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ORIGINAL ARTICLE

Neural activation underlying emotional interference of cognitive control in rotating shift workers: moderating effects of the prefrontal cortex response on the association between sleep disturbance and depressive symptoms

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Abstract

Study Objectives: This study investigated the altered neural function involved in emotional interference and its role in linking sleep disturbance and depressive/anxiety symptoms in rotating shift workers.

Methods: Sixty rotating shift workers and 61 controls performed the emotional Stroop task in three blocks (emotional-related, sleep-related, and neutral words) during functional magnetic resonance imaging (fMRI) assessments. Sleep disturbance and depressive/anxiety symptoms were assessed using self-report measures and sleep diaries. Actigraphy was used to assess the sleep and circadian variables. fMRI scans were performed to compare brain activation during the emotional Stroop task. The proposed moderating models were tested using the PROCESS macro in SPSS software.

Results: A significant condition effect on reaction time was detected. Regardless of the group, reaction times were longer in the negative emotional word and sleep-related conditions than in the neutral word condition. Whole-brain analysis revealed that rotating shift workers show greater neural activation in the left dorsolateral prefrontal cortex (DLPFC) compared with controls while performing the emotional Stroop task with negative emotional words. Sleep disturbance was more strongly associated with depressive symptoms when activation of the left DLPFC was higher during the emotional Stroop task with negative words.

Conclusions: The left DLPFC may play important roles in increased sensitivity to emotional information, possibly due to circadian misalignment, and has moderating effects on the association between sleep disturbance and depressive symptoms in rotating shift workers. These findings will help to identify possible brain regions where interventions can be performed to correct sleep and mood problems in rotating shift workers.

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Graphical Abstract

Neural activation underlying emotional interference of cognitive control in rotating shift workers: Moderating effects of the prefrontal cortex response on the association between sleep disturbance and depressive symptoms

Study Objective

This study investigated the altered neural function involved in emotional interference and its role in linking sleep disturbance and depressive/anxiety symptoms in rotating shift workers.

Methods

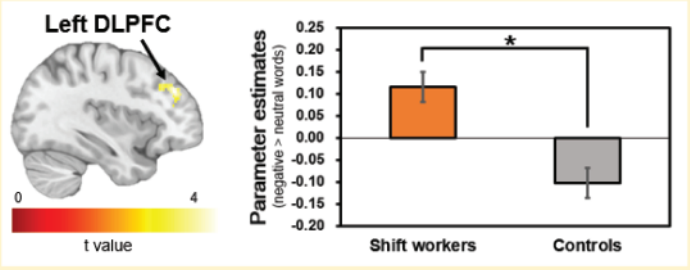
Sixty rotating shift workers and 61 controls performed the emotional Stroop task in three blocks (emotional-related, sleep-related, and neutral words) during functional magnetic resonance imaging (fMRI) assessments. fMRI scans were performed to compare brain activation during the emotional Stroop task.

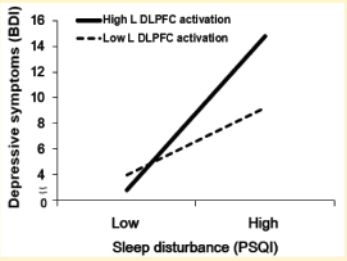
Measures

Sleep disturbance and depressive/anxiety symptoms were assessed using Pittsburgh Sleep Quality Index (PSQI), Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI). Nocturnal polysomnography, sleep diary and actigraphy were used to assess the sleep and circadian variables.

Conclusions

The left DLPFC may play important roles in increased sensitivity to emotional information, possibly due to circadian misalignment.





Findings

1) Whole-brain analysis revealed that rotating shift workers show greater neural activation in the left dorsolateral prefrontal cortex (DLPFC), compared with controls, while performing the emotional Stroop task with negative emotional words.

2) Sleep disturbance was more strongly associated with depressive symptoms when activation of the left DLPFC was higher during the emotional Stroop task with negative words.

Statement of Significance

Rotating shift patterns interfere with circadian chronobiological rhythms, causing an increased risk of depression compared to daytime shift rosters. Although shift workers are vulnerable to sleep or mood problems, the neurobiological mechanisms underpinning the vulnerabilities that originate from circadian misalignment are unclear. This study focused on the altered neural function involved in emotional interference and its role in linking sleep disturbance and depressive/anxiety symptoms in rotating shift workers. Shift workers had greater activation of the left dorsolateral prefrontal cortex (DLPFC) compared to controls in response to negative emotional words, indicating increased vulnerability to emotional information. Additionally, activation of the left DLPFC strengthened the association between self-reported sleep disturbance and depressive symptoms. These findings emphasize the role of DLPFC function in sleep and emotional problems in shift workers. Our results suggest that neurobiological factors, such as activation of the DLPFC reflecting cognitive conflict due to emotional interference, may link sleep disturbance and depression in shift workers. Moreover, given the growing body of evidence showing the promise of neuromodulation techniques for treating various sleep or mood problems, our results suggest that neural substrates should be targeted to relieve emotional vulnerability derived from circadian misalignment.

Key words: circadian misalignment; emotional Stroop task; fMRI; left DLPFC; rotating shift work

Introduction

Throughout industrialized society, 24/7 operations are essential for healthcare, production, and service delivery industries. It is estimated that 15%–30% of working adults have a nontraditional shift that falls outside the hours of 7:00 am to 6:00 pm [1]. Shift workers experience desynchronization between homeostatic sleep pressure and circadian rhythmicity, which results in an increased risk of sleep disturbance [2, 3]. Greater sensitivity to sleep disturbance after a circadian challenge increases the risks of shift work disorder (SWD) and subsequent depressive mood in shift workers [4]. Previous studies have reported that 8.1%–43.0% of shift workers meet the criteria for SWD, which is defined as difficulty sleeping when sleep is allowed and/or excessive sleepiness during the desired waking period [5, 6]. Additionally, according to a recent meta-analysis, shift workers have a 1.33-fold greater risk of depression compared with daytime workers [1]. Therefore, it is important to identify vulnerabilities that originate from the circadian misalignment of shift workers.

Because of frequent circadian challenges, shift workers may be preoccupied with sleep; thus, they closely monitor their internal and external environments for sleep-related threats. This focused attention on sleep-related stimuli makes workers vulnerable to sleep problems and depression [7]. In addition, disrupted sleep/wake stability is associated with negative emotions and delayed affective recovery from negative events [8–10]. Therefore, selective attention to negative affective cues may be another vulnerability in shift workers.

One method to estimate the degree of selective attentional processes is the emotional Stroop task. In the emotional Stroop task, participants are asked to indicate the colors of various words as quickly as possible when neutral and emotionally salient words are displayed. Longer response times to emotionally salient words are considered Stroop interference: the more emotionally valenced level (e.g., more emotionally intense) of the word, the more cognitive performance is impaired [11]. Therefore, vulnerabilities in impaired cognitive performance of shift workers (e.g., due to attentional biases from sleep-related or emotionally

salient words) can be assessed using the emotional Stroop task. In addition, the emotional Stroop task has been widely used in functional magnetic resonance imaging (fMRI) studies to identify brain activation related to Stroop interference. A recent meta-analysis of neuroimaging studies using the emotional Stroop task reported that the lateral prefrontal cortex (LPFC), medial prefrontal cortex, and dorsal anterior cingulate cortex are associated with cognitive conflict caused by negative emotional words [12].

Previous studies have suggested that sleep disturbance or sleep loss leads to negativity bias (e.g., tendency for negative emotional information) in various emotional processes, including recognizing response/reactivity to emotional information, identifying emotions that should be regulated, and regulating unwanted emotions [13, 14]. Furthermore, negativity bias is an important feature of anxiety and depression [15]. For example, individuals with depression and anxiety show interpretation bias and attentional bias to negative information. Many fMRI studies have also reported that sleep disturbance increases negativity bias through changes in emotional brain networks, particularly in the frontolimbic system [16, 17].

Therefore, we aimed to identify differences between rotating shift workers and nonshift workers in the patterns of neural activation reflecting cognitive conflict caused by sleep-related and emotionally salient words; for this purpose, we used fMRI to investigate brain activation during the emotional Stroop task in rotating shift workers and nonshift workers. Given the associations among sleep, emotions, and neural function [18, 19], we designed moderating models to identify the effect of specific neural activation (during the emotional Stroop task in response to sleep-related and emotionally salient words [vs. neutral words]) on the association between sleep disturbance and depressive/anxiety symptoms in rotating shift workers. To test the moderating model, we measured the levels of sleep disturbance, depressive symptoms, and anxiety symptoms using the Pittsburgh Sleep Quality Index (PSQI), Beck Depression Inventory (BDI), and Beck Anxiety Inventory (BAI), respectively. In particular, the PSQI was used as an indicator of sleep disturbance in this study because it evaluates typical sleep habits during the past month. It may represent a general variable related to self-reported sleep quality, including all cross-sectional aspects of circadian change of rotating shift workers [20]. In addition, several studies have consistently shown the correlation between PSQI and BDI/BAI scores [21–24].

Given that rotating shift workers have greater sensitivity to negative emotional or sleep-related information compared with controls [1, 3], we hypothesized that shift workers would have increased activation in regions implicated in cognitive control of emotions and emotional interference, including the LPFC, medial prefrontal cortex, and dorsal anterior cingulate cortex while processing emotionally salient and sleep-related words (vs. neutral words) [12]. Furthermore, we predicted that the association between sleep disturbance and depressive/anxiety symptoms would depend on the activity levels of the specific brain regions related to Stroop interference in response to emotionally salient or sleep-related stimuli in rotating shift workers.

Methods

Participants

Participants were recruited from June 2017 to December 2019 through advertisements at Seoul National University Hospital and Samsung Medical Center. Rotating shift workers were defined as individuals who had work schedules that changed from one shift to another on a three-shift rotating basis from day to night shifts. We only included those who worked as shift workers for more than 6 months. Controls included participants who did not have sleep disturbance and did not engage in shift work. Therefore, controls had nighttime sleep, and rotating shift workers had either night or daytime sleep according to their shifts. To screen for psychiatric or sleep disorders in the shift worker and control groups, the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders-IV was conducted by trained psychologists at the start of the study, and nocturnal polysomnography was performed within about a week after the study started. Rotating shift workers on the night shift were not permitted to undergo PSG during the day immediately following the nighttime shift. Exclusion criteria were as follows: history of serious medical or neurological illness; Apnea-Hypopnea Index score ≥15 or Periodic Limb Movement Index score ≥15; Axis I psychiatric disorder other than a shift work type of circadian rhythm sleep disorder (SWD) (as defined by the Diagnostic and Statistical Manual of Mental Disorders-IV); sleep disorder other than SWD (based on the International Classification of Sleep Disorders-3 criteria); visual acuity ≤0.7, regardless of vision correction; pregnancy; and any contraindication for an MRI scan. Sixty-five shift workers and 64 controls were initially recruited. Eight participants were excluded because of sleep disorder (n = 2 [two controls with Apnea-Hypopnea Index scores ≥15]), T1 structural imaging problems (e.g., tumor) (n = 2 [one shift worker, one control]), task-related errors (n = 2 [two shift workers]), or poor image quality related to excessive head motion (n = 2 [two shift workers]). Thus, our final sample comprised 60 rotating shift workers (46 women; mean ± *SD* age, 30.67 ± 6.75 years) and 61 controls (42 women; mean ± *SD* age, 31.67 ± 7.40 years). All shift workers maintained rotating shift patterns during the time they completed sleep diaries, and they underwent polysomnography, actigraphy, and an fMRI study. This study was approved by the Institutional Review Board of Seoul National University Hospital. All participants provided written informed consent before participating in the study.

Self-reported measurements

Participants were asked to report directly using self-reported questionnaires at the start of the study. The levels of depressive and anxiety symptoms were assessed using BDI and the BAI, respectively [25, 26]. The Epworth Sleepiness Scale (ESS) was used to assess daytime sleepiness by asking participants whether they were likely to fall asleep while engaged in eight different activities [27]. PSQI was used to measure self-reported sleep disturbance. The PSQI is a self-reported questionnaire that comprises 19 retrospective questions regarding the past 7 days; it includes seven sleep domains for self-reported sleep quality, sleep latency, sleep duration, habitual sleep efficiency (SE), sleep disturbance, use of sleep medications, and daytime dysfunction [20]. Additionally, the Insomnia Severity Index was used to assess the severities of nighttime and daytime components of insomnia [28]. Participants began writing a sleep diary at the beginning of the study. A sleep diary was used to estimate various sleep parameters, such as total sleep time, *SE*, wake time after sleep onset, and sleep onset latency (SOL). The sleep diary served as a daily record of important sleep-related information during the past 2 weeks.

Actigraphy-based measurement of sleep and circadian variables

Actigraphy is a validated method to objectively measure sleep parameters and mean motor activity over several days to several weeks using a noninvasive accelerometer. Actigraphy was provided to the participants at the start of the study. All data from Actiwatch 2 (Phillips Respironics; Murrysville, PA, USA), worn on the participant's nondominant wrist for 7 consecutive days, were collected in 30-s epochs. Actiware version 6.0.9 was used to calculate the actigraphic data and sleep variables. Together with the sleep diary data, rest and excluded intervals (take-off duration) were manually marked in the software by technicians who were blinded to the other variables.

A cosinor analysis was performed using the raw actigraphic records to calculate the cosinor variables, including mesor (midline of the oscillating curve, where lower values suggest less activity and rhythmicity), amplitude (half of the peak-to-nadir difference in the fitted curve, where lower amplitude suggests a dampened circadian rhythm), *F*-statistic (robustness of the circadian activity, where a higher value suggests a more rhythmic or robust rhythm), and the acrophase (time of the peak of the curve during the day, where a later time suggests more phase delay). The following nonparametric variables were also calculated: most active 10-h period (M10; lower M10 counts indicate lower activity levels), interdaily stability (IS; higher IS indicates good synchronization with light and other environmental cues), intradaily variability (IV; higher IV indicates greater rhythm fragmentation), relative amplitude (higher relative amplitude indicates a more robust 24-h rest-activity rhythm), and the least active 5-h period (L5; lower L5 counts indicate less restful sleep). Detailed information related to the cosinor and nonparametric analyses was provided in a previous study [29, 30].

fMRI emotional Stroop task and word stimuli

Participants performed the emotional Stroop task, which was adapted from the classic Stroop task [31]. The emotional Stroop task has been widely used to measure affective interference on cognitive control through attentional bias for emotionally valanced words [12]. Considering that our study investigated the neural correlates of rotating shift work, which is a known risk factor for sleep problems, we modified the emotional Stroop task by including sleep-related words. Thus, our emotional Stroop task included three emotional blocks, three sleep blocks, and three neutral blocks. Each block began with the presentation of a fixation cross for 2 s. In each block, nine words were each presented for 1.5 s, followed by a 0.5-s interstimulus interval. Thus, each block lasted 20 s, followed by jittered intervals (fixation dot) of 14–20 s. The words were presented randomly during each block. Participants were instructed to indicate the ink color of each word by pressing one of four buttons (1 = blue, 2 = yellow, 3 = green, and 4 = red). We used 27 negative emotional words (e.g., grief, lonely, bomb, and terrorist), 27 sleep-related words (fatigue, sleepy, pillow, and insomnia), and 27 neutral words (e.g., pen, table, shoes, and cabbage). The sleep-related words were selected from previous studies that used the attention and emotional Stroop tasks [7, 32]; the terms were translated into Korean [33]. Negative emotional words and neutral words were selected from the Korean Affective Word list [34] and the Korean version of the California Verbal Learning Test [35], respectively. Eighty-one words were finally selected based on valence ratings and word characteristics (i.e., frequency and length of the word). The valence ratings on a 7-point Likert scale ranging from –3 (very negative) to 3 (very positive) were collected from our pilot study. Negative emotional words (*M*[*SD*] = –1.91[0.73]) were rated more negatively than either sleep-related words (*M*[*SD*] = 0.31[1.28] or neutral words (*M*[*SD*] = 0.24[0.22]) ($F_{(2, 80)}$ = 58.47, $p < .001$). The word frequency was collected from a survey [36]. No significant differences in the frequency ($F_{(2, 80)}$ = 1.97, $p = .15$) or length ($F_{(2, 80)}$ = 1.50, $p = .23$) of the words were observed among the three word types.

fMRI data analysis

fMRI data acquisition and preprocessing. fMRI was performed about 2 months after polysomnography was completed. All shift workers maintained their rotating shift patterns during the time they completed sleep diaries, polysomnography, actigraphy, and fMRI. fMRI data were collected during the daytime between 10 am and 4 pm for the shift workers and controls. However, shift workers were not allowed to undergo the fMRI scan on the day immediately after their nighttime shift. Before collecting the fMRI data, we confirmed whether participants were alert using the Stanford Sleepiness Scale (SSS) to measure their sleepiness level. When the SSS score was more than 2 (scale rating 2: functioning at a high level but not fully alert), participants were encouraged to go to the restroom, walk around, or drink a cup of water until the score dropped below 1 point (scale rating 1: feeling active, vital, alert, or wide awake). The total time of fMRI assessment took at least 3 h, including evaluation of sleepiness, task instruction and practice, scanning, postscan questionnaires, and debriefing.

The fMRI data were acquired with a 3T whole-body Tim Trio scanner (Siemens AG, New York, NY, USA), using a 12-channel birdcage head coil and interleaved T2*-weighted echo planar imaging (repetition time = 2000 ms, echo time = 30 ms, flip angle = 90°, slice thickness = 4.0 mm, in-plane resolution = 3.4 × 3.4 mm, no gap, 32 axial slices, field of view = 220 mm, 175 volumes). High-resolution structural images were also collected with a T1-weighted 3D gradient-echo pulse sequence with magnetization-prepared rapid gradient-echo sequencing (repetition time = 1670 ms, echo time = 1.89 ms, flip angle = 9°, slice thickness = 1.0 mm, in-plane resolution = 1.0 × 1.0 mm, field of view = 250 mm).

The fMRI data were preprocessed using SPM12 (Wellcome Trust Centre for Neuroimaging, London, UK). The data were slice time-corrected, motion-corrected, coregistered with the high-resolution structural image, normalized to the Montreal Neurological Institute space, and smoothed using a 6-mm full width at half-maximum Gaussian kernel. Coregistered and normalized fMRI data were visually inspected for quality control. Artifact Detection Tools (http://www.nitrc.org/projects/artifact_detect/) were used to identify outlier volumes. Outliers with a significant head motion by each participant were detected if the composite motion was greater than 2 mm or larger global mean intensity was detected (i.e., difference in global mean intensity across functional volumes >3 *SD*). As mentioned above, two participants were excluded from the final analysis because their outlier volumes were greater than 20% of the total volume. The outliers of each participant were also entered into the first-level general linear model as nuisance regressors to remove possible artifacts.

First-level analysis. First-level general linear model analyses were conducted for each participant. Three regressors pertaining to the presentation of words (negative emotional words, sleep-related

words, and neutral words) were entered into the model. Other regressors were created, corresponding to the fixation cross and fixation dot, but these were of no interest. Regressors were defined based on boxcar functions that were convolved with the canonical hemodynamic response function. Six head motion parameters and outliers were included in each participant's general linear model to control for the effects of head motion and outliers. High-pass filtering was applied to remove low-frequency drifts.

Three contrast images were calculated for each participant to compare brain activation while performing the emotional Stroop task with negative emotional words versus neutral words, with sleep-related words versus neutral words, and with negative emotional words versus sleep-related words. These contrast images were submitted to the second-level group analysis.

Second-level group analysis. We conducted whole-brain analyses using two-sample *t*-tests to identify regions with group differences (rotating shift workers vs. healthy controls) in neural activation, in association with affective interference in the context of the "negative emotional words > neutral words" contrast, and in association with sleep-related interference in the context of the "sleep-related words > neutral words" contrast. The clusterwise correction was performed in 3dClustSim, with smoothing estimated via 3dFWHMx in AFNI using the "acf" procedure (https://afni.nimh.nih.gov/, version 20.03.01) [37]. Cluster size was determined using 10 000 Monte Carlo simulations, second nearest-neighbor clustering, and a two-sided threshold. Both the cluster-defining threshold and cluster size necessary to achieve a cluster-wide corrected $p < .05$ are reported below (see the fMRI whole-brain results section).

Statistical analysis

Statistical analyses were conducted using SPSS 25.0 software. The *t*-test and chi-squared test were used to detect differences in demographic, clinical, sleep, and circadian characteristics between rotating shift workers and controls. The PROCESS macro in SPSS 25.0 was employed to examine the moderation model, in which the interaction between sleep disturbance (measured by the PSQI) and neural activation reflecting Stroop interference predicted depressive symptoms in rotating shift workers. Significant interactions were tested using the Johnson–Neyman procedure implemented in PROCESS [38]. The moderation model was adjusted for sex and length of working as a shift worker.

Results

Demographic, clinical, sleep, and circadian characteristics

The demographic, clinical, sleep, and circadian characteristics are presented in Table 1. Rotating shift workers had higher ESS scores and longer SOLs (ESS: $p < .05$, SOL: $p < .01$) on the self-reported sleep variables measured by the sleep diary compared with controls. In addition, they had lower *SE* on the objective sleep variables measured by actigraphy compared with controls ($p < .05$). In terms of circadian variables, rotating shift workers had higher levels of mesor, M10, and L5 (mesor: $p < .001$, M10: $p < .001$, L5: $p < .001$) and lower levels of amplitude, *F*-stat, relative amplitude, IS, and IV (amplitude: $p < .01$, *F*-stat: $p < .001$, relative amplitude: $p < .001$, IS: $p < .001$, IV: $p < .001$), compared with controls.

Table 1. Demographic, clinical, sleep, and circadian characteristics

	All participants, *N* = 121, *M* ± *SD* or *n* (%)			
Variables	Shift workers, *n* = 60	Controls, *n* = 61	Test	*p*
Demographic information				
Age, years	30.67 ± 6.75	31.67 ± 7.40	*t* = 0.78	.437
Female sex	46 (76.7)	42 (68.9)	χ^2 = 0.93	.335
Time as a shift worker, months	63.31 ± 57.79			
Self-reported emotional problems				
BDI	7.80 ± 6.44	5.67 ± 5.31	*t* = 1.97	.051
BAI	6.96 ± 6.72	7.69 ± 6.97	*t* = –0.54	.591
Self-reported sleep problems				
ESS	9.13 ± 3.99	7.57 ± 3.73	*t* = 2.22	<.05
PSQI	6.75 ± 2.77	5.74 ± 3.30	*t* = 1.83	.070
ISI	9.47 ± 5.24	7.72 ± 6.04	*t* = 1.70	.092
Sleep diary				
TST, min	401.47 ± 59.40	407.92 ± 55.69	*t* = 0.53	.596
SE, %	86.01 ± 6.74	84.62 ± 9.81	*t* = 0.76	.453
WASO, min	30.15 ± 18.01	27.56 ± 21.38	*t* = 0.64	.527
SOL, min	19.25 ± 12.96	12.64 ± 8.94	*t* = 2.70	<.01
Actigraphy: sleep variables				
TST, minutes	403.03 ± 47.89	421.08 ± 56.73	*t* = 1.66	.100
SE, %	77.19 ± 7.33	80.56 ± 5.36	*t* = 2.58	<.05
WASO, min	52.60 ± 20.85	47.45 ± 20.94	*t* = 1.17	.246
SOL, min	35.55 ± 22.40	36.14 ± 19.44	*t* = 0.13	.896
Actigraphy: circadian variables				
Mesor	99.48 ± 18.09	81.95 ± 22.19	*t* = 4.20	<.001
Amplitude	48.47 ± 24.80	61.53 ± 17.31	*t* = 3.02	<.01
Acrophase	16.05 ± 3.41	16.42 ± 1.23	*t* = 0.75	.455
F-stat	1169.21 ± 914.27	2064.40 ± 931.27	*t* = 4.54	<.001
M10	129.55 ± 33.00	110.48 ± 30.00	*t* = 2.83	<.001
L5	35.58 ± 22.46	7.71 ± 4.93	*t* = 9.18	<.001
Interdaily stability	0.31 ± 0.15	0.49 ± 0.09	*t* = 7.48	<.001
Intradaily variability	0.71 ± 0.18	0.90 ± 0.22	*t* = 4.49	<.001
Relative amplitude	0.57 ± 0.24	0.87 ± 0.09	*t* = 8.67	<.001
Reaction time (miliseconds)				
Negative emotional words	704.47 ± 105.06	681.79 ± 110.27	*t* = 1.11	.269
Sleep-related words	678.14 ± 100.13	662.02 ± 102.23	*t* = 0.84	.403
Neutral words	652.73 ± 81.68	641.05 ± 105.34	*t* = 0.65	.514
Accuracy (%)				
Negative emotional words	93.50 ± 15.42	93.35 ± 17.83	*t* = 0.05	.961
Sleep-related words	94.48 ± 14.43	92.46 ± 17.36	*t* = 0.67	.505
Neutral words	93.96 ± 16.60	93.00 ± 16.21	*t* = 0.31	.760

BDI: Beck Depression Inventory, BAI: Beck Anxiety Inventory, BIS: Barratt Impulsiveness Scale, ESS: Epworth Sleepiness Scale, IS: interdaily stability, ISI: Insomnia Severity Index, IV: intradaily variability, L5: least active 5-h period, M10: most active 10-h period, PSQI: Pittsburgh Sleep Quality Index, TST: total sleep time, *SE*: sleep efficiency, WASO: wake time after sleep onset, SOL: sleep onset latency

Behavioral results

Reaction time. A group (rotating shift workers vs. controls) × condition (negative emotional vs. sleep-related vs. neutral words) repeated-measures analysis of variance revealed a significant main effect of condition ($F_{(2, 218)} = 42.93$, $p < .001$, partial $\eta^2 = 0.28$). Pairwise comparisons showed that regardless of

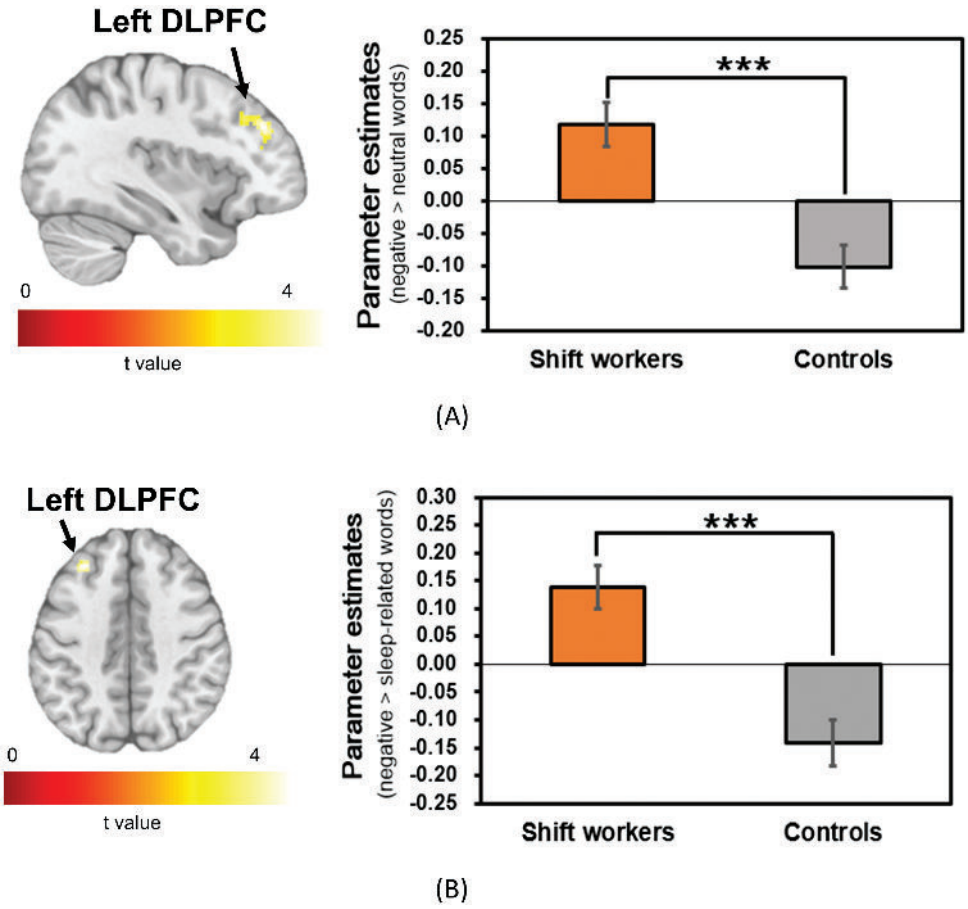


Figure 1. Activation of the left dorsolateral prefrontal cortex (DLPFC) in response to negative emotional words (vs. neutral or sleep-related words) when shift workers and controls performed the emotional Stroop task. (A) Activation of the left DLPFC in response to negative emotional words vs. neutral words, $^{*}p < .05$. (B) Activation of the left DLPFC in response to negative emotional words and sleep-related words, $^{*}p < .05$.

the group, reaction times were longer in the negative emotional word (*M*[*SD*] = 693.44[107.74]) and sleep-related word (*M*[*SD*] = 670.30[101.02]) conditions than in the neutral word condition (*M*[*SD*] = 647.05[93.69]) (all $p < .001$). A significant difference in reaction time was detected between the negative emotional word and sleep-related word conditions ($p < .001$). However, no significant main effects of the group or group × condition interaction were observed (all $p > .35$) (Table 1).

Accuracy. A group (rotating shift workers vs. controls) × condition (negative emotional vs. sleep-related vs. neutral words) repeated-measures analysis of variance revealed no significant main effects of the condition, group, or group × condition interaction effect on accuracy (all $p > .1$) (Table 1).

Table 2. Moderating effects of activating the left dorsolateral prefrontal cortex on the association between self-reported sleep disturbance and depressive symptoms in shift workers

Predictors	ΔR^2	*b*	*SE*	*t*	*p*
Main effects	0.45				
Sleep disturbance (PSQI)		1.65	0.26	6.35	<.001
Left DLPFC activation		4.04	2.41	1.68	.100
Sex		−1.40	1.56	−0.90	.371
Time as a shift worker		0.03	0.01	2.65	.011
Interactive effects	0.04				
Sleep disturbance (PSQI) × Left DLPFC activation		2.40	1.14	2.10	.041
Model $R^2 = 0.49$, $F_{(5,52)} = 9.93$, $p < .001$					

Adjustment for sex and length of working as a shift worker.

fMRI whole-brain analysis results

Group differences in neural correlates of negative emotional words versus neutral words. Whole-brain analysis revealed that rotating shift workers had greater neural activation in the left DLPFC, compared with controls, while performing the emotional Stroop task with negative emotional words (vs. neutral words) (cluster size = 228, peak coordinate: $x = -36$, $y = 40$, $z = 30$, peak *t*-value= 4.44, cluster-defining threshold, $p < .001$; cluster size > 90 voxels to achieve a clusterwise corrected $p < .05$) (Figure 1A). However, the controls did not present greater activation in any region compared with rotating shift workers while performing the emotional Stroop task with negative emotional words (vs. neutral words). The results remained unchanged after adjusting for depressive symptoms.

Group differences in neural correlates of sleep-related words vs. neutral words. Whole-brain analysis revealed no group differences in neural activation while performing the emotional Stroop task with sleep-related words (vs. neutral words) (cluster-defining threshold, $p < .001$; cluster size >89 voxels to achieve a clusterwise corrected $p < .05$).

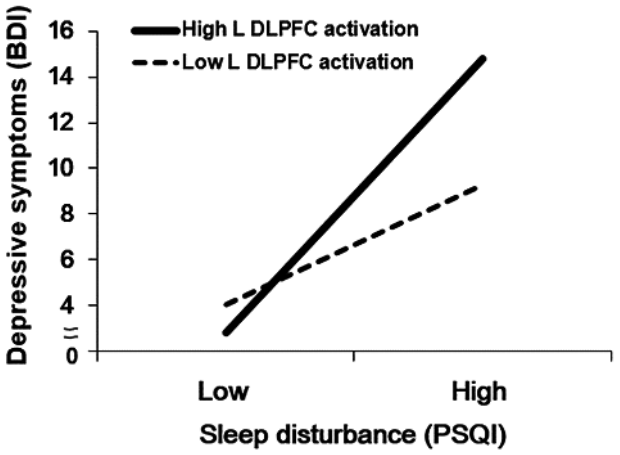


Figure 2. Moderating effects of activating the left dorsolateral prefrontal cortex on the association between sleep disturbance and depressive symptoms in shift workers.

Group differences in neural correlates of negative emotional words vs. sleep-related words. We also tested whether rotating shift workers exhibited different neural activation compared with controls while performing the emotional Stroop task with negative emotional words (vs. sleep-related words). Rotating shift workers had greater activation in the left DLPFC, compared with controls while performing the emotional Stroop task with negative emotional words (vs. sleep-related words) (cluster size = 75, peak coordinate: $x = -30$, $y = 32$, $z = 44$, peak t-value = 4.16, cluster-defining threshold, $p < .001$; small volume correction using the DLPFC mask, cluster size >17 voxels to achieve a clusterwise corrected $p < .05$) (Figure 1B).

Moderation analysis results

Sleep disturbance × left DLPFC activation in response to negative emotional stimuli predicts depressive symptoms in rotating shift workers. The results of the moderation analysis are summarized in Table 2. Activation of the left DLPFC while performing the emotional Stroop task with negative emotional words (vs. neutral words) significantly moderated the association between the PSQI score and depressive symptoms after controlling for sex and length of working as a shift worker ($p = .041$). A simple slope analysis using the Johnson–Neyman technique revealed that a sleep disturbance was more strongly associated with depressive symptoms when left DLPFC activation was higher (+1 *SD*: $b = 2.29$, $SE = 0.45$, $p < .001$) than when left DLPFC activation was lower (–1 *SD*: $b = 1.00$, $SE = 0.35$, $p = .006$) while performing the emotional Stroop task with negative emotional words (vs. neutral words) (Figure 2).

Sleep disturbance × left DLPFC activation in response to negative emotional stimuli predicts anxiety symptoms in rotating shift workers. Activation of the left DLPFC while performing the emotional Stroop task with negative emotional words (vs. neutral words) did not significantly moderate the association between the PSQI score and anxiety symptoms after controlling for sex and length of working as a shift worker ($p = .071$).

Discussion

The present study used fMRI to examine the differences in the patterns of neural activation between rotating shift workers and controls during the emotional Stroop task with negative emotional or sleep-related words (vs. neutral words). Rotating shift workers showed greater left DLPFC activation in response to negative emotional words (vs. neutral words) compared with healthy controls. No significant differences in brain activation were detected in response to sleep-related words (vs. neutral words). Furthermore, the greater left DLPFC activation in response to negative emotional words strengthened the association between sleep disturbance and depressive symptoms in rotating shift workers.

Rotating shift workers had higher ESS scores and longer SOLs on the self-reported sleep variables as measured by the sleep diary compared with controls. In addition, they had lower *SE* on the objective sleep variables measured by actigraphy compared to controls. Although not statistically significant, shift workers had higher PSQI scores compared to controls ($p = .070$). These results indicate that rotating shift workers experience disrupted sleep and excessive sleepiness during their working hours. Although rotating shift workers performed higher levels of activity (higher levels of mesor and M10), they experienced less restful sleep (higher L5). This result could reflect the dampened 24-h rest-activity rhythm and circadian misalignment caused by rotating shift work. Many studies have shown that rotating shift workers are more vulnerable to difficulty sleeping and reduced alertness while at work, and have less robust circadian rhythms [6, 39]. These results suggest that the participants in the current study well reflect the characteristics of rotating shift workers.

When participants performed the emotional Stroop task, rotating shift workers showed greater activation of the left DLPFC in response to negative emotional words. The DLPFC is the primary neural circuit related to controlling cognitive and executive functions [40]; thus, greater activation of the left DLPFC in rotating shift workers in response to negative emotional words may indicate that rotating shift workers require more effort to perform cognitive tasks under negative emotional contexts than controls. Several explanations exist for these results. First, dysregulated circadian gene expression outside of the suprachiasmatic nucleus (e.g., in the PFC) may be associated with the cognitive control of emotions through the rhythmic activity of monoamine neurotransmitters. Otsuka et al. [41] reported that circadian misalignment disrupts the expression rhythms of the clock and immediate early genes in the PFC, resulting in depressive-like behaviors in rats. Because clock genes control the dopaminergic system [42] and the function of the PFC is associated with cognitive control and emotion regulation [40, 43], greater activation of the PFC may reflect integration of the clock function and cognitive control of emotions. Second, although not statistically significant, the BDI scores showed that shift workers tended to be more depressed than controls ($p = .051$). Thus, depressive symptoms in rotating shift workers could be a factor that contributes to greater Stroop interference caused by emotionally salient stimuli. Further studies using larger samples would be necessary to provide confirmation of the current analysis.

No differences in the patterns of brain activation were detected in response to sleep-related words between rotating shift workers and healthy controls when they performed the emotional Stroop task. Additionally, the behavioral results revealed that shift workers did not have increased sensitivity to sleep-related stimuli. These results are inconsistent with our hypothesis and previous results showing that shift workers are more vulnerable to sleep disturbances because the homeostatic

pressure to sleep and the circadian alerting signal become uncoupled [44]. There are several possible explanations for these unexpected results. First, shift workers in the current study showed longer SOL on sleep diaries and lower *SE* on actigraphy compared to controls. However, insomnia severity was not significantly different between shift workers and controls (ISI: $p = .092$). In the current study, the shift worker group was likely composed of relatively healthy shift workers who rarely raised concerns or expressed distress about sleep. Therefore, they may not be sensitive to sleep-related words. Second, as most participants in the current study were young adults, sleep problems derived from shift rosters may have been underestimated. Older shift workers experience more difficulty sleeping during the early part of the day after night shifts. Aging is also associated with increased *morningness* due to age-related shortening of the circadian rhythm and reduced sleep duration [45]. Therefore, future studies should include participants from a wide range of age groups to better understand the effects of shift work on sleep problems.

In the current study, activation of the left DLPFC in response to negative emotional words moderated the relationship between sleep disturbance and depressive symptoms in rotating shift workers. This result indicates that the association between sleep disturbance measured by the PSQI and depressive symptoms was stronger when left DLPFC activation was high in response to negative emotional words than when left DLPFC activation was low. Individuals who report greater self-reported sleep disturbance tend to have greater negative bias with disruptions in sustained attention [46, 47]. Consequently, the negativity bias and disrupted sustained attention result in depression [48, 49]. However, not all individuals who experienced self-reported sleep disturbances are depressed. Our results suggest that neurobiological factors, such as activation of the DLPFC, representing more cognitive effort due to emotional interference may be related to negative bias and may play a critical role linking self-reported sleep disturbance and depressive symptoms in shift workers. Therefore, in line with the growing body of evidence showing the potential promise of neuromodulation techniques for treating various sleep and mood problems [50, 51], the left DLPFC may be a target region to relieve depressive symptoms derived from sleep disturbance in shift workers.

This study had several limitations. First, it was cross-sectional; therefore, inflated associations and reverse causality are possible. Second, regardless of emotional valence, high emotional arousal stimuli may be more salient than neutral and sleep-related stimuli. Therefore, positive high arousal words should have been included in the emotional Stroop task to identify a potential negativity bias in shift workers more precisely. Third, although we tried to exclude the influence of shift worker sleepiness before the fMRI scan, the shift workers may have been sleepy when completing the Stroop task in the MRI scanner. However, we did not find any group differences in behavioral performance, including reaction time and accuracy. These results indicate that sleepiness may not be a factor that differentiates neural responses to emotional words. Additionally, the ESS scores were not correlated with activation of the left DLPFC ($r = 0.146$, $p = .343$) in shift workers. Fourth, we did not collect information about the interval from the most recent shift until the PSG and fMRI assessment. Depending on the interval lapsed, levels of circadian disruption and social/environmental factors can differ even within the same rotating shift worker. Fifth, since the mean days of all shift workers' actigraphic records were 6.85 (*SD* 1.02), actigraphy data might not be enough to examine the possible effects of individual shift work schedules on circadian disruption. Further research should collect actigraphic data for a sufficient period to fully reflect shift work patterns.

To the best of our knowledge, this study was one of the first fMRI studies conducted on study subjects performing the emotional Stroop task to elucidate the brain region reflecting emotional interference of cognitive control in rotating shift workers. Furthermore, we investigated the role of the DLPFC in the context of sleep and emotions. The results broaden our understanding of sleep and mood problems derived from circadian misalignment and contribute to the literature related to the etiology and management of SWD.

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Disclosure Statement

The authors declare that they have no conflict of interest.

Author Contributions

Y.J.L. and S.J.K. designed and directed the project. Y.J.L. and S.J.K. contributed to project management. H.Y.L., J.E.J, and K.H.L. processed the data and designed and performed the data analyses. K.H.L. verified the analytical methods. S.Y.K. wrote the manuscript. All authors provided critical feedback and helped shape the research, analysis, and manuscript.

Data Availability

Anonymized data will be made available to other qualified researchers upon reasonable request to the corresponding author.

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