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## Resting-state network dysconnectivity in ADHD: A system-neuroscience-based meta-analysis

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### ABSTRACT

**Objectives:** Neuroimaging studies report altered resting-state functional connectivity in attention deficit/hyperactivity disorder (ADHD) across multiple brain systems. However, there is inconsistency among individual studies.

**Methods:** We meta-analyzed seed-based resting state studies of ADHD connectivity within and between four established resting state brain networks (default mode, cognitive control, salience, affective/motivational) using Multilevel Kernel Density Analysis method.

**Results:** Twenty studies with 944 ADHD patients and 1121 controls were included in the analysis. Compared to controls, ADHD was associated with disrupted within-default mode network (DMN) connectivity – reduced in the core (i.e. posterior cingulate cortex seed) but elevated in the dorsal medial prefrontal cortex sub-system (i.e. temporal pole-inferior frontal gyrus). Connectivity was elevated between nodes in the cognitive control system. When the analysis was restricted to children and adolescents, additional reduced connectivity was detected between DMN and cognitive control and affective/motivational and salience networks.

**Conclusions:** Our data are consistent with the hypothesis that paediatric ADHD is a DMN-dysconnectivity disorder with reduced connectivity both within the core DMN sub-system and between that system and a broad set of nodes in systems involved in cognition and motivation.

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ADHD; MRI; brain imaging; connectivity; resting-state

## Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a common neuro-developmental disorder of childhood, which often persists into adolescence and adulthood (Willcutt 2012). It is characterised by developmentally inappropriate expressions of excessive inattention, hyperactivity, and impulsivity, either occurring individually or in combination (American Psychiatric Association 2013). Despite recent advances in ADHD neuroscience, the pathophysiological mechanisms, which underpin the disorder, remain to be fully characterised (Faraone and Biederman 2016). In recent years studies have started to test the idea that ADHD is caused by altered patterns of connectedness between different regions of the brain that need to work in simultaneously to properly regulate thought and actions (Castellanos and Aoki 2016). These

networks, which are a defining feature of intrinsic brain organisation, can be studied by analysing patterns of temporal synchronisation of oscillatory activity (within the BOLD signal) between different brain regions during rest – so called resting-state functional connectivity (rsFC; Biswal et al. 1995; Greicius et al. 2003).

To date, such studies have focussed on connectivity within four well-established large-scale networks named as default mode network (DMN), cognitive control network (CCN), salience network (SN), and affective/motivational network (AMN). Specific aberrations within and between these networks suggest alterations in the functional organisation and integrity of the brain that may explain deficits in cognitive and affective functioning displayed by individuals with ADHD. DMN consists of three sub-systems

(Andrews-Hanna et al. 2010; Doucet et al. 2011; Thomas Yeo et al. 2011). The midline core sub-system (anterior medial prefrontal cortex, posterior cingulate cortex, and portions of the inferior parietal lobule) is related to self-relevant and affective decisions. The dorsal medial prefrontal cortex (dmPFC) sub-system (dorsal medial prefrontal cortex, lateral temporal cortex, temporal parietal junction, and temporal pole) is active when participants think about their own or other people's mental states. The medial temporal lobe (MTL) sub-system (hippocampal formation, parahippocampal cortex, ventromedial prefrontal cortex, retrosplenial cortex, posterior inferior parietal lobule) underpins decisions requiring a mental scene based on memory. Most studies found reduced resting state connectivity between DMN hubs in ADHD (Cao et al. 2006; Castellanos et al. 2008; Uddin et al. 2008; Mennes et al. 2011; Qiu et al. 2011; Chabernaud et al. 2012; Tomasi and Volkow 2012) – especially mPFC and PCC (Wang et al. 2009; Fair et al. 2010; Sun et al. 2012). This has been hypothesised to cause excessive mind-wandering and attentional difficulties during task performance (Metin et al. 2015). It has also been suggested to be implicated in impaired inter-temporal decision making in ADHD (Sonuga-Barke et al. 2016). Some studies have reported the opposite pattern of results – ADHD-related DMN elevated connectivity (Barber et al. 2015). To date, there is no study that decomposed their analyses by DMN sub-systems for ADHD.

The salience network (SN), consists of dorsal anterior cingulate (dACC) and fronto-insular cortices. These act in concert to code the salience of stimuli and allow emotional monitoring (Seeley et al. 2007). Tian et al. (2006) reported ADHD elevated connectivity among dACC and SN and thalamus, cerebellum, insula, and brainstem during resting. The cognitive control network (CCN), also known as the executive-control network, links dorsolateral frontal, parietal neo-cortices and the dorsal basal ganglia (i.e. caudate nucleus) and is involved in top-down regulation of emotion and attention (Zhou et al. 2007). Executive function deficits seen in children and adults with ADHD is thought to be related to reduced connectivity found in this network (Cao et al. 2006; Cao et al. 2009; for a review Cubillo et al. 2012). An affective/motivational network (AMN) includes ventral striatum, amygdala, and ACC. This network processes the valence of positive and negative events and emotions (Etkin et al. 2011). ADHD-related dysconnectivity has been reported across multiple nodes in this network (ACC) (Cao et al. 2006; Zang et al. 2007), inferior frontal gyrus (Cao et al. 2006; Zang et al. 2007; Wang et al. 2009),

cerebellum (Cao et al. 2009; Liu et al. 2010). ADHD-related elevated connectivity was reported between putamen and thalamus (Mills et al. 2012) and reduced connectivity between putamen and fronto-striato-thalamic, fronto-temporal and sensorimotor circuits (Cao et al. 2009; Sato et al. 2013).

Although the number of studies examining rsFC in ADHD has increased over recent years, many of the studies have inadequate results for consistency and reproducibility. To overcome this problem, we performed a seed-based network meta-analysis of studies related with resting state connectivity in ADHD. We chose to focus on seed-based studies, as these are by far the most common in the literature. These studies identify a region of interest and examine either the level of connectivity between that and other pre-specified seeds (seed-to-seed) or other parts of the brain (seed-to-voxel). Other data-driven methods – with no pre-specification of regions of interest (RoI) – such as independent component analysis (van de Ven et al. 2004) or approaches using graph theory (Wang 2010), and machine-learning have only been employed relatively rarely and so meta-analysis of studies using these approaches is not yet viable.

## Methods

### Literature search

The literature search was conducted in accordance with the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) standards (in Supplementary Appendix Figure A.1).

### Study screening and selection

A comprehensive literature search was conducted between 06 March 2017 and 27 January 2020 PubMed, and Web of Science using keywords ('ADHD' OR 'Inattention' OR 'hyperactivity' OR 'Attention-Deficit/Hyperactivity Disorder' OR 'attention deficit') AND ('resting' OR 'resting state' OR 'connectivity' OR 'functional connectivity' OR 'FC' OR 'rs-fMRI' OR 'resting-state fMRI' OR 'resting-state functional connectivity' OR 'rs-FC' OR 'spontaneous brain activity'). The reference sections of review papers were manually checked for relevant articles.

First, duplicate papers from different databases were removed. Then, titles, abstracts, and full texts, respectively, were assessed independently by two authors to identify studies that potentially meet the inclusion criteria. The method section of potentially eligible studies was screened by two authors and the studies using non-seed based methods were removed.

Finally, two authors checked whether the remaining studies had a seed within predefined Rols. Details of the protocol for this systematic meta-analysis were registered on PROSPERO (International prospective register of systematic reviews) (2018).

### **Inclusion criteria**

Original fMRI studies using whole-brain seed-based (seed-seed or seed-voxel) resting-state functional connectivity to compare ADHD and healthy control (HC) groups were eligible for inclusion (other rsFC methods employing statistical approaches such as independent component analysis, were excluded because data cannot be integrated with seed-based data). The summary of methods implemented in studies included in the meta-analysis can be seen in [Supplementary Appendix Table A.4](#). Authors were contacted for information when a published study did not report peak effect coordinates for the seed region of interests, and the studies were excluded if the authors did not respond back. Only studies, which had a seed within our pre-defined Rols, were included. For this reason, we excluded five studies that had seeds in the different networks such as sensorimotor.

### **Exclusion criteria**

Studies were excluded if they; (1) had no typically developing control group; (2) were based on a non-seed-based method; (3) could not identify standard resting state networks of interest in the whole sample; and (4) had irretrievable peak Rol coordinates. Studies excluded and the reasons for exclusion are listed in the [Supplementary Appendix](#) (Table A.2).

### **Data processing**

The current meta-analysis was coordinate-based (Wager et al. 2007; Wager et al. 2009; Salimi-Khorshidi et al. 2009) and identified coordinates showing significant differences in resting state functional connectivity between ADHD and control groups. Data extraction and coding stages were as follows: First, the seeds were identified, a-priori, as being part of predefined networks. Then, coordinates for the center-of-mass of each seed Rol (32 seeds) and the peak of each significant between-group effect (213 effects) were extracted from each study and converted into Montreal Neurological Institute space if needed (Brett et al. 2001). Following this, each seed was categorised as being part of a specific brain-network. This was based on the location of its center-of-mass within previously published a-priori network masks determined by a

previous whole-brain network segmentation (including SN, DMN, AMN, and CCN) in 1000 participants (see [figure 1A](#) and in [Supplementary Appendix Table A.3](#); Buckner et al. 2011; Thomas Yeo et al. 2011; Choi et al. 2012). Based on previous studies, elevated connectivity, where individuals with ADHD showed greater connectivity than healthy controls ( $\text{ADHD} > \text{HC}$ ) was defined as larger positive or diminished negative rsFC in ADHD compared with HC; reduced connectivity ( $\text{ADHD} < \text{HC}$ ) was defined as reduced positive or greater negative rsFC in ADHD compared with HC.

### **2.3. Statistical analysis**

The meta-analysis was performed using Multilevel Kernel Density Analysis, a Matlab (Mathworks, Natick, MA) toolbox that utilises Statistical Parametric Mapping (n.d.). MKDA weights reported coordinates by the between-group contrast instead of the activation foci, thereby partially preventing the influence of variations in thresholding of activation foci operating in different studies (Wager et al. 2009). The group contrasts for each study were specified as  $\text{ADHD} > \text{HC}$  or  $\text{HC} > \text{ADHD}$  subjects. The peak coordinates and network seed Rols in each study were mapped onto the MNI template (Mazziotta et al. 2001) and the studies reporting their results in Talairach coordinates were subjected to an additional tal2mni method in SPM toolbox (Lancaster et al. 2007; Mazziotta et al. 2001). All coordinates were convolved with a spherical kernel of radius 10 mm thresholded with a maximum value of 1 if a coordinate resides within 10 mm of any other focus (Kaiser et al. 2015; Kober et al. 2008; Wager et al. 2004). Subsequently, a Monte Carlo analysis was performed ( $n=15,000$  iterations) to establish the Family-Wise Error Rate (FWER) threshold. This simulation checks whether a specific voxel could have been identified by chance with random assignment of activation points to the Rols while at the same time correcting for multiple comparisons. This method uses a grey matter mask to limit randomised data points and increase confidence and threshold level. An FWER threshold is reached when the  $p < .05$  standard is obtained (Kober et al. 2008). The two types of density maps were used for thresholding with respect to both their height and extent based on previous meta-analyses (Kaiser et al. 2015; Dong et al. 2018). While extent-based thresholding, which has a low spatial specificity, provides information about the presence of a significant cluster with respect to its size (Woo et al. 2014), height-based thresholding is used to determine an individual voxel's peak-level inference (Kaiser et al. 2015). Together, these measures complement each other and alleviate potential

confounds. Our findings are presented as within- and/or between-network abnormalities for ADHD patients. If both seed and target regions were inside the same a-priori defined network, it was classified as a within-network abnormality – if they were in different networks it was classified as a between-network abnormality. Given the current debate about the neurobiological differences between paediatric and adult ADHD – a sensitivity analysis was run excluding adult studies. We initially intended to include a sensitivity analysis of the impact of medication by limiting the analysis to studies with medication naïve patients. Unfortunately, there were insufficient number of such studies.

## Results

### Included studies

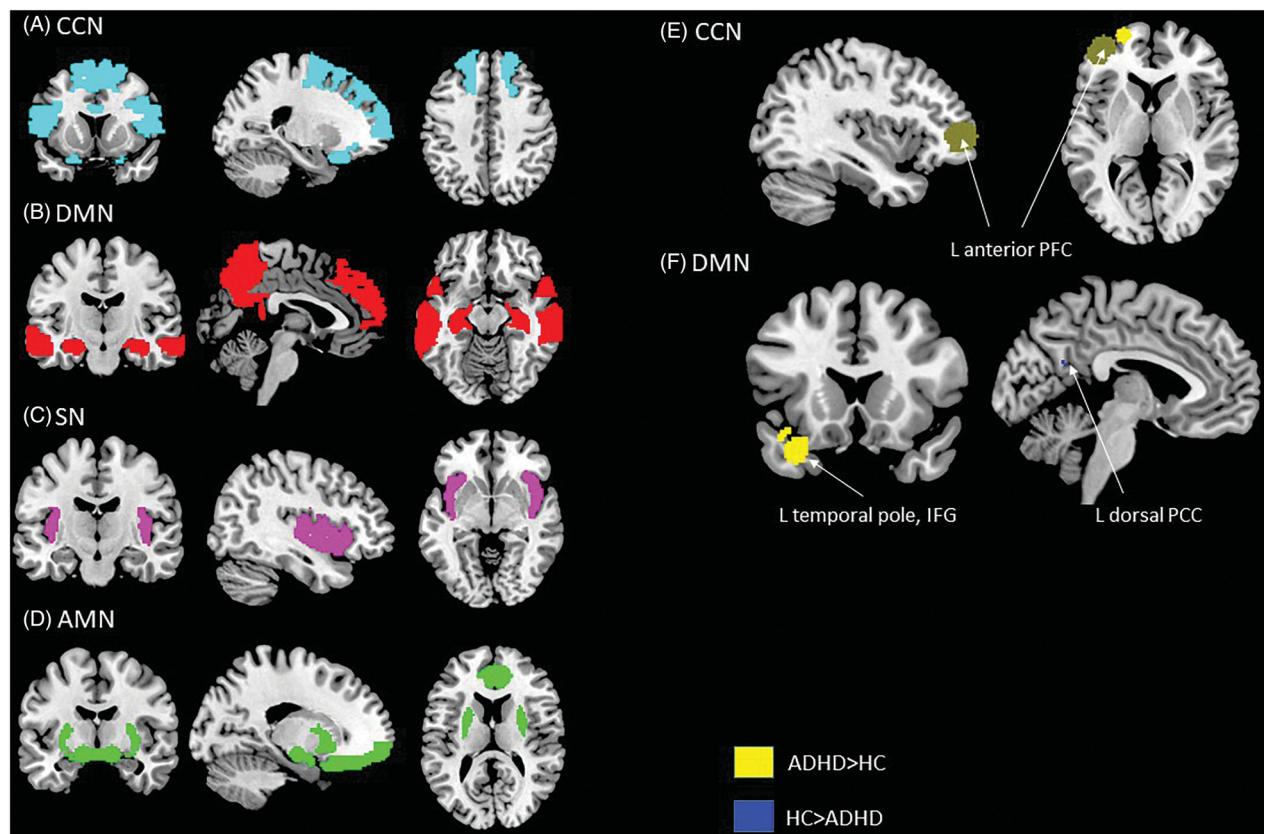
Twenty studies met the inclusion criteria, reporting data on 944 separate individuals with ADHD and 1121 healthy controls. The flowchart of the literature

search/study selection and the demographic characteristics of studies included in the meta-analysis are shown in the *Supplementary Appendix (Figure A.1, Table A.1 and text A.1)*. In 16 studies, the age of participants with ADHD was below 18 years and designated as 'child/adolescent'. Four studies focussed on adults only (18 years or older). The individuals with ADHD from ten studies were drug naïve, other patients were drug-free at least for 24 hours before scanning (range: 24 hours–6 months). See table A.3 for the list of seeds included in the different networks.

### All studies

#### Default mode network

Six studies (143 ADHD v 156 controls) included DMN seeds (i.e. PCC, precuneus, mPFC, middle temporal gyrus, temporopolar area, angular gyrus, inferior parietal lobe). Some used the whole DMN (Lin and Gau 2015; Barber et al. 2015) as the seed while others used



**Figure 1.** Seeds within a priori networks and results of the meta-analysis. The figure was drawn by authors to show the seeds used in meta-analysis and the abnormal resting-state functional connectivity results of meta-analyses in the whole sample. (a) The left four columns (A, B, C, D) represent the seed regions categorised into a priori networks based on the location of its center-of-mass. (b) The right two columns (E, F) show the significant results of meta-analyses. While the yellow colour on brain images represents elevated connectivity, the blue colour is used for reduced connectivity in ADHD compared to healthy controls. All results are significant at  $p < .05$ , corrected for family-wise error rate. HC: healthy controls; ADHD: attention-deficit hyperactivity disorder; CCN: cognitive control network; DMN: default mode network; AMN: affective motivational network; SN: salience network; PFC: prefrontal cortex; IFG: inferior frontal gyrus; PCC: posterior cingulate cortex.

**Table 1.** Results of the meta-analysis of resting-state functional connectivity in ADHD – all studies.

Seed-network & thresholding	Seed anatomy	Effect network	Effect anatomy	x	y	z	Voxels	Max. p
Default Mode	hippocampus, precuneus, MTG, PCC, TPA, AG, IPL, mPFC, DMN (mPFC, AG, precuneus)							
HC > ADHD (hb)		DMN	L-dorsal PCC	-2	-58	22	2	.72
HC > ADHD (hb)		DMN	L-dorsal PCC	-6	-58	24	2	.72
ADHD > HC (hb)		DMN	L-TP, L-IFG	-34	18	-24	203	.56
Cognitive control	aPFC, dlPFC, IPS, FEF, ACC, CCN, premotor, IFC, SFG	CCN	L-anterior PFC	-22	58	6	1445	.35
ADHD > HC (eb)								

DMN: default mode network; CCN: cognitive control network; HC: healthy controls; ADHD: attention-deficit hyperactivity disorder; MTG: middle temporal gyrus; PCC: posterior cingulate cortex; TPA: temporopolar area; AG: angular gyrus; IPL: inferior parietal lobe; mPFC: medial prefrontal cortex; aPFC: anterior prefrontal cortex; dlPFC: dorsolateral prefrontal cortex; IPS: intraparietal sulcus; FEF: frontal eye field; ACC: anterior cingulate cortex; IFC: inferior frontal cortex; SFG: superior frontal gyrus; TP: temporal pole; IFG: inferior frontal gyrus; L: left; R: right.

All results are significant at  $p < .05$ , corrected for family-wise error rate. Maximum P is the maximum proportion of studies exhibiting the effect at the peak density weighted by sample size. The results are shown with both height-based (hb) thresholding and extent-based (eb) thresholding.

particular DMN regions (Castellanos et al. 2008; McCarthy et al. 2013; Posner et al. 2014; Icer et al. 2018) such as mPFC, PCC, hippocampus or precuneus (Supplementary Table A.3). There was evidence of disrupted connectivity for ADHD in DMN sub-systems (see Table 1 and Figure 1(B)). In the core DMN subsystem, dorsal PCC hub displayed reduced connectivity. An elevated connectivity was evident in the dmPFC sub-systems involving the temporal pole/inferior frontal gyrus. These effects were observed in a height threshold level.

### Cognitive control network

Seven studies (252 ADHD v 232 controls) included CCN seeds in ACC, anterior PFC, dorsolateral PFC, IPS, FEF, premotor, inferior frontal cortex (IFC), superior frontal gyrus (SFG), and one study used the whole CCN (Francx et al. 2015). ADHD related alterations were observed only in the left anterior PFC (elevated connectivity) when using medium thresholds (Table 1 and Figure 1(B)).

### Salience network

Seven studies (157 ADHD v 163 controls) included salience network nodes consisting of the dorsal anterior cingulate cortex (dACC), temporo-parietal junction, left and right insula (VFC), and cingulo-opercular network (dorsal anterior insula, supramarginal gyrus, dorsal medial frontal cortex, ACC, supplementary motor cortex) in their analysis. No significant ADHD-related effects were observed.

### Affective/motivational network

Nine studies (592 ADHD v 779 controls) included AMN seeds – NAcc, VTA, ACC, orbitofrontal cortex (OFC), striatum, putamen, caudate, globus pallidus, and amygdala – in their analysis. No significant ADHD-related effects were observed.

### Child and adolescent studies only

Four studies were excluded with adult participants (Castellanos et al. 2008; McCarthy et al. 2013; Lin and Gau 2015; Zhao et al. 2017). Within network patterns seen for the whole set of studies were replicated in the child/adolescent studies (see Table 2, Figure 2). In addition, reduced connectivity within the DMN was more extensive – now including both the MTL (specifically hippocampus) and PFC sub-systems (temporal cortex) as well as the core. Moreover, there was also reduced connectivity between the DMN and both CCN (specifically DLPFC, anterior PFC, FEF, premotor cortex, orbitofrontal and inferior frontal gyrus) and AMN regions (caudate, amygdala, subgenual cingulate and nucleus accumbens). This extended to DMN seeds and visual regions (middle occipital gyrus, primary visual cortex). Furthermore, reduced connectivity was found between the MTL subsystem and temporal and fusiform gyrus in the SN.

### Discussion

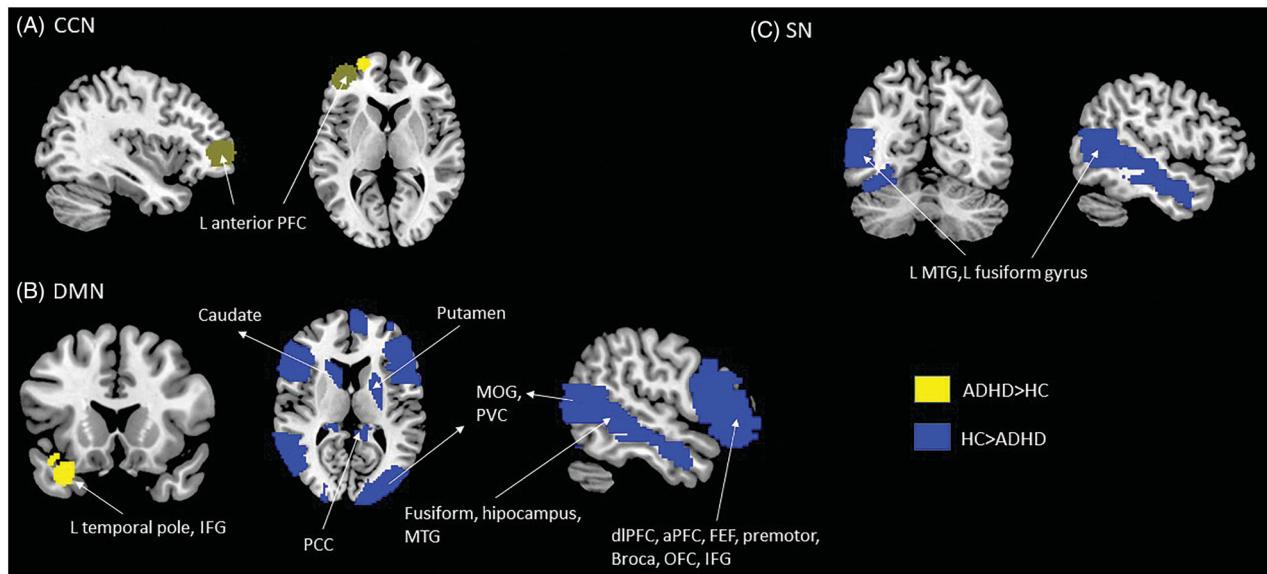
We examined the functional integrity of the ADHD brain by measuring patterns of connectivity within and between established resting state networks. The results supported the existence of alterations primarily within two networks: DMN and CCN. First, ADHD was associated with reduced connectivity within the DMN core. This suggests that the DMN was less well defined functionally in individuals with ADHD than in typically developing individuals with diminished network integrity suggesting inefficient organisation. This result is consistent with prior individual studies of both children (Wang et al. 2009; Sun et al. 2012) and adults with ADHD (Castellanos et al. 2008; Uddin et al. 2008) – the most frequently reported finding being reduced connectivity within the DMN core (Broyd et al. 2009; Posner et al. 2014). Alteration in DMN activation has also been reported in task-based fMRI studies (Metin

**Table 2.** Results of the meta-analysis of resting-state functional connectivity in children and adolescents with ADHD.

Seed-Network & Threshholding	Seed Anatomy	Effect Network	Effect Anatomy	x	y	z	Voxels	Max. p
<b>Default mode</b>	hippocampus, precuneus, MTG, PCC, TPA, AG, IPL, mPFC, DMN (mPFC, AG)							
ADHD > HC (hb)		DMN	L-TP, L-IFG	-34	18	-24	203	.72
HC > ADHD (hb)		CCN	OFC	-6	56	-18	515	1.00
HC > ADHD (hb)		DMN	R-fusiform gyrus, R-hippocampal gyrus, R-MTG	42	-38	-12	1405	1.00
HC > ADHD (hb)		AMN	R-caudate, R-amygadala, R-subgenual cingulate, R-NAcc	8	8	-8	1030	1.00
HC > ADHD (hb)		DMN	L-amygadala, L-hippocampus, L-putamen	-26	-6	-12	515	1.00
HC > ADHD (hb)		CCN	R-IFG	40	-68	14	451	1.00
HC > ADHD (hb)		VN/DMN	L-middle occipital gyrus, PVC, L-ventral PCC	-4	-64	14	704	1.00
HC > ADHD (hb)		CCN	R-dIPFC, R-anterior PFC	12	62	26	390	1.00
HC > ADHD (hb)		CCN	L-FEF, L-Broca, L-premotor	-44	12	30	515	1.00
HC > ADHD (hb)		CCN	FEF, L-premotor	-34	16	50	514	1.00
HC > ADHD (hb)		CCN	R-FEF	20	40	48	353	1.00
<b>Salience</b>	dACC, TPJ, VFC, insula, CON (insula, SMG, ACC, SMC, dMFC)							
HC > ADHD (hb)		DMN	L-MTG, L-fusiform gyrus	-54	-46	-2	484	1.01
<b>Cognitive Control</b>	aPFC, dIPFC, IPS, FEF, ACC, CCN, premotor, IFC, SFG							
ADHD > HC (eb)		CCN	left aPFC	-22	62	12	488	.40
ADHD > HC (eb)		CCN	left aPFC	-40	50	4	709	.21

DMN: default mode network; AMN: affective/motivational network; SN: salience network; CCN: cognitive control network; VN: visual network; ADH: attention-deficit hyperactivity disorder; HC: healthy controls; MTG: middle temporal gyrus; PCC: posterior cingulate cortex; TPA: temporopolar area; AG: angular gyrus; IPL: inferior parietal lobe; mPFC: medial prefrontal cortex; ACC: anterior cingulate cortex; dACC: dorsal anterior cingulate cortex; TPJ: temporoparietal junction; VFC: ventral frontal cortex; CON: cingulo-opercular network; SMG: supramarginal gyrus; SMC: supplementary motor complex; dMFC: dorsal medial prefrontal cortex; aPFC: anterior prefrontal cortex; dIPFC: dorsolateral prefrontal cortex; IPS: intraparietal sulcus; FEF: frontal eye field; IFC: inferior frontal cortex; SFG: superior frontal gyrus; TP: temporal pole; IFG: inferior frontal gyrus; OFC: orbitofrontal cortex; NAcc: nucleus accumbens; PVC: primer visual cortex; L: left; R: right.

All results are significant at  $p < .05$ , corrected for family-wise error rate. Maximum P is the maximum proportion of studies exhibiting the effect at the peak density weighted by sample size. The results are shown with both height-based (hb) thresholding and extent-based (eb) thresholding.



**Figure 2.** Results of the meta-analysis in children and adolescents. The figure was drawn by authors to show the abnormal resting-state functional connectivity results of meta-analyses in children and adolescents with ADHD. While the yellow colour on brain images represents elevated connectivity, the blue colour is used for reduced connectivity in ADHD compared to healthy controls. All results are significant at  $p < .05$ , corrected for family-wise error rate. HC: healthy controls; ADHD: attention-deficit hyperactivity disorder; CCN: cognitive control network; DMN: default mode network; SN: salience network; PFC: prefrontal cortex; IFG: inferior frontal gyrus; PCC: posterior cingulate cortex; MOG: middle occipital gyrus; PVC: primary visual cortex; dIPFC: dorsolateral prefrontal cortex; aPFC: anterior prefrontal cortex; FEF: frontal eye field; OFC: orbitofrontal cortex; MTG: middle temporal gyrus.

et al. 2015; see Cortese et al. 2012 for a meta-analytical review). Specifically, certain DMN regions have been shown to be hyper-activated in children and adults with ADHD during information processing (Cortese et al. 2012) – a finding that resonates with the evidence of ADHD-related altered connectivity in the PFC sub-system and the Default Mode Interference Hypothesis of ADHD whereby insufficient attenuation of the DMN during goal-oriented tasks may contribute to the disruption of cognitive performance in ADHD (Sonuga-Barke and Castellanos 2007). Besides, individuals with ADHD have been found to have elevated levels of connectivity between DMN seeds and left temporal, inferior frontal regions implicated in language processing (Pulvermüller 2005). These alterations may be related to language problems encountered in ADHD (Korrel et al. 2017).

There was evidence of ADHD-related increased connectivity between regions within the CCN – specifically relating to the left anterior PFC regions. This result is consistent with some previous studies (Costa Dias et al. 2013). However, the findings of reduced activation in fronto-parietal circuits during inhibitory tasks are more difficult to reconcile with the current result (Dickstein et al. 2006; Rubia 2013). Interestingly, the implicated region (Brodmann 10) is involved in multi-tasking and elevated connectivity may underpin a compensatory strategy whereby individuals with ADHD learn to engage in multiple tasks at the same time (Burgess et al. 2003, 2007). This region is also commonly implicated in prospection, meta-cognition and envisioning the future (Burgess and Wu 2013). An elevated connectivity of this region with other pre-frontal regions may explain deficits in these abilities in ADHD. Alternatively, it may be a consequence of the chronic application of greater mental effort required to control for generally reduced information processing abilities seen in ADHD (Metin et al. 2012).

When adult studies were dropped in the sensitivity analysis – the key findings detailed above were replicated and extended in a number of ways. Most strikingly, childhood ADHD was associated with reduced connectivity between the DMN and other resting state brain networks as well as within the DMN. For instance, there was clear evidence of reduced connectivity between DMN seeds and the CCN. This finding is consistent with the previous results from individual studies reported diminished connectivity between DMN seeds and cognitive control network areas (Castellanos et al. 2008; Cao et al. 2009). This represents a potential neural basis for executive deficits and attentional lapses seen in ADHD (Willcutt et al.

2005). In the restricted age analysis we also observed that DMN seeds had reduced connectivity with caudate, amygdala, subgenual cingulate and nucleus accumbens regions of AMN in children with ADHD compared to healthy controls. One may speculate that this is related to either emotion dysregulation (Shaw et al. 2014) or deficits in the monitoring of the salience of motivational significance of stimuli (van Meel et al. 2011) seen in ADHD. Furthermore, there was ADHD-related reduced connectivity between salience network seeds and temporal gyrus and fusiform gyrus regions of MTL DMN compared to typically developing children. This may explain why children with ADHD have been shown to be less able process stimulus salience during conscious rest (Durston et al. 2003).

Overall, it is fair to say that the ADHD-related reduced network integrity was more apparent when the sample was restricted to children and adolescents. This finding is consistent with a developmental lag hypothesis and the normalisation of dysconnectivity as individuals grow (Shaw et al. 2007). The feasibility of this account is supported by previous literature, which has shown that resting state brain networks continue to mature throughout adolescence (Kelly et al. 2009; Dosenbach et al. 2010; Uddin 2010; Fransson et al. 2011; Jolles et al. 2011). Correspondingly, a recent study showed that ADHD adults had similar connectivity patterns to those observed in typically developing young individuals (Sato et al. 2012). There is evidence that DMN activity matures with increasing age (Dosenbach et al. 2010) and could be associated with cognitive maturation (Rubia 2013).

The current study had a number of strengths. It was the first meta-analysis to adopt a systems neuroscience approach to examine the intrinsic functional connectivity of the brain of individuals with ADHD. The meta-analysis was conducted using Multilevel Kernel Density Analysis (MKDA), which has the advantages because this method uses the studies or contrasts rather than individual peak coordinates as the unit of analysis. Other methods may not take into account the nested nature of peaks within a contrast. Densely populated local peaks may seem independent at first. However, this may be disadvantageous when averaging over studies with small sample sizes, thereby creating rougher statistical images. MKDA, on the other hand, takes the multi-level nature of data into consideration through its study-based analysis. Other advantages include straightforward interpretation of its statistics, weighted contrast maps based on sample size and study quality, and the use of family-wise error rate (FWE) to overcome false positive

results (Wager et al. 2007; Kober et al. 2008; Wager et al. 2009).

There were also a number of limitations that need to be considered when interpreting the results. First, we could not analyse the effect of medication on connectivity, due to limited number of studies with medication naïve patients. Second, we could not account for the effects of a number of other variables known to be related to ADHD. These include low IQ, sex and comorbidity. Third, we could not include results from studies which used different connectivity methods other than the seed-based analysis (like ICA, ReHo etc.), due to the insufficient number of these studies. As the literature grows, a separate meta-analysis for each analytic approach should be conducted. Fourth, although we performed a meticulous meta-analysis using MKDA method estimates the results after FWE error correction based on multiple iterations using Monte-Carlo simulations, the number of included studies was only 20 and this might have limited the sensitivity of analyses for several networks. Since MKDA based on the number of study sample and contrast rather than publication number, we believe the results of this meta-analysis is representative; although, it contains few publications. Furthermore, there is also a meta-analysis, which contains very close number of eligible publication to our study (25 publication: Kaiser et al. 2015). We, therefore, recommend that the meta-analysis should be repeated in the future when there are more studies published.

In summary, we identified within-network alterations in connectivity in two resting state networks implicated in neuropsychological processes known to be impaired in ADHD: DMN and CCN. DMN effects were more extensive and robust – largely characterised by within-network reduced connectivity. CCN alterations were limited to within-network elevated connectivity between two specific nodes. When adult studies were excluded, more widespread and conspicuous alterations within DMN and between it and other networks were observed.

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No potential conflict of interest was reported by the author(s).

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