

# BRAIN COMMUNICATIONS

## Exploring white matter functional networks in children with attention-deficit/hyperactivity disorder

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Attention-deficit/hyperactivity disorder has been identified to involve the impairment of large-scale functional networks within grey matter, and recent studies have suggested that white matter, which also encodes neural activity, can manifest intrinsic functional organization similar to that of grey matter. However, the alterations in white matter functional networks in attention-deficit/hyperactivity disorder remain unknown. We recruited a total of 99 children, including 66 drug-naive patients and 33 typically developing controls aged from 6 to 14, to characterize the alterations in functional networks within white matter in drug-naive children with attention-deficit/hyperactivity disorder. Using clustering analysis, resting-state functional MRI data in the white matter were parsed into different networks. Intrinsic activity within each network and connectivity between networks and the associations between network activity strength and clinical symptoms were assessed. We identified eight distinct white matter functional networks: the default mode network, the somatomotor network, the dorsal attention network, the ventral attention network, the visual network, the deep frontoparietal network, the deep frontal network and the inferior corticospinal-posterior cerebellum network. The default mode, somatomotor, dorsal attention and ventral attention networks showed lower spontaneous neural activity in patients. In particular, the default mode network and the somatomotor network largely showed higher connectivity with other networks, which correlated with more severe hyperactive behaviour, while the dorsal and ventral attention networks mainly had lower connectivity with other networks, which correlated with poor attention performance. In conclusion, there are two distinct patterns of white matter functional networks in children with attention-deficit/hyperactivity disorder, with one being the hyperactivity-related hot networks including default mode network and somatomotor network and the other being inattention-related cold networks including dorsal attention and ventral attention network. These results extended upon our understanding of brain functional networks in attention-deficit/hyperactivity disorder from the perspective of white matter dysfunction.

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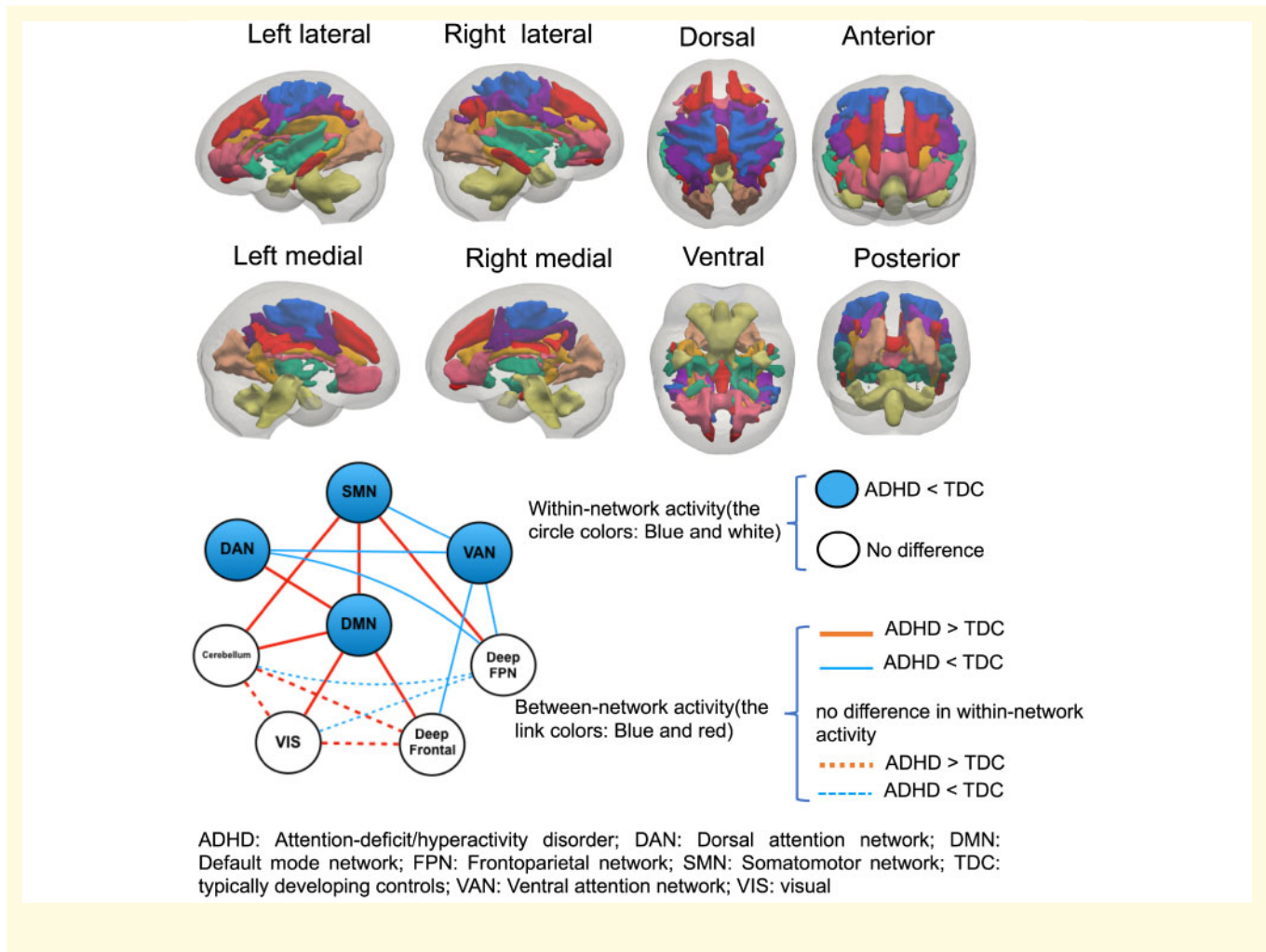
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**Abbreviations:** ADHD = attention-deficit/hyperactivity disorder; BOLD = blood-oxygen-level-dependent; CPRS = Conners' Parent Rating Scale; DAN = dorsal attention network; DMN = default mode network; FPN = frontoparietal network; GM = grey matter; IVA-CPT = Integrated Visual and Auditory Continuous Performance Test; SMN = somatomotor network; TDC = typically developing controls; VAN = ventral attention network; WM = white matter



## Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a prevalent neurodevelopmental disorder typically diagnosed in childhood and adolescence that is characterized by impaired attention and/or impulsiveness–hyperactivity (Faraone et al., 2015). Previous neuroimaging studies have led to the prominence of neural circuits or neural networks, rather than isolated brain regions, as substrates for ADHD neuropathology (Konrad and Eickhoff, 2010; Castellanos and Proal, 2012; Gallo and Posner, 2016; Samea et al., 2019). For example, many resting-state fMRI studies have consistently reported reduced functional connectivity within the default mode network (DMN), impaired anti-correlation between the DMN and the frontoparietal network (FPN) and decreased functional connectivity in attention networks (Kessler et al., 2014).

A recent large (700 patients with ADHD and 580 controls) meta-analysis (Gao et al., 2019) of seed-based resting-state functional connectivity studies confirmed functional connectivity alterations in several networks, including the DMN, the FPN, the affective network, the somatosensory network and the ventral attention network (VAN), among patients with ADHD. Moreover, dysfunction of these grey matter (GM) networks has been shown to be associated with ADHD symptoms and several disrupted neurocognitive functions (de Lacy et al., 2018).

Recent studies (Ding et al., 2013, 2016; Ji et al., 2017; Huang et al., 2018) have provided robust evidence that blood-oxygen-level-dependent (BOLD) signal fluctuations in white matter (WM) are modulated by neural activity and are detectable with fMRI. WM has the vascular capacity to support hemodynamic changes detected by fMRI even with a lower density of vasculature than GM; the

neural activity in WM is mainly linked to spiking, which reflects action potentials, and there is evidence provided that spiking activity may be sufficient for inducing hemodynamic responses (Gawryluk *et al.*, 2014). Therefore, these suggest that fMRI signal in WM is BOLD and is modulated by neural activity.

There is evidence supporting the functional contribution of WM. The BOLD signal in WM tracts was first detected during both event-related task and resting state and was found to be greater under stimulation than in a resting state (Wu *et al.*, 2017; Ding *et al.*, 2018). The detectability of neural activities was later confirmed in specific WM tracts, which strongly correlated with neural signals in cortical regions that are connected by these tracts (Li *et al.*, 2019). The existence of an intrinsic functional network organization of WM tracts was revealed with a hierarchical structure of temporally correlated fMRI signal in WM and further demonstrated that WM functional networks interact in a similar way as GM networks (Marussich *et al.*, 2017; Peer *et al.*, 2017). More recently, functional connectome architecture in WM including small-world topology, high-degree hubs, and a non-random modular organization was also reported (Li *et al.*, 2019). These results converged to provide evidence that WM networks underlying different GM networks carry synchronized activity within themselves and bear different functions. Dysfunction of WM has been detected in neuropsychiatric disorders such as epilepsy and schizophrenia (Jiang *et al.*, 2019a, b), however no study had been carried out to explore the functionality of WM in ADHD yet.

Therefore, in this study, we explored large-scale WM functional networks for the first time by applying a clustering approach to resting-state fMRI data in children with ADHD and typically developing controls (TDC). In particular, we compared differences in spontaneous activity within each network and functional connectivity between networks between children with ADHD and TDC, we studied the relationships between WM network and clinical symptoms, and we further investigated their relationship with known GM networks. As prior studies have shown wide-spread disruptions of WM microstructure in pathways connecting prefrontal and parietooccipital areas with the striatum and the cerebellum (Silk *et al.*, 2009; Qiu *et al.*, 2012; Hong *et al.*, 2014; Wu *et al.*, 2014) and have reported altered interactions among DMN, FPN and attentional networks as aforementioned, we hypothesized that children with ADHD would present dissociated connectivity between DMN and FPN, hyperactive DMN and hypoactive attentional networks in WM and that these functional abnormalities in WM networks would be associated with clinical symptoms of ADHD.

## Materials and methods

### Subjects

The Ethics Committee of The First Affiliated Hospital of Wenzhou Medical University approved this study.

All participants and their parents were fully informed about the purpose and procedures of this study, and written informed consent was obtained from the parents.

A total of 99 children (66 drug-naive ADHD and 33 TDC) between the ages of 6 and 14 were recruited at the Department of Psychiatry, The First Affiliated Hospital of Wenzhou Medical University from June 2013 to March 2018. ADHD diagnosis was evaluated with the Diagnostic and Statistical Manual of Mental Disorders 5th Edition (American Psychiatric Association, 2013) and the schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version (K-SADS-PL) (Kaufman *et al.*, 2000). TDC were recruited from local primary schools and were screened by the same psychiatrists. All subjects were right-handed and were required to have a full-scale IQ above 90 on the Wechsler Intelligence Scale for Children—Chinese Revision (Gong and Cai, 1994).

Children in both groups were excluded if they were left-handed, had a history of neurological illness, had a comorbidity of other Diagnostic and Statistical Manual of Mental Disorders 5th Edition mental disorders, were receiving psychotropic medications or had significant head trauma. The first-degree relatives reported no history of psychiatric diagnosis. We excluded eight children (ADHD  $n=7$ ; TDC  $n=1$ ) with framewise displacement  $>0.2$  mm during fMRI scanning and two children (ADHD  $n=1$ ; TDC  $n=1$ ) because their resting-state functional signal was  $>3$  standard deviations from their own group's mean. Thus, our final sample included 58 children with ADHD (47 males and 11 females; mean age  $9.10 \pm 2.22$  years) and 31 TDC (21 males and 10 females; mean age  $8.87 \pm 1.52$  years) matched with the ADHD group by age and gender. Demographic details are listed in Table 1.

The parents of all enrolled children completed the Chinese version of the revised Conners' Parent Rating Scale (CPRS) to evaluate the behavioural problems of children with ADHD. This scale has been proven to have good reliability and validity among Chinese children with ADHD (Conners *et al.*, 1998; Su *et al.*, 2001). An Integrated Visual and Auditory Continuous Performance Test (IVA-CPT) (Tinius, 2003) was used to measure sustained attention and response control at the auditory and visual levels. We obtained six indexes—full-scale control/attention quotient, visual control/attention quotient and auditory control/attention quotient—for further analysis.

### Image acquisition

All subjects were scanned using a GE signal HDx 3T MR scanner with an eight-channel phase-array head coil. The data for each subject consisted of an 8-min resting-state EPI scan (31 axial slices, slice thickness = 4 mm, slice gap = 0.2 mm, repetition time = 2000 ms, echo time = 30 ms, flip angle =  $90^\circ$ , matrix size =  $64 \times 64$  and field of view = 192 mm) and a high-resolution

**Table 1** Demographic and clinical characteristics of TDC and children with ADHD

Clinical Values	Group		Statistics	
	ADHD	TDC	<i>t</i> / $\chi^2$	<i>P</i>
Sample size	58	31		
Age (years), mean (SD)	9.10 (2.22)	8.87 (1.52)	0.58	0.56
Sex (male:female)	47:11	21:10	1.98	0.16
IQ scores, mean (SD)	117.91 (12.37)	121.45 (14.11)	-1.22	0.22
Conners' Parent Rating Scale, mean (SD)				
Conduct problem	1.07 (0.49)	0.43 (0.43)	6.05	<0.001
Psychosomatic	0.38 (0.41)	0.13 (0.22)	3.77	<0.001
Anxiety	0.48 (0.38)	0.34 (0.27)	1.74	0.09
Study problem	1.88 (0.61)	0.64 (0.59)	9.34	<0.001
Hyperactivity-impulsivity	1.50 (0.68)	0.51 (0.48)	8.01	<0.001
Hyperactivity index	1.42 (0.53)	0.49 (0.39)	8.67	<0.001
Continuous Performance Test, mean (SD)				
Full-scale control quotient	72.24 (23.99)	79.61 (22.94)	-1.40	0.16
Visual control quotient	75.24 (25.26)	81.74 (24.07)	-1.18	0.24
Auditory control quotient	74.48 (23.80)	80.32 (23.80)	-1.10	0.27
Full-scale attention quotient	71.55 (22.85)	94.39 (20.38)	-4.66	<0.001
Visual attention quotient	73.36 (22.56)	93.45 (18.70)	-4.24	<0.001
Auditory attention quotient	72.43 (25.16)	94.61 (20.45)	-4.49	<0.001

T<sub>1</sub>-weighted structural scan acquired with a spoiled gradient-recalled echo sequence (repetition time = 7200 ms, echo time = 2.2 ms, 176 axial slices, slice thickness = 1 mm, flip angle = 7°, matrix size = 256 × 256, field of view = 256 mm).

## Data preprocessing

Preprocessing was performed using SPM8 ([www.fil.ion.ucl.ac.uk/spm](http://www.fil.ion.ucl.ac.uk/spm)), DPABI (<http://rfmri.org/dpabi>) and open MATLAB scripts (<http://mind.huji.ac.il/white-matter.aspx>). T<sub>1</sub> images were skull-stripped, segmented into WM, GM and cerebrospinal fluid and then normalized to the Montreal Neurological Institute template.

The preprocessing steps for functional images included the following: (1) removal of the first 10 time points for signal stabilization; (2) slice time correction; (3) realignment to the median volume and coregistration with the structural image; all registrations were visually inspected; (4) removal of linear trends to correct for signal drift; (5) nuisance regression, including 24-parameter motion correction (6 rigid-body motion parameters, their values at the previous time point and the 12 corresponding squared values) and the mean cerebrospinal fluid signals. The WM and global brain signals were not regressed out because this could have eliminated signals of interest; (6) we also used a rigorous approach to minimize the potential effects of head motion as suggested by recent publications (Power *et al.*, 2012, 2014; Yan *et al.*, 2013), namely temporal scrubbing using motion 'spikes' (framewise displacement >0.2 mm) as separate repressors to effectively censor the data at the spike without further changing the correlation values; (7) band-pass filtering (0.01–0.15 Hz) to reduce non-neuronal contributions to BOLD fluctuations; (8) spatial smoothing (4-mm FWHM)

on the WM and GM separately to avoid mixing their signals; (9) normalization to the Montreal Neurological Institute template and spatially resampling to a voxel size of 3 × 3 × 3 mm<sup>3</sup> using the DARTEL. We also examined head motion differences between the ADHD group and the TDC group using the two-sample *t*-test, and the group-level statistical analysis showed no difference (Supplementary Table 1).

## Construction of WM functional networks

WM network clustering was performed using an analysis pipeline that was described in a previous study (Peer *et al.*, 2017). In brief, the steps were as follows: WM and GM masks were created to select voxels for clustering across all the children: We used the T<sub>1</sub> segmentation results of each subject to create WM and GM masks, which are used in following clustering analysis. We identified each voxel as WM, GM or cerebrospinal fluid based on its maximum probability in the segmentation images, which resulted in WM, GM and cerebrospinal fluid mask for each subject. Then, we averaged these masks across subjects and for each voxel we calculated the percentage of subjects that was classified as WM or GM. For WM, voxels identified in >60% of subjects were used for group-level mask, whereas for GM, threshold of >20% was used. Meanwhile, we only keep voxels identified as WM or GM and containing functional data in >80% of the subjects. Finally, we used the Harvard-Oxford atlas (Desikan *et al.*, 2006) to remove subcortical structures including thalamus, caudate nucleus, putamen, globus pallidus and nucleus accumbens from WM mask. Pearson's correlation coefficients between each WM voxel and other WM voxels were computed for each subject



and then averaged across all 89 subjects to obtain a group-level correlation matrix. *K*-means clustering was performed on the average group-level correlation matrix to identify the clusters of WM voxels with similar connectivity patterns to the rest of the voxels. The number of clusters ranged from 2 to 22, and the stability of clustering was measured for each number of clusters by Dice's coefficient.

## Functional activity within WM networks

Signal amplitudes were extracted from each WM network using Fourier transform (MATLAB's FFT function). The resulting frequency graphs were averaged separately across subjects in the ADHD and TDC groups to produce an average frequency–power graph for each network. For each WM network, the averaged amplitudes were obtained for each subject, which were then used to compare the differences between the ADHD and TDC groups.

## Functional connectivity between WM networks

We extracted the average time courses from each WM network by averaging across all voxels belonging to the network for each subject. The Pearson's correlation between the average time courses of any two WM networks was computed for each subject and then transformed to the Fisher *z*-score for the statistical analysis.

Furthermore, we assessed the functional relationships between WM and GM networks to explore whether the WM networks act in concert with GM networks. We first identified a number of functional networks within the GM by the same clustering procedure. Then, average time courses from each GM network were extracted. The temporal correlations were calculated between each GM network and each WM network.

## Correlations between WM functional networks and clinical measures

We further investigated the relationships between clinical measures (CPRS scores and IVA-CPT scores) and functional connectivity and signal amplitudes by Pearson correlation analysis with age as a covariant.

## Statistical analysis

For demographic data, we performed two-sample *t*-test or  $\chi^2$  test to investigate group differences. For the functional activity within WM networks and functional connectivity between WM networks, we used the analysis of covariance with age and gender as covariates to detect the differences between ADHD and TDC.

We analysed the relationships between clinical measures (CPRS scores and IVA-CPT scores) and functional connectivity and signal amplitudes by Pearson correlation analysis with age as a covariant.

For all analyses,  $P < 0.05$  was used to determine significance. To address concerns that may arise from multiple comparisons across the eight networks, we used Bonferroni correction with the threshold of  $P < 0.05$ .

## Data availability

Data from this study are available for researchers upon reasonable request.

## Results

### WM networks

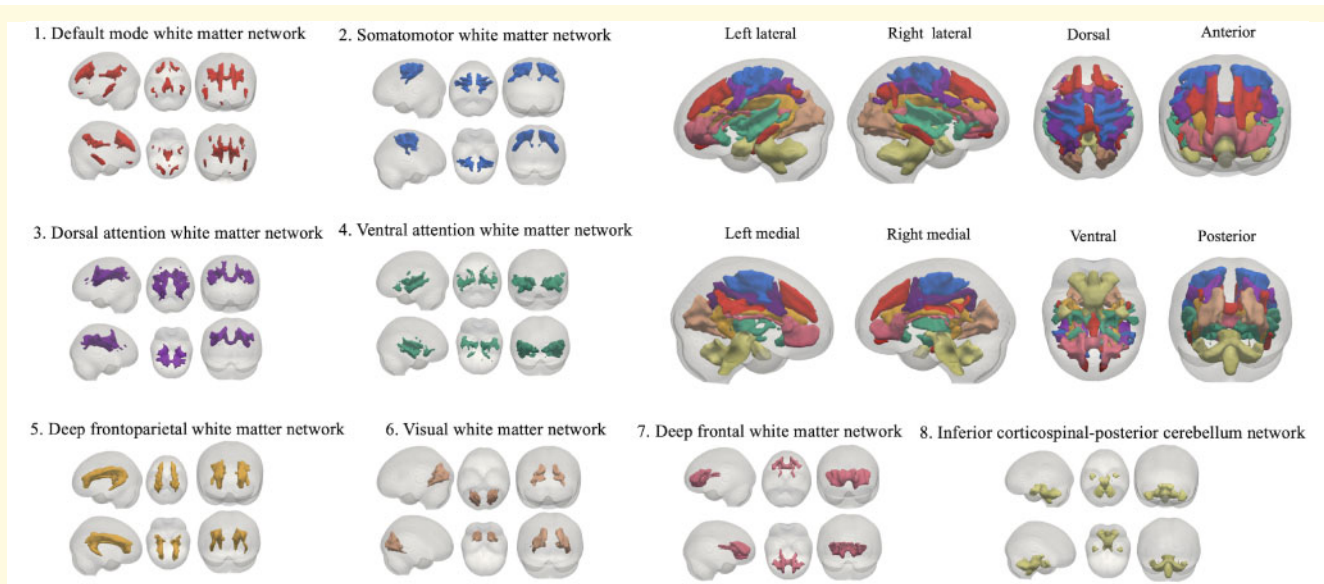
Using a clustering approach on the resting-state voxelwise correlation matrices of WM, we identified the eight most stable and proper WM functional segregations among our subjects according to Dice's coefficient (Supplementary Fig. 1). Therefore, we conducted analyses based on the resulting eight networks and defined them according to the correspondence between our WM networks and the known resting-state GM networks (Yeo *et al.*, 2011). The identified networks were the DMN, the somatomotor network (SMN), the dorsal attention network (DAN), the VAN, the visual network, the deep FPN, the deep frontal network and the inferior cortico-spinal-posterior cerebellum network. The presentation of the eight networks is presented in Fig. 1.

### Functional activity within WM networks

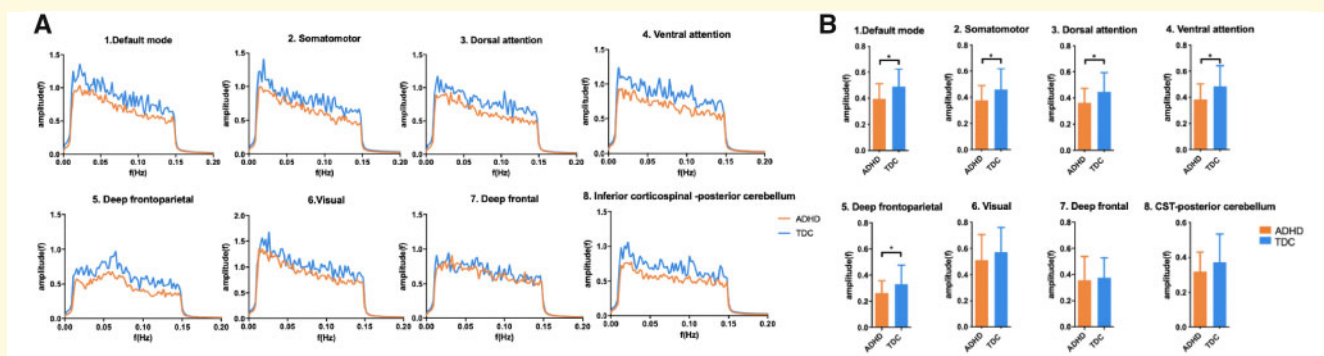
For all WM networks, the signal amplitudes were derived by Fourier transform, and the values corresponding to the frequency are shown in Fig. 2A. A decreasing trend in amplitude with increased frequency was found in each network, suggesting greater activity in WM at lower frequencies. All the networks except for the deep FPN exhibited maximal activity at the lowest frequency of 0.01 Hz, whereas the deep FPN showed a maximal amplitude at  $\sim 0.07$  Hz. Compared with TDC, children with ADHD showed lower amplitudes in all the networks, with the DMN, the SMN, the deep FPN, the DAN and the VAN exhibiting significant differences after correction (Fig. 2B).

### Functional connectivity between WM networks

For each group, an  $8 \times 8$  matrix of pairwise network correlation coefficients was calculated (Fig. 3A). These matrices were then compared between the two groups to



**Figure 1** Eight WM functional networks were identified by clustering analysis: (1) the DMN, (2) the SMN, (3) the DAN, (4) the VAN, (5) the visual network, (6) the deep FPN, (7) the deep frontal network and (8) the inferior corticospinal-posterior cerebellum network.



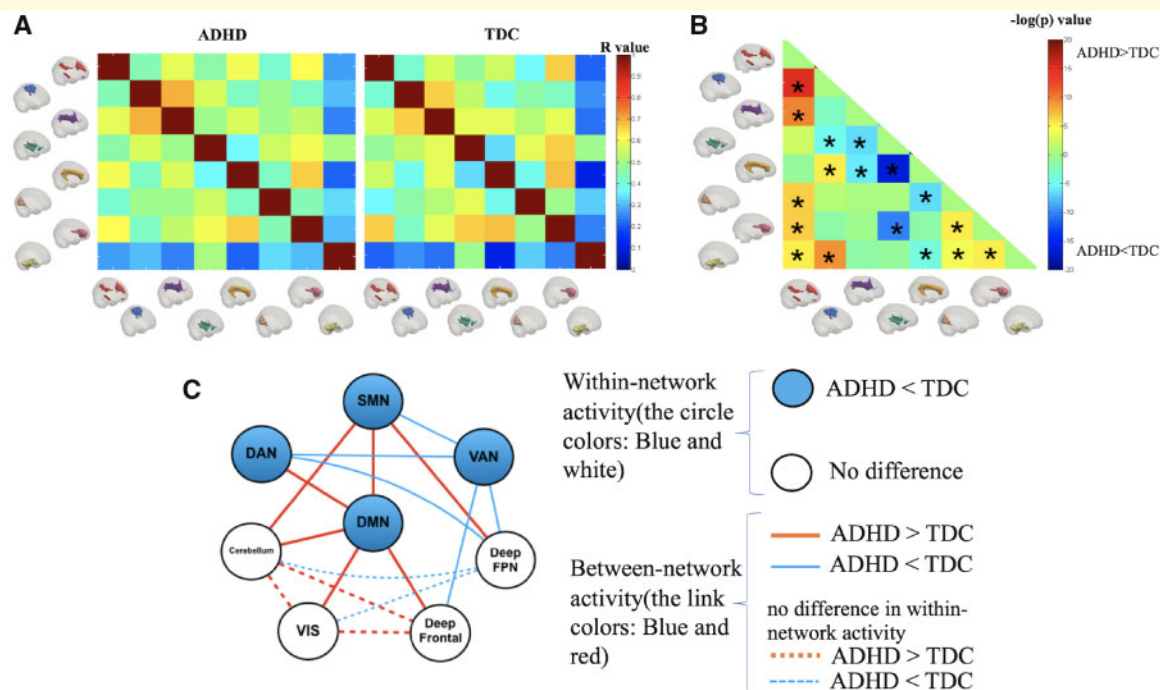
**Figure 2** Analysis of signal amplitude for each WM functional network. (A) Power–frequency graphs showing spontaneous neural activity in each WM network. (B) Differences in the average amplitude of each network between children with ADHD and TDC. Asterisks represent significant differences with age and gender as covariates (\* $P < 0.05$ , Bonferroni corrected).

reveal differences in functional connectivity, as noted in Fig. 3B. We identified that the between-network connectivity of the following 10 network pairs was significantly higher in children with ADHD: DMN–SMN, DMN–DAN, DMN–cerebellum, DMN–Visual, DMN–deep frontal, SMN–deep FPN, SMN–cerebellum, Visual–cerebellum, Visual–deep frontal and cerebellum–deep frontal. In contrast, children with ADHD showed lower connectivity between the following seven network pairs: VAN–SMN, VAN–DAN, VAN–deep FPN, VAN–deep frontal, deep FPN–DAN, deep FPN–Visual and deep FPN–cerebellum. Detailed illustrations of between-group differences in all networks are provided in Supplementary Fig. 2.

To better illustrate the ADHD pattern of the within- and between-network activities compared with TDC, the results are summarized in Fig. 3C, showing abnormalities

in both within-network and between-network activities. These abnormalities existed in one intrinsic network (DMN), two sensory networks (SMN and VIS), three task-control networks (DAN, VAN and deep FPN) and two other networks (cerebellum and deep frontal). In the ADHD group, the DMN and the SMN mainly showed higher connectivity with other networks, whereas the DAN and the VAN generally exhibited lower connectivity, which suggests that abnormal WM networks exhibit two distinct patterns, with DMN and SMN as ‘hot’ networks and the DAN and the VAN as ‘cold’ networks.

We also examined the relationship between WM and GM networks by calculating the temporal correlations between each WM network and each GM network. We found that most WM networks showed high ( $r > 0.6$ ) functional connectivity with their corresponding GM



**Figure 3 Connectivity between the WM network.** (A) Matrices of the Pearson correlation coefficient showing the between-network connectivity for each group. (B) Differences in between-network connectivity. Hot colour means ADHD > TDC, and cool colour means ADHD < TDC. Asterisks represent significant differences with age, gender as covariates ( $P < 0.05$ , Bonferroni corrected). (C) Summary of WM network activities, including within-network activity reflected by signal amplitude and between-network activity revealed by the Pearson correlation. The node represents the WM network (blue: lower amplitude in the ADHD group, white: no difference in the amplitude between groups), and the link represents the connectivity between networks (red: increased connectivity in ADHD, blue: decreased connectivity in ADHD).

networks, which may suggest good activity coupling between WM and GM networks and further validates the existence of WM functional networks (Supplementary Fig. 3).

### Correlation between WM network functional connectivity and clinical measures

We next explored the relationship of significantly increased or decreased functional connectivity with CPRS scores and IVA-CPT scores for all subjects. We found that increased connectivity of the DMN and the SMN was positively correlated with the hyperactivity-impulsivity score and the hyperactivity index in the CPRS and negatively correlated with the attention quotient in the IVA-CPT. In contrast, decreased connectivity of the DAN and the VAN had a positive correlation with the attention quotient in the IVA-CPT but a negative correlation with the hyperactivity-impulsivity score and the hyperactivity index in the CPRS (Fig. 4A, Supplementary Table 2 and Supplementary Fig. 4).

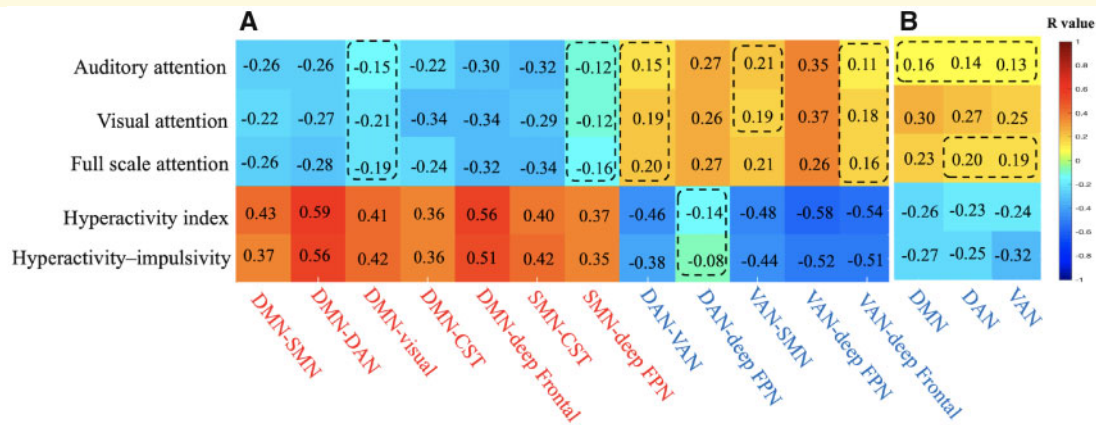
We also found that the within-network activity of the DMN, the DAN and the VAN, which showed lower amplitudes in children with ADHD, was negatively

correlated with hyperactivity behaviour and positively correlated with poor attention performance (Fig. 4B, Supplementary Table 2 and Supplementary Fig. 4).

## Discussion

In this study, we uncovered for the first time the intrinsic functional organization of WM in children with ADHD using clustering analysis with rs-fMRI data in WM. We revealed that children with ADHD illustrated decreased intrinsic neural activity in four of the eight distinct WM networks, i.e. the DMN, the SMN, the DAN and the VAN, which are defined according to the correspondence with the known GM networks. The DMN and the SMN seem to be ‘hot’ networks that showed higher connectivity with other networks and were correlated with more severe hyperactive behaviour, while the DAN and the VAN were considered ‘cold’ networks that showed lower connectivity with other networks and were correlated with poor attention performance. Taken together, our findings extend upon the existing understanding of brain functional networks in ADHD from the perspective of WM functional networks and suggest two patterns of WM network alterations that might underlie ADHD psychopathology of hyperactivity and attention deficit.





**Figure 4** Correlation between (A) functional connectivity, (B) within-network activity and scores of hyperactivity behaviour and attention. The rows indicate functional connectivity/within-network activity, with red indicating higher activity in ADHD and blue indicating lower activity in ADHD, while the columns indicate clinical measures in terms of hyperactivity behaviour and attention performance. The number in each cell is the correlation coefficient ( $r$ ) with red cells indicating a positive correlation and blue cells indicating a negative correlation. The dashed box indicates a nonsignificant correlation ( $P > 0.05$ ).

Previous studies have provided microstructural and functional evidence of abnormalities within circuits or networks in patients with ADHD. Diffusion MRI studies found altered fractional anisotropy in several distributed WM tracts, including frontostriatal fibre tracts (Wu *et al.*, 2014), the corticospinal tract (Bu *et al.*, 2019) and other WM bundles (Hong *et al.*, 2014), which indicates the existence of disrupted WM microstructure. Regarding functional aspects, reduced functional connectivity within regions of the DMN (Posner *et al.*, 2014; Gao *et al.*, 2019), the DAN (Zhu *et al.*, 2008; Cortese *et al.*, 2012; McCarthy *et al.*, 2013), the VAN and the FPN (Hart *et al.*, 2013; Yerys *et al.*, 2019) has been reported. The reduced signal amplitude within the WM functional network in our study supported and extended upon these findings of abnormalities in ADHD from the perspective of WM dysfunction, suggesting reduced neural activities in WM underlying disrupted WM microstructural and hypoactivity of the GM network. In contrast, for the motor network of GM, strong connectivity (O'Halloran *et al.*, 2018) within the motor cortex, as well as atypical strength and patterns (McLeod *et al.*, 2016) of functional connections within and between hemispheres, has been reported. It is plausible that decreased neural activity in the SMN of WM, as observed in our study, could affect information transmission between cortical regions and thus be associated with alterations in how the motor network is connected within and between hemispheres.

In addition to different within-network activity from TDC, we identified abnormal between-network connectivity in children with ADHD. Notably, increased connectivity was mainly observed in the DMN and the sensory networks (i.e., the SMN and visual network), while decreased connectivity was observed for the task-control networks (i.e., the DAN, VAN and deep FPN). Previous

fMRI studies of ADHD examining the interaction between the DMN and other networks have revealed deficient regulation of DMN activity from task-control networks (Sonuga-Barke and Castellanos, 2007; Fair *et al.*, 2010; McCarthy *et al.*, 2013; Posner *et al.*, 2014; Sidlauskaitė *et al.*, 2016), and similar findings for DMN were also presented in individuals with familial risk for depression and patients with OCD (Posner *et al.*, 2016, 2017). Normally, the DMN can be deactivated during external goal-directed tasks and activated during internally focused cognition. Persistent DMN hyperactivity in ADHD interferes with sustained attention, which manifests as mind-wandering and lapses or errors in goal-directed behaviour (Gallo and Posner, 2016). In our study, we found that the DMN of WM had increased connectivity with all other WM networks and absent connections with the FPN of WM, and the increased between-network connectivity for DMN was correlated with increased inattention. Our results suggest that the DMN interference model in ADHD is further supported and extended by WM system since diminished connectivity between DMN and FPN (cognitive control network) also exists in BOLD signal from WM. As previous fMRI study of GM network of ADHD has indicated that mind-wandering dominated by interference of DMN may impair the normal attention function (Posner *et al.*, 2014), here, we postulated that DMN in WM plays a similar important role in attention regulation as it does in GM.

Motor and sensory circuits have been implicated in the pathophysiology of ADHD (Valera *et al.*, 2010; Proal *et al.*, 2011; O'Halloran *et al.*, 2018). Previous studies using intrinsic functional connectivity analysis have reported high network centrality in the somatomotor cortex (Di Martino *et al.*, 2013) and the visual cortex (Wang *et al.*, 2009) in patients with ADHD. Thus, it is



plausible that the functional connectivity in the motor and visual networks of WM could be abnormal. Carmona *et al.* (2015) revealed an increased degree of functional connectivity in the somatomotor cortex and the visual cortex and a decreased degree of connectivity in executive control systems in children with ADHD. In the current study, we found that the motor-sensory system of WM, which contains the SMN, the visual network and the cerebellum, showed increased connectivity with most networks but decreased connectivity for two network pairs—visual-FPN and SMN-VAN. Therefore, the current study not only provides evidence for the predominance of sensorimotor processing and less interaction with attentional and executive control regions in ADHD but also suggests that WM activity may play a corresponding role in cortical activity.

In addition to increased connectivity, we observed several decreased between-network connectivity, predominantly in the task-control network. Compared with TDC, we found significantly decreased between-network connectivity in children with ADHD in both the DAN and the VAN. The DAN functions in goal-directed top-down attention processing, while the VAN supports the identification of salient or novel environmental factors. Normally, activation of the DAN and the VAN increases together when reorientation of attention is required. Hypofunction of these two networks has been proposed in ADHD (Castellanos and Proal, 2012; Cortese *et al.*, 2012; McCarthy *et al.*, 2013). Clinical symptoms of ADHD- and ADHD-related deficits in adaptive switching to external salient stimuli have been linked to deficient VAN engagement and disrupted information exchange between the VAN and the DAN (Helenius *et al.*, 2011; Cubillo *et al.*, 2012). Our finding regarding decreased connectivity of the WM of the attention network is in line with that of GM. We speculate that the decreased connectivity between WM networks underpins deficits in the function of the GM network. Thus, we provide further evidence of deficiency of the DAN and the VAN in attention processing. Moreover, the decreased connectivity between the deep FPN and other networks, especially between the deep FPN and attention networks, identified in our study might suggest less engagement of the FPN of WM in ADHD. Since sustained attention requires both engagement of the FPN, the DAN and the VAN and suppression of the DMN, our results suggest a similar disrupted functional connectivity pattern within the WM network, which could play a role in distractibility in ADHD.

Our findings must be considered in light of some limitations. First, the limited number of TDC in the current study may bias the clustering results. It is necessary to include a larger and more balanced sample in further research to examine the stability of the current results. Second, as fibre tracts cross each other, mixed signals from different functional systems may be detected in the same WM locations. Therefore, it is difficult to clarify

the precise source of the fMRI signals in the WM. We would like to compare the WM network with WM tracts identified by diffusion tensor imaging to further confirm the overlap between functional networks and fibre tracts in future studies. Third, the conclusion should be taken with caution since we recruited ADHD children without comorbidities and treatment to reduce clinical confounding factors, which make our sample differ from typical ADHD population. Fourth, though there may be profound differences between ADHD presentations and importance of subtyping analysis, we were not able to perform subtyping analysis due to small sample size and imbalance number of subjects in each group. Further studies are needed to examine alterations in functional WM networks for ADHD subtypes.

## Conclusion

In summary, we for the first time characterized the intrinsic functional organization of WM networks in children with ADHD. Our findings demonstrated two distinct WM network patterns—the DMN and the SMN as ‘hot’ networks and the DAN and the VAN as ‘cold’ networks—suggesting that abnormal WM network interactions may be implicated in hyperactivity and attention deficit. These results offer a new perspective for studying WM in ADHD and help further understand the network basis of ADHD.

## Supplementary material

Supplementary material is available at *Brain Communications* online.

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## Competing interests

The authors report no competing interests.

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