NeuroImage: Clinical 7 (2015) 68–81

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Connectivity supporting attention in children with attention deficit hyperactivity disorder

Anita D. Barber [a,b,*], Lisa A. Jacobson [a,b], Joanna L. Wexler [a], Mary Beth Nebel [a,b], Brian S. Caffo [c], James J. Pekar [a,b], Stewart H. Mostofsky [a,b]

[a] Kennedy Krieger Institute, Baltimore, MD, USA
[b] Johns Hopkins University School of Medicine, Baltimore, MD, USA
[c] Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

ARTICLE INFO

Article history:
Received 20 May 2014
Received in revised form 4 November 2014
Accepted 14 November 2014
Available online 20 November 2014

Keywords:
ADHD
Intra-subject variability
Attention
Resting-state connectivity
Network
Default mode network

ABSTRACT

Intra-subject variability (ISV) is the most consistent behavioral deficit in Attention Deficit Hyperactivity Disorder (ADHD). ISV may be associated with networks involved in sustaining task control (cingulo-opercular network: CON) and self-reflective lapses of attention (default mode network: DMN). The current study examined whether connectivity supporting attentional control is atypical in children with ADHD. Group differences in full-brain connection strength and brain–behavior associations with attentional control measures were examined for the late-developing CON and DMN in 50 children with ADHD and 50 typically-developing (TD) controls (ages 8–12 years).

Children with ADHD had hyper-connectivity both within the CON and within the DMN. Full-brain behavioral associations were found for a number of between-network connections. Across both groups, more anti-correlation between DMN and occipital cortex supported better attentional control. However, in the TD group, this brain–behavior association was stronger and occurred for a more extensive set of DMN–occipital connections. Differential support for attentional control between the two groups occurred with a number of CON–DMN connections. For all CON–DMN connections identified, increased between-network anti-correlation was associated with better attentional control for the ADHD group, but worse attentional control in the TD group. A number of between-network connections with the medial frontal cortex, in particular, showed this relationship. Follow-up analyses revealed that these associations were specific to attentional control and were not due to individual differences in working memory, IQ, motor control, age, or scan motion.

While CON–DMN anti-correlation is associated with improved attention in ADHD, other circuitry supports improved attention in TD children. Greater CON–DMN anti-correlation supported better attentional control in children with ADHD, but worse attentional control in TD children. On the other hand, greater DMN–occipital anti-correlation supported better attentional control in TD children.

1. Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is a developmental disorder (Castellanos et al., 2002; Fair et al., 2010; Krain and Castellanos, 2006; Shaw et al., 2013), which is usually identified in childhood and often persists into adulthood. Characteristic deficits of inattention, hyperactivity, and impulsivity contribute to a range of potential problems: poor academic achievement, substance abuse, obesity, risky behavior, difficulty achieving long-term goals, and/or mood disorders (Cortese et al., 2013; Garner et al., 2013; Shaw et al., 2012). Investigations of behavioral markers have targeted increased intra-subject variability (ISV) in reaction times (RTs) as the most consistent behavioral deficit associated with ADHD (Castellanos et al., 2005; Castellanos and Tannock, 2002). Elevated ISV in ADHD has been found across a number of tasks (Adamo et al., 2012; Tamm et al., 2012) and is broadly associated with ADHD symptomatology (Gomez-Guerrero et al., 2011). In healthy adults, elevated ISV is associated with reduced anti-correlation between the DMN and cognitive control networks both during task and at rest (Kelly et al., 2008), suggesting that this between-network antagonism is important for attentional control trait behavior. Identification of the neural systems that contribute to this behavioral deficit in ADHD, especially early in development, is key for understanding the best course of treatment for the disorder.

Pathophysiology of ADHD is diverse. Early studies focused on fronto-striatal pathways, while more recent attention has been on the default mode network (DMN) and its antagonistic relationship with cognitive control networks (Bush et al., 2005). Atypical integrity of the DMN has been found in a number of resting state studies (Castellanos et al.,

* Correspondence to: 716 North Broadway, Baltimore, MD 21205, USA. Tel: +1 443 923 9278; fax: +1 443 923 9279.
E-mail address: adbarber@jhu.edu (A.D. Barber).

http://dx.doi.org/10.1016/j.nicl.2014.11.011

2008; Fair et al., 2010; Sun et al., 2012; Uddin et al., 2008). Reduced anti-correlation between the DMN and cognitive control networks has been found during both rest (Castellanos et al., 2008; Sun et al., 2012) and task (Fassbender et al., 2009; Liddle et al., 2011) and is related to symptomatic (Castellanos et al., 2008) and behavioral (Fassbender et al., 2009) measures. In particular, reduced anti-correlation between the dorsal medial frontal cortex (dMFC) and the DMN is a consistent finding (Castellanos et al., 2008; Sun et al., 2012), suggesting that this antagonistic relationship may be integral to ADHD pathology.

The dMFC consists of both the anterior/middle cingulate cortex (BA 32/24) and supplementary motor complex (SMC: BA 6) and plays a role in control and error processing (Nee et al., 2011). This region forms part of the cingulo-opercular network (CON) (Dosenbach et al., 2007), which also includes the bilateral dorsal anterior insula (DAI, BA 13) and bilateral supramarginal gyrus (SMG, BA 40). While the dMFC has been of interest for its altered function (Bush, 2010; Castellanos et al., 2008; Suskauer et al., 2008) and structure (Shaw et al., 2013) in ADHD, the rest of the network may also play a role in ADHD pathology (Grayson et al., 2014). Anti-correlation between the CON and the DMN is late-developing (Barber et al., 2013), which may be important for the developmental course of the disorder.

Given their established pathophysiology in ADHD, the CON and DMN are candidate networks for involvement in attention deficits associated with ADHD. The CON supports sustained attention over task blocks (Dosenbach et al., 2007), while the DMN supports self-reflective thought (Buckner et al., 2008; Raichle et al., 2001). Therefore, these networks likely play a role in ISV-related attention deficits (Castellanos et al., 2005; Castellanos and Tannock, 2002). The current study examines full-brain connectivity with the CON and DMN to identify altered connectivity related to attentional control in children with ADHD. In addition to examining group differences in CON and DMN connectivity, brain–behavior associations with ISV and related measures are examined for the two groups.

2. Material and methods

2.1. Participants

50 ADHD and 50 typically-developing (TD) children (ages 8–12 years) were matched on the following variables (Table 1): age, gender, handedness, socio-economic status, verbal comprehension index (VCI), and perceptual reasoning index (PRI). The two groups were matched on VCI and PRI rather than Full-Scale IQ (WISC-IV), since the latter measure includes traits that are characteristic of ADHD dysfunction (i.e. working memory and processing speed) (Theiling and Petermann, 2014). Only subjects with movement less than 3 mm translation and 3° rotation in any direction over the course of the resting scan were included in the current sample. The two groups were matched for scan movement for which they did not significantly differ (mean absolute motion summed across the six motion parameters, $t_{98} = 0.45$, $p = 0.15$, ADHD mean = 2.03, SD = 1.05; TD mean = 1.76, SD = 0.86, mean frame-wise displacement: $t_{98} = 1.8$, $p = 0.08$, ADHD mean = 0.31, SD = 0.21; TD mean = 0.25, SD = 0.14). Scan motion was additionally accounted for by the use of the CompCor method of nuisance regression, which is an effective alternative to removing motion-contaminated scans (Muschelli et al., 2014). TD children had no history of intellectual disability, developmental language disorder, reading disability, pervasive developmental disorder, visual impairment, neurological disorder, or psychiatric diagnosis, as confirmed using the DICA-IV (Reich, 2000). Children with ADHD met criteria for the disorder on both the DICA-IV (Reich, 2000) and Conners Parent Rating Scale-Revised (Conners et al., 1998). 39 children met criteria for combined type, 1 met criteria for hyperactive/impulsive type, and 10 met criteria for inattentive type. The DICA-IV was also used to assess comorbidity. Children were excluded if they met criteria for conduct disorder, mood disorder, generalized anxiety disorder, separation anxiety disorder, or obsessive–compulsive disorder. Five children in each group had a simple phobia and 17 children with ADHD met criteria for oppositional defiant disorder. 35 children with ADHD were prescribed stimulant medications and were required to withhold medication for 48 h prior to testing. This study was approved by the Johns Hopkins Medical Institutional Review Board. Written consent was obtained from a parent or legal guardian and verbal assent was obtained from the participating child.

Table 1
Demographic information.

	ADHD $n = 50$		Control $n = 50$		
	Mean	SD	Mean	SD	p
Sex (% male)	64.0		62.0		0.836
Handedness (% right)	90.0		86.0		0.360
Age	9.81	1.31	9.99	1.01	0.430
WISC-IV					
VCI	115.16	14.20	118.52	10.82	0.186
PRI	109.82	14.99	108.52	12.18	0.635
ADHD					
CPRS-R N scale	73.92	8.80	46.25	4.58	< 0.001
Reaction time (GNG)					
Mean RT	412.10	81.66	390.60	12.82	0.216
Omission rate	0.05	0.05	0.02	0.03	< 0.001
Commission rate	0.47	0.19	0.41	0.19	0.083
RT — SD	149.98	88.85	127.30	53.06	0.004
RT — ISV	0.40	0.17	0.33	0.12	0.014
RT — Mu	275.18	45.06	289.64	85.56	0.293
RT — Sigma	28.03	16.03	30.13	27.49	0.642
RT — Tau	136.92	69.27	100.97	51.18	0.004

Note. WISC-IV = Wechsler Intelligence Scale for Children, Fourth Edition; VCI = Verbal Comprehension Index, Standard score; PRI = Perceptual Reasoning Index, Standard score; CPRS-R: Conners' Parent Rating ScaleRevised, Total ADHD Symptoms scale (N Scale), *T*-score; GNG = Go/No-go test; RT = reaction time (ms).

2.2. Imaging acquisition and preprocessing

Images were acquired on a Philips 3 T scanner. A high-resolution anatomical scan (MPRAGE, 8-channel head coil, TR = 7.99 ms, TE = 3.76 ms, Flip angle = 8°) and a resting state functional scan (2D-SENSE EPI, 8-channel head coil, TR = 2500 ms, TE = 30 ms, Flip angle = 70°, voxel-size = 3 mm^3, ascending axial slices, no slice gap) were acquired from each participant. The functional scan lasted 5 min 20 s during which participants fixated on a center cross.

Preprocessing of functional images was performed using SPM8 and Matlab scripts (Fig. S1). This included slice time correction, motion correction, co-registration, segmentation, and normalization. Nuisance variables were removed from each voxel, including cerebrospinal fluid and white matter signals identified using the CompCor method (Behzadi et al., 2007), global mean signal, and twelve motion parameters (representing affine parameters acquired from the SPM motion correction step for absolute x, y, and z translation and roll, pitch, and yaw rotation movement from the first scan as well as the six derived differential (scan-to-scan) parameters). Functional images were spatially-smoothed using a 6-mm full-width at half-maximum kernel and then temporally filtered (bandpass 0.01–0.1 Hz).

2.3. Functional connectivity data analysis

A network-based approach was taken in which several seed regions, which represent key nodes of a network, were identified for the CON and DMN. Time-courses were extracted and full-brain connectivity maps were created for each seed. Within each participant, the full-brain connectivity maps for each network seed were then averaged for each network. This approach assumes that nodes within a network show similar connectivity profiles and work together to support similar cognitive functions. To determine whether this was actually the case, previous papers employing this approach (Barber et al., 2013; Fox et al., 2005) corroborated the method of averaging region maps by

performing a conjunction analysis of overlapping significant connectivity for multiple seed regions within a network. Both approaches, the average connectivity and conjunction approach, show correspondence in regions displaying significant activation. For the current study, primary analyses were performed using the method of averaging seed connectivity maps separately for the CON and DMN. Conjunction analyses were then performed to determine those voxels that had significant connectivity across several of the individual network seed full-brain connectivity maps and to examine correspondence with mean connectivity maps.

6-mm radius seeds were placed in five CON regions: bilateral DAI, bilateral SMG, and anterior cingulate cortex; and three DMN regions: medial prefrontal cortex (MPFC), posterior cingulate cortex (PCC), and angular gyrus. See Table S1 for seed coordinates. The CON regions were centered at peak coordinates from a previous study examining developmental changes in resting state connectivity between late childhood and adulthood (Barber et al., 2013). The DMN regions were centered at peak coordinates (converted to MNI space (Lancaster et al., 2007)) from a previous study examining resting-state connectivity of task negative (i.e. DMN) regions (Fox et al., 2005). Mean time-courses were extracted and full-brain connectivity maps were created for each seed. Connectivity maps were then Fisher's Z-transformed. For each subject, the five CON maps and three DMN maps were averaged to make one mean CON and one mean DMN map.

Second-level *t*-tests were performed to examine differential connectivity for the two groups with the CON and DMN (i.e. TD > ADHD and ADHD > TD). Second-level group analyses were thresholded at a voxel-level of $p < .01$. To correct for multiple comparisons across the 2 second-level analyses (i.e. 2 networks), cluster-level thresholding was performed at $p < 0.025$ (i.e. 0.05/2 network maps) according to the Random Field Theory (Kiebel et al., 1999).

In addition to testing for significant effects in the mean network maps, conjunction analyses were performed for each of the seed maps to determine whether there were overlapping significant effects for connectivity with each seed region within a network. These conjunction maps were created for the 5 CON seed regions and 3 DMN seed regions separately. At the second-level, each seed map was thresholded (i.e. using a voxel-level threshold of $p < 0.05$ and a cluster-level threshold of $p < 0.025$ (i.e. $p < 0.05/2$) to correct for the two network statistical maps). Each voxel of the conjunction map was then labeled with a number corresponding to the number of seed regions that showed a significant connectivity difference between the two groups in that voxel (i.e. 1–5 for the CON and 1–3 for the DMN).

To determine whether significant regions formed part of the CON or DMN, second-level *t*-tests were performed within the TD group to test for those connections that were greater than 0 in the mean CON and mean DMN maps. Mean network connectivity maps were examined within the TD group, since this group's network maps represent the typical network structure. It was, however, expected that the average connectivity maps would be similar for the two groups for both networks. This network analysis was thresholded at a voxel-level of $p < 0.001$ and a cluster-level of $p < 0.025$ (i.e. 0.05/2 network maps). Conjunction analyses were performed across all of the seed region maps within each network to determine the number of seed maps with significant connectivity in each voxel. Each seed map was thresholded at a voxel-level of $p < 0.05$ and a cluster level of $p < 0.025$ (i.e. 0.05/2 network maps). The TD group mean network maps were used to visually inspect whether regions with significantly different connectivity values for the two groups fell within the CON or DMN. In addition, mean connectivity values with the identified CON and DMN regions were used for follow-up analyses examining within-network and between-network connectivity (see Section 2.5).

2.4. Brain–behavior associations

All children completed a Go/No-go task outside of the scanner. On each trial, a spaceship stimulus was presented for 300 ms followed by a 2000 ms fixation. Children were instructed to press a button with their right index finger when a green spaceship appeared and to withhold their response when a red spaceship appeared. The Go:No-go ratio was 4:1.

Brain–behavior associations were performed for three Go/No-go variables related to lapses of attention: ISV, Tau (Ex-Gaussian distribution), and Omission Error Rate (OER). ISV was the standard deviation of the RT divided by the mean RT for each participant. Ex-Gaussian indices, Mu, Sigma, and Tau, were computed (Leth-Steensen et al., 2000; Vaurio et al., 2009). Specifically, Tau characterizes the exponential part of the distribution (Cousineau et al., 2004) and reflects the proportion of slow RT responses made. Both ISV and Tau were computed for correct Go trials. In addition to these two measures of RT variability, OER was also considered. Epstein et al. (2010) showed that RT slowing occurs around the time of omission errors, suggesting that both reflect the same cognitive process. OER was the proportion of Go trials in which participants failed to make a response. Although the three attentional control measures (ISV, Tau, and OER) reflect related cognitive constructs, all three were considered independently to determine whether this is actually the case. Some studies have suggested that Tau, which reflects the proportion of very slow RT trials, may be more indicative of ADHD pathology than ISV itself (Leth-Steensen et al., 2000). This is based on the assumption that ADHD individuals make occasional long RTs (i.e. lapses of attention) but otherwise look typical in their RT distribution. Omissions (i.e. incorrect Go trials) are those trials on which the RT was so slow that a response was never made and therefore, may reflect an extreme case of an attention lapse.

Separate SPM first-level models were created for each of the behavioral covariates (ISV, Tau, and OER) and for each network (CON and DMN). Second-level models examined the associations between full-brain connectivity and each covariate. Regression was performed to test common and differential associations in the two groups. The brain–behavior analyses were multiple-comparisons corrected across the 6 second-level maps (i.e. 3 behavioral covariates × 2 networks). Therefore, cluster-level thresholding was performed at $p < 0.0083$ (i.e. 0.05/6 statistical maps) according to the Random Field Theory (Kiebel et al., 1999). In addition to examining brain–behavior associations in the mean network maps, conjunction maps were created for the 5 CON seed regions and 3 DMN seed regions separately. These analyses identified voxels in which there was a significant association between attentional control (i.e. ISV, Tau, or OER) and connectivity for multiple seed regions within a network. Both significant associations in both groups (i.e. covariate effect in both groups) and associations that were significantly different for the two groups (i.e. group × covariate interaction) were tested. At the second-level, each seed map was thresholded (i.e. using a voxel-level threshold of $p < 0.05$ and a cluster-level threshold of $p < 0.0083$ (i.e. $p < 0.05/6$) to correct for the six statistical maps). Each voxel of the conjunction map was then labeled with a number corresponding to the number of seed regions that showed a significant behavioral effect in that voxel (i.e. 1–5 for the CON and 1–3 for the DMN).

2.5. Follow-up analyses

2.5.1. Follow-up examination of regions identified in brain–behavior analyses

Mean connectivity values were extracted for each region that had significantly different brain–behavior associations for the two groups. This was done first to confirm the network affiliation of the region and second to determine whether other variables could account for the brain–behavior associations. To determine network affiliation, *t*-tests were performed to test whether connectivity of the region with each network was significantly different from 0. In addition, *t*-tests were performed to determine whether connectivity was greater within the CON map than within the DMN map or vice versa.

To determine whether other factors (i.e. behavioral measures, age, or participant scan motion) may account for the observed brain–behavior

associations, multiple regression analyses were performed within each group and for each region. Mean connectivity value was the dependent variable and the appropriate behavioral measure (ISV, Tau, or OER) was the independent variable. To determine whether brain–behavior associations were specific to attentional control or may be more related to other behavioral impairments, three behavioral covariates were included: Working Memory Index (WMI), Full-Scale IQ (FSIQ), and Total PANESS score (Denckla, 1985), a measure of children's basic motor abilities. All three of these measures significantly differed between the two groups and including them in the multiple regression model allowed us to determine whether brain–behavior associations were specific to attentional control, were indicative of another type of behavioral impairment (e.g. working memory or motor dysfunction), or were related to more general impairment. In addition to these behavioral measures, age was included in each model along with four summary measures of motion (mean and maximum absolute motion and mean and maximum differential scan-to-scan frame-wise displacement). Summary motion measures were calculated by summing across the six motion parameters (x, y, z, roll, pitch, and yaw in millimeters) at each time-point and then taking the average or maximum value for each subject's scan run.

2.5.2. Associations with mean network connectivity

Mean connectivity values for the two networks were extracted for two follow-up analyses: 1. to determine whether the between-network associations with attentional control were specific to those regions identified in the full-brain analyses or whether they were network-wide, 2. to determine whether greater CON–DMN anti-correlation may compensate for increased within-network DMN connectivity, and 3. to determine whether stimulant medication plays a role in the observed brain–behavior associations. For these analyses, masks were made of those voxels that were significantly greater than 0 for the TD group for the mean CON and mean DMN maps. Average connectivity values were then extracted across all voxels for the within-CON mask and the within-DMN mask. Average between-network CON–DMN values were obtained by averaging all of the voxel values in the mean TD DMN mask extracted from the CON maps. This resulted in one within-CON, one within-DMN, and one between-CON–DMN connectivity value per subject. Simple regression analysis was then performed to examine the association of the mean network connectivity values with the three attentional control behavioral measures and with the other mean network connectivity values.

Previous studies have found that stimulant medication increases the anti-correlation between DMN and other cognitive control networks during task performance (Peterson et al., 2009; Tomasi et al., 2009). Most of the children with ADHD in the current sample were on stimulant medication (35 out of 50). Although there was a 48 hour wash-out period before behavioral and scan testing, long-term use of stimulant medication may still have had an effect on associations with between CON–DMN connectivity. To determine whether this was the case, three matched groups were compared: a TD group, a medication naïve ADHD group, and a medicated ADHD group. 15 subjects were included in each group and the three groups were matched for gender, handedness, age, VCI, PRI, SES, and four measures of scan motion (Table S4). Within each group, regression analyses were performed to examine the association of CON–DMN connectivity with the three measures of attentional control (ISV, Tau, and OER) and with within-network connectivity.

3. Results

3.1. Behavioral results

Table 1 summarizes performance on the Go/No-go task. The two groups were not significantly different in mean RT ($t_{98} = 1.25$, $p = 0.22$), commission error rate ($t_{98} = 1.25$, $p = 0.083$) or on the Mu ($t_{98} = -1.06$, $p = 0.29$) or Sigma ($t_{98} = -0.47$, $p = 0.64$) fits of the Ex-Gaussian RT distribution. Children with ADHD had significantly greater ISV ($t_{98} = 2.51$, $p = 0.014$), OER ($t_{98} = 3.30$, $p = 0.0013$), and Tau ($t_{98} = 2.95$, $p = 0.004$) than TD children.

3.2. Functional connectivity results

Fig. 1 and Table 2 display regions showing group differences in connectivity for both the CON and DMN. For the CON, connectivity was significantly greater for the ADHD than TD group with a region of the dMFC. This region spanned the supplementary motor area (SMA), pre-SMA, and cingulate cortex (BA 6/24). For the DMN, connectivity was significantly greater for the ADHD than the TD group across a number of DMN regions. This included the MPFC, which encompassed the bilateral superior frontal gyrus, medial superior frontal gyrus, anterior cingulate cortex, and middle frontal gyrus (BA 9/10/32). This also included the bilateral precuneus (BA 7/31) and the left angular gyrus (BA 39). In addition, children with ADHD had significantly greater connectivity between the DMN and the left inferior orbitofrontal cortex (OFC: BA 47) and the left superior temporal pole (BA 38). There were no regions with greater connectivity for the TD group in either network.

Conjunction analyses showed correspondence with those regions identified in the mean connectivity analyses. For the TD CON and TD DMN networks, those regions identified in the mean maps generally overlapped with those regions that were significant across all of the network seed maps (Fig. 1, panels a and c). In addition, those regions that had greater connectivity in the ADHD group than TD group for the mean maps, likewise had greater connectivity in the ADHD group for most, or all, network seed regions (Fig. 1, panels b and d).

3.3. Brain–behavior results

3.3.1. Brain–behavior associations across both groups

Associations with ISV, Tau, and OER were examined for the CON and DMN connectivity maps. For the CON, no regions had significant associations with any of the behavioral variables within both of the two groups. For the DMN, a number of between-network connections were associated with attention abilities in both groups (Fig. 2 and Table 3). Greater anti-correlation between the DMN and occipital regions were associated with both reduced ISV and reduced Tau for both groups. For ISV, the occipital region spanned the Lingual Gyrus, Calcarine Sulcus, Cuneus, Superior Occipital Gyrus, Middle Occipital Gyrus, and the Fusiform Gyrus (BA 18/19/30/17/7/31); whereas for Tau, the occipital region was confined to the Lingual and Fusiform Gyri (BA 18/19). For OER, greater anti-correlation between DMN and lateral frontal cortex (middle frontal gyrus and inferior frontal gyrus opercularis and triangularis (BA 9)) was associated with lower OER in both groups.

Conjunction analysis revealed that the occipital region that had significant associations for connectivity with DMN in the mean maps and ISV, likewise had significant associations for connectivity with DMN connectivity in 2–3 of the DMN seed maps and ISV (Fig. 2). This was not the case for the occipital region that had significant associations for connectivity with DMN in the mean maps and Tau (Fig. 2). Inspection of the individual seed maps revealed that there was a large occipital region that had significant associations for connectivity with the PCC seed and Tau, but this was not the case for the other two DMN seed regions. Therefore, identification of this region in the mean DMN connectivity maps was largely driven by PCC connectivity associations with Tau. Likewise for the middle/inferior frontal region that had significant associations in connectivity with the DMN and OER, the brain–behavior associations were not significant for each of the DMN seed region maps. For this region, an overlapping region cluster was identified in each of the seed region statistical maps; however it did not reach significance in any of the three seed region maps. Therefore, identification of this region in the average DMN connectivity map was due to consistent sub-threshold brain–behavior associations in the corresponding DMN seed region maps rather than a highly significant association in any one of the three DMN seed region maps.

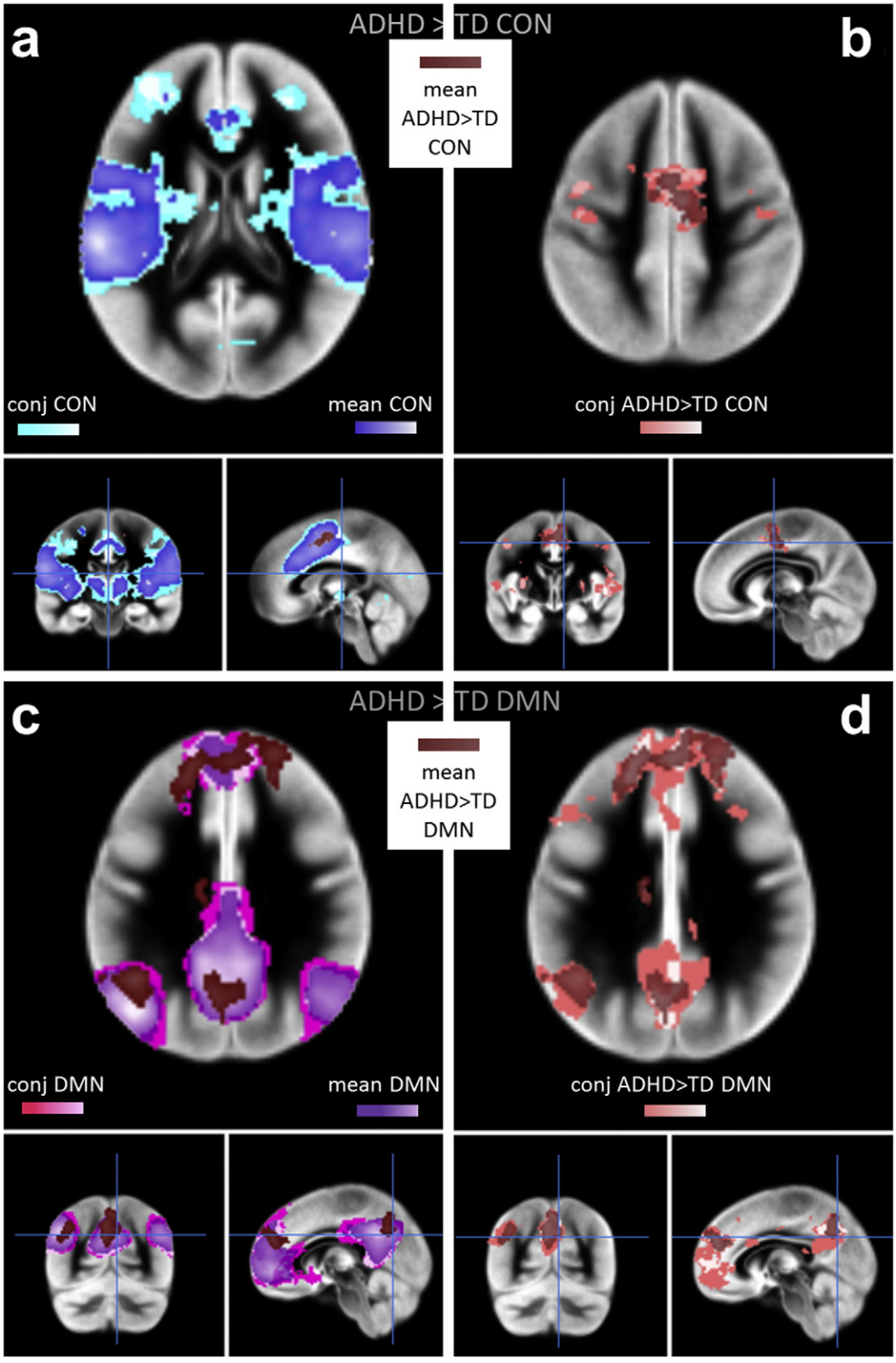

Fig. 1. Regions that have group differences in connectivity for the CON and DMN. Panels a and b show group differences for the CON. Panels c and d show group differences for the DMN. Regions with connectivity that is significantly greater than zero for the mean TD CON maps are displayed in royal blue and for the mean TD DMN maps in purple. The group differences for the mean network maps are displayed in burgundy. The conjunction maps are displayed for the TD CON in cyan blue and for the TD DMN in pink. Panels b and d show the group differences for the mean network maps (in burgundy) overlaid on the conjunction maps of the group differences (in salmon). The group difference conjunction maps display those voxels that had significantly different connectivity between the two groups for several seed maps in the network (i.e. 3–5 in the CON and 2–3 in the DMN).

Table 2
Regions with significant group differences in connectivity with the CON and DMN.

Contrast	Behavior	Region	Hemisphere	BA	*p*-Value	Size	*Z*-value	x	y	z
ADHD > TD	—	Supplementary motor area	Both	24/6	0.005	687	3.85	12	−10	44
CON		Middle cingulate gyrus					3.74	8	−4	60
							3.55	−10	0	42
ADHD > TD	—	Superior frontal gyrus	Both	9/10/32	0.000	1780	5.37	−12	44	40
		Superior medial frontal gyrus					4.27	−6	48	16
		Anterior cingulate gyrus/middle frontal gyrus					4.25	−2	48	26
		Inferior orbital frontal cortex	Left	38/47	0.010	610	4.63	−32	22	−28
		Superior temporal pole					4.3	−46	20	−12
							3.95	−40	28	−8
		Precuneus	Both	7/31	0.001	935	4.51	0	−58	40
							3.9	−6	−62	30
							3.74	2	−66	50
		Angular gyrus	Left	39	0.006	661	4.18	−44	−56	34
							4.04	−48	−52	28
							3.99	−38	−66	40

3.3.2. Differential brain–behavior associations for the two groups

For the CON, connectivity with a region of the MPFC was differentially associated with ISV in the two groups (Fig. 3 and Table 4). This MPFC region encompassed the superior frontal gyrus, superior medial frontal gyrus, the anterior cingulate cortex, and the middle frontal gyrus (BA 9/32/10). Greater anti-correlation between the CON and this MPFC region was associated with lower ISV in the ADHD group, but higher ISV in the TD group. A left cerebellar region showed the opposite brain–behavior association for the two groups. This region spanned lobule VI and lobule VIIA-Crus I of the left cerebellum. Greater connectivity between the CON and this region was associated with lower ISV in the ADHD group, but higher ISV in the TD group.

For the DMN, connectivity with two regions of the dMFC had group differences in their associations with ISV (Fig. 4 and Table 4). The first was a more dorsal region spanning the bilateral supplementary motor area (SMA) and the superior frontal and middle frontal gyrus (BA 6). The second region included the middle cingulate gyrus (BA 24/32) and SMA (BA 6). For both of these regions, greater connectivity with the DMN was associated with higher ISV in the ADHD group, but lower ISV in the TD group. The dMFC is a node of the CON, and therefore, this differential ISV association provides evidence that CON-DMN connections differentially support attention in the two groups. One region spanning the bilateral cuneus and the superior and middle occipital gyrus (BA 18/19) also showed a differential association between the two groups. Greater anti-correlation between the DMN and this occipital region was associated with lower ISV in the TD group, but showed no significant association in the ADHD group.

For the DMN, two regions had differential brain–behavior associations with Tau for the two groups. The first region was an area of the dMFC that spanned the anterior cingulate, superior medial frontal, and middle cingulate cortices (BA 32/9/24). This region mainly overlapped with CON regions, but also showed some overlap with the DMN at its anterior boundary. The second region was an area of the left parietal cortex that spanned the inferior parietal lobule and SMG (BA 40). Greater DMN anti-correlation with both of these regions was associated with lower Tau in the ADHD group and higher Tau in the TD group. Differential brain–behavior associations for these two regions provide further support that CON-DMN connections differentially support attentional control in the two groups.

Conjunction analyses revealed overlap in multiple seed maps for those regions displaying differential brain–behavior associations for the two groups. Significant differential brain–behavior associations were found for most network seed maps (i.e. 3–5 seed maps for the CON and 2–3 seed maps for the DMN) in regions that overlapped with those found in the mean network maps (Figs. 3 and 4). This was the case for all regions with differential brain-behavior associations except the left cerebellar region in which connectivity with the CON was differentially associated with ISV for the two groups (Fig. 4a and 4c). Examination of the results for the component seed maps revealed that this differential association in the two groups was significant in the left anterior insula and anterior cingulate maps. A subthreshold cluster was identified for each of the other cingulo-opercular seed region maps. Therefore, while this differential association was not significant in all of the CON seed maps, there was a weak differential association for all of the network seed maps.

3.4. Follow-up analyses

3.4.1. Follow-up examination of regions identified in brain–behavior analyses

Full-brain analyses revealed that attentional control was generally supported by between-network connections. To confirm that those regions with significantly different brain–behavior associations for the two groups were indeed between-network connections, mean connectivity values for each region were extracted both within the mean CON and mean DMN statistical maps. *t*-Tests were then performed to determine whether connectivity with each network was significantly different from 0. In addition, *t*-tests were performed to determine whether connectivity was greater within the CON map than within the DMN map or vice versa. The results are summarized in Table S2. For most of the regions identified in the full-brain behavioral analysis, the results supported the conclusion that these were between-network connections. Only the MPFC–DMN connection that was differentially associated with Tau, was not significantly more connected for either network (i.e. this region was marginally more connected with the DMN than CON in the ADHD group ($p < 0.037$, uncorrected); and was not significantly more connected with either network in the TD group). Although this region displayed a similar brain–behavior association to that of the other between CON–DMN regions identified, its network affiliation was not as clearly identifiable as that of the other regions. It may be that this region is a transition zone between the two networks. It lies between the MPFC region in which between-network connectivity with the CON was differentially associated with ISV and the two dMFC regions in which between-network connectivity with the DMN was differentially associated with ISV. Although this region has a similar relationship with attentional control to that of the nearby dMFC regions, it is located on the boundary of the two networks.

For those regions with differential brain–behavior associations in the full-brain analysis, multiple regression was performed to determine whether a number of covariates could account for the association with attentional control. This was done in each group separately with the mean region connectivity as the dependent variable and the

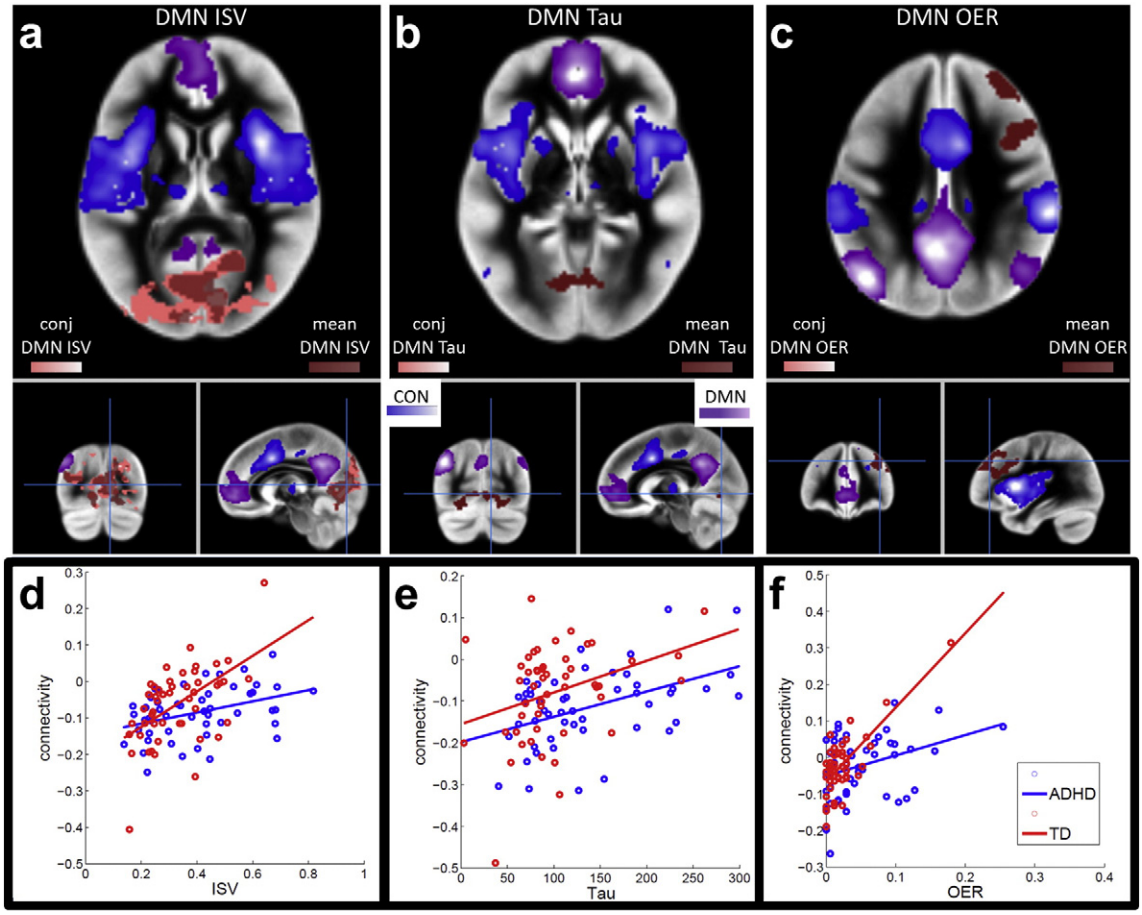

Fig. 2. Regions that have significant brain–behavior associations in both groups for the CON and DMN. All brain–behavior associations are overlaid on the mean TD CON maps (in royal blue) and mean TD DMN maps (in purple). The regions with significant associations between connectivity and attentional control are displayed in burgundy. The brain–behavior conjunction maps (in salmon) display those voxels that had significant associations with attentional control for several seed maps in the network (i.e. 3–5 in the CON and 2–3 in the DMN). Panels a, b, and c display those regions that had associations with ISV, Tau, and OER, respectively. The corresponding panels below plot the average connectivity in the region with significant brain–behavior associations (in burgundy) and attentional control values for each subject. The regression fit lines are plotted in blue for the ADHD group and in red for the TD group. ISV = intra-subject variability, OER = omission error rate.

appropriate behavioral variable (ISV, Tau, or OER) in addition to Total PANESS, a measure of children's motor control abilities, WMI, FSIQ, age, and four motion variables as independent variables. The standardized beta coefficient and *p*-value for the attention control variable and full-model R and p-value are displayed in Table S3. For all models, the attentional control measure was the most significant independent variable in the model and the standardized beta coefficients had opposite signs for the two groups. In most cases, the attention control variable continued to have a highly significant relationship with mean connectivity in the region even when controlling for all other variable in the model. The only case in which the attentional control variable no longer had a significant effect in the multiple regression models was in the ADHD group for the CON–MPFC region. The brain–behavior association with ISV was still in the opposite direction for the two groups and was highly significant for the TD group. However, the relationship was only a trend ($p < 0.079$) for ISV in the ADHD group. Therefore, the additional covariates mitigated this particular brain–behavior association in the ADHD group, but the differential association between the two groups was still robust. For the differential association of DMN–occipital connectivity with ISV in the two groups, the effect was likewise in the

Table 3
Regions with significant brain–behavior associations within both groups for the CON and DMN.

Contrast	Behavior	Region	Hemisphere	BA	*p*-Value	Size	*Z*-value	x	y	z
Both groups DMN	ISV	Lingual gyrus/calcarine sulcus	Both	18/19/30	0.000	5121	4.31	22	−60	8
		Cuneus/superior occipital gyrus		17/7/31			4.28	20	−70	28
		Middle occipital gyrus					4.21	20	−54	2
		Fusiform gyrus								
	Tau	Lingual gyrus/fusiform gyrus	Both	18/19	0.006	660	3.69	6	−70	−4
							3.21	−26	−66	−12
							3.15	18	−70	−8
	OER	Middle frontal gyrus	Right	9	0.000	1305	4.34	34	28	20
		Inferior frontal gyrus opercularis					4.23	50	14	42
		Inferior frontal gyrus triangulas					4.16	34	22	44

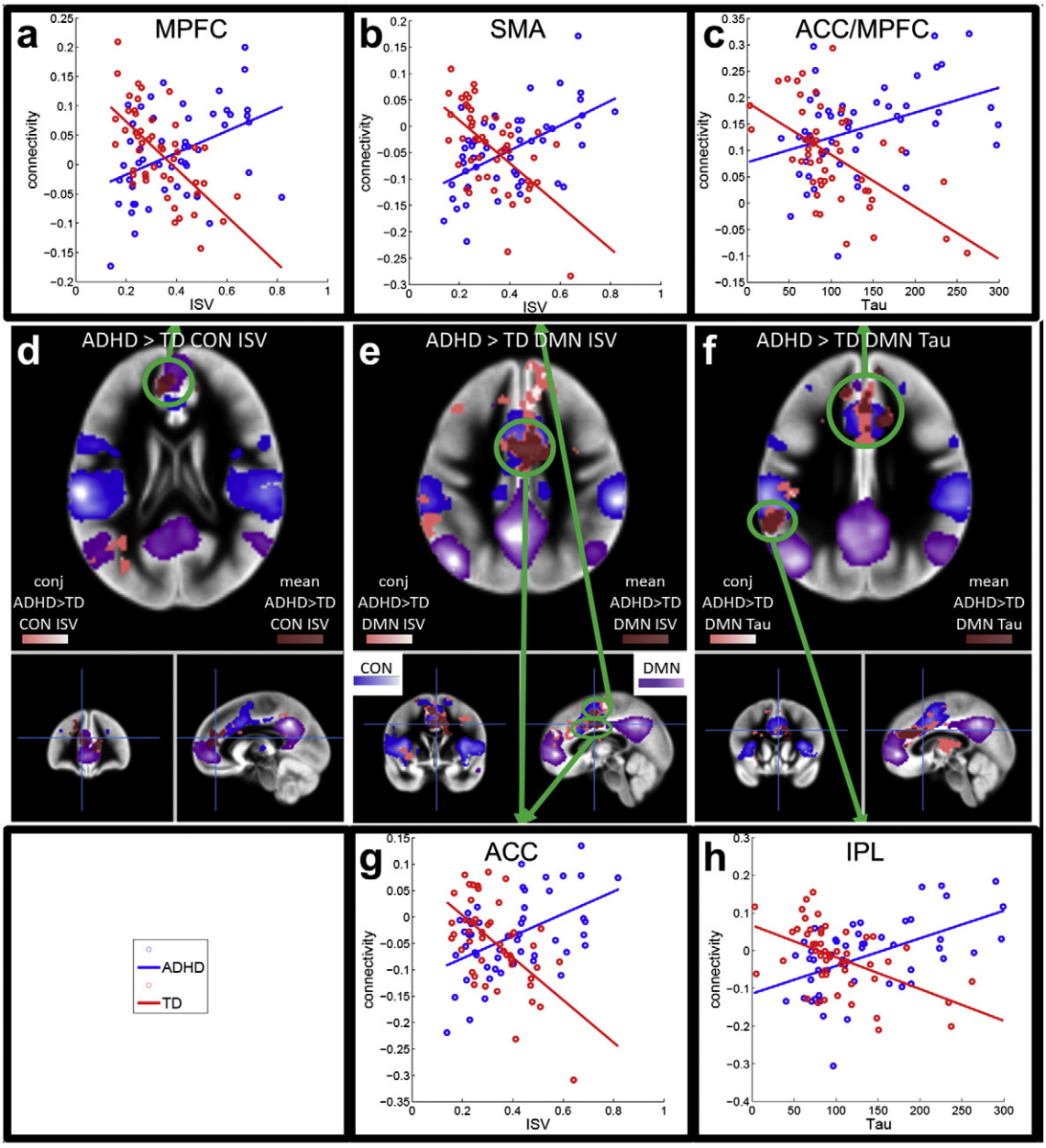

Fig. 3. Regions that have significantly different brain–behavior associations in the two groups (ADHD > TD) for the CON and DMN. All brain–behavior associations are overlaid on the mean TD CON maps (in royal blue) and mean TD DMN maps (in purple). The regions with significant associations between connectivity and attentional control are displayed in burgundy. The brain–behavior conjunction maps (in salmon) display those voxels that had significant associations with attentional control for several seed maps in the network (i.e. 3–5 in the CON and 2–3 in the DMN). Panels d, e, and f display those regions with associations between CON connectivity and ISV, DMN connectivity and ISV, and DMN connectivity and Tau, respectively. The corresponding panels above and below plot the average connectivity in the region with significant brain–behavior associations (in burgundy) and attentional control values for each subject. The regression fit lines are plotted in blue for the ADHD group and in red for the TD group. MPFC = medial prefrontal cortex, SMA = supplementary motor area, ACC = anterior cingulate cortex, IPL = inferior parietal lobule, ISV = intra-subject variability.

opposite direction for the two groups, but not significant in the ADHD group. In this case, the inclusion of additional covariates did not change the effect since this region only displayed a significant brain–behavior association in the TD group in the original full-brain analysis.

3.4.2. Associations with mean network connectivity

Network connectivity values were extracted across the CON and DMN for several reasons. First, it was assessed whether the between-network associations with attentional control were specific to those regions identified in the full-brain analyses or whether they were network-wide. Second, to determine whether greater CON–DMN anti-correlation may compensate for increased within-network DMN connectivity, simple regression was performed for average between CON–DMN connectivity and average within-network DMN connectivity in each group. Third, to assess whether stimulant medication plays a role in brain–behavior associations, children on and off stimulant medication were examined.

To address the first point, associations with mean between CON–DMN connectivity and attentional control were examined. For the ADHD group, between-network connectivity was significantly associated with the first two behavioral variables (ISV: $R = 0.393$, $p = 0.0048$, Tau: $R = 0.348$, $p = 0.0134$) and was associated at trend level for OER ($R = 0.262$, $p = 0.0661$); however in the TD group, none of these associations held (ISV: $R = -0.116$, $p = 0.4231$, Tau: $R = 0.014$, $p = 0.9229$,

Table 4
Regions with significantly different brain–behavior associations for the two groups for the CON and DMN.

Contrast	Behavior	Region	Hemisphere	BA	*p*-Value	Size	*Z*-value	x	y	z
ADHD > TD CON	ISV	Superior gyrus	Left	9/32/10	0.000	939	3.85	−18	38	32
		Superior medial frontal gyrus					3.74	−28	20	34
		Middle frontal gyrus/anterior cingulate gyrus					3.55	−30	18	42
TD > ADHD CON	ISV	Cerebellum, Crus I lobule/6th lobule	Left		0.004	691	4.07	−30	−50	−36
							4.05	−16	−66	−26
							3.94	−36	−60	−34
ADHD > TD DMN	ISV	Supplementary motor area	Both	6	0.001	923	4.22	20	−16	52
		Superior frontal gyrus/middle frontal gyrus					4.11	4	−12	62
		Precentral gyrus					4.11	24	−16	66
		Middle cingulate gyrus/	Both	24/32/6	0.000	1071	4.16	−2	2	38
		Supplementary motor area					3.76	8	4	36
							3.52	0	0	52
	Tau	Anterior cingulate cortex	Both	9/32/24	0.003	719	3.97	0	28	24
		Superior medial frontal gyrus					3.73	2	38	24
		Middle cingulate cortex					3.67	14	20	30
		Inferior parietal lobule	Left	40	0.002	759	3.89	−60	−46	34
		Supramarginal gyrus					3.72	−54	−48	18
							3.64	−38	−36	48
TD > ADHD	ISV	Cuneus/superior occipital gyrus	Both	18/19	0.004	691	4.25	18	−82	28
		Middle occipital gyrus					3.52	28	−70	24
							3.51	24	−84	22

OER: $R = -0.031$, $p = 0.8328$). This confirms that stronger between CON–DMN anti-correlation is associated with better attentional control in the ADHD group. Although these brain–behavior associations were not significant in the TD group, the direction of the relationship was in the opposite direction for ISV and OER in the two groups.

To address the second point, regression was performed with average between-network connectivity as a dependent variable and average within-network connectivity for the CON and DMN as the independent variable for each group. It was found that for the ADHD group, between-network connectivity was significantly associated with within-DMN connectivity ($R = -0.336$, $p = 0.0172$) and was associated with within-CON connectivity at a trend level ($R = -0.263$, $p = 0.0653$); however these associations were not present in the TD group (DMN: $R = -0.168$, $p = 0.2437$, CON: $R = 0.067$, $p = 0.6455$). In addition, the association of within and between-network connectivity suggests that those individuals with ADHD that have stronger CON–DMN anti-correlation also tend to have stronger within-network connectivity particularly within the DMN.

To examine the role of medication status on associations with between CON–DMN connectivity three matched groups were compared: a medicated ADHD group, a medication naïve ADHD group, and a TD group (Table S4). The results are reported in Table S5. For the medicated ADHD group, between CON–DMN connectivity was associated with within-network DMN connectivity ($R = -0.678$, $p = 0.0055$), but not within-network CON connectivity ($R = -0.353$, $p = 0.1963$). In addition, between-network connectivity was significantly associated with all three behavioral variables (ISV: $R = 0.586$, $p = 0.0216$; Tau: $R = 0.630$, $p = 0.0119$; OER: $R = 0.546$, $p = 0.0354$). For the medication-naïve ADHD group, between-network connectivity was associated with within-DMN connectivity at a trend level ($R = -0.484$, $p = 0.0672$) and was significantly associated with within-CON connectivity ($R = -0.718$, $p = 0.0026$); however, it was not significantly associated with any of the behavioral variables (ISV: $R = 0.071$, $p = 0.8008$; Tau: $R = 0.032$, $p = 0.9086$; OER: $R = 0.124$, $p = 0.6600$). For the TD group, between-network connectivity was associated with ISV ($R = -0.535$, $p = 0.04$). This relationship was in the opposite direction of that seen in the medicated ADHD group. Between-network connectivity was not associated with within-network connectivity for either network (DMN: $R = -0.070$, $p = 0.8047$; $R = 0.043$, $p = 0.8784$) or with the other attentional control variables (Tau: $R = -0.397$, $p = 0.1429$; OER: $R = 0.031$, $p = 0.9135$).

4. Discussion

The current study examined full-brain connectivity with the CON and DMN in children with ADHD and TD controls. Children with ADHD had hyper-connectivity within both networks. The dMFC, in particular, was more connected with the rest of the CON in the ADHD group, which is consistent with previous findings that this region has atypical function (Bush, 2010; Castellanos et al., 2008; Shaw et al., 2013; Tian et al., 2006). For the DMN, hyper-connectivity was found across several network regions, consistent with previous hypotheses that atypical DMN connectivity contributes to inattention (Castellanos et al., 2008; Sonuga-Barke and Castellanos, 2007).

Full-brain associations between connection strength and attentional control were examined for the two networks. Attentional control was assessed using summary measures of participant response variability and omission errors during a Go/No-go task performed outside of the scanner. Therefore, these analyses examined connections that support trait differences in attentional control abilities rather than directly examining state changes in connectivity that support attentional control performance.

A number of connections, particularly those between the DMN and task positive regions other than the CON, were commonly associated with attentional control abilities in the two groups. Greater anti-correlation between the DMN and visual cortex was associated with lower response variability in both groups; while greater anti-correlation between the DMN and right lateral frontal cortex was associated with lower omission errors in both groups. Differential brain–behavior associations for the two groups were found for a separate set of DMN–visual connections and a number of CON–DMN connections. Greater anti-correlation in the DMN–visual connections supported better attention, but only in the TD group. On the other hand, greater anti-correlation in the CON–DMN connections supported better attention in the ADHD group, but worse attention in the TD group. These brain–behavior relationships were robust even when controlling for other potentially-related behavioral and nuisance variables (i.e. working memory abilities, motor control abilities, general intelligence, age, and motion artifact).

4.1. Altered network function in ADHD

The finding that connections within the CON and within the DMN are more connected in the ADHD group is consistent with some

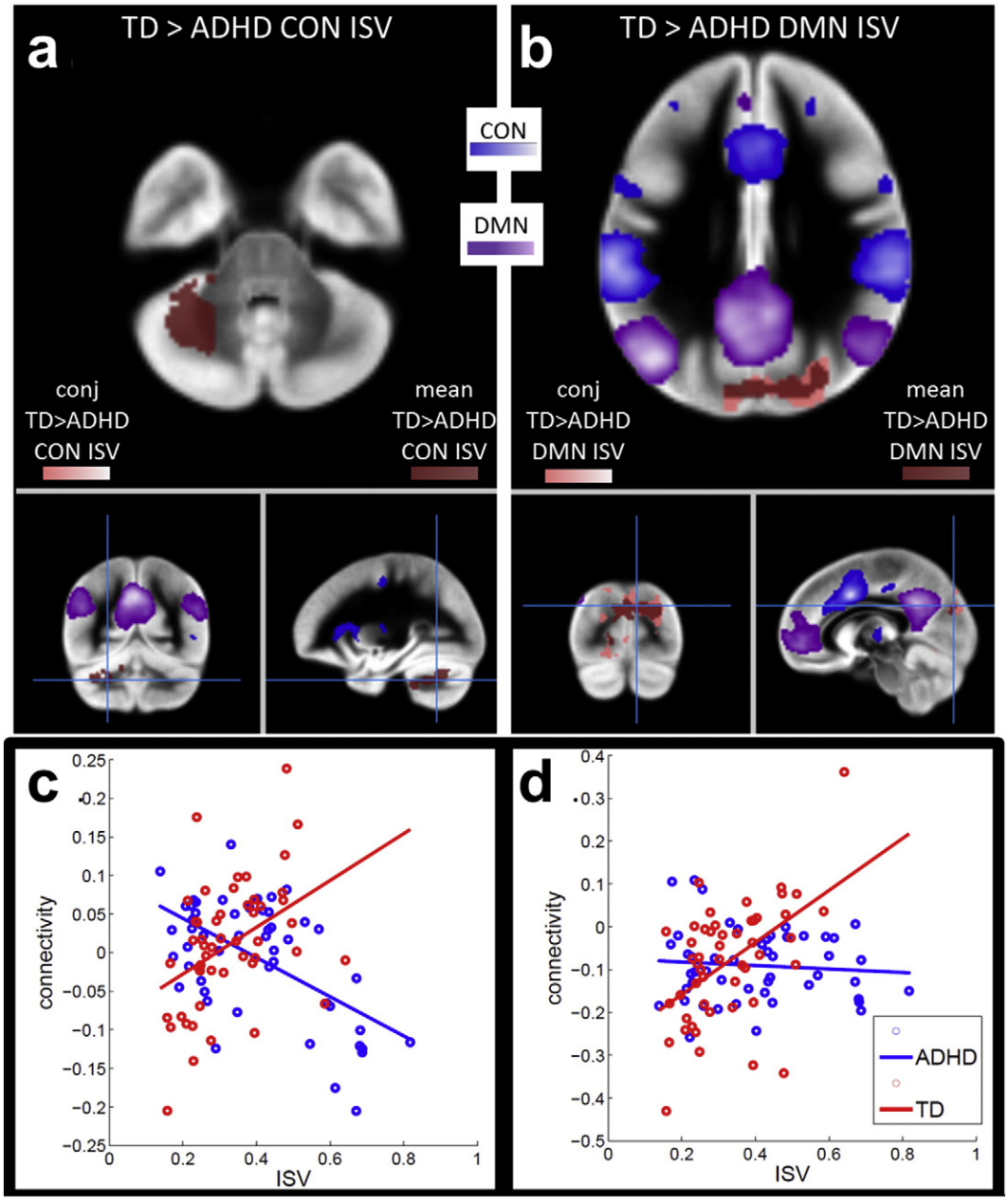

Fig. 4. Regions that have significantly different brain–behavior associations in the two groups (TD > ADHD) for the CON and DMN. All brain–behavior associations are overlaid on the mean TD CON maps (in royal blue) and mean TD DMN maps (in purple). The regions with significant associations between connectivity and attentional control are displayed in burgundy. The brain–behavior conjunction maps (in salmon) display those voxels that had significant associations with attentional control for several seed maps in the network (i.e. 3–5 in the CON and 2–3 in the DMN). Panels a and b display those regions that had associations with CON connectivity and ISV (panel a), and DMN connectivity and ISV (panel b), respectively. The corresponding panels below plot the average connectivity in the region with significant brain–behavior associations (in burgundy) and attentional control values for each subject. The regression fit lines are plotted in blue for the ADHD group and in red for the TD group. ISV = intra-subject variability.

(McCarthy et al., 2013; Sun et al., 2012; Tian et al., 2006), but not all findings (Castellanos et al., 2008; Fair et al., 2010; Uddin et al., 2008). This discrepancy may be due to demographic and/or methodological factors between studies. The current study used samples that were well-matched for gender, handedness, age, PRI, VCI, and scan motion. In addition, the ADHD sample was recruited to have no concurrent comorbidities (with the exception of oppositional defiant disorder), learning disorders, or other neurological disorders.

Atypical DMN connectivity has been previously associated with inattention (Castellanos et al., 2008, 2009) and therefore, DMN hyper-connectivity could contribute to ADHD-related deficits in attentional control. That is, even though brain–behavior associations were not found for the within-network DMN connections, DMN hyper-connectivity could contribute to group differences in attentional control. In that case, children with ADHD would have significantly worse attentional control abilities due to a predominance of self-reflective thought which leads to increased interference during cognitive control tasks. However, we found evidence that DMN hyper-connectivity did not result in inattention. While no direct association was found for within-network DMN connectivity and attentional control, those children with ADHD that had greater CON–DMN antagonism tended to have stronger connectivity within the DMN. Therefore, greater network integrity within the DMN does not appear to result in worse attentional control, but instead may be a by-product of mechanisms to cope with inattention. In support of this view, this effect was seen only in those children that took stimulant medications. In medicated children with ADHD, increased CON–DMN

anti-correlation was associated with better attentional control and increased hyper-connectivity within the DMN; however it was not associated with either in non-medicated children with ADHD or TD children. More discussion of the role of stimulant medication is included in Section 4.5 below.

4.2. Circuitry supporting attentional control

The current study found that for both groups, attentional control abilities were largely supported by between-network connections. Between-network connectivity was determined based on spatial overlap with the CON or DMN. For many children, the identified between-network connections were in fact positive and not negative (e.g. average between CON–DMN Z-transformed correlation values ranged from −0.197 to 0.0843). For those connections identified as supporting attentional control in both of the groups, greater anti-correlation promoted better attentional control. This was the case for both of the DMN-occipital regions that were associated with ISV and Tau for the two groups, as well as the DMN-right lateral frontal region associated with OER for the two groups. Interestingly, ISV and Tau were supported by DMN connections to a region of the occipital cortex that spatially overlapped for both measures. The ISV measure was associated with a broader region of occipital cortex, which extended dorsally into the Calcarine Sulcus, Cuneus, and Middle and Superior Occipital Gyri, than the Tau measure. This confirms that both ISV and Tau are related constructs and are supported by the same neural pathways. OER, on the other hand, was supported by a distinct set of connections; consisting of DMN-right lateral frontal between-network connections. This finding suggests that omission errors are not simply an extreme case of Tau (i.e. trials in which the participant waited so long for a response that no response was executed). Instead, these behavioral measures may reflect different aspects of task control. ISV and Tau may be related to the efficiency of perceptual decision processes (i.e. DMN suppression by visual cortex); whereas OER may be related to the efficiency of task decision processes (i.e. DMN suppression by lateral frontal cortex).

In addition to those between-network connections that commonly supported attentional control in both groups, a number of connections, mostly between the CON and DMN, differentially supported attentional control in the two groups. In the ADHD group, all of the identified CON–DMN connections showed a similar brain–behavior relationship as those connections mentioned above (i.e. greater between-network anti-correlation was related to better attentional control). However, in the TD group, those children with greater between CON–DMN anti-correlation had worse attentional control. Therefore, greater CON–DMN antagonism is adaptive for children with ADHD, but maladaptive for TD children. The relationship found in the ADHD group is not consistent with the interpretation that DMN hyper-connectivity leads to a predominance of self-reflective thought and attention lapses. If that were the case, DMN hyper-connectivity would be associated with attention lapses and decreased, not increased, CON-DMN antagonism.

Another possible reason that CON–DMN connections differentially support attentional control in the two groups is that CON–DMN antagonism may only support attentional control as an alternate mechanism when it is not well-supported by DMN–occipital antagonism. In this case, TD children with good attentional control do not need to recruit the CON for task performance, and therefore, exhibit less CON–DMN antagonism at rest. In children with ADHD, good attentional control may not be as well-supported by antagonism between the DMN and occipital regions, and therefore, may rely on antagonism between CON and DMN regions instead. There are two pieces of evidence to support this claim in the current study. First, the current results identified an occipital region in which greater anti-correlation with the DMN was associated with better attentional control in TD children, but was not associated with attentional control in children with ADHD. Second, for those DMN–occipital connections that supported attentional control in both groups, the strength of the brain–behavior relationship was weaker in children with ADHD. Therefore, unlike TD children, who rely primarily on DMN–occipital antagonism for attentional control; children with ADHD, additionally, need to rely on CON–DMN antagonism for attentional control. Support for this account comes from the finding that TD children with increased DMN–occipital anti-correlation also had decreased CON–DMN anti-correlation; however, no such association was found in children with ADHD (Fig. 5). Therefore, in children with ADHD, greater CON–DMN antagonism may provide primary support for attentional control. On the other hand, in TD children, suppression of the DMN by CON regions may only occur when occipital regions do not properly suppress the DMN (i.e. in those children with poor attentional control).

4.3. Dysfunction in medial frontal cortex

Both group comparisons of connection strength and brain–behavior associations performed across the full-brain revealed dysfunction in a wide area of the medial frontal cortex in children with ADHD. For a large MPFC region, within-DMN connectivity was stronger in children with ADHD. This region was located within the boundary of the DMN at the dorsal extent of the MPFC, while an even broader area of the MPFC, extending more ventrally, displayed this hyper-connectivity in the conjunction maps. Another medial frontal region, the dMFC, also displayed increased within-network connectivity in the ADHD group. This region clearly showed spatial correspondence with the CON and had increased within-CON connectivity in the children with ADHD.

Behavioral associations likewise revealed dysfunction in a large extent of the medial frontal cortex, with a spatial extent ranging from the MPFC to the dMFC. CON–MPFC connections differentially supported ISV in the two groups. This MPFC region spatially-overlapped with the DMN and had significantly stronger within-DMN connectivity than within-CON connectivity in both groups (Table S2). In addition, dMFC–DMN connections differentially supported ISV for the two groups. These were also identified as between-CON–DMN connections in the two groups. Another medial frontal region was identified in which connectivity with the DMN was differentially associated with Tau in the two groups. This region was spatially positioned between the MPFC–CON and dMFC–DMN regions just mentioned. This region also partially spatially overlapped with both the DMN and CON. Examination of its within-network connectivity revealed that, while its connectivity was significantly greater than 0 for both networks, neither the within-CON nor within-DMN connectivity was stronger. The results suggest that this region may correspond to a transition zone between the two networks. Nonetheless, this dMFC–DMN region had the same association with behavior for the two groups as the other medial frontal regions mentioned (i.e. more anti-correlation with the DMN was associated with better attentional control in the ADHD group, but worse attentional control in the TD group).

The current results suggest that a large area of the medial frontal cortex exhibits dysfunctional connectivity and atypical support of attentional control in children with ADHD. Previous studies have likewise identified the dMFC as a region with atypical function using both task fMRI (Bush et al., 1999; Christakou et al., 2013; Rubia et al., 2014; Suskauer et al., 2008) and resting state connectivity (Castellanos et al., 2008; Sun et al., 2012; Tian et al., 2006). In addition, structural imaging studies have found that this region is atypical in ADHD (Shaw et al., 2013). Therefore, although the current results suggest atypical support of attentional control may be network-wide, occurring across CON–DMN connections more generally, the medial frontal cortex, in particular, clearly plays an integral role in ADHD pathology.

4.4. Network-wide associations

The strength of the full-brain analysis approach was that it was not confined to particular regions or networks. However, from this approach it was not clear whether the CON–DMN associations were network-wide or were particular to the identified regions. Several

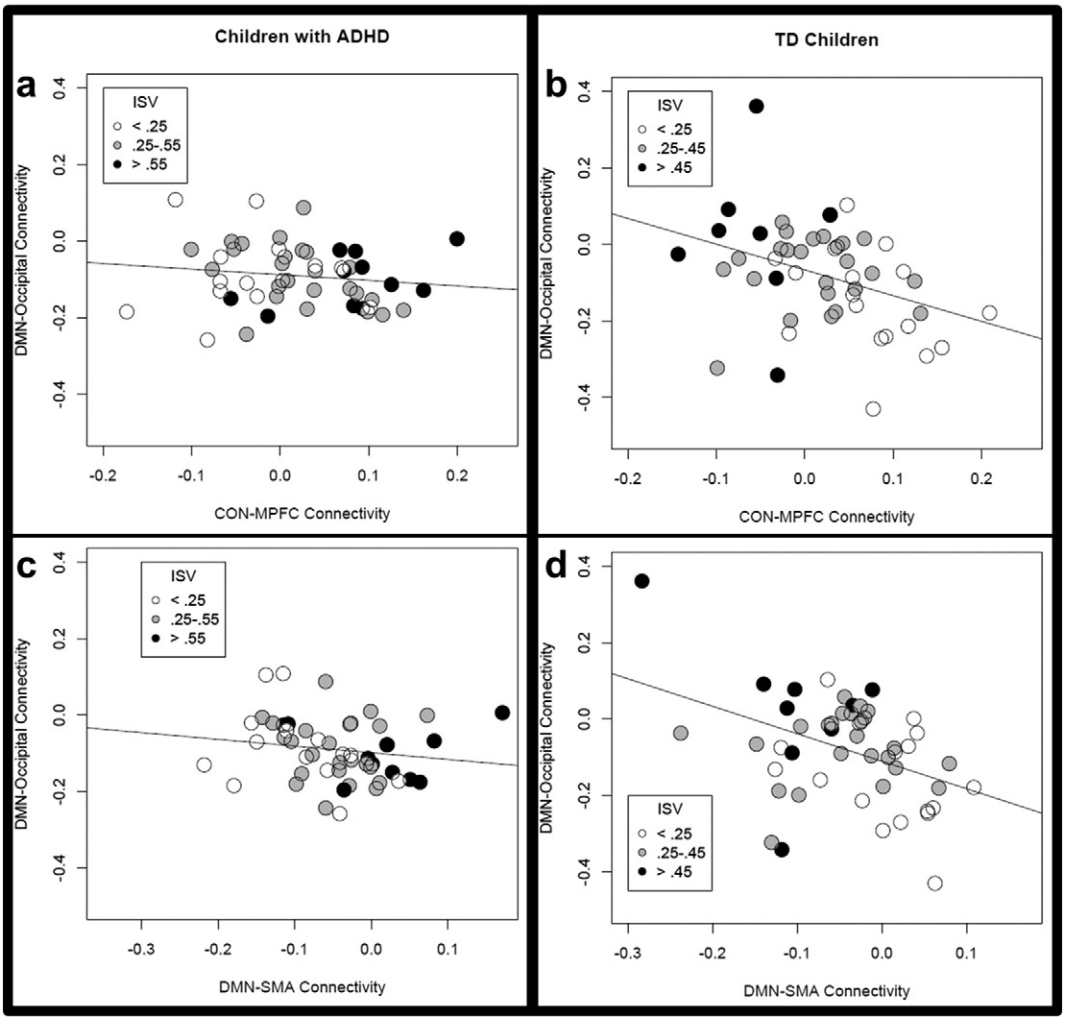

Fig. 5. In TD children, there is an association between DMN-occipital connectivity and between-network connectivity with medial frontal regions (panels b and d). Those children with greater DMN-occipital anti-correlation have less between CON-DMN connectivity and have lower ISV. This relationship does not exist in children with ADHD (panels a and c).

sub-threshold connections were identified that were also consistent with the pattern of differential CON–DMN support of attentional control in the two groups. To determine whether this relationship generalized to connectivity across the two networks, average within-network CON and DMN connectivity and average between CON–DMN connectivity values were extracted for each subject. Again, brain–behavior associations were performed for the three attentional control measures for each group. This analysis revealed that CON–DMN connectivity was significantly associated with both ISV and Tau (and marginally-associated with OER) for the ADHD group, but not the TD group. This suggests that, in children with ADHD, CON–DMN support for attentional control is network-wide.

4.5. Role of medication

A post-hoc analysis was performed to examine whether stimulant medication may play a role in the current findings. Previous studies have suggested that medication may affect dMFC function as well as DMN suppression (Liddle et al., 2011). Therefore, it is not clear whether the current findings may be attributed to ADHD pathology or may be more directly related to medication status. The majority of children with ADHD in the current study (35 out of 50 children) were taking stimulant medication. Although there was a 48-hour wash-out period, the effects of stimulant medications may have lasting effects on network integrity and task performance. Examination of the effect of medication status revealed that CON–DMN antagonism was associated with attentional control only in the medicated ADHD group. CON–DMN support for attentional control may, therefore, be a by-product of stimulant medication and may be due to dopaminergic influence on circuitry supporting attentional control. This interpretation is supported by previous findings that striatal dopamine concentrations affect the degree of DMN suppression during task (Fusar-Poli et al., 2012; Peterson et al., 2009; Tomasi et al., 2009). The results are, however, preliminary and more research should be conducted to determine whether children's baseline (pre-medication) abilities or the wash-out period itself could play a role in the current findings.

5. Conclusions

Children with ADHD exhibit hyper-connectivity both within the CON and the DMN and exhibit atypical support for attentional control by between-network CON–DMN connections. This corroborates previous findings that these systems have altered function in ADHD. Greater CON–DMN antagonism was associated with better attentional control for children with ADHD; however, it was associated with poor attentional control for TD children. Attentional control may be supported by CON–DMN antagonism as a compensatory mechanism since it is not well supported by DMN–occipital antagonism in children with ADHD. While greater DMN–occipital antagonism supported better attentional control in both groups; this relationship was stronger and

was found for a wider area of occipital cortex in TD children. In addition, TD children showed a trade-off between DMN–occipital antagonism and CON–DMN antagonism. Those TD children with greater DMN–occipital antagonism had reduced CON–DMN antagonism and better attentional control. In children with ADHD, there was no such trade-off suggesting that they rely more heavily on CON–DMN antagonism for attentional control.

Acknowledgements

Funding for this research was provided by NIH R01 MH078160, R01 MH085328, and P41 EB015909.

Appendix A. Supplementary data

Supplementary material for this article can be found online at http://dx.doi.org/10.1016/j.nicl.2014.11.011.

References

Adamo, N., Di Martino, A., Esu, L., Petkova, E., Johnson, K., Kelly, S., Castellanos, F.X., Zuddas, A., 2012. Increased response-time variability across different cognitive tasks in children with ADHD. J. Atten. Disord. 18, 434–446. http://dx.doi.org/10.1177/1087054712439419225087759.

Barber, A.D., Caffo, B.S., Pekar, J.J., Mostofsky, S.H., 2013. Developmental changes in within- and between-network connectivity between late childhood and adulthood. Neuropsychologia 51 (1), 156–167. http://dx.doi.org/10.1016/j.neuropsychologia.2012.11.01123174403.

Behzadi, Y., Restom, K., Liau, J., Liu, T.T., 2007. A component based noise correction method (CompCor) for BOLD and perfusion based fMRI. Neuroimage 37 (1), 90–101. http://dx.doi.org/10.1016/j.neuroimage.2007.04.04217560126.

Buckner, R.L., Andrews-Hanna, J.R., Schacter, D.L., 2008. The brain's default network: anatomy, function, and relevance to disease. Ann. N. Y. Acad. Sci. 1124, 1–38. http://dx.doi.org/10.1196/annals.1440.01118400922.

Bush, G., 2010. Attention-deficit/hyperactivity disorder and attention networks. Neuropsychopharmacology 35 (1), 278–300. http://dx.doi.org/10.1038/npp.2009.12019759528.

Bush, G., Frazier, J.A., Rauch, S.L., Seidman, L.J., Whalen, P.J., Jenike, M.A., Rosen, B.R., Biederman, J., 1999. Anterior cingulate cortex dysfunction in attention-deficit/hyperactivity disorder revealed by fMRI and the counting Stroop. Biol. Psychiatry 45 (12), 1542–1552. http://dx.doi.org/10.1016/S0006-3223(99)00083-910376114.

Bush, G., Valera, E.M., Seidman, L.J., 2005. Functional neuroimaging of attention-deficit/hyperactivity disorder: a review and suggested future directions. Biol. Psychiatry 57 (11), 1273–1284. http://dx.doi.org/10.1016/j.biopsych.2005.01.03415949999.

Castellanos, F.X., Kelly, C., Milham, M.P., 2009. The restless brain: attention-deficit hyperactivity disorder, resting-state functional connectivity, and intrasubject variability. Can. J. Psychiatry 54 (10), 665–67219835673.

Castellanos, F.X., Lee, P.P., Sharp, W., Jeffries, N.O., Greenstein, D.K., Clasen, L.S., Blumenthal, J.D., James, R.S., Ebens, C.L., Walter, J.M., Zijdenbos, A., Evans, A.C., Giedd, J.N., Rapoport, J.L., 2002. Developmental trajectories of brain volume abnormalities in children and adolescents with attention-deficit/hyperactivity disorder. JAMA 288 (14), 1740–174812365958.

Castellanos, F.X., Margulies, D.S., Kelly, C., Uddin, L.Q., Ghaffari, M., Kirsch, A., Shaw, D., Shehzad, Z., Di Martino, A., Biswal, B., Sonuga-Barke, E.J., Rotrosen, J., Adler, L.A., Milham, M.P., 2008. Cingulate-precuneus interactions: a new locus of dysfunction in adult attention-deficit/hyperactivity disorder. Biol. Psychiatry 63 (3), 332–337. http://dx.doi.org/10.1016/j.biopsych.2007.06.02517888409.

Castellanos, F.X., Sonuga-Barke, E.J., Scheres, A., Di Martino, A., Hyde, C., Walters, J.R., 2005. Varieties of attention-deficit/hyperactivity disorder-related intra-individual variability. Biol. Psychiatry 57 (11), 1416–1423. http://dx.doi.org/10.1016/j.biopsych.2004.12.00515950016.

Castellanos, F.X., Tannock, R., 2002. Neuroscience of attention-deficit/hyperactivity disorder: the search for endophenotypes. Nat. Rev. Neurosci. 3 (8), 617–628. http://dx.doi.org/10.1038/nrn89612154363.

Christakou, A., Murphy, C.M., Chantiluke, K., Cubillo, A.I., Smith, A.B., Giampietro, V., Daly, E., Ecker, C., Robertson, D., Murphy, D.G., Rubia, K., 2013. Disorder-specific functional abnormalities during sustained attention in youth with attention deficit hyperactivity disorder (ADHD) and with autism. Mol. Psychiatry 18 (2), 236–244. http://dx.doi.org/10.1038/mp.2011.18522290121.

Conners, C.K., Sitarenios, G., Parker, J.D., Epstein, J.N., 1998. The revised Conners' Parent Rating Scale (CPRS-R): factor structure, reliability, and criterion validity. J. Abnorm. Child Psychol. 26 (4), 257–268. http://dx.doi.org/10.1023/A:1022602400621970051 8.

Cortese, S., Ramos Olazagasti, M.A., Klein, R.G., Castellanos, F.X., Proal, E., Mannuzza, S., 2013. Obesity in men with childhood ADHD: a 33-year controlled, prospective, follow-up study. Pediatrics 131 (6). http://dx.doi.org/10.1542/peds.2012-054023690516.

Cousineau, D., Brown, S., Heathcote, A., 2004. Fitting distributions using maximum likelihood: methods and packages. Behav. Res. Methods Instrum. Comput. 36 (4), 742–756. http://dx.doi.org/10.3758/BF03202065551564142 0.

Denckla, M.B., 1985. Revised neurological examination for subtle signs. Psychopharmacol. Bull. 21, 773–800.

Dosenbach, N.U., Fair, D.A., Miezin, F.M., Cohen, A.L., Wenger, K.K., Dosenbach, R.A., Fox, M.D., Snyder, A.Z., Vincent, J.L., Raichle, M.E., Schlaggar, B.L., Petersen, S.E., 2007. Distinct brain networks for adaptive and stable task control in humans. Proc. Natl. Acad. Sci. U.S.A. 104 (26), 11073–11078. http://dx.doi.org/10.1073/pnas.07043201041757692 2.

Epstein, J.N., Hwang, M.E., Antonini, T., Langberg, J.M., Altaye, M., Arnold, L.E., 2010. Examining predictors of reaction times in children with ADHD and normal controls. J. Int. Neuropsychol. Soc. 16 (1), 138–147. http://dx.doi.org/10.1017/S1355617709991111198498 82.

Fair, D.A., Posner, J., Nagel, B.J., Bathula, D., Dias, T.G., Mills, K.L., Blythe, M.S., Giwa, A., Schmitt, C.F., Nigg, J.T., 2010. Atypical default network connectivity in youth with attention-deficit/hyperactivity disorder. Biol. Psychiatry 68 (12), 1084–1091. http://dx.doi.org/10.1016/j.biopsych.2010.07.00320728873.

Fassbender, C., Zhang, H., Buzy, W.M., Cortes, C.R., Mizuiri, D., Beckett, L., Schweitzer, J.B., 2009. A lack of default network suppression is linked to increased distractibility in ADHD. Brain Res. 1273, 114–128. http://dx.doi.org/10.1016/j.brainres.2009.02.07019281801.

Fox, M.D., Snyder, A.Z., Vincent, J.L., Corbetta, M., Van Essen, D.C., Raichle, M.E., 2005. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc. Natl. Acad. Sci. U.S.A. 102 (27), 9673–9678. http://dx.doi.org/10.1073/pnas.050413610215976020.

Fusar-Poli, P., Rubia, K., Rossi, G., Sartori, G., Balottin, U., 2012. Striatal dopamine transporter alterations in ADHD: pathophysiology or adaptation to psychostimulants? A meta-analysis. Am J. Psychiatry 169 (3), 264–272. http://dx.doi.org/10.1176/appi.ajp.2011.1106094022294258.

Garner, A.A., O'Connor, B.C., Narad, M.E., Tamm, L., Simon, J., Epstein, J.N., 2013. The relationship between ADHD symptom dimensions, clinical correlates, and functional impairments. J. Dev. Behav. Pediatr. 34 (7), 469–477. http://dx.doi.org/10.1097/DBP.0b013e3182a39890240420 78.

Gómez-Guerrero, L., Martín, C.D., Mairena, M.A., Di Martino, A., Wang, J., Mendelsohn, A.L., Dreyer, B.P., Isquith, P.K., Gioia, G., Petkova, E., Castellanos, F.X., 2011. Response-time variability is related to parent ratings of inattention, hyperactivity, and executive function. J. Atten. Disord. 15 (7), 572–582. http://dx.doi.org/10.1177/1087054709356379206860 98.

Grayson, D.S., Ray, S., Carpenter, S., Iyer, S., Dias, T.G., Stevens, C., Nigg, J.T., Fair, D.A., 2014. Structural and functional rich club organization of the brain in children and adults. PLoS ONE 9 (2), e88297. http://dx.doi.org/10.1371/journal.pone.008829724505468.

Kelly, A.M., Uddin, L.Q., Biswal, B.B., Castellanos, F.X., Milham, M.P., 2008. Competition between functional brain networks mediates behavioral variability. Neuroimage 39 (1), 527–537. http://dx.doi.org/10.1016/j.neuroimage.2007.08.00817919929.

Kiebel, S.J., Poline, J.B., Friston, K.J., Holmes, A.P., Worsley, K.J., 1999. Robust smoothness estimation in statistical parametric maps using standardized residuals from the general linear model. Neuroimage 10 (6), 756–766. http://dx.doi.org/10.1006/nimg.1999.050810600421.

Krain, A.L., Castellanos, F.X., 2006. Brain development and ADHD. Clin. Psychol. Rev. 26 (4), 433–444. http://dx.doi.org/10.1016/j.cpr.2006.01.00516480802.

Lancaster, J.L., Tordesillas-Gutiérrez, D., Martinez, M., Salinas, F., Evans, A., Zilles, K., Mazziotta, J.C., Fox, P.T., 2007. Bias between MNI and Talairach coordinates analyzed using the ICBM-152 brain template. Hum. Brain Mapp. 28 (11), 1194–1205. http://dx.doi.org/10.1002/hbm.2034517266101.

Leth-Steensen, C., Elbaz, Z.K., Douglas, V.I., 2000. Mean response times, variability, and skew in the responding of ADHD children: a response time distributional approach. Acta Psychol. (Amst.) 104 (2), 167–190. http://dx.doi.org/10.1016/S0001-6918(00)00019-610900704.

Liddle, E.B., Hollis, C., Batty, M.J., Groom, M.J., Totman, J.J., Liotti, M., Scerif, G., Liddle, P.F., 2011. Task-related default mode network modulation and inhibitory control in ADHD: effects of motivation and methylphenidate. J. Child Psychol. Psychiatry 52 (7), 761–771. http://dx.doi.org/10.1111/j.1469-7610.2010.02333.x21073458.

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. J.A.M.A. Psychiatry 70 (12), 1329–1337. http://dx.doi.org/10.1001/jamapsychiatry.2013.21742413273 2.

Muschelli, J., Nebel, M.B., Caffo, B.S., Barber, A.D., Pekar, J.J., Mostofsky, S.H., 2014. Reduction of Motion-related artifacts in resting state fMRI using a CompCor. Neuroimage 96, 22–35. http://dx.doi.org/10.1016/j.neuroimage.2014.03.02824657780.

Nee, D.E., Kastner, S., Brown, J.W., 2011. Functional heterogeneity of conflict, error, task-switching, and unexpectedness effects within medial prefrontal cortex. Neuroimage 54 (1), 528–540. http://dx.doi.org/10.1016/j.neuroimage.2010.08.02720728547.

Peterson, B.S., Potenza, M.N., Wang, Z., Zhu, H., Martin, A., Marsh, R., Plessen, K.J., 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 (11), 1286–1294. http://dx.doi.org/10.1176/appi.ajp.2009.0805072419755575.

Raichle, M.E., MacLeod, A.M., Snyder, A.Z., Powers, W.J., Gusnard, D.A., Shulman, G.L., 2001. A default mode of brain function. Proc. Natl. Acad. Sci. U.S.A. 98 (2), 676–682. http://dx.doi.org/10.1073/pnas.98.2.67611209064.

Reich, W., 2000. Diagnostic interview for children and adolescents (DICA). J. Am. Acad. Child Adolesc. Psychiatry 39 (1), 59–66. http://dx.doi.org/10.1097/00004583-200001000-00017106380 68.

Rubia, K., Alegria, A., Brinson, H., 2014. Imaging the ADHD brain: disorder-specificity, medication effects and clinical translation. Expert Rev. Neurother. 14 (5), 519–538. http://dx.doi.org/10.1586/14737175.2014.90752624738703.

Shaw, M., Hodgkins, P., Caci, H., Young, S., Kahle, J., Woods, A.G., Arnold, L.E., 2012. A systematic review and analysis of long-term outcomes in attention deficit

hyperactivity disorder: effects of treatment and non-treatment. BMC Med. 10, 99. http://dx.doi.org/10.1186/1741-7015-10-9922947230.

Shaw, P., Malek, M., Watson, B., Greenstein, D., de Rossi, P., Sharp, W., 2013. Trajectories of cerebral cortical development in childhood and adolescence and adult attention-deficit/hyperactivity disorder. Biol. Psychiatry 74 (8), 599–606. http://dx.doi.org/10.1016/j.biopsych.2013.04.00723726514.

Sonuga-Barke, E.J., Castellanos, F.X., 2007. Spontaneous attentional fluctuations in impaired states and pathological conditions: a neurobiological hypothesis. Neurosci. Biobehav. Rev. 31 (7), 977–986. http://dx.doi.org/10.1016/j.neubiorev.2007.02.00517445893.

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-naive boys with attention deficit hyperactivity disorder. Psychiatry Res. 201 (2), 120–127. http://dx.doi.org/10.1016/j.pscychresns.2011.07.00122424873.

Suskauer, S.J., Simmonds, D.J., Caffo, B.S., Denckla, M.B., Pekar, J.J., Mostofsky, S.H., 2008. fMRI of intrasubject variability in ADHD: anomalous premotor activity with prefrontal compensation. J. Am. Acad. Child Adolesc. Psychiatry 47 (10), 1141–1150. http://dx.doi.org/10.1097/CHI.0b013e3181825b1f18724253.

Tamm, L., Narad, M.E., Antonini, T.N., O'Brien, K.M., Hawk Jr., L.W., Epstein, J.N., 2012. Reaction time variability in ADHD: a review. Neurotherapeutics 9 (3), 500–508. http://dx.doi.org/10.1007/s13311-012-0138-522930417.

Theiling, J., Petermann, F., 2014. Neuropsychological profiles on the WAIS-IV of ADHD adults. J. Atten. Disord http://dx.doi.org/10.1177/1087054713518241244448224.

Tian, L., Jiang, T., Wang, Y., Zang, Y., He, Y., Liang, M., Sui, M., Cao, Q., Hu, S., Peng, M., Zhuo, Y., 2006. Altered resting-state functional connectivity patterns of anterior cingulate cortex in adolescents with attention deficit hyperactivity disorder. Neurosci. Lett. 400 (1-2), 39–43. http://dx.doi.org/10.1016/j.neulet.2006.02.02216510242.

Tomasi, D., Volkow, N.D., Wang, R., Telang, F., Wang, G.J., Chang, L., Ernst, T., Fowler, J.S., 2009. Dopamine transporters in striatum correlate with deactivation in the default mode network during visuospatial attention. PLoS ONE 4 (6), e6102. http://dx.doi.org/10.1371/journal.pone.000610219564918.

Uddin, L.Q., Kelly, A.M., Biswal, B.B., Margulies, D.S., Shehzad, Z., Shaw, D., Ghaffari, M., Rotrosen, J., Adler, L.A., Castellanos, F.X., Milham, M.P., 2008. Network homogeneity reveals decreased integrity of default-mode network in ADHD. J. Neurosci. Methods 169 (1), 249–254. http://dx.doi.org/10.1016/j.jneumeth.2007.11.03118190970.

Vaurio, R.G., Simmonds, D.J., Mostofsky, S.H., 2009. Increased intra-individual reaction time variability in attention-deficit/hyperactivity disorder across response inhibition tasks with different cognitive demands. Neuropsychologia 47 (12), 2389–2396. http://dx.doi.org/10.1016/j.neuropsychologia.2009.01.02219552927.