Effect of jet lag on brain white matter functional connectivity

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Abstract

Background: A long-haul flight across more than five time zones may produce a circadian rhythm sleep disorder known as jet lag. Little is known about the effect of jet lag on white matter (WM) functional connectivity (FC).

Objective: The present study is to investigate changes in WM FC in subjects due to recovery from jet lag after flying across six time zones.

Methods: Here, resting-state functional magnetic resonance imaging was performed in 23 participants within 24 hours of flying and again 50 days later. Gray matter (GM) and WM networks were identified by k-means clustering. WM FC and functional covariance connectivity (FCC) were analyzed. Next, a sliding window method was used to establish dynamic WM FC. WM static and dynamic FC and FCC were compared between when participants had initially completed their journey and 50 days later. Emotion was assessed using the Positive and Negative Affect Schedule and the State Anxiety Inventory.

Results: All participants were confirmed to have jet lag symptoms by the Columbian Jet Lag Scale. The static FC strengths of cingulate network (WM7)-sensorimotor network and ventral frontal network-visual network were lower after the long-haul flight compared with recovery. Corresponding results were obtained for the dynamic FC analysis. The analysis of FCC revealed weakened connections between the WM7 and several other brain networks, especially the precentral/postcentral network. Moreover, a negative correlation was found between emotion scores and the FC between the WM7 and sensorimotor related regions.
Conclusions: The results of this study provide further evidence for the existence of WM networks and show that jet lag is associated with alterations in static and dynamic WM FC and FCC, especially in sensorimotor networks. Jet lag is a complex problem that not only is related to sleep rhythm but also influences emotion.

Key words: circadian rhythm disorder; jet lag; functional connectivity; white matter

Introduction

The circadian rhythms of a person (commonly referred to as the “body clock”) are generally synchronous with the light–dark solar cycle (American Academy of Sleep Medicine, 2005). A long-haul flight across more than five time zones may, however, break this balance and produce a circadian rhythm disorder known as jet lag (Morgenthaler et al., 2007). The main manifestation of jet lag is excessive daytime sleepiness (Sack, 2010), and additional symptoms may include altered mood (Drust et al., 2005), gastrointestinal distress, fatigue, and cognitive impairments such as memory and concentration deficits (Gander et al., 1993; Drust et al., 2005; Herxheimer, 2014). All these symptoms will generally resolve once a person is re-entrained to the light–dark solar cycle in the place to which they have traveled, a process that generally takes 1 week or more and maybe prolonged depending upon individual differences and factors such as flight direction (Weingarten and Collop, 2013).

Previous research to elucidate the potential mechanisms that produce jet lag has focused on the measurement of behavior (Sack, 2010) and body chemistry (Carter and Juurlink, 2012). To our knowledge, there have been only two studies on the effects of jet lag on brain function; one found a reduction in functional connection (FC) in the default mode network (Coutinho et al., 2015), the other found decreased FC between the thalamus and cortex (Zhang et al., 2020). These findings are supported by a resting-state functional magnetic resonance imaging (RS-fMRI) study in which circadian rhythm was altered in participants by sleep disturbance and deprivation (Dijk, 2012) and from which it was also reported that the occipital pole, sensorimotor cortex, and subcortical regions, namely basal ganglia and thalamus, are also modulated by circadian rhythm (Muto et al., 2016).

When it comes to white matter (WM), the most-used method is diffusion tensor imaging (DTI) analysis that studies the structural changes of WM. A previous DTI study suggested that WM also plays an important role in maintaining circadian rhythm and reported alterations in the frontal and temporal lobe of WM and cingulate gyrus and corpus callosum following sleep deprivation (Rosenberg et al., 2014). Although DTI studies can reveal the details of WM structure, they cannot provide direct evidence of its function in vivo. Since jet lag is a transient physiological state, it will be more important to study its effect on WM function. Recently, it has been shown that it is possible to study brain WM function by using fMRI based on the so-called blood oxygen level-dependent (BOLD) signal (Peer et al., 2017; Ding et al., 2018; Li et al., 2019), and it has been shown that the BOLD signal can identify the contribution of different WM tracts (Ding et al., 2013; Ding et al., 2016) as well as internal capsule and corpus callosum (Mazerolle et al., 2008; Fabri et al., 2011; Gawryluk et al., 2011) in specific cognitive tasks. Moreover, WM networks have also been detected using RS-fMRI (Ding et al., 2018), and changes in WM FC have been reported in patients with epilepsy (Jiang et al., 2019), stroke (Wang et al., 2019), and Parkinson’s Disease (Ji et al., 2019). In the present study, the FC of WM will be used to detect neuron changes in jet lag. More importantly, recent studies found that the WM had a similar fluctuation of the BOLD signal with GM (Ding et al., 2016; Peer et al., 2017; Ding et al., 2018) that has been shown to vary over various timescales. The dynamic FC of WM is anticipated to shed important further insight into brain network properties.

The goal of the present study is to investigate changes in WM FC in participants due to recovery from jet lag, as measured using the Colombia Jet Lag Questionnaire, after flying across six time zones. According to the previous findings, the aggregation of BOLD signals in the resting state produces a pattern similar to that of the WM bundle (Mezer et al., 2009). A k-means approach will be used to identify the WM and GM networks of the brain after which the first objective is to study the underlying changes in WM networks due to recovery from jet lag. This will comprise analysis of changes in the FC of the WM networks and also of changes in FC between the WM and GM networks. The second objective is to extend the analysis to investigate corresponding changes in functional covariance connectivity (FCC) between the WM networks. The so-called FCC (Zhang et al., 2016; Jiang et al., 2019) has been computed to describe the correlation between any two WM networks based on the correlation between the WM network and multiple GM networks. The FCC can reflect a complex information interaction between WM and GM. The third objective acknowledges that the BOLD signal has components with a range of timescales (Chang and Glover, 2010). We thus perform an analysis of whether there may be changes in the dynamic FC of WM networks associated with jet lag. The fourth objective is to detect the relationship between the symptoms and the WM network FC. The significant correlation between FC and jet lag symptoms is analyzed by partial correlation, with gender and age as covariates.
Materials and Methods

Participants

Twenty-three right-handed participants (12 females and 11 males, mean age 28.9 ± 5.7 years, range 23 to 46 years) who were due to fly across six time zones were recruited to this study at West China Hospital of Sichuan University. All the participants flew from Chengdu to Hawaii and then flew directly from Hawaii to Chengdu after a 6-day stay at the 2017 annual meeting of the ISMRM. The average duration of each flight was 16 hours. The first test was conducted within 24 hours after the participants returned to China (between 6:00 a.m. and 8:00 a.m. Hawaiian time). Participants were re-examined 50 days after the first test, and the second scan time point is the same as the first time in the solar cycle. Under the guidance of psychologists, all the participants completed the questionnaire first and then completed the MRI scan. Exclusion criteria were a history of psychiatric or neurological disorder, claustrophobia, and any contraindications for MRI scans including pregnancy, taking drugs to sleep, air travel in the month before testing, focal brain lesions on T1-weighted images, and head motion exceeding 1.5 mm in translation or 1.5° in rotation during fMRI scanning. MRI was performed within 24 hours of the participant’s completing the flight, and the protocol was repeated 50 days later at the same time of day. On both occasions, questionnaires were administered, namely the Colombia Jet Lag Questionnaire (Spitzer et al., 1999), the Positive and Negative Affect Schedule (Benedetti et al., 2017), the State Anxiety Inventory (Touitou et al., 2016), and the Epworth Sleepiness Scale (Bollettini et al., 2017), to assess emotional status, level of anxiety, and daytime sleepiness. To exclude participants with sleep disorders, the Pittsburgh sleep quality index (Buysse et al., 1989) was also used to evaluate sleep quality, and scores greater than eight were considered abnormal. The study was approved by the West China Hospital Ethics Committee of Sichuan University and before any investigations were performed each participant gave fully informed written consent of their willingness to participate (Fig. 1).

MRI image acquisition

MRI data were acquired using a Siemens 3.0 tesla system (Tim Trio, Siemens Healthineers, Erlangen, Germany) equipped with a standard eight-channel head coil. The main scanning parameters for the RS-fMRI echo-planar imaging sequence were as follows: repetition time (TR) 2 seconds, echo time (TE) 30 ms, flip angle 90°, slice thickness 3.8 mm, matrix 64 × 64, field of view (FOV) 240 × 240 mm (i.e. voxel size of 3.75 × 3.75 × 3.8 mm) and a total of 205 volumes each comprising 33 contiguous slices were acquired in a time of 6 minutes 50 seconds. Participants were asked to close their eyes, not think about anything, and stay awake. Besides, a 3D T1-weighted image was obtained with acquisition parameters TR 1.96 seconds, TE 2.26 ms, and flip angle 90°, for 175 contiguous slices.
with thickness 1 mm, and FOV of 256 × 256 mm (i.e. array of contiguous cubic voxels with sides of 1 mm).

MRI data processing

Processing of the MRI data was performed using SPM12 (www.fil.ion.ucl.ac.uk/spm) and DPARSFA (http://rfmri.org/DPARSF) in MATLAB. First, the anatomical images were segmented into GM, WM, and cerebrospinal fluid (CSF) using the SPM12 New Segment algorithm (Ashburner, 2007). Next, the RS-fMRI data were processed as follows: (i) the first 10 volumes were removed to ensure the signal had reached equilibrium, (ii) a slice-timing correction was applied, (iii) images were motion corrected to the middle image in the series, and participants with translation >1.5 mm or >1.5° rotation were excluded, but no participant was excluded, (iv) the timing and motion-corrected RS-fMRI images were coresgistered with the anatomical image, and GM and WM masks obtained by setting the threshold to 0.7 in the Prior Probability Map in SPM12 were applied, (v) signal drift was corrected according to the best fitting linear trend, (vi) a 0.01 to 0.10 Hz bandpass filter was applied to remove non-neuronal contributions to the BOLD signal fluctuations, and (vii) a nuisance signal that included information from the 24-parameter motion correction and the variation in the mean signal of the CSF was removed (Friston et al., 1996). To further minimize the effect of head motion, motion "spikes" with a high framewise displacement (FD) >1 were removed (Jiang et al., 2019). To avoid eliminating signals of interest, signals from WM and global brain were not included in the regression (Peer et al., 2017; Ji et al., 2019). Then, (viii) signals from GM and WM within the respective masks were respectively smoothed using a full-width half maximum filter of size 4 mm. To avoid mixing of GM and WM signals, we used the segmentation results of each participant to identify GM and WM voxels. Then the SPM12 smoothing algorithm was applied to two groups of images. Finally, we used the smoothing data from GM and WM voxels to merge the two images into full-function images (Peer et al., 2017). Finally, (ix) the processed images were normalized to the standard Montreal Neurological Institute (MNI) template and resampled to 3-mm cubic voxels.

Extraction of GM and WM networks

Group-level GM and WM masks were produced from the results of the segmentation of the high-resolution T1-weighted images. Application of the maximum probability method ensured that voxels defined as WM were identified in more than 60% of participants. Subcortical regions including the thalamus, caudate nucleus, putamen, globus pallidum, and nucleus accumbens as anatomically defined according to the Harvard-Oxford Atlas (Desikan et al., 2006) were removed from the group-level WM mask. The final group-level GM mask with 41 007 voxels and WM mask with 19 646 voxels were coregistered to the MNI template, and it was ensured that there was no overlap between the two masks.

Next, the k-means clustering algorithm was used to identify the GM and WM functional networks in the processed RS-fMRI data (Peer et al., 2017). To establish a specific individual and group-averaged matrix, we calculated Pearson correlation coefficients between each WM voxel and other WM voxels. The interchanging grid method was used to resample the WM mask and extract any second voxels along the rows and columns of the image and move one between slices to avoid losing the entire data column. For each WM voxel, the correlation with all subsampling mask nodes was calculated to obtain a correlation matrix with size 19 646 × 4998. A group-level correlation matrix was obtained by averaging the results of all participants. The same procedure was applied to generate the group-level GM correlation matrix with a size of 41 007 × 5668. For the correlation between each voxel, the data used for cross-participant averaging were only taken from participants whose two voxels were identified as WM during segmentation, so the contribution from GM signal was excluded. Then, k-means clustering (distance metric-correlation, 10 replicates) was performed for the respective group-level GM and WM matrices.

To identified the most stable of the k (the number of clusters), the stability of the clustering solution for each number of clusters, from 2 to 22 were measured (Peer et al., 2017). The group-level WM correlation matrix was randomly divided into four folds with 19 646 × 1045 (in WM network) elements per fold, and k-means clustering was performed from 2 to 22 clusters. The similarity of the clustering solutions was measured using Dice’s coefficient, which was used to compare Adjacency Matrices. Finally, the average Dice’s coefficient that represents clustering stability was calculated from the four Adjacency Matrices corresponding to each cluster size. A k value with a Dice’s coefficient of greater than 0.85 was considered a stable solution.

FC between WM networks

A $K_{White} \times K_{White}$ matrix was produced for each participant by computing Pearson’s correlation coefficient for the average time courses between pairs of WM networks. The process was repeated for GM.

FC and FCC between WM and GM networks

The FC between WM and GM networks was analyzed by computing the $K_{White} \times K_{Gray}$ Pearson’s correlation coefficient matrix between each WM network and each GM network (Ding et al., 2018) with appropriate masking. The FCC between any two WM networks based on the correlation between the WM network and multiple GM networks was analyzed. The FCC is defined as the Pearson’s
correlation coefficient between $F_{ij}$ (meaning the FC values between WM$_i$ and all GM networks) and $F_{ij}$ (meaning the FC values between WM$_j$ and all GM networks).

**Dynamic WM networks**

The WM showed a similar fluctuation of the BOLD signal with GM (Ding et al., 2016; Peer et al., 2017; Ding et al., 2018) and dynamic FC can quantify the characteristics of FC indicators over time (Hutchison et al., 2013), which will improve the understanding of the basic characteristics of the brain WM networks in jet lag. We, therefore, performed an analysis of the temporal variation of WM signals to determine what may be called the dynamic WM functional network. In particular, a sliding window approach with a window length of 50 TRs and step 5 TRs was used to produce 30 $K_{\text{white}} \times K_{\text{white}}$ matrices per participant, and the k-means clustering algorithm was applied again to cluster the dynamic FCs into five FC states.

**Statistical analysis**

One-sample t-tests were used to determine the significant static GM and WM networks, dynamic WM networks, and WM FCC present in the cohort of participants immediately after the long-haul flight and 50 days later, and the false discovery rate (FDR) (Benjamini, 1995) was used to correct for multiple comparisons ($P < 0.05$, FDR corrected). The paired t-tests were used to determine significant differences in the parameters between the two time points (FDR corrected). A partial correlation analysis was performed between the significant changes in FC and FCC, and jet lag symptoms (i.e., emotional status and level of anxiety) while controlling for the gender and age of the participants.

**Results**

**Emotional status, anxiety level, and sleepiness scores**

First of all, the Pittsburgh sleep quality index showed that all participants had no problem with a sleep disorder (mean scores of $4.10 \pm 1.49$). The Colombia Jet Lag Questionnaire was assessed 5 days after travel. The results showed that the symptoms of jet lag decreased significantly in the first four days, and there was no significant difference between the scores on the fourth and fifth days (mean scores are $15.30 \pm 9.92$ (first day), $9.83 \pm 7.76$ (second day), $P < 0.001$, $t_{22(1-2)} = 4.97$; $6.56 \pm 5.66$ (third day), $P < 0.001$, $t_{22(1-2)} = 4.12$; $4.52 \pm 6.18$ (fourth day), $P = 0.028$, $t_{22(1-4)} = 2.35$; $3.43 \pm 4.73$ (fifth day), and $P = 0.077$, $t_{22(1-5)} = 1.85$). Based on the Colombia Jet Lag Questionnaire, all 23 participants were defined as having jet lag symptoms (mean scores of $15.30 \pm 9.92$) at the time of the first MRI data acquisition. According to the results of the Epworth Sleepiness Scale, participants showed varying degrees of drowsiness (a mean score of $9.00 \pm 2.27$) after the long-haul flight. Besides, paired t-tests revealed that on average participants had significantly lower positive emotional status ($P < 0.001$, $t_{22} = -4.47$, FDR corrected) and higher anxiety ($P = 0.013$, $t_{22} = 2.87$, FDR corrected) compared to 1 month later (Table 1).

**GM and WM networks**

The results of the k-means clustering revealed that among the k values of 2–22 there were 11 k values in WM clustering and 4 k values in GM clustering that can represent the most stable functional segregation. Based on high stability and Dice’s coefficient of $>0.85$, the segregations were assigned to represent 15 WM networks and 7 GM networks (Jiang et al., 2019). Following the convention of anatomic localization (AAL template), the 15 WM networks (Fig. 2) are named as WM1, occipital network; WM2, inferior longitudinal fasciculus network; WM3, precentral/postcentral network; WM4, cerebellum network; WM5, brainstem network; WM6, posterior corpus callosum network; WM7, cingulate network; WM8, superior longitudinal fasciculus network; WM9, middle frontal network; WM10, dorsal frontal and genu of corpus callosum network; WM11, anterior temporal network; WM12, corona radiate network; WM13, orbitofrontal and inferior temporal network; WM14, ventral frontal network; and WM15, inferior frontoparietal network. The present networks WM6, WM8, WM10, and WM15 are located in the same regions as the WM1 network in previous research (Peer et al., 2017), while the other WM networks can also be identified in previous research (Peer et al., 2017) and the seven GM networks (Fig. 3) are defined following the previous findings of GM functional networks: GM1, attention network; GM2, default network; GM3, frontoparietal network; GM4, visual network; GM5, cerebellum network; GM6, temporal-orbitofrontal network; and GM7, sensorimotor network.

**Changes in FC between WM networks**

Analysis of the changes in FC between WM networks revealed that a significant reduction had occurred during jet lag in the FC between WM7 and WM1 ($P = 0.0031$), WM2 ($P = 0.0013$), WM3 ($P < 0.001$), WM5 ($P < 0.001$), WM12 ($P = 0.0019$), and WM13 ($P < 0.001$), and between WM3 and WM4 ($P = 0.0029$), with FDR correction (see Fig. 4).

**Changes in FC and FCC between WM and GM networks**

Analysis of changes in FC and FCC between WM and GM networks during jet lag revealed a significant reduction in FC between WM7 and GM7 ($P = 0.006$) and between WM14 and GM4 ($P = 0.002$), and in FCC between WM7 and WM3 ($P = 0.0003$) (Fig. 5). All were corrected by FDR. No significant increase in FC or FCC was observed during jet lag compared with 50 days recovery.
Table 1: Demographic data, behavioral, and neuroendocrine characteristics of participants.

| Characteristic                  | Jet lag         | 50-day follow-up | P value |
|--------------------------------|-----------------|------------------|---------|
| Sample size                    | 23              | NA               | NA      |
| Age (years)                    | 28.9 ± 5.7      | NA               | NA      |
| Gender (M/F)                   | 11/12           | NA               | NA      |
| Handedness (R/L)               | 23/0            | NA               | NA      |
| Framewise displacement (FD)    | 0.19 ± 0.10     | 0.18 ± 0.09      | 0.347   |
| Positive emotion               | 17.47 ± 6.13    | 25.69 ± 7.87     | <0.001* |
| Negative emotion               | 14.43 ± 4.67    | 13.73 ± 4.25     | 0.423   |
| Anxiety score                  | 43.04 ± 11.17   | 36.56 ± 9.99     | 0.013*  |
| Colombia Jet Lag               | 15.30 ± 9.92    | NA               | NA      |
| Epworth Sleepiness             | 9 ± 2.27        | NA               | NA      |

Data are presented as the mean ± standard deviation. The P value was obtained using a paired t-test.
*Region considered significant after multiple-comparison correction.

Changes in dynamic WM networks

The difference in five connectivity states identified for the dynamic FC of the WM networks is displayed in Fig. 4. Comparing jet lag to 50 days recovery, for state 1 there is a significant reduction in the dynamic FC between WM3 and WM7 (P = 0.047), WM10 (P = 0.019), and WM14 (P = 0.028) and also between WM1 and WM14 (P = 0.024), and between WM9 and WM11 (P = 0.036). Similarly, for states 3, 4 and 5 significant reductions in dynamic FC between WM7 and WM3 (P_{state3} = 0.002, P_{state4} = 0.027, P_{state5} = 0.009) is observed after the long-haul flight. However, there are also some differences in these states. In particular, a significant lower dynamic FC is observed between WM1 and WM10 (P = 0.021) and WM14 (P = 0.031), and between WM9 and WM11 (P = 0.031) in state 2 after FDR correction. The significant reduction of FC between WM1 and WM4 (P = 0.004), WM7 (P = 0.006), WM10 (P = 0.014), and WM14 (P = 0.015), between WM3 and WM4 (P = 0.038), and WM14 (P = 0.027), between WM7 and WM11 (P = 0.013), and between WM11 and WM14 (P = 0.035) in state 3 after multiple correction, as well as between WM3 and WM9 (P = 0.037), between WM4 and WM13 (P = 0.006), and between WM2 and WM14 (P = 0.038) in state 5 after FDR correction. The only significant higher dynamic FC of the WM networks occurred in state 1 between WM7 and WM10 (P = 0.013) and in state 3 between WM8 and WM15 (P = 0.033). The changes in dynamic FC reflect changes in the non-static characteristics of WM resting-state networks.
Correlation between changes in symptoms and FC of WM networks

During jet lag, a significant negative correlation is observed between positive emotion and the FC between WM7 and WM1 ($r = -0.474; P = 0.03$) and WM3 ($r = -0.589; P = 0.02$, FDR corrected) although the latter finding is corrected for multiple comparisons. A highly significant correlation is observed between positive emotion and the FC between WM7 and GM7 ($r = -0.720; P < 0.008$, FDR corrected) during jet lag. No significant correlations were observed for negative emotion, anxiety, or sleepiness score. To validate that the correlations do not reflect unspecific associations, we performed partial correlation analysis between positive emotion scores and the significant FC after recovery and no significant correlations were observed (FC between WM7 and WM1 ($r = 0.339; P = 0.13$), between WM7 and WM3 ($r = 0.149; P = 0.52$) and between WM7 and GM7 ($r = 0.253; P = 0.27$)).

Discussion

Analysis using the Colombia Jet Lag Questionnaire confirmed that all 23 participants showed jet lag symptoms, of which the most prominent symptoms were drowsiness and anxiety. A comprehensive analysis of the static and dynamic FC of WM resting-state networks revealed the cingulate network (WM7) and the precentral/postcentral network (WM3) to be the brain networks most implicated in producing the symptoms associated with jet lag. In particular, after the long-haul flight that produced jet lag, analysis of the brain WM resting-state networks reveals that a significant reduction has occurred (i) in FC between WM7 and other WM networks, namely WM1, WM2, WM3, WM5, WM12, and WM13, and between WM3 and WM4, (ii) in FC between WM7 and GM4, (iii) in FCC between WM7 and WM3, (iv) in dynamic FC between WM7 and WM1, WM2, WM3, and WM12 for state 1 (as well as similar effects for states 2, 4, and 5), and (v) a significant negative correlation between positive emotion and FC between WM7 and WM3 and a highly significant correlation between positive emotion and FC between WM7 and GM7, and one will note that effects relating to WM7 and WM3 are present in all of (i)–(v). Additionally, the ventral frontal network (WM14) is implicated in that (i) there is a significant reduction in FC and between WM14 and GM4 and (ii) in dynamic FC between WM5 and WM10 and WM14 for state 1. In all cases, FC decreases during jet lag compared to recovery.

The cingulate network is known to play an important role in information processing (Amir et al., 2005). The function of the cingulate has been reported to be disrupted in participants with both sleep disorders (Tomasi et al., 2009) and mood disorders (Amir et al., 2005; Wang et al., 2017). Furthermore, a DTI study of participants categorized as early (EC), late (LC), or intermediate (IC) chronotypes, where ECs tend to wake up early in the morning and find it difficult to remain awake beyond their usual bedtime, and LCs go to bed late and have difficulty getting up, revealed decreased WM fractional anisotropy of cingulate gyrus in participants with the LC chronotype (Rosenberg et al., 2014) who have symptoms such as sleep disturbance and vulnerability to...
Figure 4: Static FC and dynamic FC between WM networks. The static FC revealed that a significant reduction had occurred in the FC between the cingulate network (WM7) and occipital network (WM1), inferior longitudinal fasciculus network (WM2), precentral/postcentral network (WM3), brainstem network (WM5), corona radiate network (WM12), and orbitofrontal and inferior temporal network (WM13), and between the precentral/postcentral network (WM3) and cerebellum network (WM4) during jet lag. The difference in five connectivity states identified for the dynamic FC of the WM networks is displayed, and significant reduction was found between the cingulate network (WM7) and other WM networks.

Figure 5: Changes in FC and FCC between WM and gray matter (GM) networks. The left circle of FCC revealed a significant reduction between the cingulate network (WM7) and the precentral/postcentral network (WM3). The other two circles showed the lower FC between the cingulate network (WM7) and sensorimotor network (GM7) and between the ventral frontal network (WM14) and visual network (GM4) during jet lag.

depression that are also associated with jet lag (Rosenberg et al., 2014). On the contrary, participants with sleep deprivation were reported to show increased FC (Liu et al., 2018) and increased FC density (Sterpenich et al., 2017) in pre- and postcentral regions bilaterally and which was suggested to reflect a compensatory mechanism (Huang et al., 2012). At the time of experiencing jet lag participants showed significantly decreased positive emotion and increased anxiety, and with the former being negatively correlated with the FC of WM7 with both WM3
and GM7, suggesting that the cingulate may play a crucial role in the expression of emotions and maintenance of positive mood.

The cingulate network (WM7) showed reduced FC with five (WM1, WM2, WM3, WM5, WM12, and WM13) WM networks that were extracted from the RS-fMRI data during jet lag. In the case of WM1, both static and dynamic FC are reduced during jet lag. WM1 is the occipital network and supports language processes, visual function, and visual cognition-related functions (Bell-McGinty et al., 2004; Zhao et al., 2016). A previous imaging study found that brain functional activity in the occipital lobe diminished in the late evening (Gorfine and Zisapel, 2009) providing good evidence that the function of the occipital network is modulated by the circadian rhythm (Gorfine and Zisapel, 2009; Muto et al., 2016). In the present study, the decreased connectivity between the cingulate and occipital network was found to be negatively correlated with positive emotion scores. However, since this correlation does not survive after correction for multiple corrections further experiments are needed to confirm the validity of the finding.

The reduced FC between the cingulate network (WM7) and inferior longitudinal fasciculus network (WM2) in participants with jet lag is consistent with the results of the study of participants with excessive daytime sleepiness (Ashraf-Ganjouei et al., 2019) as well as patients with depression (Ghazi Sherbaf et al., 2018), schizophrenia (Phillips et al., 2009), and autism spectrum disorder (Boets et al., 2018). Additionally, decreased FC was observed between the cingulate network (WM7) and the orbitofrontal and inferior temporal network (WM13). The orbitofrontal has previously been reported to show reduced activity following sleep deprivation and to contribute to the regulation of positive emotional sensitivity (Gujar et al., 2011). Together, these findings provide support for the finding that jet lag is associated with disruption of emotional processing. This interpretation is supported by the fact that the inferior longitudinal fasciculus network WM2 provides connections between the occipital and anterior temporal lobe and is known to contribute to emotion processing (Herbet et al., 2018).

Finally, a significant reduction in FC was observed between WM7 and WM5, and WM12. WM5 refers to the brainstem network and WM12 to the corona radiate network. The brainstem is a crucial component of arousal systems (Yoo et al., 2007), which may be influenced by jet lag. The present finding that reduced FC between WM7 and WM5 may indicate the jet lag effect on arousal function. The corona radiate contains fibers that project from the internal capsule to the cerebral cortex and has been reported to play a role in executive function, attention, and processing of emotions (Yin et al., 2013), and abnormal fractional anisotropy of the corona radiate has been reported in patients with emotion-related disorder (Karababa et al., 2015; Lu et al., 2018). The reduced FC between WM7 and WM12 may be associated with emotion, and further study is needed to explore the relationship.

Analysis of dynamic FC can potentially provide more detailed information on brain connectivity than stationary FC, revealing whether connectivity patterns persist through time or come and go. The analysis revealed that the decrease in FC between WM7 and other WM networks was present at most of the temporal frequencies in the RS-fMRI signal, as has previously been observed in circadian sleep (Kyeong et al., 2017), LE chronotype (Horne and Norbury, 2018), and sleep-related disorder (Yang et al., 2018), and these changes were reported to correlate with emotion (Wang et al., 2017). However, increased FC was observed in state 1 and state 3, indicating that significant temporal fluctuations may occur in the WM networks. Further research is needed to determine the neurophysiology underlying these fluctuations.

Several limitations need to be considered. First, the sample size is relatively small and we will continue to recruit participants who have taken a flight of similar duration and direction across multiple time zones. Second, no data are available before the participants experienced jet lag. We will add a control group matched for age and sex. Finally, understanding the physiological basis of the BOLD signal in WM is still limited at present. In a systematic review of the literature, the authors suggest that WM function may depend on energy requirements for spiking activity, resting potential maintenance, and neuronal processing, while artifacts from sources such as motion, partial volume, and physiological noise contribute least (Gawryluk et al., 2014), but further study is needed.

Conclusion

As far as we are aware this is the first study of the effects of jet lag on the static and dynamic resting-state networks of the WM of the brain and their FC with each other and with GM networks. The most significant finding was the reduction of static FC and FCC between the cingulate network (WM7) and the precentral/postcentral network (WM3). The cingulate network was considered to be affected by jet lag because the dynamic FC of the cingulate network was significantly reduced, and significant negative correlations were found between the FC of the cingulate network and precentral/postcentral network (both in GM and WM) and positive emotion scores. In conclusion, these findings provide evidence that changes in WM FC, especially in the cingulate network, may be associated with a decrease in positive emotions as a symptom of jet lag.

Author Contributions

J.A.S., Q.G., and Z.J. designed the project. Z.J. and F.Z. completed the collection of images and behavioral data. Z.Y., K.Q., and F.Z. analyzed and summarized the data. J.A.S.,...
N.R., and Q.G. explained the results and commented on the manuscript. F.Z. and N.R. wrote and edited the manuscript. Q.G. and Z.J. supervised all aspects of the project.

Conflict of interest
One of the authors, Q.G., is also the editor-in-chief of Psychoriadology. He was blinded from reviewing or making decisions on the manuscript.

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