

# Functional Connectivity of White Matter and Its Association with Sleep Quality

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**Purpose:** Functional magnetic resonance imaging (fMRI) has been widely adopted to investigate the neural activity in gray matter (GM) in the field of sleep research, but the neural activity in white matter (WM) has received much less attention. The current study set out to test our hypothesis that WM functional abnormality is associated with poor sleep quality.

**Participants and Methods:** K-means clustering analysis was performed on 78 healthy adults drawn from the Human Connectome Project dataset to extract stable WM functional networks (WM-FNs) and GM-FNs. The differences in functional connectivity within WM-FNs and between WM- and GM-FNs, as well as the power spectrum between good sleep quality group (Pittsburgh Sleep Quality Index (PSQI) <6, daytime dysfunction = 0) and poor sleep quality group (PSQI >6, daytime dysfunction >0) were examined between groups with good and poor sleep quality. Additionally, linear relationships between sleep quality and altered functional characteristics of WM-FNs were evaluated.

**Results:** Functional connectivity between middle and superficial WM-FNs, short- and long-range functional connectivity between WM- and GM-FNs were decreased in poor sleepers and negatively correlated with PSQI score. The mean amplitudes of right sensorimotor WM networks at whole, high and low frequency bands were higher in poor sleepers and were positively correlated with PSQI score.

**Conclusion:** WM functional abnormality is associated with poor sleep quality. The neurobiological mechanisms that underlie the functional alterations of WM-FNs in poor sleepers need to be investigated in future studies.

**Keywords:** human connectome project, sleep quality, white matter, functional connectivity, functional magnetic resonance imaging

## Introduction

Sleep plays an essential role in the restoration and preservation of optimal brain function, although its functions remain to be fully elucidated. Poor sleep quality or sleep loss not only has a negative influence on attention, cognition, emotion and motion,<sup>1,2</sup> but also increases the risk of neurological,<sup>3,4</sup> psychiatric<sup>5,6</sup> and cardiovascular diseases.<sup>7,8</sup>

The neural mechanisms that underlie poor sleep quality have been investigated in many aspects, such as gray matter (GM) structure and function, white matter (WM) integrity and immune system,<sup>9–11</sup> yet how WM functional activity is related to sleep quality has received much less attention, especially in humans. Brain WM consists of axons and myelin sheath that facilitate electrical signal transmission between neurons. Animal studies have shown that sleep loss reduces myelin thickness and down-regulates transcripts involving myelin formation.<sup>12–14</sup> In humans, poor sleep quality and sleep disorders were found to be associated with lower WM integrity in multiple brain regions.<sup>15–17</sup> In addition, reduced WM structural connectivity has been demonstrated to be associated with poor sleep quality.<sup>18,19</sup> Considering the complicated interplay between brain structure and function, these findings lead us to the hypothesis that WM structural alterations related to poor sleep quality may in turn lead to WM functional abnormality.

Relative to the abundance of studies assessing the links between WM structural characteristics and sleep quality/quantity, research investigating the role of WM functional activity played in sleep remains limited in humans.

Currently, the blood oxygenation level-dependent functional MRI (BOLD-fMRI) technique has been proven to be a powerful tool to assess whole brain functional activity.<sup>20</sup> In recent decades, BOLD-fMRI has been used to accumulate knowledge on how sleep quality/sleep disorder affects neural activity and network organization in GM.<sup>21,22</sup> However, to our knowledge, no studies have evaluated the association between WM functional activity and sleep quality using WM BOLD signals. This may be ascribed to the engrained belief in the field of fMRI research that BOLD signals in WM have no physiological information and usually are regressed out as “nuisance” during BOLD-fMRI data preprocessing. Recent studies have demonstrated that BOLD signals in WM are robustly detectable under resting state and task conditions, providing evidence that BOLD signals in WM are related to brain functional activity and deserve greater attention.<sup>23,24</sup>

In this study, we drew 78 well-screened young healthy adults from the Human Connectome Project (HCP) repository to test our hypothesis that functional alterations of WM are associated with poor sleep quality indexed by WM functional connectivity and spontaneous activity. Functional connectivity is a powerful tool to detect the coupled activity between different brain areas/networks.<sup>25</sup> Accumulating studies have demonstrated that the functional connectivity in GM alters under poor sleep quality,<sup>26</sup> sleep/wake states,<sup>27</sup> sleep deprivation,<sup>28</sup> and sleep disorders.<sup>29</sup> Frequency characteristics embedded in spontaneous BOLD signal fluctuations may reflect different neural activities and physiological functions.<sup>30</sup> Power spectrum analysis has found that fluctuation amplitudes of WM functional networks (FNs) change with sleep/wake states.<sup>31</sup> Yet the relationship between frequency characteristics in WM and sleep quality has not been investigated. To this end, WM-FNs were obtained using clustering analysis based on WM BOLD-fMRI signals, and functional connectivity within WM-FNs and between WM- and GM-FNs were calculated. Fast Fourier transform was used to calculate the power spectrum at different frequency bands for each WM-FN. Then, the alterations of the abovementioned parameters were investigated between groups with good and poor sleep quality.

## Materials and Methods

### Participants

Young adult participants were selected from the Human Connectome Project (HCP) Data S1200 release. Individuals with severe neurodevelopmental disorders (eg autism), documented neuropsychiatric disorders (eg schizophrenia or depression) or neurologic disorders (eg Parkinson's disease), diabetes and high blood pressure were excluded to minimize the possible confounding effects of these diseases on the data analysis.<sup>32</sup> Additionally, participants with identified HCP quality control issues (QC\_Issue) or without resting-state fMRI data were also excluded from this study, resulting in 162 participants for the subsequent sleep measure. We had access to the HCP database through a signed agreement with Washington University–University of Minnesota Consortium of the Human Connectome Project. The data usage in this study was approved by the Institutional Review Board of Washington University. Informed consent was obtained from all participants. This retrospective study has been exempted by the local Institutional Review Board in compliance with the exemption policy that data sources are publicly available or the information is recorded by the HCP investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects. We confirm that our study complies with the Declaration of Helsinki.

### Sleep Measures

Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI), a self-reported questionnaire to measure seven components of sleep: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleep medication, and daytime dysfunction. To investigate the effect of sleep quality on WM functional networks, PSQI total score and its seventh sub-item score (Comp\_7, daytime dysfunction) were adopted to further screen the selected 162 participants. Participants with PSQI total score of <6 and Comp 7=0 were selected as good sleepers ( $n = 55$ , 31 males, aged  $28.4 \pm 4.1$  years), whereas people with PSQI total score of >6 and Comp 7 >0 were selected as poor sleepers ( $n = 23$ , 12 males, aged  $29.0 \pm 3.6$  years).<sup>33</sup> Finally, 78 participants were included in the following analysis.

## MRI Data Acquisition

The MRI data were obtained from the public HCP repository (<https://db.humanconnectome.org>) as part of the HCP 1200 subjects release. The data were acquired on a 3T Siemens Skyra scanner with a 32-channel head coil (Siemens AG, Erlangen, Germany). Resting state fMRI (rsfMRI) data were acquired using a multi-band gradient echo-planar imaging sequence with parameters of TR 720ms, TE 33.1 ms, 2 mm isotropic voxel size, 1200 volumes. Each rsfMRI session consisted of 2 runs with left-to-right and right-to-left phase encoding directions. T1 weighted images were acquired using a 3D magnetization-prepared rapid gradient echo (MPRAGE) sequence with parameters of TR 2.4 s, TE 2.14 s, and 0.7mm isotropic voxel size.

## Preprocessing of MRI Data

The MRI data obtained from HCP repository were preprocessed through the minimal preprocessing pipeline (MPP).<sup>34</sup> Briefly, T1-weighted images were preprocessed including gradient distortion correction, bias field correction, nonlinear registration to MNI space and parcellation following Freesurfer pipeline. MMP steps for rsfMRI data included motion correction, distortion correction and nonlinear registration to MNI space. Then the preprocessed rsfMRI data underwent regression of nuisance variables, including head movement parameters from the output of MPP pipeline, as well as five principal components extracted from each subject's CSF mask using a component-based noise correction method (CompCor),<sup>35</sup> and followed by a linear trend correction and band-pass temporal filtering (0.01–0.15Hz). The rsfMRI data were spatially smoothed (FWHM = 4) within WM mask and GM mask separately to avoid mixing WM and GM signals.

## Clustering of WM and GM Functional Networks

WM parcellation derived from Freesurfer across all subjects was averaged. Voxels identified in >60% of the subjects were selected to generate a group-level WM mask in order to keep as many valuable voxels due to individual differences in WM.<sup>23,31</sup> A group-level GM mask was reconstructed in a similar manner. Then the group-level WM and GM masks were compared with fMRI data; voxels having functional data of less than 80% of the subjects were removed. The resulting group-level WM and GM masks had 66,888 and 60,012 voxels, respectively.

To reduce the computational demands, the group-level WM mask was downsampled in an interchanging grid manner.<sup>23</sup> Specifically, every second voxel along the image rows and columns was kept and shifted by 1 between slices to reduce missing columns of data. Pearson's correlation coefficients between each group-level WM voxel and downsampled voxels were calculated, resulting in a correlation matrix ( $66,888 \times 10,796$ ) for each subject. Then a group-level correlation matrix was obtained by averaging the correlation matrices across all subjects. K-means clustering (distance metric correlation, 10 replicates) was performed on the group-level correlation matrix, with k ranging between 2 and 22. In order to obtain the most stable number of WM networks, the group-level correlation matrix was randomly divided into four folds along the column dimension. For each k, clustering was performed on each fold, and the adjacency matrix was calculated. Dice's coefficient was calculated to compare the similarity of every pair of these four adjacency matrices. Then, the Dice's coefficients were averaged to assess the stability of clustering for each k. For the GM, similar k-means clustering and stability analysis were performed to identify the stable GM functional networks.

## Functional Connectivity of WM Functional Networks

After clustering analysis, the mean rsfMRI time courses for each WM-FN and GM-FN were extracted by averaging the time courses across all voxels within the same network for each subject. Then, Pearson's correlation coefficients between each pair of WM-FNs were calculated and transformed to Fisher's z score. In addition, Pearson's correlation coefficients between every pair of WM-FN and GM-FN were also calculated to evaluate the relationship between WM and GM.

## Power Spectral Analysis of WM Functional Networks

Spontaneous oscillations of BOLD signals at different frequency bands may reflect different neural activities and physiological functions.<sup>30,36</sup> Consistent with a previous study on WM BOLD signals, the whole band (band A: 0.01–

0.15 Hz) was further divided into two sub-bands (band B: 0.01–0.08 Hz; band C: 0.08–0.15 Hz).<sup>37</sup> Signal amplitudes in each frequency were calculated using Fourier transform (MATLAB's FFT function), and then the amplitudes at each frequency band were averaged for each WM- and GM-FN of each subject.

## Statistical Analyses

The group difference in sex was tested using chi-square test, and the differences in age, PSQI total score, daytime dysfunction score, functional connectivity within WM-FNs and between WM-FNs and GM-FNs, and frequency characteristics between good sleepers and poor sleepers were tested using two sample *t*-test ( $P < 0.05$ , false discovery rate (FDR) corrected). Pearson's correlation analysis was used to measure the relationship between PSQI total score and significant functional connectivity as well as frequency characteristics ( $P < 0.05$ , Bonferroni corrected).

## Results

### Demographic Characteristics

Demographic information and sleep quality data are summarized in Table 1. There were no significant differences between good sleepers and poor sleepers in age ( $t = -0.653$ ,  $P = 0.516$ ) or sex ( $\chi^2 = 0.115$ ,  $P = 0.734$ ), but the poor sleepers showed higher PSQI total score ( $t = -16.327$ ,  $P < 0.001$ ) and daytime dysfunction score (Comp\_7,  $t = -17.472$ ,  $P < 0.001$ ).

### Identification of WM and GM Functional Networks

K-means clustering was adopted to identify WM-FNs and GM-FNs from 78 healthy young adults. Dice's coefficients at different  $k$  are shown in Figure 1. The local peaks of the Dice's coefficients that represented the most stable clustering were located at  $k = 2, 5, 7, 14$  (Figure 1A) for WM, and at  $k = 2, 4, 10, 12$  for GM (Figure 1B). In order to characterize the most detailed information of WM-FNs and GM-FNs,  $k = 14$  and  $k = 12$  clusters were adopted for WM and GM, respectively, in the following analysis.

The 14 WM-FNs included one cerebellar network and 13 cerebral networks (Figure 2A). Consistent with previous studies, the WM-FNs could be classified as deep, middle and superficial layers based on the spatial locations (Figure 2B).<sup>23</sup> The detailed information about these WM-FNs is summarized in Table 2. Twelve GM-FNs were identified, closely corresponding to known cortical network sub-divisions,<sup>38–40</sup> which were labeled as visual network (GM1), posterior cerebellar network (GM2), anterior cerebellar network (GM3), default mode network A (GM4), sensorimotor network (GM5), control network A (GM6), ventral attention network (GM7), control network B (GM8), default mode network B (GM9), putamen–pallidum network (GM10), thalamus–caudate network (GM11), and limbic–temporal network (GM12) (Figure 3).

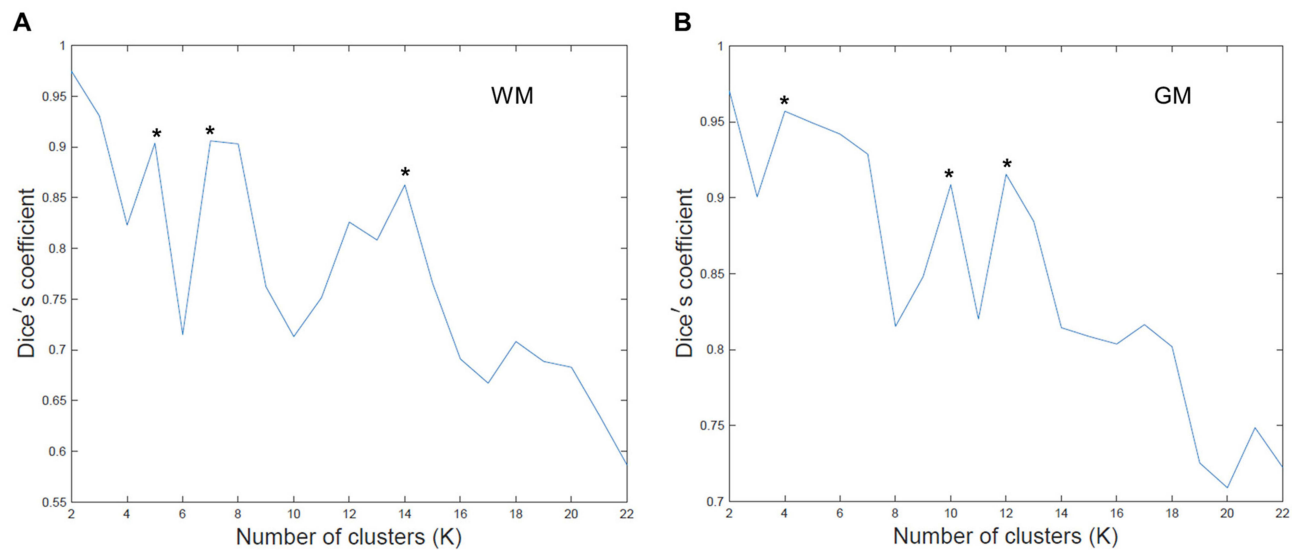
### Functional Connectivity Within WM-FNs

The relationship between different WM-FNs was evaluated by functional connectivity. Based on two sample *t*-tests, five pairs of WM functional networks showed a significant difference between good sleepers and poor sleepers (Figure 4). Functional connectivity between posterior corona radiata (WM13) and bilateral superior temporal and motor (WM4, WM8) and left sensorimotor (WM9) networks, between visual (WM7) and left sensorimotor (WM9), between anterior

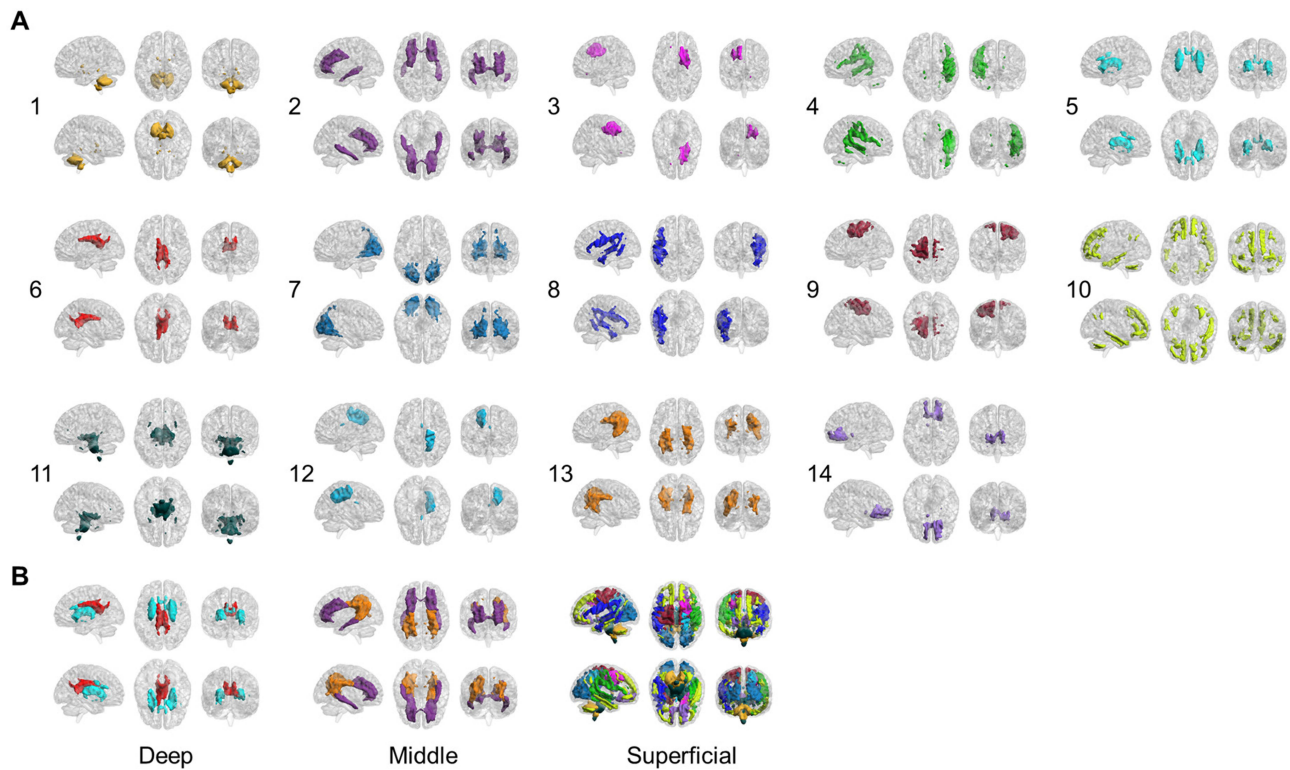
**Table 1** Demographic Characteristics of Good Sleeper and Poor Sleeper Groups

Demographics	Good Sleeper	Poor Sleeper	t or $\chi^2$	P
N	55	23	–	–
Age (y)	28.4 ± 4.1	29.0 ± 3.6	–0.653	0.516
Sex (male/female)	31/24	12/11	0.115	0.734
PSQI total score	2.9 ± 1.4	9.4 ± 1.9	–16.327	<0.001
Daytime dysfunction	0 ± 0	1.3 ± 0.6	–17.472	<0.001

**Abbreviation:** PSQI, Pittsburgh Sleep Quality Index.



**Figure 1** Dice's coefficients at different clustering number K for WM (A) and GM (B). \* Indicates the local peaks that represented the most stable clustering results.



**Figure 2** (A) Six views for each of the 14 WM functional networks. (B) WM functional networks can be spatially classified as deep, middle and superficial layers.

corona radiata network (WM2) and right superior temporal and motor (WM4) were significantly decreased in poor sleepers ( $P < 0.05$ , FDR corrected).

## Functional Connectivity Between WM-FNs and GM-FNs

To further explore the relationship between WM-FNs and GM-FNs, functional connectivity was also calculated between each pair of WM-FN and GM-FN. The two groups showed no differences in functional connectivity between WM-FNs



**Table 2** Spatial Information of WM Functional Networks

Label	WM Network	Layer
WM1	Cerebellar network	Superficial
WM2	Anterior corona radiata network	Middle
WM3	Right superior frontal network	Superficial
WM4	Right superior temporal-motor network	Superficial
WM5	Internal-external capsule network	Deep
WM6	Body of corpus callosum network	Deep
WM7	Occipital network	Superficial
WM8	Left superior temporal-motor network	Superficial
WM9	Left sensorimotor network	Superficial
WM10	Tempofrontal network	Superficial
WM11	Brainstem network	Superficial
WM12	Right sensorimotor network	Superficial
WM13	Posterior corona radiata network	Middle
WM14	Orbitofrontal network	Superficial

**Abbreviation:** WM, white matter.

and GM-FNs after FDR correction for multiple comparisons. But the poor sleepers showed a decreased trend in functional connectivity between posterior corona radiata (WM13) and cortical visual network (GM1) ( $P < 0.01$ , uncorrected) and subcortical networks including putamen-pallidum network (GM10) ( $P < 0.01$ , uncorrected) and thalamus-caudate network (GM11) ( $P < 0.01$ , uncorrected), between orbitofrontal network (WM14) and two cerebellar networks (GM2, GM3) ( $P < 0.005$ , uncorrected) (Figure 5).

## Frequency Characteristics of WM-FNs

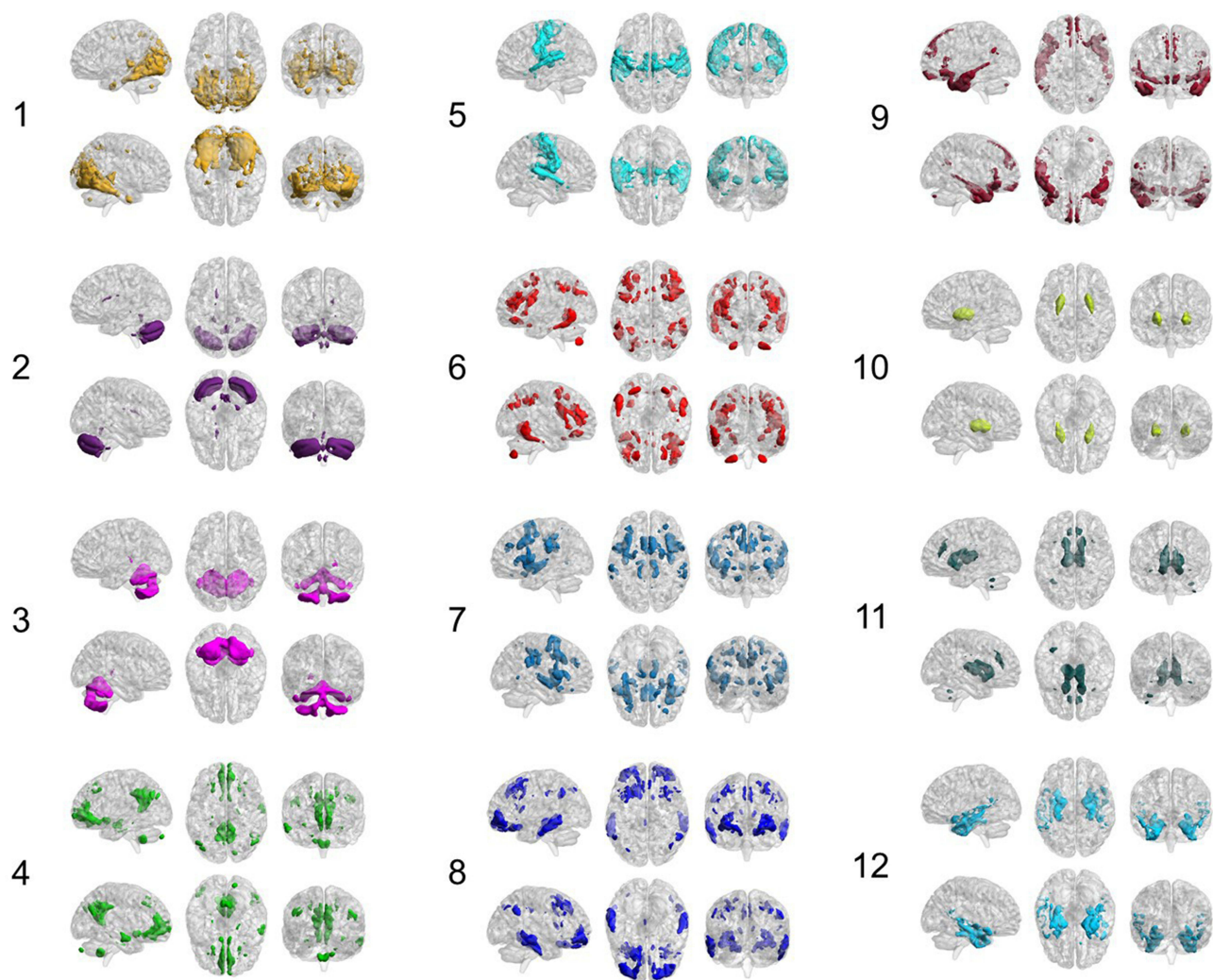
Based on the power spectral analysis, for both groups, all WM-FNs showed a gradual decrease in amplitude with increased frequency. The superficial and deep WM-FNs showed maximal amplitude at  $\sim 0.01$ Hz, whereas the middle layer WM-FNs (WM2 and WM13) showed maximal amplitude at  $\sim 0.07$ Hz (Figure 6A). The amplitudes at the whole frequency (band A: 0.01–0.15Hz) and high frequency (band C: 0.08–0.15Hz) were increased in the right sensorimotor network (WM12) in poor sleepers, whereas the amplitude at low frequency (band B: 0.01–0.08Hz) showed an increased trend in poor sleepers without passing FDR correction ( $P < 0.05$ , uncorrected) (Figure 6B).

## Relationship Between PSQI Total Score and Altered Characteristics of WM-FNs

Pearson's correlation analysis was used to measure the association between PSQI total score and significant altered functional connectivity within WM-FNs and between WM-FNs and GM-FNs, as well as the frequency characteristics. The mean amplitudes of WM12 in the whole band (band A: 0.01–0.15Hz), low frequency band (band B: 0.01–0.08Hz) and high frequency band (band C: 0.08–0.15Hz) were found to be positively correlated with PSQI total score ( $P < 0.05$ , Bonferroni corrected) (Figure 7A). Functional connectivities between WM networks including WM13–WM4 and WM13–WM8 were negatively correlated with PSQI total score ( $P < 0.05$ , Bonferroni corrected), while functional connectivities between WM9–WM7 and between WM4–WM2 showed a negative correlated trend with PSQI total score ( $P < 0.05$ , uncorrected) (Figure 7B). In addition, functional connectivities between WM and GM networks including WM13–GM1 and WM14–GM3 were negatively correlated with PSQI total score ( $P < 0.05$ , Bonferroni corrected), functional connectivities including WM13–GM10, WM13–GM11 and WM14–GM2 showed a negative correlated trend with PSQI total score ( $P < 0.05$ , uncorrected) (Figure 7C).

## Discussion

White matter, as a major component of human brain tissue, plays a crucial role in optimal brain function. Despite this, WM activity has been overlooked and misunderstood in the field of fMRI research.<sup>41</sup> Recent studies suggest that WM BOLD signal is strongly related with WM microstructure, energy demanding and neurovascular coupling,<sup>42–44</sup> although



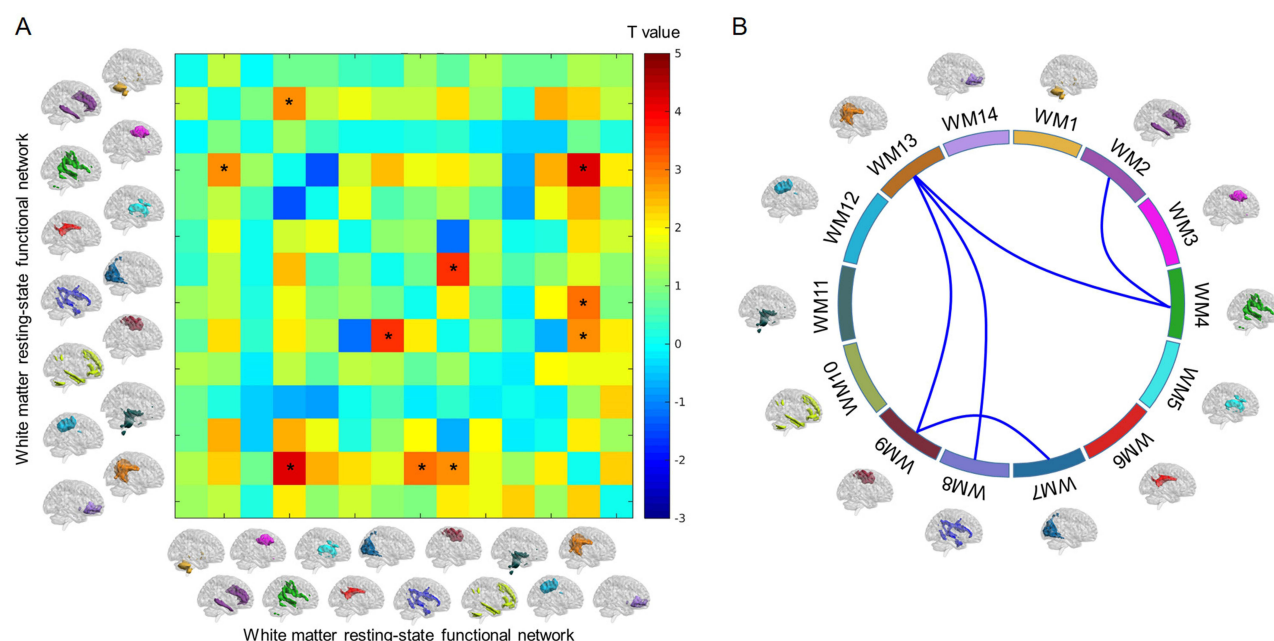
**Figure 3** Spatial layout of 12 identified GM functional networks. 1: visual network; 2: posterior cerebellar network; 3: anterior cerebellar network; 4: default mode network A; 5: sensorimotor network; 6: control network A; 7: ventral attention network; 8: control network B; 9: default mode network B; 10: putamen–pallidum network; 11: thalamus–caudate network; 12: limbic–temporal network.

the precise biophysical basis of the BOLD signal in WM remains to be fully revealed. In this study, the association between sleep quality and functional characteristics of WM-FNs was investigated. Fourteen distinct WM-FNs were identified by k-means clustering analysis based on WM BOLD signals. Then, the functional connectivity within the WM-FNs and between WM-FNs and GM-FNs, as well as power spectral characteristics, were compared between good sleep quality group and poor sleep quality group. In addition, the correlations between PSQI total score and the significantly altered characteristics of WM-FNs were also evaluated.

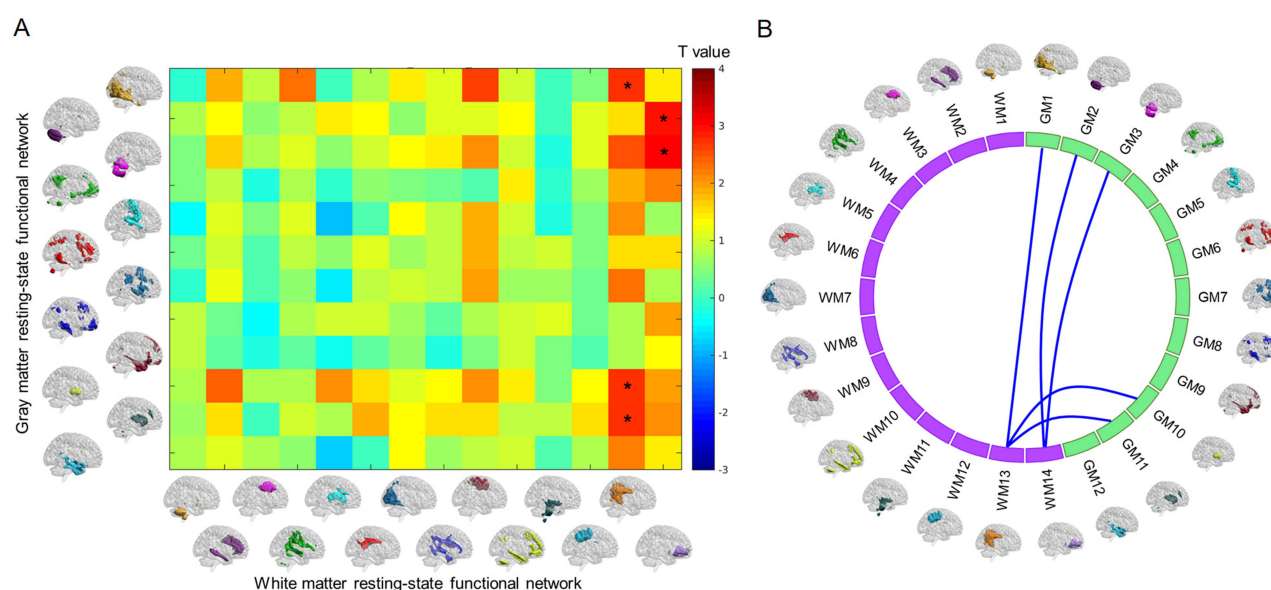
## Decreased Functional Connectivity Within WM-FNs is Associated with Poor Sleep Quality

Compared to good sleepers, poor sleepers showed decreased functional connectivity mainly between anterior/posterior corona radiata and bilateral superior temporal-motor networks and left sensorimotor networks (WM13–WM4, WM13–WM8, WM13–WM9, WM2–WM4), as well as visual and left sensorimotor networks (WM7–WM9).

As corona radiata relays information to and from the widespread cerebral cortex, the decreased functional connectivity between corona radiata and sensorimotor, superior temporal-motor networks found in this study may underlie the functional neural basis for the cognitive and behavioral deficits of poor sleepers. Despite a lack of documentation on the



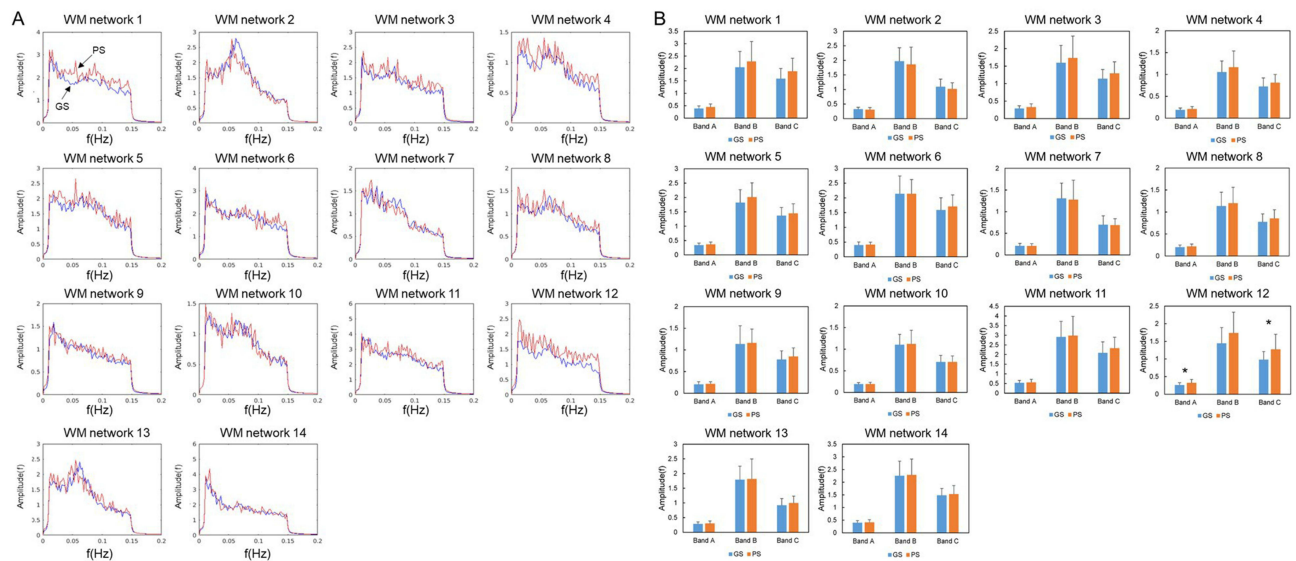
**Figure 4 (A)** Differences in functional connectivity within WM-FNs between good sleepers and poor sleepers. The color bar shows T value of two sample t-test. \*Represents significant difference after FDR correction. **(B)** Five pairs of WM-FNs that showed significant difference in functional connectivity between good sleepers and poor sleepers.



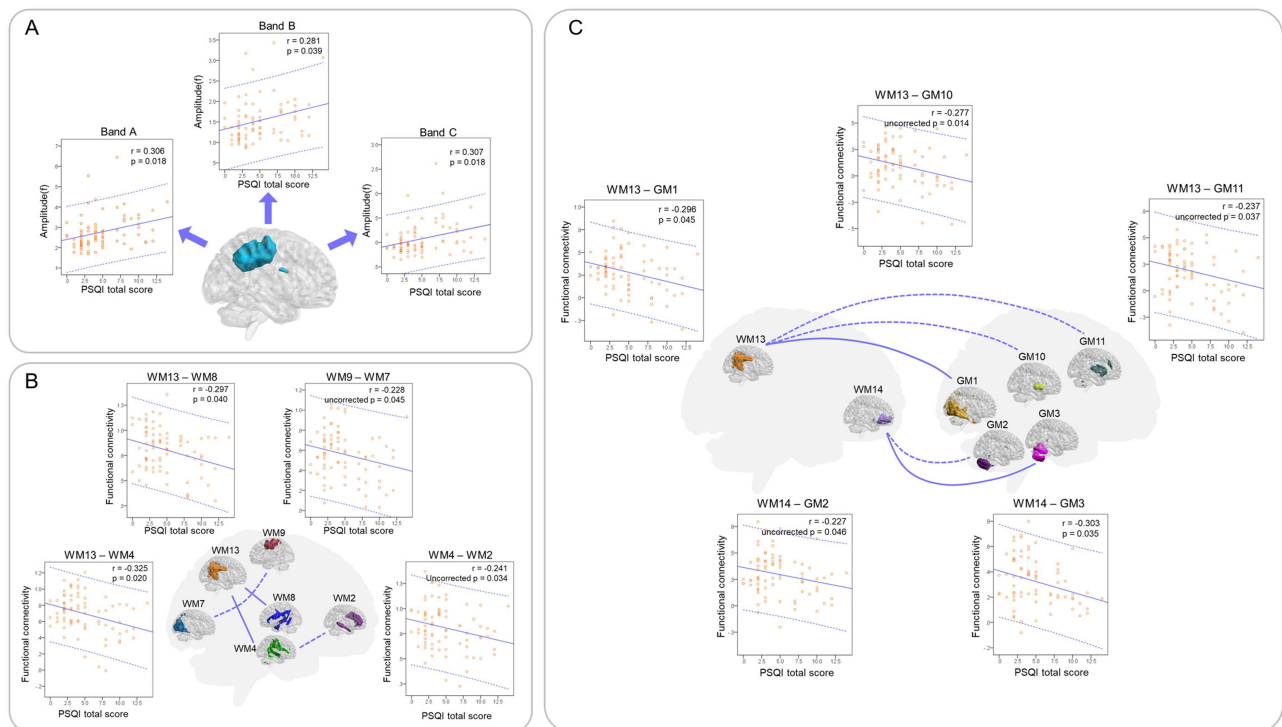
**Figure 5 (A)** Differences in functional connectivity between WM and GM functional networks between good sleepers and poor sleepers. The color bar shows T value of two sample t-test. \*Represents statistical significance ( $P < 0.05$ , uncorrected). **(B)** Five pairs of functional connectivity between WM-FNs and GM-FNs showed a decreased trend in poor sleepers.

functional abnormality in WM-FNs, impaired structural integrity in corona radiata was found in subjects with poor sleep quality, insomnia or major depressive disorders.<sup>15,45,46</sup> Dysfunction of neural activity may arise at the local or network level as a result of the impaired structural integrity of WM. Accumulative studies have identified that structural alterations of corona radiata are linked with behavioral deficits, particularly in attention and cognitive control.<sup>47–49</sup> Therefore, the decreased functional connectivity within the WM-FNs in this study, especially those involving corona radiata, may serve as a convergent neural basis mediating the behavioral consequences of sleep. Furthermore, these





**Figure 6** (A) Power spectrum of 14 WM functional networks for good sleepers and poor sleepers. (B) Differences of mean amplitude in three frequency bands between good sleepers and poor sleepers. GS: good sleepers; PS: poor sleepers; Band A 0.01–0.15 Hz; Band B 0.01–0.08 Hz; Band C 0.08–0.15 Hz. \*Represents the statistical significance after FDR correction ( $P < 0.05$ , FDR corrected).



**Figure 7** Correlations between PSQI total score and altered characteristics of WM functional networks. (A) The amplitudes of three frequency bands of WM8 network were positively correlated with PSQI total score ( $P < 0.05$ , Bonferroni corrected). (B) Two white matter functional connectivities were negatively correlated with PSQI total score (WM13–WM8, WM13–WM8,  $P < 0.05$ , Bonferroni corrected). Functional connectivity between WM9–WM7 and between WM2–WM4 showed negative correlated trend with PSQI total score ( $P < 0.05$ , uncorrected), but did not pass the Bonferroni correction (illustrated as dotted lines in glass brain). (C) Two functional connectivities between GM and WM were negatively correlated with PSQI total score (WM13–GM1, WM14–GM3,  $P < 0.05$ , Bonferroni corrected). Functional connectivity between WM13–GM10, between WM13–GM11 and between WM14–GM2 showed negative correlated trend with PSQI total score ( $P < 0.05$ , uncorrected), but did not pass the Bonferroni correction (illustrated as dotted lines in glass brain). The fitted dotted lines represent 95% confidence interval.

decreased functional connectivities between posterior corona radiata and bilateral superior temporal-motor networks (WM13–WM4, WM13–WM8) were negatively correlated with PSQI total score, suggesting the lower the functional connectivity, the poorer the sleep quality. The links between WM functional connectivity and cognition and behavioral performance should be investigated in future studies.

## Decreased Functional Connectivity Between WM-FNs and GM-FNs is Associated with Poor Sleep Quality

Poor sleepers showed a trend of decreased functional connectivity in two pathways: short-range and long-range pathways. The short-range communication included functional connectivity between posterior corona radiata (WM13) and visual cortex, subcortical nuclei including putamen, pallidus, thalamus and caudate (GM1, GM10, GM11). The long-range communication includes orbitofrontal network (WM14) and two cerebellar networks (GM2 and GM3). It should be noted that these alterations did not survive in the FDR correction; however, in the subsequent correlation analysis, the functional connectivity between WM13–GM1 and between WM14–GM3 showed significant negative correlations with PSQI total score, while those between WM13–GM10, between WM13–GM11, and between WM14–GM2 showed a trend of negative correlation ( $P < 0.05$ , uncorrected).

The subcortical nuclei above are usually involved in networks with functions of sleep and arousal regulation. The thalamus acts as a relay station to process the information between the cortex and sleep–wake control regions of the lower brain, playing a dual-role in controlling wakefulness and sleep.<sup>50</sup> The caudate nuclei have been suggested to be a key region for sleep because of their role in reward/sensory processing and regulation of cortical excitability. Reduced recruitment of caudate (reduced BOLD response) during executive functioning was associated with hyper-arousal severity in patients with insomnia.<sup>51</sup> Caudate volume was also found to be significantly correlated with sleep duration.<sup>52</sup> The putamen receives afferent input from different cortical regions and projects efferent output to the cortex through the thalamus.<sup>53</sup> Atrophic changes in the putamen were significantly associated with higher arousal in patients with chronic insomnia.<sup>54</sup> A positron emission tomography (PET) study reported that sleep benefit in patients with Parkinson's disease is associated with the dopamine transporter expression in putamen.<sup>55</sup> An animal study found that lesions in globus pallidus remarkably reduced sleep by ~45%, suggesting that globus pallidus promotes sleep.<sup>56</sup> Taken together, the structural and functional disruptions in the above subcortical nuclei may alter the neural activity in these regions, which in turn contribute to poor sleep quality. The decreased functional connectivity between posterior corona radiata and these subcortical nuclei found in this study reflects the desynchronized neural activity, indicating impaired communication in the short-range pathway for subjects with poor sleep quality. Given the weak correlation between the functional connectivity of the subcortical nuclei and posterior corona radiata with PSQI total score, caution should be taken in the deduction of sleep quality based on functional connectivity. Further study incorporating molecular and electrophysiological evidence would be helpful to clarify the biological relevance of the WM-FNs variations to sleep quality.

Decreased functional connectivity associated with poor sleep quality was also found in long-range pathways in this study involving orbitofrontal networks and cerebellum networks. Although the link between the functional connectivity of this long-range pathway and sleep quality remains to be elucidated, the breakdown of the functional connectivity of this pathway was found to underlie the negative symptoms (such as lack of motivation, expressive deficits and anhedonia) or suboptimal cognitive control in patients with schizophrenia or emotional disorders.<sup>57,58</sup> This evidence suggests behaviorally dependent network activity of the pathway between prefrontal cortex and cerebellum mediating emotional intelligence and cognitive adjustment. Since these symptoms are shared in subjects with sustained poor sleep quality or insomnia, the decreased functional connectivity of the orbitofrontal–cerebellar pathway may underlie the subjective perceptions of daytime performance. In addition, WM structural changes in orbitofrontal regions affected by sleep deprivation and habitual sleep durations have been found in previous studies.<sup>45,59</sup> Cerebellum has been increasingly recognized to closely interact with neocortex.<sup>60,61</sup> Malfunction of cerebellum can change the sleep–wake cycle, leading to sleep disorders and impaired memory formation and consolidation.<sup>62</sup> The decreased functional connectivity between orbitofrontal and cerebellar cortex implied a disrupted interaction between cerebellum and cerebral cortex, and such

disruption may also contribute to poor memory performance, which is commonly seen as a consequence of sleep deprivation and poor sleep quality.<sup>63</sup>

## Altered Frequency Characteristics of WM-FNs is Associated with Sleep Quality

For both good sleepers and poor sleepers, middle layer WM-FNs showed a distinct activity pattern with maximal amplitude at ~0.07Hz, whereas superficial and deep WM-FNs showed maximal amplitude at ~0.01Hz. Such a distinct pattern was also found in previous studies on WM BOLD signals,<sup>23,31,37</sup> ascribed to specific functions of the middle networks or the heterogeneous characteristics of the BOLD hemodynamic response function in WM. Nonetheless, there was no confirmative explanation for this phenomenon, which should be investigated in future studies.

The mean amplitudes of the right sensorimotor WM network at whole (band A) and high (band C) frequency bands were higher in poor sleepers compared to good sleepers, whereas the mean amplitude at the low frequency band also showed an increased trend in poor sleepers. Furthermore, the mean amplitudes at these three frequency bands were positively correlated with PSQI total score. In the majority of GM BOLD-fMRI studies, the spontaneous low frequency oscillations were mainly focused on the conventional low frequency range (0.01–0.1Hz). Oscillations within different frequency bands showed distinct spatial profiles and were linked to various neural processes and physiological functions.<sup>30,36</sup> Considering the differences in energy demands of different cell types, vascular characteristics, and tissue microstructure between GM and WM, the oscillations in WM at different frequency bands may have distinct physiological origins.<sup>42</sup> The amplitude of right sensorimotor WM-FN increased with poor sleep quality, indicating abnormality of WM activity or signal transmission along sensorimotor fiber tracts, which may be linked to impaired sensory and motor functions in poor sleepers.

## Limitations

There are several limitations in the present study. First, limited to the cross-sectional design, we cannot confirm the causal relationship between poor sleep quality and the altered characteristics of WM-FNs, although the negative impact of poor sleep quality on WM integrity has been reported in previous longitudinal sleep deprivation studies.<sup>16,64</sup> Second, cognitive and psychological tests were not included in this study. The association between cognition and alterations of WM-FNs should be explored in future studies to reveal the underlying neural mechanism of cognitive deficits due to poor sleep quality. Third, WM-FNs were derived from k-means clustering analysis based on group-level WM mask. It will be useful in future studies to derive WM-FNs using other approaches, such as independent component analysis, to test the generalization of the findings in this study.

## Conclusion

The current work represents the distinct differences in functional connectivity within WM-FNs and between WM-FNs and GM-FNs, as well as power spectral characteristics of WM-FNs between good sleepers and poor sleepers. These differences are highly correlated with sleep quality. Our findings highlight the importance of functional activity of WM in sleep research. This will be of great interest to the sleep field, leading to investigations on the cellular or physiological mechanisms of WM-FNs.

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## Disclosure

The authors report no conflicts of interest in this work.

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