	22 (8)	9.6 ± 2.6 (NA)	9.8 ± 2.6 (NA)	C = 44; I = 32; H = 1; NOS = 6	22 (ODD, AD)	88
Kucyi <i>et al.</i> (2015)	23 (13)	23 (15)	24.3 ± 3.9 (>18)	24.2 ± 2.9 (>18)	C = 12; I = 10; H = 1	NA	70
Lin <i>et al.</i> (2015)	25 (5)	25 (6)	9.9 ± 1.8 (7–14)	10.0 ± 2.1 (7–14)	NA	32 (ODD)	NA
Lin and Gau (2016)	24 (11)	24 (11)	30.4 ± 9.0 (18–52)	30.1 ± 9.2 (18–52)	NA	NA	0
Oldehinkel <i>et al.</i> (2016)	169 (46)	122 (68)	17.9 ± 3.1 (NA)	17.0 ± 3.0 (NA)	C = 69; I = 83; H = 17	31 (ODD, CD)	77
Uytun <i>et al.</i> (2016)	9 (0)	9 (0)	NA (9–16)	NA (9–16)	All C	0	0
Uytun <i>et al.</i> (2016)	9 (0)	9 (0)	NA (9–16)	NA (9–16)	NA	100 (CD/ODD)	0
Mizuno <i>et al.</i> (2017)	31 (0)	30 (0)	10.6 ± 2.2 (NA)	9.7 ± 2.0 (7–14)	C = 24; I = 7	10 (ODD)	100
Zhao <i>et al.</i> (2017)	28 (13)	30 (13)	27.1 ± 5.5 (>18)	25.9 ± 3.8 (>18)	C = 7; I = 21	0	21
<i>Total Subjects</i>	700	580					

C, combined type; I, inattentive type; H, hyperactive-impulsive type; NOS, not otherwise specified; DCD, developmental coordination disorder; ODD, oppositional defiant disorder; CD, conduct disorder; MDD, major depressive disorder; AD, anxiety disorder; SAD, separation anxiety disorder; SD, standard deviation; NA, not available.

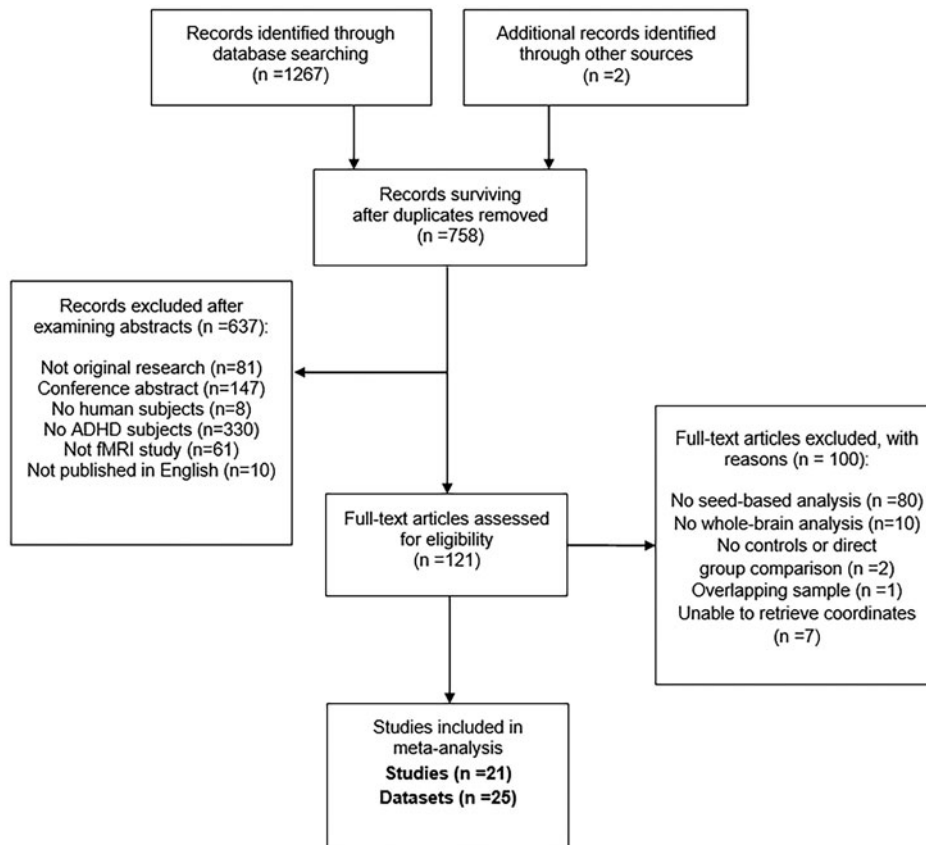


Fig. 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) flow diagram of the search strategy and retrieved studies. ADHD, attention-deficit/hyperactivity disorder; fMRI, functional magnetic resonance imaging.

found hyperconnectivity between DMN seeds and regions of the bilateral insula, which were located in the VAN, along with the left STG in the SSN. In addition, within-DMN seeds exhibited hypoconnectivity with the right medial prefrontal cortex (MPFC). In addition, we also found hyperconnectivity within the FPN, which peaked in the anterior cingulate cortex (ACC). The analysis was not repeated for AN studies because all samples were children or adolescents.

Heterogeneity analyses and publication bias

No significant between-group heterogeneity was found in the results for the DMN and AN. For the FPN results, significant between-group heterogeneity was detected in the SFG and the putamen. None of the clusters reported above showed a significant publication bias based on Egger's test ($p > 0.05$). Funnel plots are presented in online Supplementary Fig. S2.

Meta-regression analyses

Regression analyses showed that the mean age (DMN: available in all studies but two; FPN: available in all studies but one), the percentage of male patients (available in all studies) and the percentage of medication-naïve patients (DMN: available in all studies; FPN: available in all studies but one) were not associated with ADHD-related rsFC changes, at least linearly. Meta-regression analysis for AN studies was not possible as the number of studies was insufficient.

Jackknife sensitivity analyses

For the results of the main analysis, jackknife sensitivity analyses revealed that the result in the left MFG remained significant in all combinations of datasets, while the remaining resultant clusters

remained significant in all but 1 combination of datasets (online Supplementary Table S4). The results of the jackknife sensitivity analyses for the subgroup analysis of nonadult samples are listed in online Supplementary Table S6.

Discussion

The present meta-analysis motivates a consistent pattern of large-scale brain network impairments in ADHD in which the FPN plays a key role in regulating the functions of other networks (Fig. 3). Our finding of imbalanced connectivity between the FPN and regions of the DMN and VAN (also referred to as 'SN') supports the well-known triple-network dysfunction model of pathophysiology associated with multiple psychiatric disorders (Menon, 2011), including ADHD, and may underlie the symptoms of inattention that characterize ADHD. Beyond this model, we also found dysconnectivity between these three networks and two other functional networks: the somatosensory network (SSN) and the affective network (AN). These findings suggest the non-negligible roles of the SSN and AN in the abnormal network interactions that may account for ADHD-related motor hyperactivity and impulsive symptoms.

Hyperconnectivity was observed in individuals with ADHD between the DMN and the FPN along with hypoconnectivity within the DMN itself, a network involved in self-related activity (Buckner *et al.*, 2008), especially spontaneous mind-wandering (Fox *et al.*, 2015; Bozhilova *et al.*, 2018). Weaker within-DMN connectivity has been a common finding in ADHD and may reflect weakness in the integration of inner activity. In original studies, DMN-FPN hyperconnectivity was reported to be associated with reduced negative functional connectivity in ADHD

Table 2. Meta-analysis of abnormal resting-state functional connectivity in ADHD subjects compared with TD controls

Seed-network	Seed anatomy	Effect network	Effect anatomy	MNI coordinates	Voxels	SDM Z-value	<i>p</i> value
DMN	Caudate, MPFC, PCC						
	Hippocampus, IPL						
	Cerebellum, Precuneus						
ADHD > TD		FPN, DMN	Right SMG extending to the AG	62, -48, 38	451	1.217	0.0003
		AN	Left STG	-34, 10, -28	248	1.039	0.0007
ADHD < TD		DMN	Left MFG	-34, 14, 50	584	-1.537	<0.0001
		AN	Right SCC	2, 12, -4	540	-1.397	<0.0001
FPN	ACC, FO, SMG, aPFC						
	DLPFC, SFG, Caudate						
ADHD > TD		AN	Left OFC	-8, 64, -20	372	1.055	0.0010
		DMN	Right caudate	8, 6, -2	110	1.015	0.0017
ADHD < TD		VAN	Right putamen	30, -4, 0	925	-1.533	0.0002
		VAN	Left insula	-38, -10, 8	581	-1.334	0.0008
		DAN, SSN	Left precentral gyrus	-38, -6, 56	152	-1.251	0.0012
		SSN	Right precentral gyrus	38, -18, 48	119	-1.143	0.0019
AN	NAcc, Amygdala, OFC						
	Ventral striatum, Caudate						
ADHD > TD		FPN, DMN	Left DLPFC	-22, 60, 0	444	1.366	<0.0001
		DMN	Left MFG	-42, 2, 48	202	1.088	0.0008

MNI, Montreal Neurological Institute; SDM, seed-based d mapping; DMN, default mode network; VAN, ventral attention network; DAN, dorsal attention network; FPN, frontoparietal network; SSN, somatosensory network; AN, affective network; ACC, anterior cingulate cortex; FO, frontal operculum; SMG, supramarginal gyrus; AG, angular gyrus; NAcc, nucleus accumbens; DLPFC, dorsolateral prefrontal cortex; SFG, superior frontal gyrus; OFC, orbitofrontal cortex; aPFC, anterior prefrontal cortex; PCC, posterior cingulate cortex; MPFC, medial prefrontal cortex; IPL, inferior parietal lobe; MFG, middle frontal gyrus; STG, superior temporal gyrus; SCC, subcallosal cingulate cortex; DLPFC, dorsolateral prefrontal cortex

subjects compared to TDCs (Sun *et al.*, 2012; Lin and Gau, 2016). This finding is consistent with that of an earlier resting-state fMRI study showing a reduced or absent anticorrelation between the DMN and the FPN in ADHD (Castellanos *et al.*, 2008). The authors postulated that this functional alteration may underlie the attentional lapses in ADHD as mind-wandering mediated by the DMN may disrupt or interfere with the normal functioning of the frontoparietal control network. However, this hypothesis requires further verification from evidence of the behavioral correlates of DMN-FPN dysfunctional interactions. A recent study suggested that ADHD-related mind-wandering can be explained by deficient control of task-related cognition instead of excessive generation of task-unrelated thoughts, which may partly derive from dysfunction in the intrinsic architecture of the FPN rather than the DMN (Vatanev *et al.*, 2019). Therefore, the roles of the DMN and FPN in the neural correlates of mind-wandering in ADHD require further clarification.

The present study also revealed hypoconnectivity in ADHD between the FPN and the insula, which is a critical part of the salience network ('VAN' in this study) and implicated in the evaluation of motivational salience stimuli (Lopez-Larson *et al.*, 2012; Vasic *et al.*, 2014). According to a network model of insula function, when a salient event is detected, the insula plays a role in switching between other functional networks to facilitate access to attention and working memory resources (Menon and Uddin, 2010). Therefore, impairments of connectivity between the insula

and frontoparietal control network may lead to inappropriate behavioral responses to salient stimuli, which potentially cause the core ADHD symptoms of inattention. Meanwhile, the FPN also exhibited hypoconnectivity with the putamen. As one of the main structures composing the striatum, the putamen primarily regulates motor function via connections with cortical motor areas (Di Martino *et al.*, 2008; Cai *et al.*, 2014) and supports high-level cognitive functions such as working memory (Chang *et al.*, 2007) and language processing (Booth *et al.*, 2007). Previous meta-analyses revealed hypoactivation in the DLPFC, insula and putamen during attention tasks (Hart *et al.*, 2013) and inhibition tasks (Norman *et al.*, 2016) in patients with ADHD relative to controls. Therefore, the abnormal connectivity between FPN regions and the insula as well as the putamen may underlie the deficits of attention and inhibition control that characterize ADHD.

Furthermore, hypoconnectivity was also observed between the FPN and the precentral gyrus, which is an important part of the sensorimotor system and is involved in multiple executive functions, such as sustained attention, response inhibition and task switching (Dibbets *et al.*, 2010; Lei *et al.*, 2015). Hyperactivation of the precentral gyrus has been shown to be associated with impaired motor inhibition in ADHD (Cortese *et al.*, 2012). The abnormal connectivity between the precentral gyrus and the FPN may be related to deficits of motor inhibition control in ADHD.

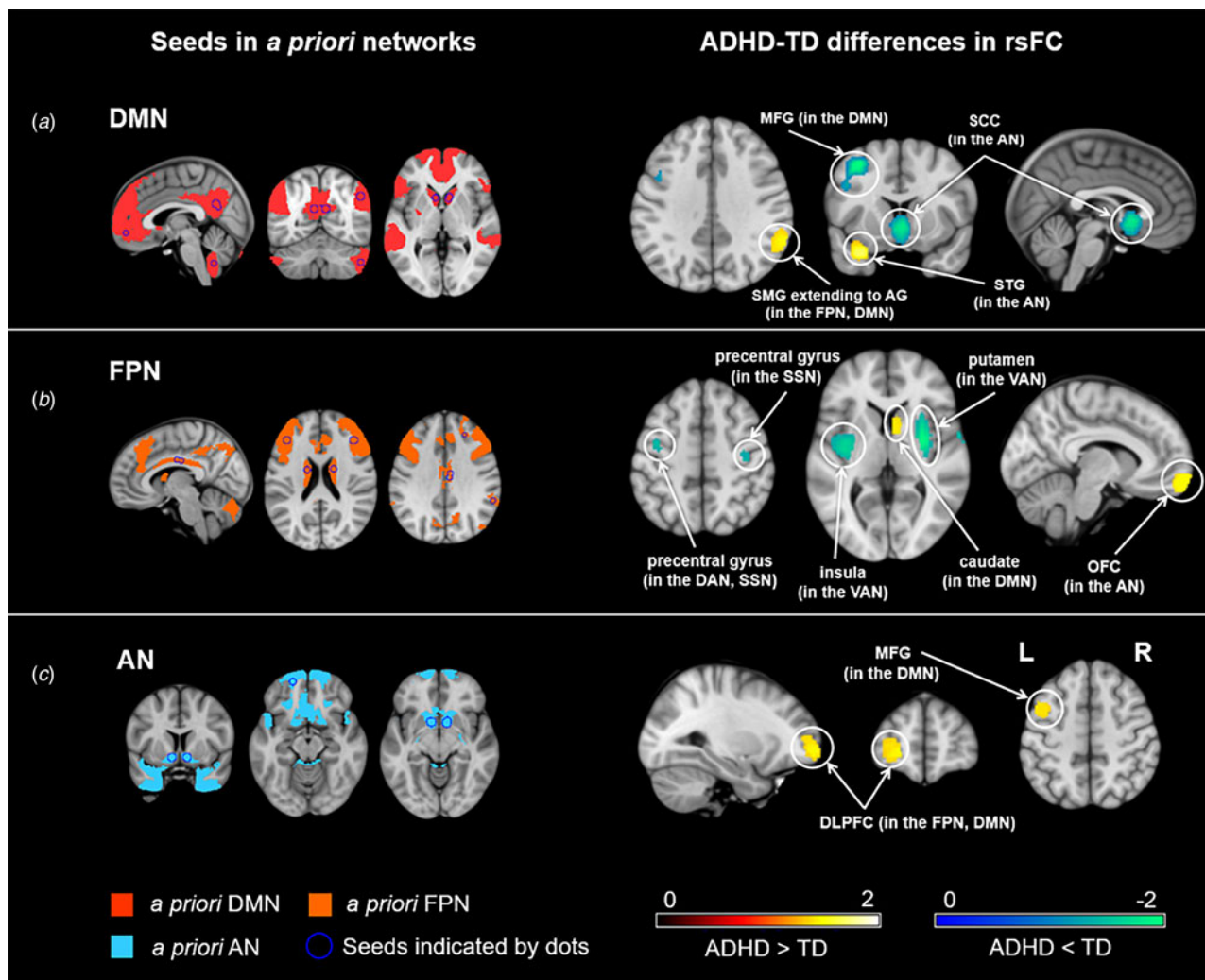


Fig. 2. Meta-analysis of abnormal resting-state functional connectivity (rsFC) for three seed-networks in attention-deficit/hyperactivity disorder (ADHD). The left 3 columns illustrate the seed regions of interest indicated by dots and categorized by a priori functional networks. The right 3 columns illustrate abnormal rsFC in ADHD subjects compared to typically developing (TD) individuals. DMN, default mode network; FPN, frontoparietal network; AN, affective network; DAN, dorsal attention network; VAN, ventral attention network; SSN, somatosensory network; MFG, middle frontal gyrus; STG, superior temporal gyrus; OFC, orbitofrontal cortex; SCC, subcallosal cingulate cortex; SMG, supramarginal gyrus; AG, angular gyrus; DLPFC, dorsolateral prefrontal cortex; L, left; R, right.

We also found hyperconnectivity between the AN and prefrontal regions of the DMN and the FPN. In the original study, the ADHD-related increased connectivity between the nucleus accumbens (NAcc) and the prefrontal cortex (e.g. the anterior prefrontal cortex (aPFC) and MFG) was associated with greater impulsivity (Costa Dias *et al.*, 2013). Meanwhile, the DMN and FPN both showed hyperconnectivity with regions of the AN, including the STG and the OFC. Previous findings suggested that dysfunction within a striato-amygdalo-prefrontal cortical network accounted for deficits in orienting toward, recognizing, and allocating attention to emotional stimuli, which may contribute to emotion dysregulation in ADHD (Shaw *et al.*, 2014). Therefore, the hyperconnectivity among the default, frontoparietal and affective networks found in the current study may contribute to symptoms of emotion dysregulation and impulsivity in ADHD.

The lack of data related to the VAN, DAN, SSN and visual network suggests a bias in seed selection in existing rsFC studies. Considering the statistical power, meta-analyses of studies on

these networks were not conducted, but we narratively reviewed the results of these studies. A relatively consistent finding that we identified was hypoconnectivity between the VAN seeds (e.g. the insula, VFC and putamen) and the regions of the SSN (e.g. the primary motor cortex and the precentral gyrus) in ADHD patients compared to TDCs. In addition, both hypoconnectivity and hyperconnectivity were observed between regions of the DAN and visual network. In detail, the DAN seeds (the FEF and IPS) showed hypoconnectivity with the right fusiform gyrus, while the FEF also exhibited hyperconnectivity with regions of the left occipital gyrus.

Although we did not find consistent functional connectivity alterations regarding the cerebellum in the current meta-analysis, original studies have reported that regions of the cerebellum showed dysconnectivity with the ACC, putamen, amygdala and hippocampus in ADHD (Tian *et al.*, 2006; Cao *et al.*, 2009; Karalunas *et al.*, 2014; Posner *et al.*, 2014b). Two studies using lateral cerebellar areas (e.g. Crus I/II) as the seed demonstrated that the cerebellum exhibited greater functional connectivity with

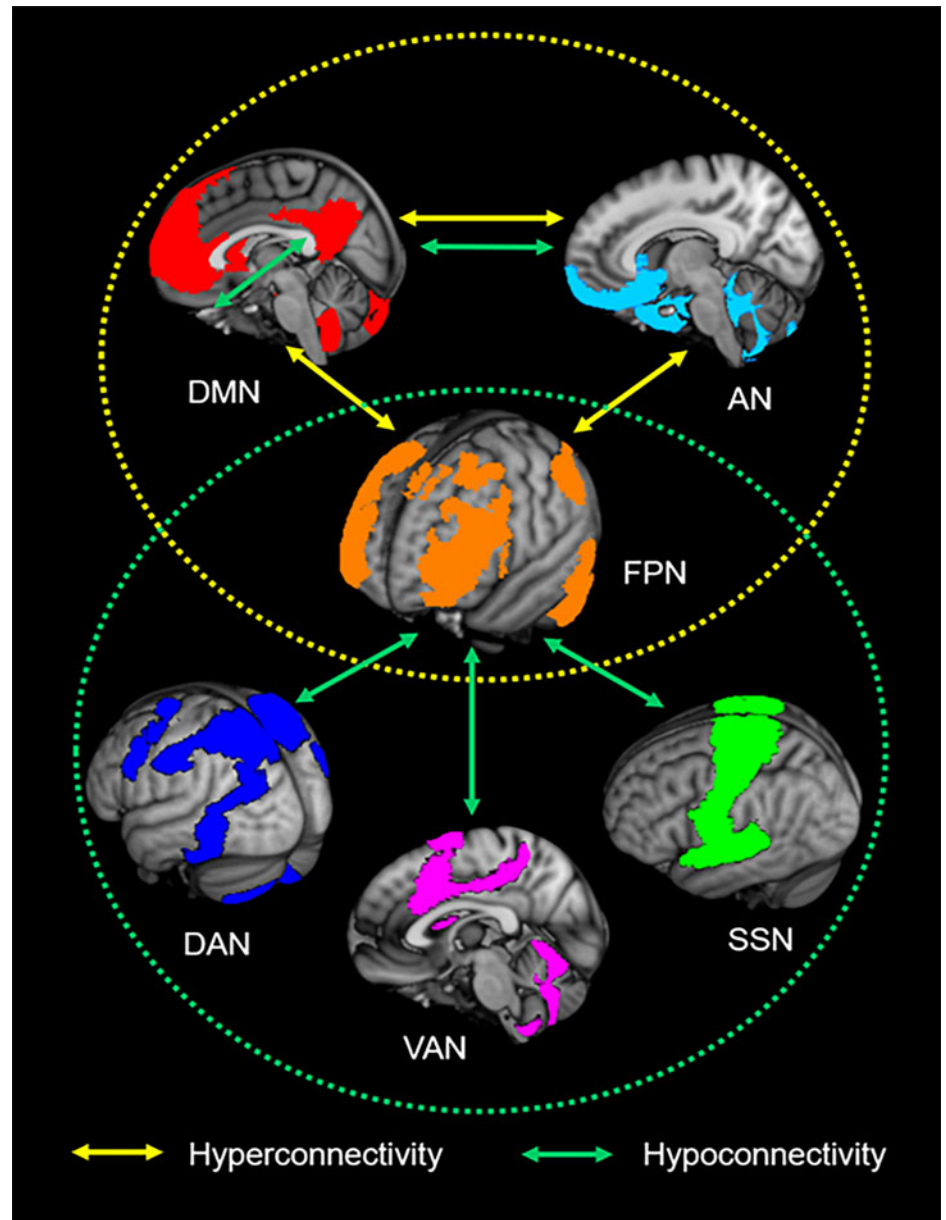


Fig. 3. Neurocognitive network dysfunction patterns of attention-deficit/hyperactivity disorder (ADHD). The yellow circle represents the aberrant interplay among the default mode network (DMN), frontoparietal network (FPN) and affective network (AN) in ADHD. The green circle represents ADHD-associated hypoconnectivity between the FPN and the dorsal attention network (DAN), ventral attention network (VAN) and somatosensory network (SSN). The overlap of the patterns suggests that the FPN is a core intrinsic network of ADHD pathophysiology.

widespread regions in the DAN, VAN and SSN in ADHD adults (Kucyi *et al.*, 2015) and lower connectivity with the left DLPFC in ADHD children (Mizuno *et al.*, 2017). These findings suggested the potential role of cerebro-cerebellar interactions in the neural mechanism of ADHD. More evidence is needed to verify these results and clarify their relations to cognitive and behavioral functions in ADHD.

In addition, mixed use of global signal regression (GSR) was noted in the studies included in current meta-analysis. Eleven of twenty-one original studies applied GSR in fMRI image preprocessing, while the other studies did not apply this method. Two studies reported results with and without applying GSR and found discrepancies between the results with GSR and those without GSR (Lin *et al.*, 2015; Zhao *et al.*, 2017), suggesting that GSR may affect group comparisons and contribute to inconsistent results. However, the effects of GSR remain confusing as various sources are attributed to the global signal (Liu *et al.*, 2017); therefore, the application of GSR in resting-state fMRI preprocessing

remains controversial. Some studies have suggested that applying GSR can reduce the effects of motion (Yan *et al.*, 2013; Power *et al.*, 2014) and increase connection specificity (Fox *et al.*, 2009; Weissenbacher *et al.*, 2009), while other studies indicate that the use of GSR may increase negative correlations (Murphy *et al.*, 2009) and thus distort estimations of group differences in rsFC (Gotts *et al.*, 2013; Hahamy *et al.*, 2014). We think that reporting results both with and without GSR may increase credibility and help enhance comprehension of the effects of GSR.

In summary, the current pattern of abnormal communication within and between large-scale functional networks highlighted the dysfunctional control of the FPN on internal thought and external stimuli, along with inhibition and motion, which may contribute to deficits in attention and inhibition control. Meanwhile, we found hyperconnectivity among the affective, default and frontoparietal networks, which may be associated with emotion dysregulation and impulsivity in ADHD. In addition, these network abnormalities seem to be rather stable and

independent of sex, age or medication state as demonstrated by the complementary analyses. These findings support the triple-network dysfunction model but also suggest the involvement of sensorimotor and affective systems that may facilitate the development of pathophysiologic symptoms in ADHD. The intrinsic network dysfunction pattern provides a potentially mechanistic framework for understanding the neuropsychology and behavioral symptoms of ADHD. However, further study is needed to directly test and verify the functional and behavioral correlations of these network alterations.

Limitations

Several limitations need to be considered in this study while also suggest future directions. First, the number of included studies for each network was relatively small. Although we employed jack-knife analyses to evaluate the robustness and reliability of the results, a cautious interpretation of the findings is necessary. Meanwhile, integrating the results for the VAN, DAN, SSN and visual network is difficult via meta-analysis due to insufficient studies. Future studies can select regions of these networks as seeds to further investigate the connectivity among these functional networks. Second, the small sample sizes in most of the included studies may bias the results. Therefore, future research should include large samples to validate these findings. Third, considerable variations exist in the data acquisition and imaging processing methods in the included studies. Different scanners, motion-correction methods and eye states all have potential effects on the results (Buckner *et al.*, 2013). Unfortunately, due to the insufficient number of studies within methodologic categories, the moderating effects of these variables were impossible to evaluate in the current study and merit future investigation. Fourth, the hemispheric distribution of the selected seed regions may be a potential source of bias; however, the current meta-analysis cannot analyze this potential bias since the number of studies is insufficient for a separate analysis. Fifth, in the absence of empirical data, conducting a meta-analysis of adult-only samples is impossible, resulting in insufficient knowledge of rsFC abnormalities in adult ADHD patients and reflecting the need for future investigations of age-related differences in rsFC in ADHD. Lastly, subgroup analyses of ADHD subtypes, comorbidities and medication use cannot be performed due to a lack of information. Although meta-regression analysis showed no relationship between the percentage of medication-naïve patients and ADHD-associated functional connectivity changes, the influence of medication should be further investigated by directly comparing medicated and medication-naïve patients.

Conclusions

To our knowledge, this is the first meta-analysis of seed-based rsFC fMRI studies to identify impairments of large-scale functional networks in ADHD. A consistent pattern of abnormal connectivity within and between intrinsic brain networks involved in spontaneous mind-wandering, attention, emotional and sensory processing and goal-directed regulation of these functions may underlie the core cognitive and affective deficits that characterize ADHD. Future studies should further explore and validate brain-behavior relationships in this disorder.

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Conflict of interest. None.

References

- American Psychiatric Association (2013) *Diagnostic and Statistical Manual of Mental Disorders*, 5th Edn. Arlington: American Psychiatric Publishing.
- Barber AD, Jacobson LA, Wexler JL, Nebel MB, Caffo BS, Pekar JJ and Mostofsky SH (2015) Connectivity supporting attention in children with attention deficit hyperactivity disorder. *NeuroImage: Clinical* 7, 68–81.
- Biswal B, Yetkin FZ, Haughton VM and Hyde JS (1995) Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magnetic Resonance in Medicine* 34, 537–541.
- Booth JR, Wood L, Lu D, Houk JC and Bitan T (2007) The role of the basal ganglia and cerebellum in language processing. *Brain Research* 1133, 136–144.
- Bozhilova NS, Michelini G, Kuntsi J and Asherson P (2018) Mind wandering perspective on attention-deficit/hyperactivity disorder. *Neuroscience and Biobehavioral Reviews* 92, 464–476.
- Buckner RL and Krienen FM (2013) The evolution of distributed association networks in the human brain. *Trends in Cognitive Sciences* 17, 648–665.
- Buckner RL, Andrews-Hanna JR and Schacter DL (2008) The brain's default network: anatomy, function, and relevance to disease. *Annals of the New York Academy of Sciences* 1124, 1–38.
- Buckner RL, Krienen FM, Castellanos A, Diaz JC and Yeo BT (2011) The organization of the human cerebellum estimated by intrinsic functional connectivity. *Journal of Neurophysiology* 106, 2322–2345.
- Buckner RL, Krienen FM and Yeo BT (2013) Opportunities and limitations of intrinsic functional connectivity MRI. *Nature Neuroscience* 16, 832–837.
- Cai W, Ryali S, Chen T, Li CS and Menon V (2014) Dissociable roles of right inferior frontal cortex and anterior insula in inhibitory control: evidence from intrinsic and task-related functional parcellation, connectivity, and response profile analyses across multiple datasets. *Journal of Neuroscience* 34, 14652–14667.
- Cao X, Cao Q, Long X, Sun L, Sui M, Zhu C, Zuo X, Zang Y and Wang Y (2009) Abnormal resting-state functional connectivity patterns of the putamen in medication-naïve children with attention deficit hyperactivity disorder. *Brain Research* 1303, 195–206.
- Castellanos FX and Aoki Y (2016) Intrinsic functional connectivity in attention-deficit/hyperactivity disorder: a science in development. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging* 1, 253–261.
- Castellanos FX, Margulies DS, Kelly C, Uddin LQ, Ghaffari M, Kirsch A, Shaw D, Shehzad Z, Di Martino A, Biswal B, Sonuga-Barke EJS, Rotrosen J, Adler LA and Milham MP (2008) Cingulate-precuneus interactions: a new locus of dysfunction in adult attention-deficit/hyperactivity disorder. *Biological Psychiatry* 63, 332–337.
- Chang C, Crottaz-Herbette S and Menon V (2007) Temporal dynamics of basal ganglia response and connectivity during verbal working memory. *Neuroimage* 34, 1253–1269.
- Choi EY, Yeo BT and Buckner RL (2012) The organization of the human striatum estimated by intrinsic functional connectivity. *Journal of Neurophysiology* 108, 2242–2263.
- Choi J, Jeong B, Lee SW and Go HJ (2013) Aberrant development of functional connectivity among resting state-related functional networks in medication-naïve ADHD children. *PLoS One* 8, e83516.
- Cortese S, Kelly C, Chabernaud C, Proal E, Di Martino A, Milham MP and Castellanos FX (2012) Toward systems neuroscience of ADHD: a meta-analysis of 55 fMRI studies. *American Journal of Psychiatry* 169, 1038–1055.
- Costa Dias TG, Wilson VB, Bathula DR, Iyer SP, Mills KL, Thurlow BL, Stevens CA, Musser ED, Carpenter SD, Grayson DS, Mitchell SH, Nigg JT and Fair DA (2013) Reward circuit connectivity relates to delay

- discounting in children with attention-deficit/hyperactivity disorder. *European Neuropsychopharmacology* **23**, 33–45.
- Dibbets P, Evers EA, Hurks PP, Bakker K and Jolles J** (2010) Differential brain activation patterns in adult attention-deficit hyperactivity disorder (ADHD) associated with task switching. *Neuropsychology* **24**, 413–423.
- Di Martino A, Scheres A, Margulies DS, Kelly AM, Uddin LQ, Shehzad Z, Biswal B, Walters JR, Castellanos FX and Milham MP** (2008) Functional connectivity of human striatum: a resting state fMRI study. *Cerebral Cortex* **18**, 2735–2747.
- Dong D, Wang Y, Chang X, Luo C and Yao D** (2018) Dysfunction of large-scale brain networks in schizophrenia: a meta-analysis of resting-state functional connectivity. *Schizophrenia Bulletin* **44**, 168–181.
- Egger M, Davey Smith G, Schneider M and Minder C** (1997) Bias in meta-analysis detected by a simple, graphical test. *BMJ* **315**, 629–634.
- Fair DA, Posner J, Nagel BJ, Bathula D, Dias TGC, Mills KL, Blythe MS, Giwa A, Schmitt CF and Nigg JT** (2010) Atypical default network connectivity in youth with attention-deficit/hyperactivity disorder. *Biological Psychiatry* **68**, 1084–1091.
- Fox MD and Greicius M** (2010) Clinical applications of resting state functional connectivity. *Frontiers in Systems Neuroscience* **4**, 19.
- Fox MD and Raichle ME** (2007) Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nature Reviews Neuroscience* **8**, 700–711.
- Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC and Raichle ME** (2005) The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proceedings of the National Academy of Sciences of the United States of America* **102**, 9673–9678.
- Fox MD, Zhang D, Snyder AZ and Raichle ME** (2009) The global signal and observed anticorrelated resting state brain networks. *Journal of Neurophysiology* **101**, 3270–3283.
- Fox KC, Spreng RN, Ellamil M, Andrews-Hanna JR and Christoff K** (2015) The wandering brain: meta-analysis of functional neuroimaging studies of mind-wandering and related spontaneous thought processes. *NeuroImage* **111**, 611–621.
- Gotts SJ, Saad ZS, Jo HJ, Wallace GL, Cox RW and Martin A** (2013) The perils of global signal regression for group comparisons: a case study of autism spectrum disorders. *Frontiers in Human Neuroscience* **7**, 356.
- Gursel DA, Avram M, Sorg C, Brandl F and Koch K** (2018) Frontoparietal areas link impairments of large-scale intrinsic brain networks with aberrant fronto-striatal interactions in OCD: a meta-analysis of resting-state functional connectivity. *Neuroscience and Biobehavioral Reviews* **87**, 151–160.
- Hahamy A, Calhoun V, Pearlson G, Harel M, Stern N, Attar F, Malach R and Salomon R** (2014) Save the global: global signal connectivity as a tool for studying clinical populations with functional magnetic resonance imaging. *Brain Connectivity* **4**, 395–403.
- Hart H, Radua J, Nakao T, Mataix-Cols D and Rubia K** (2013) Meta-analysis of functional magnetic resonance imaging studies of inhibition and attention in attention-deficit/hyperactivity disorder: exploring task-specific, stimulant medication, and age effects. *JAMA Psychiatry* **70**, 185–198.
- Hoekzema E, Carmona S, Ramos-Quiroga JA, Richarte Fernandez V, Bosch R, Soliva JC, Rovira M, Bulbena A, Tobena A, Casas M and Vilarroya O** (2014) An independent components and functional connectivity analysis of resting state fMRI data points to neural network dysregulation in adult ADHD. *Human Brain Mapping* **35**, 1261–1272.
- Hong SB, Harrison BJ, Fornito A, Sohn CH, Song IC and Kim JW** (2015) Functional dysconnectivity of corticostriatal circuitry and differential response to methylphenidate in youth with attention-deficit/hyperactivity disorder. *Journal of Psychiatry and Neuroscience* **40**, 46–57.
- Ioannidis JP, Munafo MR, Fusar-Poli P, Nosek BA and David SP** (2014) Publication and other reporting biases in cognitive sciences: detection, prevalence, and prevention. *Trends in Cognitive Sciences* **18**, 235–241.
- Kaiser RH, Andrews-Hanna JR, Wager TD and Pizzagalli DA** (2015) Large-scale network dysfunction in major depressive disorder: a meta-analysis of resting-state functional connectivity. *JAMA Psychiatry* **72**, 603–611.
- Karalunas SL, Fair D, Musser ED, Aykes K, Iyer SP and Nigg JT** (2014) Subtyping attention-deficit/hyperactivity disorder using temperament dimensions: toward biologically based nosologic criteria. *JAMA Psychiatry* **71**, 1015–1024.
- Kessler D, Angstadt M, Welsh RC and Sripada C** (2014) Modality-spanning deficits in attention-deficit/hyperactivity disorder in functional networks, gray matter, and white matter. *Journal of Neuroscience* **34**, 16555–16566.
- Kucyi A, Hove MJ, Biederman J, Van Dijk KRA and Valera EM** (2015) Disrupted functional connectivity of cerebellar default network areas in attention-deficit/hyperactivity disorder. *Human Brain Mapping* **36**, 3373–3386.
- Lei D, Du M, Wu M, Chen T, Huang X, Du X, Bi F, Kemp GJ and Gong Q** (2015) Functional MRI reveals different response inhibition between adults and children with ADHD. *Neuropsychology* **29**, 874–881.
- Li F, He N, Li Y, Chen L, Huang X, Lui S, Guo L, Kemp GJ and Gong Q** (2014) Intrinsic brain abnormalities in attention deficit hyperactivity disorder: a resting-state functional MR imaging study. *Radiology* **272**, 514–523.
- Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J and Moher D** (2009) The prisma statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* **339**, b2700.
- Lin HY and Gau SSF** (2016) Atomoxetine treatment strengthens an anti-correlated relationship between functional brain networks in medication-naive adults with attention-deficit hyperactivity disorder: a randomized double-blind placebo-controlled clinical trial. *International Journal of Neuropsychopharmacology* **19**, 1–15.
- Lin HY, Tseng WYL, Lai MC, Matsuo K and Gau SSF** (2015) Altered resting-state frontoparietal control network in children with attention-deficit/hyperactivity disorder. *Journal of the International Neuropsychological Society* **21**, 271–284.
- Liu TT, Nalci A and Falahpour M** (2017) The global signal in fMRI: nuisance or information? *NeuroImage* **150**, 213–229.
- Lopez-Larson MP, King JB, Terry J, McGlade EC and Yurgelun-Todd D** (2012) Reduced insular volume in attention deficit hyperactivity disorder. *Psychiatry Research* **204**, 32–39.
- McCarthy H, Skokauskas N, Mulligan A, Donohoe G, Mullins D, Kelly J, Johnson K, Fagan A, Gill M, Meaney J and Frodl T** (2013) Attention network hypoconnectivity with default and affective network hyperconnectivity in adults diagnosed with attention-deficit/hyperactivity disorder in childhood. *JAMA Psychiatry* **70**, 1329–1337.
- McLeod KR, Langevin LM, Goodyear BG and Dewey D** (2014) Functional connectivity of neural motor networks is disrupted in children with developmental coordination disorder and attention-deficit/hyperactivity disorder. *NeuroImage: Clinical* **4**, 566–575.
- Mennes M, Vega Potler N, Kelly C, Di Martino A, Castellanos FX and Milham MP** (2011) Resting state functional connectivity correlates of inhibitory control in children with attention-deficit/hyperactivity disorder. *Frontiers in Psychiatry* **2**, 83.
- Menon V** (2011) Large-scale brain networks and psychopathology: a unifying triple network model. *Trends in Cognitive Sciences* **15**, 483–506.
- Menon V and Uddin LQ** (2010) Saliency, switching, attention and control: a network model of insula function. *Brain Structure & Function* **214**, 655–667.
- Mills KL, Bathula D, Dias TG, Iyer SP, Fenesy MC, Musser ED, Stevens CA, Thurlow BL, Carpenter SD, Nagel BJ, Nigg JT and Fair DA** (2012) Altered cortico-striatal-thalamic connectivity in relation to spatial working memory capacity in children with ADHD. *Frontiers in Psychiatry* **3**, 2.
- Mizuno Y, Jung M, Fujisawa TX, Takiguchi S, Shimada K, Saito DN, Kosaka H and Tomoda A** (2017) Catechol-o-methyltransferase polymorphism is associated with the cortico-cerebellar functional connectivity of executive function in children with attention-deficit/hyperactivity disorder. *Scientific Reports* **7**, 4850.
- Mostert JC, Shumskaya E, Mennes M, Onnink AM, Hoogman M, Kan CC, Arias Vasquez A, Buitelaar J, Franke B and Norris DG** (2016) Characterising resting-state functional connectivity in a large sample of adults with ADHD. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* **67**, 82–91.
- Murphy K, Birn RM, Handwerker DA, Jones TB and Bandettini PA** (2009) The impact of global signal regression on resting state correlations: are anti-correlated networks introduced? *NeuroImage* **44**, 893–905.
- Norman LJ, Carlisi C, Lukito S, Hart H, Mataix-Cols D, Radua J and Rubia K** (2016) Structural and functional brain abnormalities in attention-

- deficit/hyperactivity disorder and obsessive-compulsive disorder: a comparative meta-analysis. *JAMA Psychiatry* 73, 815–825.
- Oldehinkel M, Beckmann CF, Pruim RHR, Van Oort ESB, Franke B, Hartman CA, Hoekstra PJ, Oosterlaan J, Heslenfeld D, Buitelaar JK and Mennes M** (2016) Attention-deficit/hyperactivity disorder symptoms coincide with altered striatal connectivity. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging* 1, 353–363.
- Posner J, Rauh V, Gruber A, Gat I, Wang Z and Peterson BS** (2013) Dissociable attentional and affective circuits in medication-naïve children with attention-deficit/hyperactivity disorder. *Psychiatry Research: Neuroimaging* 213, 24–30.
- Posner J, Park C and Wang Z** (2014a) Connecting the dots: a review of resting connectivity MRI studies in attention-deficit/hyperactivity disorder. *Neuropsychology Review* 24, 3–15.
- Posner J, Siciliano F, Wang Z, Liu J, Sonuga-Barke E and Greenhill L** (2014b) A multimodal MRI study of the hippocampus in medication-naïve children with ADHD: what connects ADHD and depression? *Psychiatry Research: Neuroimaging* 224, 112–118.
- Power JD, Barnes KA, Snyder AZ, Schlaggar BL and Petersen SE** (2012) Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. *Neuroimage* 59, 2142–2154.
- Power JD, Mitra A, Laumann TO, Snyder AZ, Schlaggar BL and Petersen SE** (2014) Methods to detect, characterize, and remove motion artifact in resting state fMRI. *Neuroimage* 84, 320–341.
- Radua J and Mataix-Cols D** (2009) Voxel-wise meta-analysis of grey matter changes in obsessive-compulsive disorder. *British Journal of Psychiatry* 195, 393–402.
- Radua J and Mataix-Cols D** (2012) Meta-analytic methods for neuroimaging data explained. *Biology of Mood & Anxiety Disorders* 2, 6.
- Radua J, Mataix-Cols D, Phillips ML, El-Hage W, Kronhaus DM, Cardoner N and Surguladze S** (2012) A new meta-analytic method for neuroimaging studies that combines reported peak coordinates and statistical parametric maps. *European Psychiatry* 27, 605–611.
- Radua J, Rubia K, Canales-Rodriguez EJ, Pomarol-Clotet E, Fusar-Poli P and Mataix-Cols D** (2014) Anisotropic kernels for coordinate-based meta-analyses of neuroimaging studies. *Frontiers in Psychiatry* 5, 13.
- Shaw P, De Rossi P, Watson B, Wharton A, Greenstein D, Raznahan A, Sharp W, Lerch JP and Chakravarty MM** (2014) Mapping the development of the basal ganglia in children with attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry* 53, 780–9.e11.
- Shirer WR, Ryali S, Rykhlevskaia E, Menon V and Greicius MD** (2012) Decoding subject-driven cognitive states with whole-brain connectivity patterns. *Cerebral Cortex* 22, 158–165.
- Sibley MH, Swanson JM, Arnold LE, Hechtman LT, Owens EB, Stehli A, Abikoff H, Hinshaw SP, Molina BSG, Mitchell JT, Jensen PS, Howard AL, Lakes KD, Pelham WE and Group MTAC** (2017) Defining ADHD symptom persistence in adulthood: optimizing sensitivity and specificity. *Journal of Child Psychology and Psychiatry* 58, 655–662.
- Sidlauskaite J, Sonuga-Barke E, Roeyers H and Wiersma JR** (2016) Altered intrinsic organisation of brain networks implicated in attentional processes in adult attention-deficit/hyperactivity disorder: a resting-state study of attention, default mode and salience network connectivity. *European Archives of Psychiatry and Clinical Neuroscience* 266, 349–357.
- Sripada C, Kessler D, Fang Y, Welsh RC, Prem Kumar K and Angstadt M** (2014) Disrupted network architecture of the resting brain in attention-deficit/hyperactivity disorder. *Human Brain Mapping* 35, 4693–4705.
- Sun L, Cao Q, Long X, Sui M, Cao X, Zhu C, Zuo X, An L, Song Y, Zang Y and Wang Y** (2012) Abnormal functional connectivity between the anterior cingulate and the default mode network in drug-naïve boys with attention deficit hyperactivity disorder. *Psychiatry Research: Neuroimaging* 201, 120–127.
- Tang S, Lu L, Zhang L, Hu X, Bu X, Li H, Hu X, Gao Y, Zeng Z, Gong Q and Huang X** (2018) Abnormal amygdala resting-state functional connectivity in adults and adolescents with major depressive disorder: a comparative meta-analysis. *EBioMedicine* 36, 436–445.
- Thomas R, Sanders S, Doust J, Beller E and Glasziou P** (2015) Prevalence of attention-deficit/hyperactivity disorder: a systematic review and meta-analysis. *Pediatrics* 135, e994–1001.
- Tian L, Jiang T, Wang Y, Zang Y, He Y, Liang M, Sui M, Cao Q, Hu S, Peng M and Zhuo Y** (2006) Altered resting-state functional connectivity patterns of anterior cingulate cortex in adolescents with attention deficit hyperactivity disorder. *Neuroscience Letters* 400, 39–43.
- Uytun MC, Karakaya E, Oztop DB, Gengec S, Gumus K, Ozmen S, Doganay S, Icer S, Demirci E and Ozsoy SD** (2016) Default mode network activity and neuropsychological profile in male children and adolescents with attention deficit hyperactivity disorder and conduct disorder. *Brain Imaging and Behavior* 11, 1561–1570.
- Vasic N, Plichta MM, Wolf RC, Fallgatter AJ, Sosic-Vasic Z and Gron G** (2014) Reduced neural error signaling in left inferior prefrontal cortex in young adults with ADHD. *Journal of Attention Disorders* 18, 659–670.
- Vatansver D, Bozhilova NS, Asherson P and Smallwood J** (2019) The devil is in the detail: exploring the intrinsic neural mechanisms that link attention-deficit/hyperactivity disorder symptomatology to ongoing cognition. *Psychological Medicine* 49, 1185–1194.
- Weissenbacher A, Kasess C, Gerstl F, Lanzenberger R, Moser E and Windischberger C** (2009) Correlations and anticorrelations in resting-state functional connectivity MRI: a quantitative comparison of preprocessing strategies. *Neuroimage* 47, 1408–1416.
- Wolraich M, Brown L, Brown RT, DuPaul G, Earls M, Feldman HM, Ganiats TG, Kaplanek B, Meyer B, Perrin J, Pierce K, Reiff M, Stein MT and Visser S** (2011) ADHD: clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. *Pediatrics* 128, 1007–1022.
- Yan CG, Cheung B, Kelly C, Colcombe S, Craddock RC, Di Martino A, Li Q, Zuo XN, Castellanos FX and Milham MP** (2013) A comprehensive assessment of regional variation in the impact of head micromovements on functional connectomics. *Neuroimage* 76, 183–201.
- Yeo BT, Krienen FM, Sepulcre J, Sabuncu MR, Lashkari D, Hollinshead M, Roffman JL, Smoller JW, Zollei L, Polimeni JR, Fischl B, Liu H and Buckner RL** (2011) The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *Journal of Neurophysiology* 106, 1125–1165.
- Zang YF, He Y, Zhu CZ, Cao QJ, Sui MQ, Liang M, Tian LX, Jiang TZ and Wang YF** (2007) Altered baseline brain activity in children with ADHD revealed by resting-state functional MRI. *Brain and Development* 29, 83–91.
- Zhao Q, Li H, Yu X, Huang F, Wang Y, Liu L, Cao Q, Qian Q, Zang Y, Sun L and Wang Y** (2017) Abnormal resting-state functional connectivity of insular subregions and disrupted correlation with working memory in adults with attention deficit/hyperactivity disorder. *Frontiers in Psychiatry* 8, 200.