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Brief Communication

Regional gray matter changes in shift workers: a voxel-based morphometry study

Jung Bin Kim, Ji Hyun Kim*

Department of Neurology, Korea University Guro Hospital, Korea University College of Medicine, Seoul, Republic of Korea

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ABSTRACT

Objective: Previous neuroimaging studies have shown subtle structural changes of the brain in various sleep disorders, suggesting detrimental effects of disrupted sleep–wake cycle on brain structures. We aimed to identify structural changes in shift workers relative to day workers. We hypothesized that brain structures belonging to sleep–wake modulation may be altered in shift workers.

Methods: Nineteen male shift workers (median age, 21 years) and 19 male day workers (median age, 21 years) voluntarily participated in the current study. Sleep questionnaires were obtained from all participants and compared between the groups. Voxel-based morphometry was used to compare regional gray matter volume between shift workers and day workers (corrected $p < 0.05$ with small volume correction). Separate correlation analyses were performed between regional gray matter volume change and scores of Epworth Sleepiness Scale and Pittsburgh Sleep Quality Index (Pearson's correlation, $p < 0.05$).

Results: Compared to day workers, shift workers had higher scores of Beck Depression Inventory-II, Epworth Sleepiness Scale, and Pittsburgh Sleep Quality Index. Compared to day workers, shift workers had a significant gray matter volume reduction in the pontomesencephalic tegmentum. Regional volume of the pontomesencephalic tegmentum negatively correlated with Pittsburgh Sleep Quality Index global score.

Conclusions: We observed that pontomesencephalic tegmentum volume was reduced in shift workers compared to day workers and that the smaller pontomesencephalic tegmentum volume was related to the poorer sleep quality. Our preliminary findings may be related to chronic disruption of circadian rhythm or decreased exposure to bright light in shift workers.

1. Introduction

Shift work disrupts the sleep–wake cycle and its synchrony with physiologic circadian rhythms, leading to fragmented and shorter sleep during the daytime and impaired wakefulness during working hours in shift workers [1]. Sleep disturbance and circadian rhythm disruption in shift workers have deleterious effects on physical health and quality of life [1]. Moreover, shift work schedules could negatively influence cognitive functions and job performance, and increase the risk of accidents [1]. Since sleep deprivation could lead to impaired brain functions [2], it is conceivable that sleep disturbance and disruption of circadian rhythms in shift workers may alter activity of neuronal circuitry underlying cognitive functions.

Recent magnetic resonance imaging (MRI) studies have addressed the issue of whether sleep disturbances are associated with structural changes in the brain. Severity of daytime sleepiness negatively correlated with ventromedial prefrontal gray matter (GM) volume in healthy volunteers [3]. Individuals with chronic insomnia had reduced GM volumes of prefrontal, temporal, and parietal cortices relative to good sleepers [4]. In addition, right temporal lobe volume was reduced in cabin crews with short recovery periods from jet lag, compared to those with long recovery periods [5]. These findings suggest that chronic sleep disturbance and circadian rhythm disruption may alter brain structures.

To our knowledge, there is currently no study investigating brain structural changes in shift workers. In the present study, we applied voxel-based morphometry (VBM) [6] to examine structural changes associated with shift work. We hypothesized that

* Corresponding author. Department of Neurology, Korea University Guro Hospital, Korea University College of Medicine, 152-703, Guro-dong Ro 148, Guro-gu, Seoul, Republic of Korea. Fax: +82 2 2626 2249.
E-mail address: jhkim.merrf@gmail.com (J.H. Kim).

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neuroanatomical structures relevant to sleep–wake switch [7] may be altered in shift workers relative to day workers.

2. Methods

2.1. Participants and sleep questionnaires

A total of 38 healthy military servicemen voluntarily participated in this study. Nineteen participants had been on rotating shift work according to the following schedules: nighttime wake (16:00–08:00) and daytime sleep (08:00–16:00) for two weeks, rest for 24 h, daytime wake (06:00–22:00) and nighttime sleep (22:00–06:00) for two weeks, rest for 24 h. Nineteen participants had been on standard work schedules: daytime wake (06:00–22:00) and nighttime sleep (22:00–06:00). Both groups strictly maintained the working schedules for at least six months. Neurological examination was normal in all participants. The local ethics committee of the Armed Forces Hospital approved the study, and all participants gave written informed consent.

Sleepiness and sleep quality were measured by Epworth Sleepiness Scale (ESS) and Pittsburgh Sleep Quality Index (PSQI), respectively. Depressive symptoms were measured by the Beck Depression Inventory-II (BDI-II).

2.2. Magnetic resonance image acquisition and voxel-based morphometry

Magnetic resonance (MR) images were acquired on a 1.5 T scanner (Achieva, Philips, Netherlands). For volumetric analysis, a high-resolution three-dimensional (3D) turbo field echo sequence was acquired (TR = 7 ms, TE = 3 ms, voxel dimensions = 0.5 mm^3). Clinical MR images were acquired simultaneously to identify structural abnormalities.

Data preprocessing and VBM were carried out using SPM12 software (http://www.fil.ion.ucl.ac.uk/spm). Briefly, the volumetric T1-weighted images were segmented into GM and white matter. Segmentations were produced with rigid alignment to standard MNI space and resampled to 1.5-mm^3 isotropic voxels for use with DARTEL [6]. DARTEL then iteratively registered the GM and white matter segments to an evolving estimate of their groupwise average. The native space tissue segments were then normalized to MNI space using the DARTEL transformations and modulated to account for volume changes using the Jacobian determinants. Finally, the modulated GM volumes were smoothed with a Gaussian kernel of 8-mm FWHM.

Between-group comparisons of GM volume were assessed using an analysis of covariance with total intracranial volume and age as nuisance variables. An absolute GM threshold of 0.2 was used to avoid possible edge effects around the border between GM and white matter. Statistical parametric maps were thresholded at $p < 0.001$, uncorrected for multiple comparisons at a voxel level across the whole brain. Given our *a priori* knowledge of the involvement of brainstem structures in the sleep–wake cycle [7], small-volume correction was further applied to the area of significant between-group comparison (ie, pontomesencephalic tegmentum) using a 5-mm radius with a threshold of familywise error-corrected $p < 0.05$.

2.3. Statistical analysis

Basic characteristics and questionnaires scores were compared between shift workers and day workers using an independent *t* test, Mann–Whitney *U* test, and χ^2 test, where appropriate ($p < 0.05$). Voxel values were extracted from the significant cluster in group comparison and were correlated with questionnaires scores using the Spearman or Pearson correlation ($p < 0.05$).

3. Results

Demographics and clinical data are presented in Table 1. Shift workers ($n = 19$) and day workers ($n = 19$) did not differ in age, proportion of smokers, and education years. Shift workers had higher BDI-II scores ($p = 0.022$) and ESS scores ($p = 0.029$) than day workers. The PSQI global score was higher in shift workers than in day workers ($p = 0.001$), as with domain scores of subjective sleep quality ($p = 0.006$) and daytime dysfunction ($p = 0.014$).

VBM showed a significant regional GM volume reduction in pontomesencephalic tegmentum in shift workers compared to day workers (MNI coordinate = 8/–35/–12, cluster size = 739 mm^3, peak *z* score = 3.78, voxel level–uncorrected $p < 0.001$, familywise error–corrected $p = 0.001$ after small-volume correction) (Fig. 1). No region of a significant GM volume increase was found in shift workers compared with day workers. Relative voxel values extracted from the pontomesencephalic cluster negatively correlated with PSQI global score ($r = -0.370$, $p = 0.022$) (Fig. 1), but did not correlate with age ($p = 0.848$), years of education ($p = 0.732$), ESS score ($p = 0.182$), or BDI-II score ($p = 0.187$).

4. Discussion

We observed that regional GM volume in the pontomesencephalic tegmentum was reduced in shift workers relative to day workers, and that the smaller pontomesencephalic tegmentum volume was related to poorer sleep quality.

The pontomesencephalic tegmentum region corresponds to the pedunculopontine and laterodorsal tegmental (PPT/LDT) nuclei that consist of major aggregations of cholinergic neurons and have been considered among the most important components of the reticular activating system [7]. Recently, several lines of evidence have indicated that cholinergic neurons in the PPT/LDT fire most rapidly during wakefulness and rapid eye movement (REM) sleep, and most slowly during non-REM sleep, suggesting an active role of PPT/LDT nuclei in the control system that contributes to cortical activity across the whole sleep–wake cycle, and not just to cortical activation during wakefulness and REM sleep [7–9]. Given the role of PPT/LDT in the sleep–wake cycle, lesions in the pontomesencephalic tegmentum may lead to

Table 1
Demographics and questionnaire scores in shift workers and day workers.

	Shift workers ($n = 19$)	Day workers ($n = 19$)	*p*
Age, y, median (IQR)	21 (21–22)	21 (20–22)	0.354[a]
Smokers, *n*	8	8	1.000[b]
Education years, median (IQR)	13 (13–14)	13 (13–14)	0.795[a]
Beck Depression Inventory-II, median (IQR)	10 (8–11)	7 (5–10)	0.022[a]
Epworth Sleepiness Scale, mean ± SD	10.3 ± 4.1	7.5 ± 3.4	0.029[c]
Pittsburgh Sleep Quality Index			
Global, mean ± SD	9.0 ± 2.2	6.0 ± 2.7	0.001[c]
Subjective sleep quality, median (IQR)	2 (2–3)	2 (1–2)	0.006[a]
Sleep latency, median (IQR)	1 (1–2)	1 (0–2)	0.191[a]
Sleep duration, median (IQR)	1 (0–2)	0 (0–1)	0.258[a]
Habitual sleep efficiency, median (IQR)	0 (0–1)	0 (0–1)	0.708[a]
Sleep disturbance, median (IQR)	2 (1–2)	1 (1–2)	0.109[a]
Daytime dysfunction, median (IQR)	2 (1–3)	1 (0–2)	0.014[a]

IQR, interquartile range; SD, standard deviation.
[a] Mann–Whitney *U* test.
[b] χ^2 test.
[c] Independent *t* test.