CrossMark

ORIGINAL PAPER

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

**Justina Sidlauskaite[1] · Edmund Sonuga-Barke[1,2] · Herbert Roeyers[1] ·
Jan R. Wiersema[1]**

Abstract Deficits in task-related attentional engagement in attention-deficit/hyperactivity disorder (ADHD) have been hypothesised to be due to altered interrelationships between attention, default mode and salience networks. We examined the intrinsic connectivity during rest within and between these networks. Six-minute resting-state scans were obtained. Using a network-based approach, connectivity within and between the dorsal and ventral attention, the default mode and the salience networks was compared between the ADHD and control group. The ADHD group displayed hyperconnectivity between the two attention networks and within the default mode and ventral attention network. The salience network was hypoconnected to the dorsal attention network. There were trends towards hyperconnectivity within the dorsal attention network and between the salience and ventral attention network in ADHD. Connectivity within and between other networks was unrelated to ADHD. Our findings highlight the altered connectivity within and between attention networks, and between them and the salience network in ADHD. One hypothesis to be tested in future studies is that individuals with ADHD are affected by an imbalance between ventral and dorsal attention systems with the former playing a dominant role during task engagement, making individuals with ADHD highly susceptible to distraction by salient task-irrelevant stimuli.

Introduction

Efficient allocation of attention is a prerequisite for effective information processing during task performance. This requires a control system that is responsive to the dynamic nature of task demands in terms of the need for focusing, switching and dividing attention and the ability to resist distraction [1, 2]. fMRI studies have identified the core brain regions implicated in attentional control. These include dorsal and ventral lateral frontal cortices, together with posterior parietal areas [3–5]. These regions form a twofold attentional control system comprised of dorsal and ventral attention networks (DAN and VAN), operating as an integrated supramodal top-down and bottom-up attentional gating system [3, 6]. While traditional accounts of attentional function and dysfunction have focused on task-dependent neural activity within these networks, recent formulations have stressed the importance of a task-independent network as well [7]. This network, termed the default mode network (DMN), comprises frontal and posterior midline structures (medial prefrontal cortex, posterior cingulate cortex (PCC) with adjacent precuneus) and lateral parietal and medial temporal lobe regions [7, 8]. The DMN is active during periods of rest and is attenuated following the onset of tasks [8]. The DMN is also referred to as the task-negative network, because of its anti-correlation and to some extent antagonistic relationship to activity in attention networks (also termed the task-positive network [9]). This means that effective attentional engagement requires both the "switching on" of the task-positive attention networks and the "switching off" of the DMN [10–12]. Indeed, there

✉ Justina Sidlauskaite
Justina.Sidlauskaite@UGent.be

1 Department of Experimental-Clinical and Health Psychology, Ghent University, Henri Dunantlaan 2, 9000 Ghent, Belgium

2 Developmental Brain-Behaviour Unit, Psychology, University of Southampton, Shackleton Building (B44), Highfield Campus, Southampton SO17 1BJ, UK

is compelling evidence that performance suffers when excess (residual) DMN activity is observed during attention-demanding tasks [12–14]. Recently, Menon and Uddin [15] postulated that the salience network (SN), comprising bilateral insula and anterior cingulate cortex (ACC), provides the neural substrate of a switching hub controlling the up-regulation of attention networks and the down-regulation of the DMN. Support for this view comes from a range of recent studies [16–20].

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental condition characterised in part by symptoms of distractibility and an inability to ignore irrelevant stimuli—characteristics related to deficits in attentional control [21]. While in the past explanatory models have focused on localised deficits in brain regions, such as dorsal lateral prefrontal, posterior parietal and anterior cingulate cortices, within attention systems [22], more recent studies have examined the alternative possibility that attentional failures in ADHD during task performance may relate to interference by residual DMN activity [11]. Indeed, there is now compelling evidence from fMRI and electroencephalographic (EEG) studies that individuals with ADHD show excess DMN activity during tasks and that this has an adverse effect on their performance [14, 23–25]. While the reason for this higher DMN activity during tasks remains to be determined, one possibility is that it is due to failures of the between-network switching mechanism governed by the SN [19, 26]. Currently there is no direct evidence to support this hypothesis; however, it is interesting that in more general terms SN task-related activation abnormalities have been reported in ADHD [27–30]. Furthermore a number of studies also point to ADHD-related structural and volumetric abnormalities of SN regions [31].

Building on recent evidence that patterns of intrinsic task-free brain organisation sculpt task-related neural processes [32, 33], it has been suggested that ADHD is a condition caused by underlying deficits in brain organisation [27]. Moreover, it has been proposed that the key locus of dysfunction in ADHD may lie in the abnormal coordination of the DMN and attention networks, controlled by the SN [26, 34]. In the current paper, we provide the first test of this hypothesis by exploring the intrinsic organisation of DMN, DAN, VAN and SN and their interactions in adults with ADHD by evaluating patterns of BOLD signal correlations measured during rest [32, 35, 36]. Prior resting-state studies have found reduced connectivity in ADHD between DMN regions [37–39]; for opposite findings, see Tian et al. [40], McCarthy et al. [41], as well as altered organisation of DAN and VAN [21, 41, 42]. However, no study has directly explored connectivity within and between the DMN, DAN, VAN and SN in ADHD.

We employed a hypothesis-driven anatomical, network-based, parcellation approach, which differs from more traditional seed-based voxel-wise connectivity or independent component analysis accounts. This method builds on the graph theoretical analysis approach in that it uses an anatomical atlas based on an a priori parcellation scheme to form the networks of interest and is not limited to a single seed region [43–45]. The use of several key regions instead of one seed to describe brain networks enables a more comprehensive and reliable examination of the intrinsic intra- and inter-network organisation [46]. Thus, this allows the direct comparison of the within- and between-brain network organisation in two different groups. In addition, this method ensures the reproducibility and comparability of the results across studies employing the same parcellation scheme and enables the comparison of small and unequal sized samples [46]. Our predictions were as follows: i) based on the majority of previous findings, we predicted hypoconnectivity between the regions comprising the DMN, DAN and VAN in adults with ADHD; ii) based on the assumption that ADHD-related deficits in attentional control result from dysfunctional SN–DMN and/or SN–DAN–VAN coordination, we predicted reduced connectivity between SN and DMN, as well as between SN and attention networks in ADHD.

Methods and materials

Participants

The study was approved by the Medical Ethics Committee of Ghent University Hospital. Participants gave their written informed consent before participation and received a monetary reward after participation. A total of 19 adults with an official diagnosis of ADHD obtained in a clinical setting (13 combined, 6 inattentive type) and 23 typically developing (TD) controls participated. Both groups of participants were recruited through the means of local advertising, social websites, word of mouth or from the pool of individuals who had participated in previous experiments. Participants with ADHD met the lifespan criteria for the disorder and had both an official clinical diagnosis and research diagnosis of ADHD, confirmed by the DSM-IV-based semi-structured clinical Diagnostic Interview for Adult ADHD (DIVA; [47]). In addition, all participants with ADHD scored above cut-offs on self-report measures of childhood and adult ADHD symptoms (Wender Utah Rating Scale (WURS; [48]) and self-report questionnaire on problems of inattention and hyperactivity in adulthood and childhood (Kooij and Buitelaar [49]). All TD participants scored below the cut-offs on these questionnaires. All participants in both groups had a full scale IQ in the normal

or above average range (>80) as measured by a seven sub-tests version of the Wechsler Adult Intelligent Scale [50]. Groups did not differ on IQ (TD: $M = 117.26$; SD = 10.99; ADHD: $M = 112.05$; SD = 13.60; $p = 0.187$), sex ratio (TD: 10 female; ADHD: 10 female), or age (TD: $M = 27.17$ years; SD = 8.65; ADHD: $M = 29.78$ years; SD = 9.61; $p = 0.365$). Nine participants with ADHD were taking stimulant medication (8—methylphenidate and 1—dextroamphetamine) and were asked to refrain from taking these for at least 24 h prior to the experiment. Four ADHD participants were also taking antidepressant medication which they were allowed to continue (3—selective serotonin reuptake inhibitors and 1—bupropion chloride). All participants had normal or corrected-to-normal vision, and five were left-handed (1 ADHD). The general exclusion criteria were history of brain damage, a neurologic or psychiatric condition, or IQ < 80.

fMRI data acquisition

Functional and structural images were obtained with a Siemens Magnetom Trio MRI system (Siemens Medical Systems, Erlangen, Germany) operating at 3T, using a standard 32-channel head coil. Study participants were positioned supine head first inside the scanner and instructed to relax and rest with their eyes closed. Structural high-resolution 1 mm^3 images were collected using a T1-weighted 3D MPRAGE sequence. Functional whole-brain images were collected in a single run of 180 whole-brain volumes lasting 6 min, using gradient echoplanar imaging (EPI) T2*-weighted sequence sensitive to BOLD contrast (TR = 2000 ms, TE = 29 ms, acquisition matrix = 64×64, FoV = 224 mm, flip angle = 900, slice thickness = 3 mm, voxel size $3.5 \times 3.5 \times 3.5$ mm^3, 40 axial slices). The first four EPI images of each run were discarded to reduce T1 relaxation artefacts.

fMRI data preprocessing

Data preprocessing was conducted using Statistical Parametric Mapping software (SPM8; Wellcome Trust Centre for Neuroimaging; http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). Functional images were slice-time corrected and realigned to the first EPI. Rigid body transformation correction for within-run head motion was applied, and six head motion parameters were estimated. A two-sample t test analysis on the mean of absolute values of the estimated six motion parameters revealed no significant group differences in neither translational (ADHD: $x = 0.07$ mm (SD = 0.04); $y = 0.09$ mm (SD = 0.07); $z = 0.23$ (SD = 0.28); TD: $x = 0.08$ (SD = 0.06); $y = 0.10$ (SD = 0.08); $z = 0.17$ (SD = 0.14); p's, respectively: 0.722; 0.606; 0.377) nor rotational (ADHD: roll = 0.0038

(SD = 0.0050); pitch = 0.0021 (SD = 0.0015); yaw = 0.0014 (SD = 0.0009); TD: roll = 0.0034 (SD = 0.0031); pitch = 0.0019 (SD = 0.0014); yaw = 0.0016 (SD = 0.0013); p's, respectively: 0.732; 0.579; 0.702) motion.

Next, functional-to-anatomical coregistration was performed. Spatial normalisation to the standard ($3 \times 3 \times 3$ mm) Montreal Neurological Institute (MNI) template was applied to functional and structural images. Functional data were spatially smoothed with an isotropic full-width half-maximum (FWHM) Gaussian kernel of 8 mm. Structural images were segmented into individual white matter (WM), grey matter and cerebrospinal fluid (CSF) masks. Data were band-pass filtered (0.01 Hz $< f < 0.1$ Hz), further processed and corrected using the CONN-fMRI functional connectivity toolbox (www.nitrc.org/projects/conn/) [51]. Sources of spurious variance, such as signal from WM, CSF (five dimensions) and movement parameters, extracted from the realignment process, were removed by linear regression. Importantly, CONN toolbox employs anatomical component-based noise correction method (aCompCor) [52] which has been shown to effectively reduce the physiological and other sources of noise in BOLD signal and thus has proved particularly useful in increasing the sensitivity and validity of fMRI analysis [51].

Functional resting-state connectivity analysis

Anatomically landmarked regions of interest (ROIs) corresponding to areas comprising DMN, DAN, VAN and SN [7, 9, 53] (Table 1; Fig. 1) were derived from the Automatic Anatomic Labelling (AAL) atlas implemented in the WFU Pickatlas [54–56]. After averaging over the relevant voxels, the mean signal time series were extracted from each ROI and were used to create individual ROI-to-ROI connectivity matrices between regions corresponding to DMN, DAN, VAN and SN. Fisher's transformation was applied. Although we did not directly employ graph theoretical analysis, the brain network definitions employed here correspond to the ones widely used in graph analysis studies [57]. False-positive control was implemented using false discovery rate (FDR)-corrected p values ($p < 0.05$). Adopting a ROI-to-ROI connectivity analysis, first the within-network connectivity—the product of the pairwise correlations between all the regions comprising an individual network—was calculated. This resulted in a mean composite network connectivity estimate. Second, the pairwise correlations between the regions in each pair of different networks resulting in a mean composite between-network correlation were computed. Hence the within- and between-network connectivity were separately estimated as the mean of pairwise ROI-to-ROI time-series correlations, i.e. between hubs within

Table 1 Regions corresponding to the DMN, DAN, VAN and SN and their centre of mass coordinates

Network							
DMN		DAN		VAN		SN	
Region							
Superior medial frontal gyrus	(R) [5 49 30] (L) [−8 50 30]	Middle frontal gyrus	(R) [35 33 34] (L) [−34 32 35]	Inferior frontal gyrus	(R) [49 14 21] (L) [−49 12 19]	Insula	(R) [38 6 2] (L) [−36 6 3]
Posterior cingulate gyrus	(R) [6 −41 21] (L) [−5 −42 24]	Precentral gyrus	(R) [40 −8 52] (L) [−39 5 50]	Inferior parietal gyrus	(R) [45 −46 49] (L) [−43 −45 46]	Anterior cingulate gyrus	(R) [7 37 15] (L) [−5 35 13]
		Superior parietal gyrus	(R) [25 −59 62] (L) [−24 59 58]				
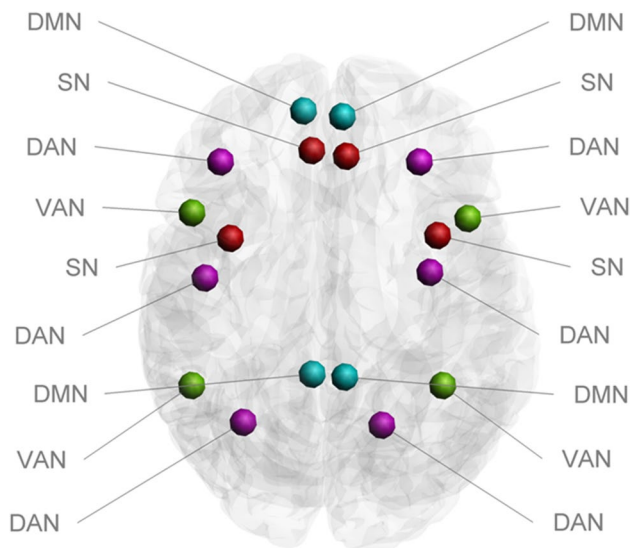
Fig. 1 The schematic outline of the regions corresponding to the DMN, DAN, VAN and SN used in the network connectivity analyses

network *a* for within-network connectivity and between hubs of network *a* and network *b* for between-network connectivity. Connectivity between all other pairs of networks was estimated in this way. Averages of within- and between-network connectivity were compared between groups.

Results

Within-network connectivity

Both groups showed strong functional connectivity between regions comprising the DMN (TD: $t(22) = 12.27$, $p < 0.001$; ADHD: $t(18) = 10.02$, $p < 0.001$), DAN (TD: $t(22) = 6.90$, $p < 0.001$; ADHD: $t(18) = 9.50$, $p < 0.001$), VAN (TD: $t(22) = 6.58$, $p < 0.001$; ADHD: $t(18) = 10.41$,

$p < 0.001$) and SN (TD: $t(22) = 18.58$, $p < 0.001$; ADHD: $t(18) = 11.10$, $p < 0.001$). Against our prediction, functional connectivity was stronger between areas comprising both the DMN and VAN in the ADHD group (DMN: $t(40) = 3.02$, $p = 0.002$; VAN: $t(40) = 2.68$, $p = 0.005$), and the same trend was observed for the areas comprising DAN ($t(40) = 1.53$, $p = 0.066$). ADHD and control groups did not differ in terms of between areas comprising the SN connectivity ($t(40) = 0.93$, $p = 0.179$). There is an ongoing debate about the regions comprising the DMN. We therefore examined whether the current results would hold when the set of regions comprising the DMN was extended to include additional frontal (bilateral medial frontal gyrus) and posterior (bilateral precuneus) regions. Re-running the analysis using the extended DMN did not change any of the results.

Between-network connectivity

Consistent with prior studies, activity within the DAN and VAN was correlated (TD: $t(22) = 8.50$, $p < 0.001$; ADHD: $t(18) = 11.22$, $p < 0.001$), and both attention networks were anti-correlated with the DMN (DAN–TD: $t(22) = -3.88$, $p < 0.001$; ADHD: $t(18) = -2.87$, $p = 0.005$; VAN–TD: $t(22) = -1.85$, $p = 0.030$; ADHD: $t(18) = -2.43$, $p = 0.010$). The DMN and SN were positively correlated (TD: $t(22) = 4.92$, $p < 0.001$; ADHD: $t(18) = 3.43$, $p < 0.001$). There was no group difference in the strength of anti-correlations between the DMN and attention networks (DMN and DAN: $t(40) = 0.40$, $p = 0.343$; DMN and VAN: $t(40) = 1.18$, $p = 0.122$) or the DMN and SN correlation ($t(40) = 0.61$, $p = 0.271$). However, the DAN and VAN were more strongly correlated in the ADHD group ($t(40) = 2.15$, $p = 0.018$). The DAN and SN were significantly anti-correlated only in the TD group (TD: $t(22) = -2.06$, $p = 0.025$; ADHD: $t(18) = 0.96$, $p = 0.174$) producing a significant group

difference ($t(40) = -2.00$, $p = 0.025$). The VAN–SN connectivity was significant only in the ADHD group (ADHD: $t(22) = 2.85$, $p = 0.005$; TD: $t(18) = 0.66$, $p = 0.25$), with a trend towards a group difference ($t(40) = 1.56$, $p = 0.06$) (Fig. 2; Table 2).

Discussion

In the current study, using resting-state connectivity analyses, we tested the hypothesis that abnormalities in the intrinsic organisation of brain regions corresponding to

Fig. 2 The schematic representation of the main intra- and inter-DMN, DAN, VAN and SN connectivity findings and differences between groups. "TD < ADHD" represents stronger connectivity in the ADHD group (significantly more positive in the ADHD group); "TD > ADHD" represents weaker connectivity in the ADHD group (significantly more negative in the control group); "ADHD = TD" represents the absence of group differences in connectivity strength. Please note that this scheme takes into account the absolute values of connectivity estimates as a measure of connectivity strength

networks implicated in attentional control—the DMN, attention networks and the SN—may lie at the heart of the pathophysiology of ADHD [26, 34]. Our network-based approach to study connectivity patterns allowed us to look at both connectivity between the key regions within networks and between these specific networks as a whole [46, 58]. There were a number of findings of note that provide further evidence of connectivity abnormalities within networks implicated in attentional control in ADHD [26].

First, we found altered connectivity in ADHD with regard to the areas comprising attention networks—DAN and VAN. Two aspects of ADHD-related intrinsic organisation of regions corresponding to DAN and VAN were particularly striking. (i) The areas forming attention networks were hyperconnected, both within each network and between the networks. Moreover, (ii) the VAN and DAN displayed differential connectivity patterns with regions corresponding to SN–SN–VAN being hyperconnected and SN–DAN hypoconnected. Please note that the terms hyper- and hypoconnected relate to the absolute value of the connectivity estimates, meaning that, for instance, significantly negative connectivity in the control group compared to non-significant positive connectivity in the ADHD group is reported as hypoconnectivity in the ADHD group based on the significant difference between groups (e.g. SN–DAN hypoconnectivity in the ADHD group). The potential significance of these findings for models of ADHD pathophysiology becomes apparent once one considers the respective roles of those brain networks during the control of goal-directed and stimulus-driven attention, as well as the importance of their effective coordination [3, 59]. In healthy individuals, the DAN and VAN systems display strong differentiation based on their specific functions to facilitate processes in attentional control [6, 60]. The DAN is involved in top-down voluntary allocation of goal-driven attention, whereas the VAN is involved in the detection of unexpected task-relevant stimuli to trigger attentional shifts, thus in stimulus-driven attention. Although they
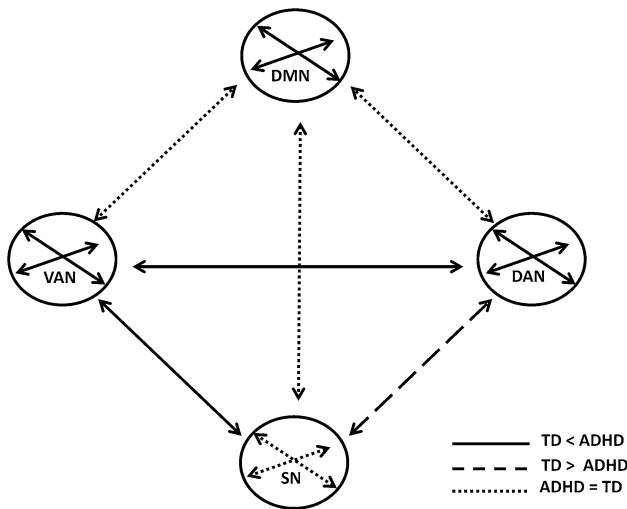
Table 2 Within- and between-network connectivity differences between the ADHD and TD group

Network	Within-network connectivity	Between-network connectivity			
		DMN	DAN	VAN	SN
DMN	ˆADHD		ADHD = TD	ADHD = TD	ADHD = TD
DAN	ˆADHD[a]	ADHD = TD		ˆADHD	ˇADHD
VAN	ˆADHD	ADHD = TD	ˆADHD		ˆADHD[a]
SN	ADHD = TD	ADHD = TD	ˇADHD	ˆADHD[a]	

* Results are presented with reference to the ADHD group

ˆ ADHD—stronger connectivity in the ADHD group (significantly more positive in the ADHD group)

ˇ ADHD—weaker connectivity in the ADHD group (significantly more negative in the TD group); ADHD = TD—no group difference

[a] – trend-level result, *DMN* default mode network, *DAN* dorsal attention network, *VAN* ventral attention network, *SN* salience network

have specialised roles, they continuously interact to control "where" and "what" one attends to [6, 59]. Our data suggest that the DAN and VAN are less segregated functionally in ADHD. This may create altered interactions between the attention networks in ADHD, where task-relevant inputs from the DAN filter stimulus-driven signals originating in the VAN, and where task-relevant stimuli trigger the VAN to interrupt and reorient the DAN to relevant stimuli. More specifically, decreased intrinsic segregation of the attention networks may alter the information exchange threshold between the two systems with VAN signals interrupting goal-directed task-relevant DAN activity. This is consistent with recent findings that increasingly point to VAN as the locus of attentional dyscontrol and enhanced distractibility in ADHD [27, 61, 62]. For instance, López et al. [63] observed that in the ADHD group, but not in controls, unattended task-irrelevant distractors elicited increased VAN-related P300 activity. Our finding of increased within-VAN connectivity and the same trend in DAN may further suggest the potentially reduced flexibility and capacity to alternate between goal-driven and relevant stimulus-driven attentional processing in ADHD.

Our finding of an imbalance between SN–DAN and SN–VAN connectivity in ADHD underscores the specificity of DAN and VAN roles in attentional control. This would be consistent with the idea that increased SN–VAN coupling produces an altered saliency attribution mechanism, where the discrimination between environmental distractors and task-relevant stimuli is muted. Therefore, in the context of ADHD, this might be hypothesised to relate to symptoms of distractibility and inability to ignore irrelevant stimuli. It is, however, difficult to directly compare our results with previous studies as a differentiation between the VAN and SN is often not made [62]. For instance, Sripada et al. [62] did not differentiate between the VAN and SN and included insula as part of the VAN. We based our analyses on the model of the SN as a between-network switching hub, as proposed by Menon and Uddin [15], which is differentiated from the attentional networks. Hence, we separated the SN, comprised of bilateral insula and anterior cingulate cortex (ACC), from the VAN–DAN system [53, 64]. The finding of a stronger SN–DAN anti-correlation in the control group, as well as a trend towards SN–VAN hyperconnectivity in the ADHD group, suggests a decreased brain network functional differentiation and adds to the frameworks where deficits in between-brain networks balance are proposed to underlie ADHD. The trend to SN–VAN hyperconnectivity in ADHD suggests that attentional control deficits may be tentatively associated with VAN alterations [61, 62].

Second, we reported stronger intra-DMN coupling in ADHD. The field has produced inconsistent results in this regard. While most studies have reported reduced DMN connectivity [37, 38, 44, 62], hyperconnectivity has also been observed [40, 41] (and one study found hyperconnectivity for some regions and hypoconnectivity for others within the DMN [65]). These inconsistencies may be due to differences between studies in analysis techniques used or sample characteristics. For instance, Castellanos et al. [37] used a seed-based approach and found decreased connectivity between two DMN regions—PCC and medial prefrontal cortex in an adult ADHD group. In the same sample of participants, Uddin et al. [44] applied a network homogeneity approach and showed ADHD-related reductions in only the posterior DMN, i.e. PCC. The method employed in the current study, however, was based on a network perspective where the DMN and other networks were formed of several key regions comprising that specific neural circuit. This was done in order to be able to estimate overall network connectivity using a comprehensive approach, which is different from previous seed-based connectivity or network homogeneity studies. Moreover, the current sample included adults, while other studies with a comparable network approach that reported disconnection between DMN regions were conducted in adolescent samples [38, 62]. The finding of intra-DMN hyperconnectivity in our ADHD sample appears to be consistent with the concept of resting-state affinity proposed as a potential mechanism behind problems in state-to-state switching [11], with hyperconnectivity within resting networks increasing affinity for that state and reducing the potential for switching to active goal-directed states. The above evidence of similar patterns of hyperconnectivity within attention networks may also be consistent with this.

Third, connectivity between DMN and attention networks, as well as connectivity between DMN and SN was unaffected in ADHD. In recent literature, there has been a strong focus on the DMN as a core feature of attentional dyscontrol in ADHD. Task-based studies have provided evidence for elevated DMN levels in ADHD during task processing [14, 24] which has been related to attentional deficits [11–13]. In terms of intrinsic network organisation, studies have suggested diminished antagonistic relationship between DMN and attention networks which may lead to excess task-related DMN [37, 62, 66, 67]. However, more recent models have introduced the crucial role of the SN to control the state-dependent switching between DMN and task-related attention networks [15]. Specifically, studies found support for a central role of the SN in attenuating the DMN and up-regulating attention networks when switching from rest to task [19, 20]. Interestingly, our results imply an intact between DMN and SN connectivity in ADHD and indicate another locus of functional disorganisation that may relate to attention deficits, namely the imbalance between SN and attention networks.

It is important to note that previous studies have suggested that brain network connectivity alterations may be differentially related to different subtypes of ADHD [68,

69]. However, due to the fact that the current ADHD sample included only six inattentive type participants, we were unable to reliably investigate this aspect. Nevertheless, the ADHD subtype–brain network connectivity relationship is an important but underinvestigated issue and, thus, it requires further examination in future studies specifically designed for that.

Our study has some limitations that are important to address. First, our network-based connectivity method highly relies on the a priori choice of brain regions to form the brain networks of interest. Hence, the results strongly depend on the brain parcellation scheme used. Second, although ADHD participants refrained from stimulant medication use for a sufficient washout period prior to their participation in the study, history and duration of stimulant and other psychoactive medication use, such as antidepressants, which may exert differential effects on the functional brain organisation, were not taken into account in the current study. Nevertheless, this is an important aspect to be investigated in future (longitudinal) studies. Moreover, it must be noted that since this is a resting-state brain network connectivity study, its findings cannot be directly compared to task-related cognitive processes, and thus, the potential links between the current results and attentional control during task performance should be seen as tentative. The role of resting-state brain network connectivity in task-related processing ought to be addressed in future experiments, combining rest- and task-related brain functional properties.

Conclusions

The current findings add to the growing evidence of altered intrinsic brain organisation in ADHD. Crucially, our results highlight the connectivity disturbances in attention networks and between them and SN as a putative locus for ADHD-related deficits in task engagement. An important target of investigation in future studies is the hypothesis that individuals with ADHD may suffer from imbalanced ventral and dorsal attention systems with the former playing a principal role during task engagement introducing increased susceptibility to salient but task-irrelevant stimuli.

Compliance with ethical standards

Conflict of interest Authors declare no potential conflict of interest.

References

1. Tortella-Feliu M, Morillas-Romero A, Balle M, Bornas X, Llabrés J, Pacheco-Unguetti AP (2014) Attentional control, attentional network functioning, and emotion regulation styles. Cogn Emot 28:769–780
2. Ziaei M, Peira N, Persson J (2014) Brain systems underlying attentional control and emotional distraction during working memory encoding. Neuroimage 87:276–286
3. Corbetta M, Shulman GL (2002) Control of goal-directed and stimulus-driven attention in the brain. Nat Rev Neurosci 3:201–215
4. Hopfinger JB, Buonocore MH, Mangun GR (2000) The neural mechanisms of top–down attentional control. Nat Neurosci 3:284–291
5. Woldorff MG, Hazlett CJ, Fichtenholtz HM, Weissman DH, Dale AM, Song AW (2004) Functional parcellation of attentional control regions of the brain. J Cogn Neurosci 16:149–165
6. Vossel S, Geng JJ, Fink GR (2014) Dorsal and ventral attention systems: distinct neural circuits but collaborative roles. Neuroscientist 20:150–159
7. Buckner RL, Andrews-Hanna JR, Schacter DL (2008) The brain's default network: anatomy, function, and relevance to disease. Ann NY Acad Sci 1124:1–38
8. Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL (2001) A default mode of brain function. Proc Natl Acad Sci USA 98:676–682
9. Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME (2005) The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc Natl Acad Sci USA 102:9673–9678
10. Lawrence NS, Ross TJ, Hoffmann R, Garavan H, Stein EA (2003) Multiple neuronal networks mediate sustained attention. J Cogn Neurosci 15:1028–1038
11. Sonuga-Barke EJS, Castellanos FX (2007) Spontaneous attentional fluctuations in impaired states and pathological conditions: a neurobiological hypothesis. Neurosci Biobehav Rev 31:977–986
12. Weissman DH, Roberts KC, Visscher KM, Woldorff MG (2006) The neural bases of momentary lapses in attention. Nat Neurosci 9:971–978
13. Bednarski SR, Zhang S, Hong K-I, Sinha R, Rounsaville BJ, Li CR (2011) Deficits in default mode network activity preceding error in cocaine dependent individuals. Drug Alcohol Depend 119:e51–e57
14. Fassbender C, Zhang H, Buzy WM, Cortes CR, Mizuiri D, Beckett L, Schweitzer JB (2009) A lack of default network suppression is linked to increased distractibility in ADHD. Brain Res 1273:114–128
15. Menon V, Uddin LQ (2010) Saliency, switching, attention and control: a network model of insula function. Brain Struct Funct 214:655–667
16. Goulden N, Khusnulina A, Davis NJ, Bracewell RM, Bokde AL, McNulty JP, Mullins PG (2014) The salience network is responsible for switching between the default mode network and the central executive network: replication from DCM. Neuroimage 99C:180–190
17. Jilka SR, Scott G, Ham T, Pickering A, Bonnelle V, Braga RM, Leech R, Sharp DJ (2014) Damage to the salience network and interactions with the default mode network. J Neurosci 34:10798–10807
18. Rilling JK, Dagenais JE, Goldsmith DR, Glenn AL, Pagnoni G (2008) Social cognitive neural networks during in-group and out-group interactions. Neuroimage 41:1447–1461
19. Sidlauskaite J, Wiersema JR, Roeyers H, Krebs RM, Vassena E, Fias W, Brass M, Achten E, Sonuga-Barke E (2014) Anticipatory

processes in brain state switching—evidence from a novel cued-switching task implicating default mode and salience networks. Neuroimage 98:359–365

20. Sridharan D, Levitin DJ, Menon V (2008) A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. Proc Natl Acad Sci USA 105:12569–12574

21. Cubillo A, Halari R, Smith A, Taylor E, Rubia K (2012) A review of fronto-striatal and fronto-cortical brain abnormalities in children and adults with Attention Deficit Hyperactivity Disorder (ADHD) and new evidence for dysfunction in adults with ADHD during motivation and attention. Cortex 48:194–215

22. Hart H, Radua J, Nakao T, Mataix-Cols D, 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

23. Helps SK, Broyd SJ, James CJ, Karl A, Chen W, Sonuga-Barke EJS (2010) Altered spontaneous low frequency brain activity in attention deficit/hyperactivity disorder. Brain Res 1322:134–143

24. Liddle EB, Hollis C, Batty MJ, Groom MJ, Totman JJ, Liotti M, Scerif G, Liddle PF (2011) Task-related default mode network modulation and inhibitory control in ADHD: effects of motivation and methylphenidate. J Child Psychol Psychiatry 52:761–771

25. Peterson BS, Potenza MN, Wang Z, Zhu H, Martin A, Marsh R, Plessen KJ, Yu S (2009) An FMRI study of the effects of psychostimulants on default-mode processing during Stroop task performance in youths with ADHD. Am J Psychiatry 166:1286–1294

26. Menon V (2011) Large-scale brain networks and psychopathology: a unifying triple network model. Trends Cogn Sci 15:483–506

27. Cortese S, Kelly C, Chabernaud C, Proal E, Di Martino A, Milham MP, Castellanos FX (2012) Toward systems neuroscience of ADHD: a meta-analysis of 55 fMRI studies. Am J Psychiatry 169:1038–1055

28. Dibbets P, Evers EAT, Hurks PPM, Bakker K, Jolles J (2010) Differential brain activation patterns in adult attention-deficit hyperactivity disorder (ADHD) associated with task switching. Neuropsychology 24:413–423

29. Dickstein SG, Bannon K, Castellanos FX, Milham MP (2006) The neural correlates of attention deficit hyperactivity disorder: an ALE meta-analysis. J Child Psychol Psychiatry 47:1051–1062

30. Lemiere J, Danckaerts M, Van Hecke W, Mehta MA, Peeters R, Sunaert S, Sonuga-Barke E (2012) Brain activation to cues predicting inescapable delay in adolescent Attention Deficit/Hyperactivity Disorder: an fMRI pilot study. Brain Res 1450:57–66

31. Lopez-Larson MP, King JB, Terry J, McGlade EC, Yurgelun-Todd D (2012) Reduced insular volume in attention deficit hyperactivity disorder. Psychiatry Res 204:32–39

32. Bressler SL, Menon V (2010) Large-scale brain networks in cognition: emerging methods and principles. Trends Cogn Sci 14:277–290

33. Deco G, Corbetta M (2011) The dynamical balance of the brain at rest. Neuroscientist 17:107–123

34. Supekar K, Menon V (2012) Developmental maturation of dynamic causal control signals in higher-order cognition: a neurocognitive network model. PLoS Comput Biol 8:e1002374

35. Damoiseaux JS, Rombouts SARB, Barkhof F, Scheltens P, Stam CJ, Smith SM, Beckmann CF (2006) Consistent resting-state networks. Proc Nat Acad Sci USA 103:13848–13853

36. De Luca M, Beckmann CF, De Stefano N, Matthews PM, Smith SM (2006) fMRI resting state networks define distinct modes of long-distance interactions in the human brain. Neuroimage 29:1359–1367

37. Castellanos FX, Margulies DS, Kelly C, Uddin LQ, Ghaffari M, Kirsch A, Shaw D, Shehzad Z, Di Martino A, Biswal B, Sonuga-Barke EJ, Rotrosen J, Adler LA, Milham MP (2008) Cingulate–precuneus interactions: a new locus of dysfunction in adult attention-deficit/hyperactivity disorder. Biol Psychiatry 63:332–337

38. Fair DA, Posner J, Nagel BJ, Barhula D, Dias TG, Mill KL, Blythe MS, Giwa A, Schmitt CF, Nigg JT (2010) Atypical default network connectivity in youth with attention-deficit/hyperactivity disorder. Biol Psychiatry 68:1084–1091

39. Konrad K, Eickhoff SB (2010) Is the ADHD brain wired differently? A review on structural and functional connectivity in attention deficit hyperactivity disorder. Hum Brain Mapp 31:904–916

40. Tian L, Jiang T, Wang Y, Zang Y, He Y, Liang M, Sui M, Cao Q, Hu S, Peng M, Zhou Y (2006) Altered resting-state functional connectivity patterns of anterior cingulate cortex in adolescents with attention deficit hyperactivity disorder. Neurosci Lett 400:39–43

41. McCarthy H, Skokauskas N, Mulligan A, Donohoe G, Mullins D, Kelly J, Johnson K, Fagan A, Gill M, Meaney J, 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

42. Zhu C-Z, Zang Y-F, Cao Q-J, Yan CG, He Y, Jiang TZ, Sui MQ, Wang YF (2008) Fisher discriminative analysis of resting-state brain function for attention-deficit/hyperactivity disorder. Neuroimage 40:110–120

43. Bullmore E, Sporns O (2009) Complex brain networks: graph theoretical analysis of structural and functional systems. Nat Rev Neurosci 10:186–198

44. Uddin LQ, Kelly AMC, Biswal BB, Margulies DS, Shehzad Z, Shaw D, Ghaffari M, Rotrosen J, Adler LA, Castellanos FX, Milham MP (2008) Network homogeneity reveals decreased integrity of default-mode network in ADHD. J Neurosci Methods 169:249–254

45. Wang L, Zhu C, He Y, Zang Y, Cao Q, Zhang H, Zhong Q, Wang Y (2009) Altered small-world brain functional networks in children with attention-deficit/hyperactivity disorder. Hum Brain Mapp 30:638–649

46. Schultz AP, Chhatwal JP, Huijbers W, Hedden T, van Dijk KR, McLaren DJ, Ward AM, Wigman S, Sperling RA (2014) Template based rotation: a method for functional connectivity analysis with a priori templates. Neuroimage 102:620–636

47. Kooij JJS, Francken MH (2010) Diagnostisch Interview Voor ADHD bij volwassenen. DIVA Foundation Den Haag

48. Ward MF, Wender PH, Reimherr FH (1993) The Wender Utah Rating Scale. An aid in the retrospective diagnosis of childhood attention deficit hyperactivity disorder. Am J Psychiatry 150:885–890

49. Kooij S, Buitelaar K (1997) Zelf-rapportage vragenlijst over aandachtsproblemen en hyperactiviteit voor volwassenheid en kindertijd

50. Ryan JJ, Ward LC (1999) Validity, reliability, and standard errors of measurement for two seven-subtest short forms of the Wechsler Adult Intelligence Scale—III. Psychol Assess 11:207–211

51. Whitfield-Gabrieli S, Nieto-Castanon A (2012) Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. Brain Connect 2:125–141

52. Behzadi Y, Restom K, Liau J, Liu TT (2007) A component based noise correction method (CompCor) for BOLD and perfusion based fMRI. Neuroimage 37:90–101

53. Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, Reiss AL, Greicius MD (2007) Dissociable intrinsic

connectivity networks for salience processing and executive control. J Neurosci 27:2349–2356

54. Eichele T, Debener S, Calhoun VD, Specht K, Engel AK, Hugdahl K, von Cramon DY, Ullsperger M (2008) Prediction of human errors by maladaptive changes in event-related brain networks. Proc Natl Acad Sci USA 105:6173–6178

55. Maldjian JA, Laurienti PJ, Kraft RA, Burdette JH (2003) An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. Neuroimage 19:1233–1239

56. Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, Mazoyer B, Joliot M (2002) Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage 15:273–289

57. Hosseini SMH, Hoeft F, Kesler SR (2012) GAT: a graph-theoretical analysis toolbox for analyzing between-group differences in large-scale structural and functional brain networks. PLoS One 7:e40709

58. Shenton ME, Kubicki M, Makris N (2014) Understanding alterations in brain connectivity in attention-deficit/hyperactivity disorder using imaging connectomics. Biol Psychiatry 76:601–602

59. Corbetta M, Patel G, Shulman GL (2008) The reorienting system of the human brain: from environment to theory of mind. Neuron 58:306–324

60. Fox MD, Corbetta M, Snyder AZ, Vincent JL, Raichle ME (2006) Spontaneous neuronal activity distinguishes human dorsal and ventral attention systems. Proc Natl Acad Sci USA 103:10046–10051

61. Helenius P, Laasonen M, Hokkanen L, Paetau R, Niemivirta M (2011) Impaired engagement of the ventral attentional pathway in ADHD. Neuropsychologia 49:1889–1896

62. Sripada C, Kessler D, Fang Y, Welsh RC, Prem Kumar K, Angstadt M (2014) Disrupted network architecture of the resting brain in attention-deficit/hyperactivity disorder. Hum Brain Mapp 35:4693–4705

63. López V, Pavez F, López J, Ortega R, Saez N, Carracaso X, Rothhammer P, Aboitiz F (2008) Electrophysiological Evidences of Inhibition Deficit in Attention-Deficit/Hyperactivity Disorder During the Attentional Blink. Open Behav Sci J 2:23–31

64. Aboitiz F, Ossandón T, Zamorano F, Palma B, Carrasco X (2014) Irrelevant stimulus processing in ADHD: catecholamine dynamics and attentional networks. Front Psychol 5:183

65. Franzen JD, Heinrichs-Graham E, White ML, Wetzel MW, Knott NL, Wilson TW (2013) Atypical coupling between posterior regions of the default mode network in attention-deficit/hyperactivity disorder: a pharmaco-magnetoencephalography study. J Psychiatry Neurosci 38:333–340

66. Cao X, Cao Q, Long X, Sun L, Sui M, Zhu C, Zuo X, Zang Y, Wang Y (2009) Abnormal resting-state functional connectivity patterns of the putamen in medication-naïve children with attention deficit hyperactivity disorder. Brain Res 1303:195–206

67. Sun L, Cao Q, Long X, Sui M, Cao X, Zhu C, Zuo X, An L, Song Y, Zang Y, 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 Res 201:120–127

68. Fair DA, Nigg JT, Iyer S, Bathula D, Mills KL, Dosenbach NUF, Schlaggar BL, Mennes M, Gutman D, Bangaru S, Buitelaar JK, Dickstein DP, Di Martino A, Kennedy DN, Kelly C, Luna B, Schweitzer JB, Velanova K, Wang Y-F, Mostofsky S, Castellanos FX, Milham MP (2012) Distinct neural signatures detected for ADHD subtypes after controlling for micro-movements in resting state functional connectivity MRI data. Front Syst Neurosci 6:80

69. Chen L, Liu Q, Zhou M, Hu X, He N, Gong Q, Huang X (2015) The distinct functional-connectivity features of combined and inattentive subtypes of ADHD. In: OHBM 2015, Hawaii