THE JOURNAL OF CHILD PSYCHOLOGY AND PSYCHIATRY

ACAMH THE ASSOCIATION FOR CHILD AND ADOLESCENT MENTAL HEALTH

Journal of Child Psychology and Psychiatry **:* (2017), pp **–** doi:10.1111/jcpp.12712

Structural and functional connectivity in children and adolescents with and without attention deficit/hyperactivity disorder

Dienke J. Bos,[1] Bob Oranje,[1] Michelle Achterberg,[2,3] Chantal Vlaskamp,[1] Sara Ambrosino,[1] Marcel A. de Reus,[1] Martijn P. van den Heuvel,[1] Serge A.R.B. Rombouts,[2,3,4] and Sarah Durston[1]

[1]Department of Psychiatry, Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht; [2]Institute of Psychology, Leiden University, Leiden; [3]Leiden Institute for Brain and Cognition (LIBC), Leiden University Medical Center, Leiden; [4]Department of Radiology, Leiden University Medical Center, Leiden, The Netherlands

Background: Attention deficit/hyperactivity disorder (ADHD) has frequently been associated with changes in resting-state functional connectivity, and decreased white matter (WM) integrity. In the current study, we investigated functional connectivity within Default Mode and frontal control resting-state networks (RSNs) in children with and without ADHD. We hypothesized the RSNs of interest would show a pattern of impaired functional integration and segregation and corresponding changes in WM structure. **Methods:** Resting-state fMRI and diffusion-weighted imaging data were acquired from 35 participants with ADHD and 36 matched typically developing peers, aged 6 through 18 years. Functional connectivity was assessed using independent component analysis. Network topology and WM connectivity were further investigated using graph theoretical measures and tract-based spatial statistics (TBSS). **Results:** Resting-state fMRI analyses showed increased functional connectivity in right inferior frontal gyrus (IFG), and bilateral medial prefrontal cortex (mPFC) within the Default Mode and frontal control networks. Furthermore, a more diffuse spatial pattern of functional connectivity was found in children with ADHD. We found no group differences in structural connectivity as assessed with TBSS or graph theoretical measures. **Conclusions:** Resting-state networks show a more diffuse pattern of connectivity in children with ADHD. The increases in functional connectivity in right IFG and bilateral mPFC in children with ADHD may reflect reduced or delayed functional segregation of prefrontal brain regions. As these functional changes were not accompanied by changes in WM, they may precede the development of the frequently reported changes in WM structure. **Keywords:** Attention deficit/hyperactivity disorder; functional connectivity; structural connectivity; Default Mode Network; developmental delay.

Introduction

Attention deficit/hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders, characterized by hyperactive, impulsive, and/or inattentive behaviors that impair the individual's performance in multiple settings (American Psychiatric Association, 2013).

In the past decade, ADHD research has increasingly focused on brain connectivity and has yielded heterogeneous results: during rest, reduced functional connectivity of the Default Mode Network (DMN) has often been reported (Fair et al., 2010; Posner, Park, & Wang, 2014; Qiu et al., 2011), as well as more complicated patterns of increased and decreased connectivity between the DMN and executive control networks (Cao et al., 2009; Fair et al., 2010, 2012; Qiu et al., 2011; Sun et al., 2012) and within limbic and affective systems (Cao et al., 2009; Castellanos, Kelly, & Milham, 2013; Posner et al., 2013; Tian et al., 2006). Studies of the white matter (WM) structure underlying these functional networks have shown similar heterogeneous findings: global WM volume has most often been reported to be decreased, but regional increases and decreases in fractional anisotropy (FA), a commonly used measure of WM microstructural organization or integrity, have been observed throughout the brain (reviewed in van Ewijk, Heslenfeld, Zwiers, Buitelaar, & Oosterlaan, 2012). Most region-of-interest studies have focused on changes in frontostriatal systems because of their role in cognitive control and reward processing (Castellanos & Proal, 2012; Durston, van Belle, & de Zeeuw, 2011). Yet reports of changes in other tracts again suggest there may be more widespread network changes in ADHD.

Many of these findings have been interpreted to reflect an immature pattern of functional connectivity, in line with the maturational delay hypothesis of ADHD (El-Sayed, Larsson, Persson, Santosh, & Rydelius, 2003; Rubia, 2007; Shaw et al., 2007). One of the most notable studies to date showed that ADHD was associated with a trajectory of cortical maturation seemingly similar to controls, but that peak cortical thickness in areas associated with cognitive control and attention was reached up to 5 years later in children with ADHD (Shaw et al., 2007). In terms of connectivity, it has been hypothesized that ADHD is associated with impairments in functional network segregation (as local connections

Conflict of interest statement: No conflicts declared.

weaken with age in typical development) and integration (distant connections typically *strengthen* with age; Fair et al., 2009, 2010; Sripada, Kessler, Fang, et al., 2014). Connections showing a delay in development may therefore (temporarily) remain either too strong or too weak, hypothetically resulting in a pattern of both increases and decreases in resting-state functional connectivity during childhood in ADHD.

Here, we set out to investigate both structural and functional connectivity, specifically of the DMN and frontal control networks, in a sample of young children and adolescents with and without ADHD. We used data-driven, whole brain approaches in order to unify findings from different modalities. We hypothesized that functional connectivity, as assessed with resting-state functional MRI (rs-fMRI), would show an immature, more diffuse pattern in ADHD. Second, we hypothesized there would be corresponding changes in regional WM connectivity and network organization, as assessed with diffusion-weighted imaging (DTI).

Method

Participants

Thirty-five right-handed children and young adolescents with a primary diagnosis of ADHD were recruited through the Department of Psychiatry at the University Medical Center in Utrecht, and through advertising. The clinical diagnosis was confirmed by a qualified researcher using the Diagnostic Interview Schedule for Children – Parent Version (DISC-P; Costello, Edelbrock, & Costello, 1985). The children with ADHD were either medication naïve or using psychostimulant medication (see Table 1). No other forms of psychoactive medication were permitted in this study. The children with ADHD that were on stimulant medication were instructed not to take their medication 24 hr prior to the MRI scan.

Thirty-six typically developing right-handed subjects were recruited through local primary schools (Bos et al., 2014). All subjects were screened by phone interview, to confirm the absence of major neurological or psychiatric disorders, as well as the absence of psychiatric conditions in their first-degree relatives. None of the control subjects were using any form of psychoactive medication. Parents of the typically developing subjects also participated in a DISC-P interview session to confirm the absence of any psychiatric condition in the subject.

Subjects were matched for age, gender, Tanner stage, and socioeconomic status (see Table 1). Tanner stage was assessed in order to preclude group differences in pubertal development. Intelligence quotient was assessed for all participants using the abbreviated version of the Wechsler Intelligence Scale for Children (WISC-III; Kort et al., 2005), using four subtests. Finally, the parent-rated Child Behavior Checklist (CBCL) was collected for all participants to measure the severity of ADHD symptoms. Differences on demographic variables were assessed using the appropriate Students' *t*- or chi-square tests.

The study was approved by the Ethics Committee of the University Medical Centre Utrecht, The Netherlands, and took into account the ethical principles for medical research involving human subjects as stated in the declaration of Helsinki (amendment of Washington, 2002). Written and oral information was provided, after which written informed consent was obtained from all parents. All children and adolescents provided written and/or verbal assent.

MRI acquisition

All participants aged 12 years or under participated in a mock MRI-scanner practice session in our laboratory, in order to reduce potential anxiety and the risk of motion artifacts (Durston et al., 2009). Children only participated in the actual MRI scan after a successful practice session.

Data were acquired using a 3.0T Phillips Achieva MR scanner (Philips Medical Systems, Best, The Netherlands). First, a high-resolution T1-weighted image was acquired (TR/TE = 10/4.6, flip angle = 8°, matrix 304 × 299, voxel size 0.75 × 0.75 × 0.8). Furthermore, two diffusion weighted imaging (DWI) sets of 30 weighted diffusion scans (b = 1,000 s/mm^2) and five unweighted B0 scans (b = 0 s/mm^2) were acquired, of which the second diffusion set was acquired with a reversed k-space read-out direction (DWI-MR using parallel imaging SENSE p-reduction 3, TR/TE = 7,035/68, EPI factor 35; FOV 240 × 240 mm, voxel size 2 mm isotropic, no gap, 75 slices). During the acquisition of the T1- and diffusion-weighted images, all participants watched a movie.

Finally, resting-state functional images were collected in a single block of 294 dynamics with a 2D-EPI SENSE sequence (TR/TE = 2,000/35, flip angle = 70°, matrix 68 × 66, voxel size 3 × 3 × 3.5), with a total duration of 10 min. Participants were instructed to focus on a fixation cross during the procedure.

Resting-state analyses: independent component analysis

Resting-state fMRI data were preprocessed using SPM8 (Wellcome Dept. of Cognitive Neurology, www.fil.ion.ucl.ac.uk) using a standard preprocessing pipeline (Bos et al., 2014).

Table 1 Demographic and clinical characteristics of the sample

	ADHD (N = 35)	TDC (N = 36)	p
Age, mean ± *SD* (range)	11.2 ± 2.6 (7.5–16.4)	12.1 ± 2.2 (6.4–15.4)	.111
Gender (M/F)	26/9	29/7	.527
Total IQ, mean ± *SD* (range)	105.5 ± 15.9 (83–141)	109.6 ± 16.4 (80–145)	.285
Parental education (years), mean ± *SD*	13.1 ± 4.0	14.3 ± 2.0	.131
Tanner stage, mean ± *SD*	1.8 ± 1.3	2.2 ± 1.4	.148
CBCL attention problems *T*-score, mean ± *SD*	64.7 ± 6.7	52.4 ± 2.6	<.001
CBCL internalizing problems *T*-score, mean ± *SD*	54.6 ± 9.1	45.8 ± 8.8	<.001
CBCL externalizing problems *T*-score, mean ± *SD*	58.6 ± 9.5	41.5 ± 7.5	<.001
Comorbid disruptive disorders (ODD)	4/35	–	
Use of psychostimulant medication	27/35	–	

ADHD, attention deficit/hyperactivity disorder; CBCL, Child Behavior Checklist; IQ, intelligence quotient; ODD, oppositional defiant disorder; *SD*, standard deviation; TDC, typically developing children.

Twelve children with ADHD and two typically developing children (TDC) were excluded due to excessive motion (Table S1). There were no between-group differences in absolute subject motion [$F(53, 3) = 0.777$, $p = .512$], framewise displacement or the number of frames repaired (Table S2). Resting-state preprocessing and motion correction are described in detail in the Appendix S1.

Functional connectivity was assessed in FSL (Smith et al., 2004) using independent component analysis by means of the multivariate exploratory linear decomposition into a fixed set of 25 independent components (MELODIC; Beckmann, DeLuca, Devlin, & Smith, 2005; Beckmann & Smith, 2004), followed by a dual regression approach (Filippini et al., 2009).

Selection of networks. Five components were discarded from statistical analysis as they represented nonneuronal noise, such as cerebrospinal fluid and WM. The remaining 20 components were classified as containing BOLD connectivity of interest (Figures S1 and S2). For the within-network statistical analyses, we selected nine components (Figure 1A) that showed spatial similarity to previously described resting-state networks (RSNs; Laird et al., 2011) including frontal and striatal regions of interest, and the DMN.

Between-group differences in within-network functional connectivity in the nine selected RSNs were tested using a general linear model with 5,000 permutations in Randomise (FMRIB Software Library Randomise v2.9), with age, gender, and

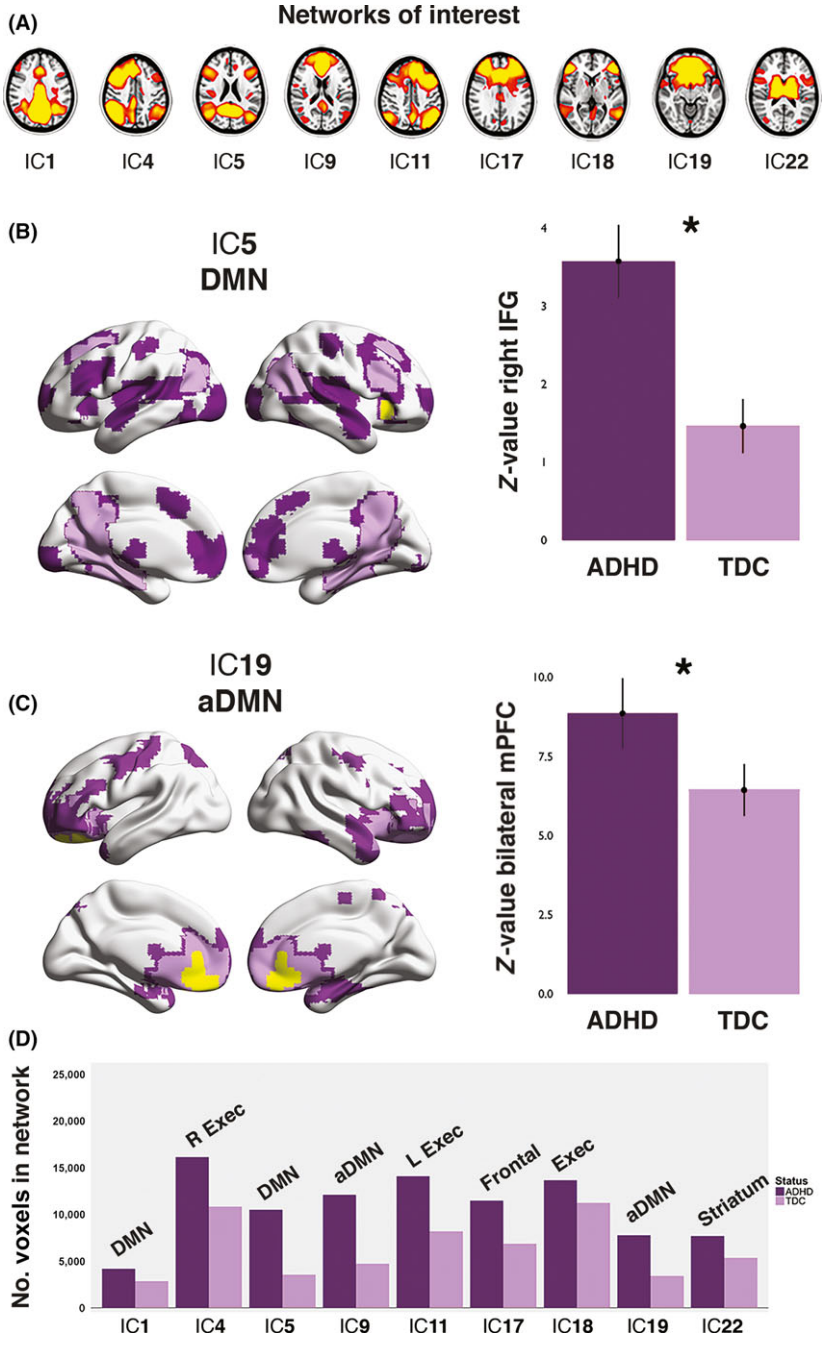

Figure 1 Panel (A) shows networks of interest for the between-group analyses of within-network functional connectivity. Panel (B) shows increased connectivity within Default Mode Network (DMN; IC05) in right inferior frontal gyrus (IFG; shown in yellow: peak cluster *T* value = 6.29, $p_{FWE} = <.001$). Panel (C) shows increased connectivity within anterior DMN (aDMN: IC19) in the bilateral medial prefrontal cortex (mPFC; yellow: peak cluster *T* value = 4.43, $p_{FWE} = .008$). Panel (D) shows an increase in the number of voxels recruited in networks of interest in participants with attention deficit/hyperactivity disorder (ADHD)

voxelwise gray matter density as covariates in all initial analyses. As there was no significant effect of gender, this covariate was consequently removed from the design. By including the individual gray matter density maps as a covariate, the results were corrected for differences in gray matter density and possible misregistrations (Oakes et al., 2007). If a between-group effect was found, the relation between functional connectivity and age was further explored within that network, with gender and voxelwise gray matter density as covariates. All results were corrected for multiple comparisons, using family-wise error (FWE) at $p < .05$ and threshold-free cluster enhancement (TFCE; Smith & Nichols, 2009). All group comparisons were masked by group main effects (i.e. those voxels that fell within the TDC and/or ADHD group-map), to restrict analyses to connectivity within the RSNs of interest. Group main effects were obtained by means of nonparametric estimation of the group means – again with age and voxelwise gray matter density as nuisance variables, using 5,000 permutations in Randomise at a FWE-threshold of $p < .05$, using TFCE.

Exploratory analysis of between-group differences in the size of the RSNs of interest were performed by calculating the average number of voxels with a $Z > 3.1$, corresponding to $p = .001$ uncorrected.

Diffusion-weighted analyses

Preprocessing steps for graph theoretical analysis of the diffusion-weighted data are described in detail in Appendix S1. Clustering coefficient (C), and characteristic path length (L) of the FA-weighted matrices were calculated using the Brain Connectivity Toolbox (Rubinov & Sporns, 2010). To correct for differences in topology based on the number of edges in the connectivity matrix, a randomization procedure was performed. For each subject, 1,000 random matrices with preserved degree sequence and an identical collection of connection weights were formed. From these randomized matrices, individual L_{random} and C_{random} values were computed by averaging over the trials. The normalized characteristic path length lambda (λ) was calculated as: $\lambda = L/L_{random}$. The normalized clustering coefficient gamma (γ) was calculated as: $\gamma = C/C_{random}$.

Statistical analyses were performed using the R statistical software package (www.r-project.org). Averages and between-group differences in mean and regional FA and mean diffusivity (MD), and (node-specific) graph theoretical measures were analyzed using a linear regression model with age as covariate.

Voxelwise statistical analysis was performed using tract-based spatial statistics (TBSS) within FSL (www.fmrib.ox.ac.uk/fsl; Smith et al., 2004; Appendix S1). Group differences in voxelwise structural connectivity (FA and MD) were tested using a general linear model with 5,000 permutations in Randomise, with age as covariate in all analyses. Results were corrected for multiple comparisons, using FWE at $p < .05$ and TFCE (Smith & Nichols, 2009).

Results

Group functional network characteristics

There were no between-group differences in between-network correlations (Figure S2). Nine components were selected for analysis of within-network connectivity. For both groups, these components included core regions of: the DMN (IC1, IC5, IC9, and IC19), the right- (IC4), left- (IC11), bilateral- (IC18), and frontal- (IC17) executive networks, and a striatal network (IC22; Figure 2A). More elaborate slice intersections are shown in Figure S1.

Within-network functional connectivity in ADHD

In ADHD, connectivity within the DMN (IC5) was increased in the right inferior frontal gyrus (IFG; Figure 1B: peak cluster T value = 5.67, $p_{FWE} = .002$, MNI-coordinates: $x = 33$, $y = 23$, $z = -4.5$, $k = 28$). These results persisted after correction for gray matter density (peak cluster T value = 6.29, $p_{FWE} = <.001$, $k = 27$). When inspecting the group main effects, the right IFG cluster was not present in the TDC, whereas it was in the children with ADHD.

Furthermore, connectivity was increased in ADHD in an anterior DMN network (IC19) in the bilateral, but mostly right medial prefrontal cortex (mPFC; Figure 1C: peak cluster T value = 4.60, $p_{FWE} = .004$, MNI-coordinates: $x = -9$, $y = 32$, $z = -18.5$, $k = 486$). Again, results persisted when a correction for gray matter density was applied (peak cluster T value = 4.43, $p_{FWE} = .008$, $k = 349$).

One small cluster in the right posterior cingulate gyrus showed reduced connectivity in ADHD within the DMN (IC1: peak cluster T value = 4.74, $p_{FWE} = .03$, MNI-coordinates: $x = -6$, $y = -31$, $z = 41$, $k = 4$), which did also survive correction for gray matter density (IC1: peak cluster T value = 5.00, $p_{FWE} = .02$, $k = 9$). There were no between-group differences in connectivity in any of the other selected RSNs of interest. Functional connectivity in the significant clusters in IC1, IC5, and IC19 was not correlated with measures of attention as assessed by the CBCL.

Structural connectivity in ADHD

Analysis of regional differences in FA or MD using TBSS yielded no significant results after FWE-correction for multiple comparisons. The graph theory approach similarly returned no differences in average FA or MD that survived false discovery rate (FDR)-correction for multiple comparisons. Furthermore, there were no between-group differences in average (normalized) clustering coefficient (C/γ) and (normalized) path length (L/λ), or node-specific differences that survived FDR-correction. Explorative correlations between the extracted Z-values of functional connectivity in the rIFG and bilateral mPFC and structural measures of node-specific normalized clustering coefficient γ in the right pars opercularis and pars triangularis, and bilateral medial orbitofrontal cortex returned no significant results.

Effects of age on connectivity in ADHD

Within IC5, functional connectivity showed a negative relationship with age ($r = -.527$, $p = >.001$) in two small clusters in the bilateral posterior cingulate cortex (PCC) in all children (Figure 2A,B: peak cluster T value = 4.45, $p_{FWE} = .006$, MNI-coordinates: $x = -12$, $y = -49$, $z = 9.5$, $k = 85$).

Furthermore, functional connectivity of bilateral mPFC was negatively correlated with age in children

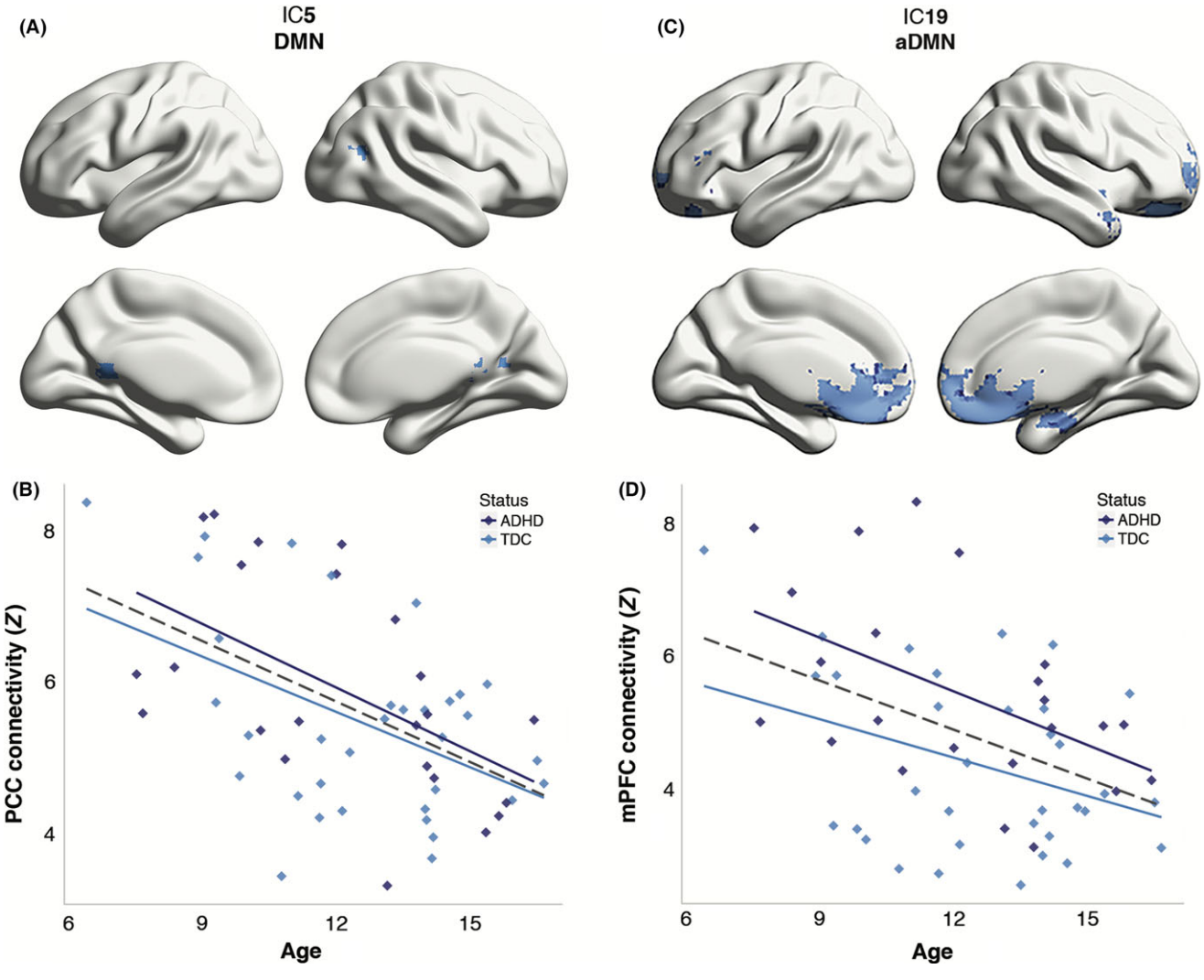

Figure 2 Functional connectivity in the medial prefrontal cortex (mPFC; IC19: panel A) showed a negative relation with age in typically developing children (TDC) and attention deficit/hyperactivity disorder (ADHD) (B). Functional connectivity in the bilateral PCC (IC05: panel C) also showed a negative relation with age (D). In both panel B and D, the mean is represented by the dotted line. (a)DMN, anterior Default Mode Network

with ADHD ($r = -.529$, $p = .009$) and TDC ($r = -.379$, $p = .027$; Figure 2C,D: peak cluster T value = 6.20, $p_{FWE} = <.001$, MNI-coordinates: $x = -6$, $y = 2$, $z = -4.5$, $k = 2{,}436$) in an area that largely overlapped with the group main effect in IC19.

Analyses of changes with age showed an increase in FA with age [TBSS: $F(1, 70) = 36.5$, $p < .001$; Graph: $F(1, 70) = 9.4$, $p = .003$], and decreases in MD [TBSS: $F(1, 70) = 19.1$, $p < .001$; Graph: $F(1, 70) = 24.1$, $p < .001$] (Figure 3). The mean values for FA and MD that were derived from the two different analysis techniques (i.e. TBSS and graph analysis) were highly correlated ($r = .743$, $p < .001$ and $r = .884$, $p < .001$, respectively).

Spatial characteristics of functional networks in ADHD

While core regions of all networks of interest overlapped between children with and without ADHD, exploration of between-group differences showed a significantly higher number of voxels included in the network in two frontal RSNs in children with ADHD: IC17 [$F(55, 1) = 5.02$, $p = .029$] and IC19 [$F(55, 1) = 4.28$, $p = .043$] (Figure 1D).

Discussion

In this study, we investigated both functional and structural connectivity of frontal control and DMNs in young children and adolescents with ADHD, compared to their typically developing peers. We found that there were increases in functional connectivity in prefrontal regions, and more widespread connectivity throughout the brain, in keeping with the delayed maturation hypothesis of ADHD. These changes in functional connectivity were not accompanied by changes in the underlying WM structure.

We found an increase in connectivity of right IFG and mPFC in ADHD within the DMN. IFG has been frequently implicated in ADHD and is a key region involved in cognitive and behavioral control (Aron & Poldrack, 2005). Increased nodal efficiency of (right) IFG has previously been reported in children with ADHD and it has been suggested that this may

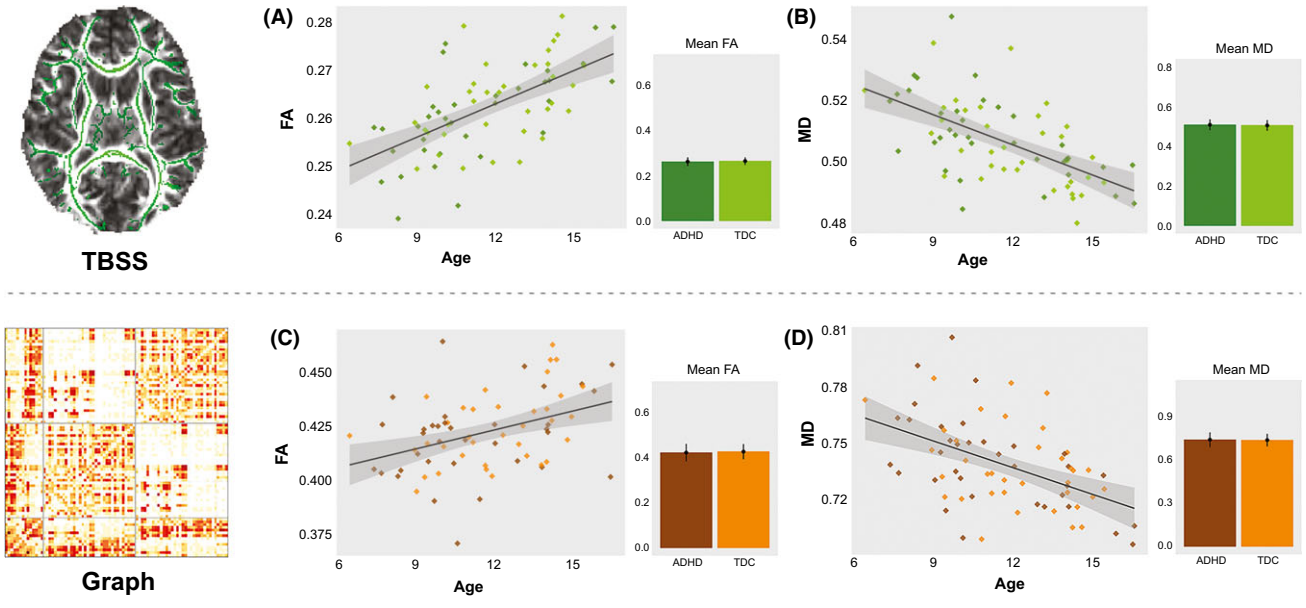

Figure 3 For the entire sample, fractional anisotropy (FA) (panel A and C) showed an increase with age, whereas MD (panel B and D) decreased with age. There were no between-group differences in mean FA or MD between children with attention deficit/hyperactivity disorder (ADHD) and typically developing children, as assessed with tract-based spatial statistics (TBSS) or graph theoretical measures

reflect greater effort in this region to achieve the same level of performance as typically developing controls (Wang et al., 2009). In addition, ADHD is associated with 'attentional lapses' related to inadequate suppression (i.e. interference) of the DMN during goal-directed behavior (Castellanos et al., 2008; Kelly, Uddin, Biswal, Castellanos, & Milham, 2008; Sonuga-Barke & Castellanos, 2007). However, while the recruitment of right IFG into DMN may point toward inadequate modulation between task-positive and task-negative networks, we did not find any evidence for such changes in between-network connectivity in the current study.

Furthermore, the recruitment of right IFG and increased connectivity of mPFC in DMN may reflect reduced functional network segregation in ADHD. In line with previous studies, we also found that mPFC connectivity decreased with age in all children (Betzel et al., 2014; Fair et al., 2009; Van Duijvenvoorde, Achterberg, Braams, Peters, & Crone, 2015). Nevertheless, on average, connectivity in mPFC remained higher in children with ADHD. Such an increase in connectivity in a region where typically a decrease with age would be expected could again be a sign of reduced functional network segregation (Fair et al., 2010; Sripada, Kessler, & Angstadt, 2014).

Typical development of functional connectivity is thought to be characterized by both segregation and integration of brain areas into coherent and efficient networks (Fair et al., 2007, 2009; Supekar, Musen, & Menon, 2009) and seems to involve a shift from a diffuse to a more focal pattern of activation in adulthood (Durston et al., 2006; Kelly et al., 2009). Specifically, Default Mode, frontal-attentional, or executive RSNs have been observed to show more diffuse, mostly increased patterns of connectivity during childhood (Jolles, van Buchem, Crone, & Rombouts, 2011). As such, the more widespread pattern of functional connectivity in ADHD could indeed reflect more immature functional network development (Sato, Hoexter, Castellanos, & Rohde, 2012; Sripada, Kessler, Fang, et al., 2014). However, whether the differences in functional connectivity observed here indeed point toward a maturational delay in prefrontal brain regions during childhood in ADHD remains to be determined as recent findings have suggested that increased connectivity in prefrontal areas may persist into adulthood (Mostert et al., 2016).

There may be multiple explanations for the observed dissociation between structural and functional network organization in this study. For one, our findings may be limited by the methods applied. At a more lenient statistical threshold, we did find differences in WM structure in regions frequently implicated in ADHD. However, these results did not survive correction for multiple comparisons and were therefore not reported. In this case, our sample size may have been too small to detect the subtle developmental differences that are associated with ADHD. During childhood and adolescence, the brain is exposed to a dynamically changing environment. While brain development is highly coordinated, great variability between individuals is still found (Walhovd, Tamnes, & Fjell, 2014). Subsequently, between-group differences in structural connectivity may have been obscured by the many developmental processes at play.

Furthermore, even though brain structure is thought to be highly predictive of function, there is not a one-to-one relationship between them (Honey, Thivierge, & Sporns, 2010; Honey et al., 2009; van den Heuvel, Mandl, Kahn, & Hulshoff Pol, 2009). During development, the relation between structure

and function strengthens and becomes more stable (Gordon et al., 2011; Hagmann et al., 2010; Supekar et al., 2010; Uddin, Supekar, Ryali, & Menon, 2011). Speculatively, fast, perhaps experience-dependent, changes in functional connectivity may precede slower changes in structural connectivity (Honey et al., 2010). Consequently, another explanation may be that (still emerging) changes in WM structural are nonspecific markers, which develop secondarily to the neurobiological pathways that lead to ADHD (Liston, Malter Cohen, Teslovich, Levenson, & Casey, 2011). Information from longitudinal cohorts is necessary to unravel the dynamics of structural and functional development in ADHD.

Our findings should be considered in light of their limitations. First, diffusion-weighted imaging relies on water diffusion as an indirect marker for axonal geometry. As such, crossing, diverging, or converging fibers pose a challenge in resolving the brain's complex fiber architecture (Jbabdi & Johansen-Berg, 2011). Moreover, motion is a known confounder in functional connectivity analyses (Power et al., 2014), and consequently a fairly large proportion of our data, in particular from individuals with ADHD, was excluded from the resting-state analyses. Motion characteristics were within acceptable limits for the remaining sample. Third, a large proportion of children with ADHD in the sample were being treated with stimulant medication. The long-term effect of methylphenidate treatment on brain connectivity continues to be an unresolved issue. Although we cannot completely rule an effect of medication on our findings, there were no significant differences between children with ADHD who did or did not receive medication (Appendix S1). If anything, methylphenidate has been suggested to normalize the trajectory of brain development and brain activation patterns (Schweren, Zeeuw, & Durston, 2013). In order to minimize the acute effects of stimulant medication on resting-state fMRI, subjects were instructed not to take their medication 24 hr prior to scanning.

In conclusion, in this study, RSNs showed a more diffuse pattern of connectivity in children with ADHD than in their typically developing peers. Furthermore, functional connectivity was increased in the right IFG and bilateral mPFC. These results can be taken to suggest that changes in functional connectivity may be associated with reduced or delayed functional network segregation, and that these functional changes may precede changes in WM structure. Future larger and longitudinal studies, perhaps also choosing a dimensional rather than categorical approach, will permit for a better characterization of developmental pathways and individual differences in the relation between DMN interference and attentional lapses in ADHD.

Supporting information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Spatial maps of all independent components (ICs) containing signal of interest.

Figure S2. Group functional network characteristics.

Table S1. Demographic data for the sample included in the resting-state study.

Table S2. Motion characteristics for the sample included in the resting-state study.

Appendix S1. Additional information.

Acknowledgements

This study was financially supported by the National Initiative Brain and Cognition (NIHC) 056-13-011, VIDI 016.076.384 and VICI 016.115.602 of the Netherlands Organization for Scientific Research (NWO) to Sarah Durston. S.R. is supported by VICI 016.130.677 of NWO. The authors thank all the participants and their parents of this study. Furthermore, they thank Juliette Weusten of the University Medical Center Utrecht, for the assistance with subject recruitment and MRI assessments, and Tilman Reinelt of the University of Bremen, for assistance in FreeSurfer processing.

Correspondence

Dienke J. Bos, Department of Psychiatry, University Medical Center Utrecht, HP A.01.126, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands; Email: d.j.bos-2@umcutrecht.nl

Key points

- Attention deficit/hyperactivity disorder (ADHD) has frequently been associated with changes in resting-state network connectivity, as well as decreased white matter (WM) integrity.
- We found increased connectivity in right inferior frontal gyrus and bilateral medial prefrontal cortex in children and adolescents with ADHD, without corresponding group differences in WM structure.
- Resting-state networks showed a more diffuse pattern of connectivity in children with ADHD, which together with increases in prefrontal functional connectivity in ADHD may reflect reduced or delayed functional segregation of prefrontal brain regions.
- The delay in functional network development may be associated with heightened Default Mode Network interference and attentional lapses in ADHD.

References

American Psychiatric Association (2013). *The diagnostic and statistical manual of mental disorders: DSM 5*. Washington, DC: Author.

Aron, A.R., & Poldrack, R.A. (2005). The cognitive neuroscience of response inhibition: Relevance for genetic research in attention-deficit/hyperactivity disorder. *Biological Psychiatry*, *57*, 1285–1292.

Beckmann, C.F., DeLuca, M., Devlin, J.T., & Smith, S.M. (2005). Investigations into resting-state connectivity using independent component analysis. *Philosophical Transactions of the Royal Society of London B: Biological Sciences*, *360*, 1001–1013.

Beckmann, C.F., & Smith, S.M. (2004). Probabilistic independent component analysis for functional magnetic resonance imaging. *EEE Transactions on Medical Imaging*, *23*, 137–152.

Betzel, R.F., Byrge, L., He, Y., Goñi, J., Zuo, X.-N., & Sporns, O. (2014). Changes in structural and functional connectivity among resting-state networks across the human lifespan. *NeuroImage*, *102*, 345–357.

Bos, D.J., van Raalten, T.R., Oranje, B., Smits, A.R., Kobussen, N.A., Van Belle, J., … & Durston, S. (2014). Developmental differences in higher-order resting-state networks in autism spectrum disorder. *NeuroImage: Clinical*, *4*, 820–827.

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

Castellanos, F.X., Kelly, A.M.C., & Milham, M.P. (2013). The restless brain: Attention-deficit/hyperactivity disorder, resting state functional connectivity and intrasubject variability. *Canadian Journal of Psychiatry*, *54*, 665–672.

Castellanos, F.X., Margulies, D.S., Kelly, C., Uddin, L.Q., Ghaffari, M., Kirsch, A., … & Milham, M.P. (2008). Cingulate-precuneus interactions: A new locus of dysfunction in adult attention-deficit/hyperactivity disorder. *Biological Psychiatry*, *63*, 332–337.

Castellanos, F.X., & Proal, E. (2012). Large-scale brain systems in ADHD: Beyond the prefrontal-striatal model. *Trends in Cognitive Sciences*, *16*, 17–26.

Costello, E.J., Edelbrock, C.S., & Costello, A.J. (1985). Validity of the NIMH Diagnostic Interview Schedule for Children: A comparison between psychiatric and pediatric referrals. *Journal of Abnormal Child Psychology*, *13*, 579–595.

Durston, S., Davidson, M.C., Tottenham, N., Galvan, A., Spicer, J., Fossella, J.A., & Casey, B.J. (2006). A shift from diffuse to focal cortical activity with development. *Developmental Science*, *9*, 1–8.

Durston, S., Nederveen, H., van Dijk, S., van Belle, J., de Zeeuw, P., Langen, M., & van Dijk, A. (2009). Magnetic resonance simulation is effective in reducing anxiety related to magnetic resonance scanning in children. *Journal of the American Academy of Child and Adolescent Psychiatry*, *48*, 206–207.

Durston, S., van Belle, J., & de Zeeuw, P. (2011). Differentiating frontostriatal and fronto-cerebellar circuits in attention-deficit/hyperactivity disorder. *Biological Psychiatry*, *69*, 1178–1184.

El-Sayed, E., Larsson, J.-O., Persson, H.E., Santosh, P.J., & Rydelius, P.-A. (2003). "Maturational lag" hypothesis of attention deficit hyperactivity disorder: An update. *Acta Paediatrica*, *92*, 776–784.

Fair, D.A., Cohen, A.L., Power, J.D., Dosenbach, N.U.F., Church, J.A., Miezin, F.M., … & Petersen, S.E. (2009). Functional brain networks develop from a "local to distributed" organization. *PLoS Computational Biology*, *5*, e1000381.

Fair, D.A., Dosenbach, N.U.F., Church, J.A., Cohen, A.L., Brahmbhatt, S., Miezin, F.M., … & Schlaggar, B.L. (2007). Development of distinct control networks through segregation and integration. *Proceedings of the National Academy of Sciences of the USA*, *104*, 13507–13512.

Fair, D.A., Nigg, J.T., Iyer, S., Bathula, D., Mills, K.L., Dosenbach, N.U.F., … & Milham, M.P., et al. (2012). Distinct neural signatures detected for ADHD subtypes after controlling for micro-movements in resting state functional connectivity MRI data. *Frontiers in Systems Neuroscience*, *6*, 80.

Fair, D.A., Posner, J., Nagel, B.J., Bathula, D., Dias, T.G.C., Mills, K.L., … & Nigg, J.T. (2010). Atypical default network connectivity in youth with attention-deficit/hyperactivity disorder. *Biological Psychiatry*, *68*, 1084–1091.

Filippini, N., Macintosh, B.J., Hough, M.G., Goodwin, G.M., Frisoni, G.B., Smith, S.M. & Mackay, C.E. (2009). Distinct patterns of brain activity in young carriers of the APOE-e4 allele. *Proceedings of the National Academy of Sciences of the USA*, *106*, 7209–7214.

Gordon, E.M., Lee, P.S., Maisog, J.M., Foss-Feig, J., Billington, M.E., Vanmeter, J., & Vaidya, C.J. (2011). Strength of default mode resting-state connectivity relates to white matter integrity in children. *Developmental Science*, *14*, 738–751.

Hagmann, P., Sporns, O., Madan, N., Cammoun, L., Pienaar, R., Wedeen, V.J., … & Grant, P.E. (2010). White matter maturation reshapes structural connectivity in the late developing human brain. *Proceedings of the National Academy of Sciences of the USA*, *107*, 19067–19072.

Honey, C.J., Sporns, O., Cammoun, L., Gigandet, X., Thiran, J.P., Meuli, R., & Hagmann, P. (2009). Predicting human resting-state functional connectivity. *Proceedings of the National Academy of Sciences of the USA*, *106*, 1–6.

Honey, C.J., Thivierge, J.-P., & Sporns, O. (2010). Can structure predict function in the human brain? *NeuroImage*, *52*, 766–776.

Jbabdi, S., & Johansen-Berg, H. (2011). Tractography: Where do we go from here? *Brain Connectivity*, *1*, 169–183.

Jolles, D.D., van Buchem, M.A., Crone, E.A., & Rombouts, S.A.R.B. (2011). A comprehensive study of whole-brain functional connectivity in children and young adults. *Cerebral Cortex*, *21*, 385–391.

Kelly, A.M.C., Di Martino, A., Uddin, L.Q., Shehzad, Z., Gee, D.G., Reiss, P.T., … & Milham, M.P. (2009). Development of anterior cingulate functional connectivity from late childhood to early adulthood. *Cerebral Cortex*, *19*, 640–657.

Kelly, A.M.C., Uddin, L.Q., Biswal, B.B., Castellanos, F.X., & Milham, M.P. (2008). Competition between functional brain networks mediates behavioral variability. *NeuroImage*, *39*, 527–537.

Kort, W., Schittekatte, M., Dekker, P.H., Verhaeghe, P., Compaan, E.L., & Bosmans, M. (2005). *Wechsler Intelligence Scale for Children – third edition, Dutch version*. London: Psychological Corporation.

Laird, A.R., Fox, P.M., Eickhoff, S.B., Turner, J.A., Kimberly, L., McKay, D.R., … & Fox, P.T. (2011). Behavioral interpretations of intrinsic connectivity networks. *Journal of Cognitive Neuroscience*, *23*, 4022–4037.

Liston, C., Malter Cohen, M., Teslovich, T., Levenson, D., & Casey, B.J. (2011). Atypical prefrontal connectivity in attention-deficit/hyperactivity disorder: Pathway to disease or pathological end point? *Biological Psychiatry*, *69*, 1168–1177.

Mostert, J.C., Shumskaya, E., Mennes, M., Onnink, A.M.H., Hoogman, M., Kan, C.C., … & Norris, D.G. (2016). Characterising resting-state functional connectivity in a large sample of adults with ADHD. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *67*, 82–91.

Oakes, T.R., Fox, A.S., Johnstone, T., Chung, M.K., Kalin, N., & Davidson, R.J. (2007). Integrating VBM into the General Linear Model with voxelwise anatomical covariates. *NeuroImage*, *34*, 500–508.

Posner, J., Park, C., & Wang, Z. (2014). Connecting the dots: A review of resting connectivity MRI studies in attention-

deficit/hyperactivity disorder. *Neuropsychology Review*, *24*, 3–15.

Posner, J., Rauh, V., Gruber, A., Gat, I., Wang, Z., & Peterson, B.S. (2013). Dissociable attentional and affective circuits in medication-naïve children with attention-deficit/hyperactivity disorder. *Psychiatry Research*, *213*, 24–30.

Power, J.D., Mitra, A., Laumann, T.O., Snyder, A.Z., Schlaggar, B.L., & Petersen, S.E. (2014). Methods to detect, characterize, and remove motion artifact in resting state fMRI. *NeuroImage*, *84*, 320–341.

Qiu, M., Ye, Z., Li, Q., Liu, G., Xie, B., & Wang, J. (2011). Changes of brain structure and function in ADHD children. *Brain Topography*, *24*, 243–252.

Rubia, K. (2007). Neuro-anatomic evidence for the maturational delay hypothesis of ADHD. *Proceedings of the National Academy of Sciences of the USA*, *104*, 19663–19664.

Rubinov, M., & Sporns, O. (2010). Complex network measures of brain connectivity: Uses and interpretations. *NeuroImage*, *52*, 1059–1069.

Sato, J.R., Hoexter, M.Q., Castellanos, X.F., & Rohde, L.A. (2012). Abnormal brain connectivity patterns in adults with ADHD: A coherence study. *PLoS ONE*, *7*, e45671.

Schweren, L.J.S., Zeeuw, P.De., & Durston, S. (2013). MR imaging of the effects of methylphenidate on brain structure and function in attention-deficit/hyperactivity disorder. *European Neuropsychopharmacology*, *23*, 1151–1164.

Shaw, P., Eckstrand, K., Sharp, W., Blumenthal, J., Lerch, J.P., Greenstein, D. & Rapoport, J.L. (2007). Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. *Proceedings of the National Academy of Sciences of the USA*, *104*, 19649–19654.

Smith, S.M., Jenkinson, M., Woolrich, M.W., Beckmann, C.F., Behrens, T.E.J., Johansen-Berg, H., ... & Matthews, P.M. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *NeuroImage*, *23*(Suppl. 1), S208–S219.

Smith, S.M., & Nichols, T.E. (2009). Threshold-free cluster enhancement: Addressing problems of smoothing, threshold dependence and localisation in cluster inference. *NeuroImage*, *44*, 83–98.

Sonuga-Barke, E.J.S., & Castellanos, F.X. (2007). Spontaneous attentional fluctuations in impaired states and pathological conditions: A neurobiological hypothesis. *Neuroscience and Biobehavioral Reviews*, *31*, 977–986.

Sripada, C.S., Kessler, D., & Angstadt, M. (2014). Lag in maturation of the brain's intrinsic functional architecture in attention-deficit/hyperactivity disorder. *Proceedings of the National Academy of Sciences of the USA*, *111*, 14259–14264.

Sripada, C., Kessler, D., Fang, Y., Welsh, R.C., Prem Kumar, K., & Angstadt, M. (2014). Disrupted network architecture of the resting brain in attention-deficit/hyperactivity disorder. *Human Brain Mapping*, *35*, 4693–4705.

Sun, L., Cao, Q., Long, X., Sui, M., Cao, X., Zhu, C., ... & Wang, Y. (2012). Abnormal functional connectivity between the anterior cingulate and the default mode network in drug-naïve boys with attention deficit hyperactivity disorder. *Psychiatry Research*, *201*, 120–127.

Supekar, K., Musen, M., & Menon, V. (2009). Development of large-scale functional brain networks in children. *PLoS Biology*, *7*, e1000157.

Supekar, K., Uddin, L.Q., Prater, K., Amin, H., Greicius, M.D., & Menon, V. (2010). Development of functional and structural connectivity within the default mode network in young children. *NeuroImage*, *52*, 290–301.

Tian, L., Jiang, T., Wang, Y., Zang, Y., He, Y., Liang, M., ... & Zhuo, Y. (2006). Altered resting-state functional connectivity patterns of anterior cingulate cortex in adolescents with attention deficit hyperactivity disorder. *Neuroscience Letters*, *400*, 39–43.

Uddin, L.Q., Supekar, K.S., Ryali, S., & Menon, V. (2011). Dynamic reconfiguration of structural and functional connectivity across core neurocognitive brain networks with development. *The Journal of Neuroscience*, *31*, 18578–18589.

van den Heuvel, M.P., Mandl, R.C.W., Kahn, R.S., & Hulshoff Pol, H.E. (2009). Functionally linked resting-state networks reflect the underlying structural connectivity architecture of the human brain. *Human Brain Mapping*, *30*, 3127–3141.

Van Duijvenvoorde, A.C.K., Achterberg, M., Braams, B.R., Peters, S., & Crone, E.A. (2015). Testing a dual-systems model of adolescent brain development using resting-state connectivity analyses. *NeuroImage*, *124*, 409–420.

van Ewijk, H., Heslenfeld, D.J., Zwiers, M.P., Buitelaar, J.K., & Oosterlaan, J. (2012). Diffusion tensor imaging in attention deficit/hyperactivity disorder: A systematic review and meta-analysis. *Neuroscience and Biobehavioral Reviews*, *36*, 1093–1106.

Walhovd, K.B., Tamnes, C.K., & Fjell, A.M. (2014). Brain structural maturation and the foundations of cognitive behavioral development. *Current Opinion in Neurology*, *27*, 176–184.

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

Accepted for publication: 21 December 2016