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fMRI brain activation in patients with insomnia disorder during a working memory task

Young-Don Son[1] · **Jae Myeong Kang**[2] · **Seong-Jin Cho**[2] · **Jung-Sun Lee**[3] · **Hee Young Hwang**[4] · **Seung-Gul Kang**[2]

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Abstract
Purpose This study used functional magnetic resonance imaging (fMRI) to investigate differences in the functional brain activation of patients with insomnia disorder (n = 21, mean age = 36.6) and of good sleepers (n = 26, mean age = 33.2) without other comorbidities or structural brain abnormalities during a working memory task.
Methods All participants completed a clinical questionnaire, were subjected to portable polysomnography (PSG), and performed the working memory task during an fMRI scan. The subjects who were suspected of major sleep disorder and comorbid psychiatric disorders except insomnia disorder were excluded. To compare the brain activation on working memory from the insomnia group with those from the good-sleeper group, a two-sample t test was performed. Statistical significance was determined using 3DClustSim with the updated algorithm to obtain a reasonable cluster size and p value for each analysis.
Results We observed higher levels of brain activation in the right lateral inferior frontal cortex and the right superior temporal pole in the insomnia group compared to good sleepers (cluster-based multiple comparison correction, $p < 0.001$, $k = 34$ @ $\alpha = 0.01$).
Conclusion Thus, patients with insomnia disorder showed increased brain activation during working memory relative to good sleepers, and this may be indicative of compensatory brain activation to maintain cognitive performance in patients with insomnia disorder without other comorbidities.

Keywords Insomnia disorder · fMRI · Working memory · Brain activation

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✉ Seung-Gul Kang
kangsg@gachon.ac.kr

[1] Department of Biomedical Engineering, College of Health Science, Gachon University, Incheon, Republic of Korea

[2] Department of Psychiatry, Gil Medical Center, College of Medicine, Gachon University, 21, Namdong-daero 774 beon-gil, Namdong-gu, Incheon 21565, Republic of Korea

[3] Department of Psychiatry, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Republic of Korea

[4] Department of Radiology, Gachon University Gil Medical Center, Incheon, Republic of Korea

Introduction

Insomnia is among the most common, distressing, and clinically important sleep disturbances. Insomnia not only impairs quality of life and everyday functioning but also affects cognitive function [1]. The biological function of sleep is thought to be related to memory integration, and its mechanism is explained by the neural plasticity and homeostasis [2].

Previous meta-analyses to investigate the effect of sleep deprivation on cognitive function showed decreased performance in most cognitive domains [3]. However, although patients with chronic insomnia often complain of various cognitive impairments [4], such tests produce varying results depending on the cognitive domain. The results of cognitive tasks assessing working memory, which are core executive function, are sometimes negative and are particularly inconsistent, which is in contrast to clinical expectations [5–8].

The possible explanation for the inconsistencies among neuropsychological working memory test results is that the neuropsychological test methods used may not have been

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sufficiently sensitive to detect the cognitive dysfunction that insomnia patients experience in their daily lives [8]. Cognitive neuroimaging studies could be used to explore alterations in cognitive processes that may not readily appear in behavioral task measures [9]. Thus, functional neuroimaging methods during cognitive tasks have been used for the investigation of brain dysfunction associated with insomnia [8, 9]. The previous studies have employed functional magnetic resonance imaging (fMRI) techniques to assess verbal working memory [8] and spatial working memory [10] abilities in patients with insomnia. The primary insomnia group showed reduced activation of the working memory task-related regions, although cognitive performance of the primary insomnia group did not differ from those of good sleepers [8]. Lower levels of activation during the spatial working memory task were also observed in several brain regions in the insomnia group [10]. However, further studies are necessary to accumulate more evidences; thus, the present study compared the fMRI brain activation between patients with insomnia disorder and good sleepers during a verbal working memory task: the *n*-back test.

The primary aim of this study was to investigate whether there is a difference in brain activation during working memory task between insomnia patients and good sleepers. We also explored whether there is a correlation between brain activation and the severity of insomnia (and objective sleep duration) in individuals with insomnia.

Materials and methods

Participants

All insomnia patients and good sleepers included in the present study were recruited from the sleep clinic at Gil Medical Center in Korea. The following inclusion criteria were used to recruit participants with insomnia disorder: (i) aged 18 − 60 years and right-handed, (ii) history of illness lasting at least 1 year and meeting the diagnostic criteria for insomnia disorder as stated in the Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders [11], (iii) a total score ≥ 8 on the Korean version of the Pittsburgh Sleep Quality Index (PSQI) at screening [12]; and (iv) not having taken any psychiatric medications or hypnotics or having been treated with cognitive behavioral therapy for insomnia (CBT-I) in the last 2 weeks. The following inclusion criteria were applied to recruit good sleepers: (i) aged 18–60 years and right-handed; (ii) no symptoms or history of psychiatric disorders and sleep disorders; (iii) a total score ≤ 4 on the PSQI at screening; and (iv) not having taken any psychotropic medications or hypnotics during their lifetime.

The following common exclusion criteria for both groups were set to exclude subjects who were not suitable for the study and to exclude factors that could act as confounders in the results: (i) suspected of a present or previous major sleep disorder other than insomnia disorder; (ii) employment as a shift worker or traveler experiencing frequent jet lag; (iii) classification as "high risk of sleep apnea" according to the Berlin Sleep Questionnaire [13] or moderate to severe sleepiness according to the Epworth Sleepiness Scale (ESS) based on a score ≥ 13 [14]; (iv) a body mass index (BMI) ≥ 30; (v) evidence of any sleep disorder except insomnia according to polysomnography (PSG) findings (e.g., apnea–hypopnea index ≥ 5, periodic limb movements in sleep ≥ 15, or rapid eye movement sleep without atonia); (vi) current or past diagnosis of other comorbid psychiatric disorders based on a clinical interview; (vii) evidence of either depression (Beck Depression Index [BDI] ≥ 16) [15] or anxiety (Beck Anxiety Index [BAI] ≥ 19) at a moderate or high level based on the screening scale; (viii) history or presence of significant neurological or medical illnesses; (ix) contraindications for 3T MRI, such as claustrophobia, metal implants, and pacemakers; (x) pregnancy, lactation, or plans to become pregnant during the study period; and (xi) structural brain abnormalities based on MRI.

All participants were screened via telephone interviews and screening scales. After screening, board-certified psychiatrists with a specialty in sleep medicine evaluated the eligibility of each participant during a face-to-face interview to assess whether the participant met the diagnostic criteria for insomnia disorder, compile the medical history of each patient, and administer a semi-structured interview for sleep and psychiatric disorders. Written informed consent was obtained from all participants prior to inclusion in the study, and the Institutional Review Board of Gil Medical Center approved all study protocols.

Clinical questionnaire

All participants completed a questionnaire to gather data on their demographic characteristics, medical and psychiatric illnesses, and sleep information. The participants also completed the Korean versions of the PSQI, ESS, Berlin Questionnaire, BDI, and BAI at screening and responded to the Korean versions of the PSQI, Insomnia Severity Index (ISI) [16], ESS, BDI, and BAI on the scanning date.

Use of PSG to identify other sleep disorders

To exclude participants with occult sleep disorders other than insomnia, an overnight PSG was performed using the Embletta X100® system (Embla; Broomfield, CO, USA). Manual scoring was performed according to the manual of the American Academy of Sleep Medicine 2.0.2. [17], using RemLogic 3.4.0® (Embla Systems; Kanata, ON, Canada) as the scoring platform.

Working memory task during fMRI scanning

A two-back working memory task was conducted during fMRI data acquisition. The test comprised three task blocks: visual fixation, motor control, and working memory tasks (Fig. 1). Each task block lasted for 30 s and at least five blocks were presented randomly over a total of 8 min. During the motor control period, the number zero was presented for 500 ms every 2 s. The working memory task was the two-back task of one numeric digit from one to nine, which were randomly presented for 500 ms every 2 s. Each task was presented via a beam projector with non-commercial presentation software that was synchronized to the trigger signal of the MR scanner. Subjects were instructed to press the buttons according to the two-back working memory task during the fMRI scanning. All button responses were recorded by an optically connected computer. Participants were instructed not to move their head throughout the entire fMRI scan. The reaction time was measured as the time from visual presentation for the task until the button-pressed response. The reaction accuracy was the ratio of the correct answer among the number of total tasks.

Statistical analyses of demographic and behavioral data

SPSS ver. 23.0 (SPSS; Chicago, IL, USA) was used to analyze the demographic and behavioral data. The chi-square test and independent *t* tests were used to compare the demographic, clinical characteristics, and working memory results across groups. p values < 0.05 were considered to indicate statistical significance for the demographic and behavioral data.

fMRI image acquisition

All fMRI was performed within 2 weeks after the PSG and was performed between 9:30 A.M. and 12:00 P.M., at least 2 h after waking up. A series of MRI scans was acquired using a 3.0-Tesla MR scanner (Magnetom Verio, Siemens; Erlangen, Germany) with a 12-element matrix head coil. T2*-weighted echo planar images were acquired with the following parameters: repetition time (TR) = 3000 ms; echo time (TE) = 30 ms; flip angle = 90°; matrix size = 66 × 66; number of slices = 42; pixel size = 3.5 × 3.5 mm^2; thickness = 3.5 mm; field of view (FOV) = 231 × 231 mm^2; number of frames = 160; and total acquisition time = 480 s. High-resolution transaxial T1-weighted structural images were acquired using 3D magnetization-prepared rapid gradient-echo (3D–MPRAGE) with the following parameters: TR = 1900 ms; TE = 3.3 ms; inversion time (TI) = 900 ms; flip angle = 9°; matrix size = 416 × 512; number of slices = 160; pixel size = 0.5 × 0.5 mm^2; thickness = 1 mm; FOV = 208 × 256 mm^2; and total acquisition time = 220 s.

Image processing and analysis of fMRI data

Before image processing, board-certified neuroradiologists reviewed the structural MR images to determine if there were structural abnormalities in any participant. All fMRI data were processed using statistical parametric mapping (SPM8). Head movement parameters for translation and rotation, compared with the first volume, were estimated for each volume and applied for realignment. After the motion correction procedure, each individual structural image was coregistered to the mean of the realigned images, and the transformed structural images were segmented into gray matter, white matter,

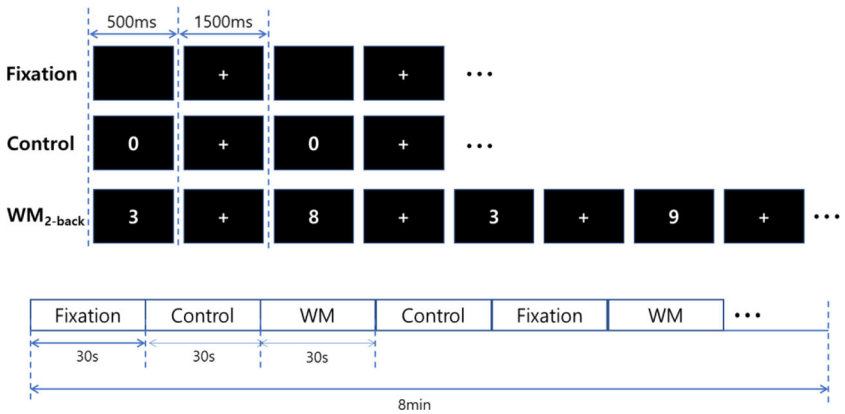

Fig. 1 Process of the two-back working memory tasks. Each task block lasted for 30 s and at least five blocks were presented randomly over a total of 8 min. The visual fixation task consisted of a series consisting of a blank or a white cross in the center. Participants were instructed to fixate on the cross during this period. The motor control task consisted of a series consisting of a zero or a white cross, and the participants were required to press the button whenever a zero appeared on the screen, to enable subtraction of the motor activation during the working memory task. The numeric two-back working memory task consisted of a series of random 1-digit numbers, which were presented for 500 ms, and a cross, which was presented for 1500 ms; participants were required to press a button inside the MR scanner if the number presented matched the number prior to the previous one. WM, working memory

and cerebrospinal fluid. The segmented data were spatially normalized to Montreal Neurological Institute (MNI) space, and the motion-corrected functional volumes were resampled to 3 mm isotropic voxels using the normalization parameters. Next, the normalized data were smoothed with a 6-mm full-width at half-maximum (FWHM) Gaussian low-pass filter.

For the individual data, a whole-brain multiple linear regression analysis was performed to analyze brain activation associated with the following three factors: visual fixation, motor control, and working memory periods. After conducting the individual analyses, the statistical results of the (working memory–motor control) contrast were used as a second-level analysis. To compare data on working memory from the insomnia group with those from the good-sleeper group, a two-sample t test was performed. The resultant regions were saved as the voxels of interest (VOIs) for the further correlation analysis with the severity of insomnia (ISI score) and total sleep time (TST) based on PSG. Furthermore, to investigate the correlation between the severity of insomnia and brain activation, a regression analysis of ISI and TST of PSG was performed.

Statistical significance was determined using 3DClustSim (AFNI, NIH, USA) with the updated algorithm issued by Eklund et al. [18] to obtain a reasonable cluster size and p value for analysis. The estimated parameters of the new exponential model were $a = 0.6823$, $b = 4.1419$, $c = 10.6853$, which were obtained by 3dFWHMx program from the detrended data set. According to the results, the cluster size threshold was set as $k = 34$ @ $\alpha = 0.01$ for two-sample t test and $k = 22$ @ $\alpha = 0.1$ for correlation analysis with ISI scores.

Results

Demographic, clinical, and PSG characteristics of participants

Of the subjects who passed the telephone screening, 47 subjects of the insomnia group and 43 subjects of the control group were excluded for the following reasons: (i) not adequate based on the screening scale (insomnia 33, good sleeper 30); (ii) were deemed ineligible after the face-to-face interview (insomnia 4, good sleeper 5); (iii) metal material in the body (insomnia 7, good sleeper 6); and (iv) abnormal PSG findings (insomnia 3, good sleeper 2). Six subjects of the insomnia group and eight subjects of the good-sleeper group withdrew their informed consent or did not attend the clinic on the scanning day. Finally, 22 patients with insomnia disorder and 27 good sleepers completed the research protocol. Additionally, one participant from each group was excluded from the analyses due to a structural abnormality on the brain MRI (arachnoid cyst in both participants).

The demographic, clinical, and PSG characteristics of the insomnia patients and good sleepers are presented in Table 1. There were no significant differences between the two groups in terms of age or sex. The average duration of illness for the insomnia-disorder group was 4.9 years (range 1–20 years).

On the day of the MRI scan, the average PSQI scores for the insomnia and good-sleeper groups were 12.2 and 2.4, respectively. The average sleep efficiency (SE) values on the PSQI were 62.9 and 95.0% in the insomnia and good-sleeper groups, respectively; and the average ISI total scores were 17.9 and 1.3 for the insomnia and good-sleeper groups, respectively. The PSG results of the insomnia group were as follows: TST = 323.4 min, SE = 80.3%, and wake after sleep onset (WASO) = 64.9 min. The PSG results of the good-sleeper group were as follows: TST = 392.1 min, SE = 94.4%, and WASO = 18.9 min.

Working memory and fMRI findings

The reaction time ($p = 0.785$) and reaction accuracy ($p = 0.359$) measured during working memory tasks during fMRI scanning did not differ significantly between the two groups. However, based on functional MRI, brain activation for the working memory task with a contrast of (working memory–motor control) was higher in the right lateral inferior frontal cortex and right superior temporal pole in the insomnia group compared with the good-sleeper group ($p < 0.001$, $k = 34$), as shown in Table 2 and Fig. 2. These significant regions were selected as VOIs for further analysis. None of the brain regions in the insomnia group showed lower brain activation for working memory tasks relative to the good-sleeper group.

Within selected VOIs, a correlation coefficient of the averaged weights in the first level analysis with sleep parameters (ISI score and TST based on PSG) was examined, and none of the sleep parameters showed any significant correlation with the VOIs (data not shown).

The regression analysis showed that the ISI total score in the insomnia group was significantly negatively correlated with brain activation in the right middle temporal cortex during the two-back task ($p < 0.001$, $k = 22$), as shown in supplementary Table S1 and Supplementary Fig. S1. TST based on PSG did not show a significant correlation with brain activation (data not shown).

Discussion

The main finding of this study is higher brain activation in the right lateral inferior frontal cortex and right superior temporal pole of the insomnia group compared with the good-sleeper group.

Table 1 Demographic, clinical, and polysomnographic characteristics of subjects

Variable	Insomnia disorder (*n* = 21)	Good sleeper (*n* = 26)	Statistics
Age years	36.6 ± 9.8	33.2 ± 7.1	$t = 1.40$, $p = 0.168$
Sex, female	12 (57.1%)	15 (57.7%)	$\chi^2 = 0.001$, $p = 0.970$
Duration of insomnia disorder, years	4.9 ± 5.7		
PSQI			
Total score	12.2 ± 3.5	2.4 ± 1.3	$t = 12.34$, $p < 0.001$
TST, min	258.1 ± 98.9	437.7 ± 45.6	$t = -7.69$, $p < 0.001$
SE, %	62.9 ± 21.3	95.0 ± 4.4	$t = -6.81$, $p < 0.001$
ISI score	17.9 ± 5.3	1.3 ± 1.8	$t = 13.67$, $p < 0.001$
BDI			
Total score	10.1 ± 4.5	2.3 ± 2.3	$t = 7.21$, $p < 0.001$
Non-sleep score	7.8 ± 4.3	1.8 ± 1.8	$t = 5.88$, $p < 0.001$
Polysomnographic data			
TST, min	323.4 ± 61.6	392.1 ± 59.7	$t = -3.86$, $p < 0.001$
SL, min	16.6 ± 14.3	5.5 ± 3.8	$t = 3.46$, $p = 0.002$
SE, %	80.3 ± 9.5	94.4 ± 3.2	$t = -6.51$, $p < 0.001$
WASO, min	64.9 ± 44.4	18.9 ± 14.3	$t = 4.56$, $p < 0.001$
AHI, number per hour	2.7 ± 1.7	2.3 ± 1.6	$t = 0.76$, $p = 0.449$

Data are mean ± standard deviation or n (%) values

PSQI Pittsburgh Sleep Quality Index, *TST* total sleep time, *SE* sleep efficiency, *ISI* Insomnia Severity Index, *BDI* Beck Depression Inventory, *SL* sleep latency, *WASO* wake after sleep onset, *AHI* Apnea–Hypopnea Index

The brain activation of the two groups significantly differed in the right lateral inferior frontal cortex and the right superior temporal pole. The inferior frontal cortex is believed to play an executive role in working memory [19, 20]. The importance of this region for working memory in insomnia has also been demonstrated in previous functional neuroimaging studies using the *n*-back task [8]. The lateral inferior frontal cortex (also known as ventrolateral prefrontal cortex) and hippocampus are known to be the main areas of visual processing of working memory [21]. One possible explanation for the significant findings in the lateral inferior frontal cortex and superior temporal pole is that the subjects might have perceived the projected numbers during the two-back working memory task as a visual image.

The previous studies suggested that insomnia patients could compensate for the cognitive dysfunction with high levels of arousal or other cognitive strategies to support a performance level that is comparable to that of good sleepers [9, 22]. We assume that increased activation of the lateral inferior frontal and superior temporal pole in our study might be due to over-recruitment of brain regions to maintain behavioral cognitive function. Similar patterns of over-recruitment of the brain regions including inferior frontal cortex, prefrontal cortex, and superior temporal gyrus without difference of

Table 2 More activated brain regions in insomnia patients relative to good sleepers during the two-back task

More activated brain regions (BAs) in insomnia	Clusters*	MNI Coordinate			*t* values	*p* values**	Effect size (Cohen's *d*)
		x	*y*	*z*			
Right lateral inferior frontal cortex (47)	59	51	27	−6	4.48	0.000	1.196
Right superior temporal pole (38)		57	9	−15	4.48	0.000	1.196

*The number of voxels within the corresponding cluster

**$p < 0.001$ indicates statistical significance (using 3dClustSim with the updated algorithm; cluster-based multiple comparison correction, $k = 34$ @$\alpha = 0.01$)

BAs Brodmann areas, *MNI152* Montreal Neurologic Institute stereotactic standard brain template, *x*, *y*, *z* = coordinates of maximum activated brain region; *t* value maximum activation intensity in a region of interest

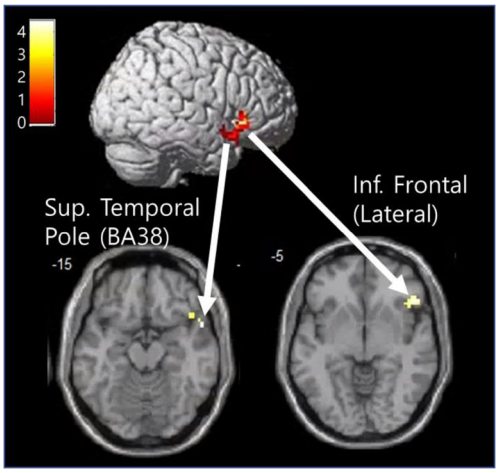

Fig. 2 Brain regions that were more activated in insomnia patients than good sleepers Higher levels of brain activation (red and yellow color) were observed in the right lateral inferior frontal cortex and right superior temporal pole in the insomnia group (cluster-based multiple comparison correction, $p < 0.001$, $k = 34$ @$\alpha = 0.01$). The number shown in each slice is the z-axis of the MNI coordinates in millimeters. MNI152, Montreal Neurologic Institute stereotactic standard brain template

behavioral performance compared to control group have been observed in mild cognitive impairment subjects [23], subjects with genetic risk for Alzheimer's disease [24], and obstructive sleep apnea patients [25, 26]. However, this concept should be supported by further studies to determine causal relationships between cognitive function and brain activation.

These findings and the interpretation are contrary to previous results in which the insomnia group, relative to good sleepers, showed decreased activation of task-related working memory regions, although their hypothesis was that insomnia patients would show increased activation during *n*-back tasks (consistent with a compensatory response to maintain performance) [8]. There are many potential explanations for the inconsistent findings, but one important reason is differences in subject characteristics, such as the severity of insomnia. In a previous study, the severity of insomnia was moderate or less, and insomnia patients showed an average of 88.6% sleep efficiency based on PSG, which did not differ from that (89.8%) of good sleepers [8]. Further studies are required since there are inconsistent findings between that study [8] and ours, and studies using our approach are limited. An fMRI study using a spatial working memory task showed significant activation modulation in different brain areas (bilateral parahippocampal gyrus, bilateral temporal cortices, and superior parietal lobule) compared to our report [10], therefore, fMRI studies investigating diverse dimensions of cognitive function will be helpful for understanding the neurocognitive functions that are affected by insomnia.

Performance on the behavioral tasks did not differ significantly between the two groups. It may be possible to identify a difference in brain function between the two groups using a more sensitive research method (i.e., fMRI) than behavioral tasks. Therefore, the absence of objective cognitive dysfunction in the insomnia group does not necessarily suggest that the brain is functioning normally. However, there are two possible reasons [8, 9] for the higher activation of the lateral inferior frontal and right superior temporal cortices in insomnia: (1) strengthened activation relative to normal baseline activation; or (2) activation during tasks in insomnia is normal, but there is decreased activation in insomnia relative to the good sleepers (as a baseline). These possibilities are controversial, since some studies reported increased glucose metabolism and cortical excitability during waking in all brain areas in primary insomnia, while other study found relatively low glucose metabolism in prefrontal area of insomnia group compared with controls [27, 28]. Therefore, future studies need to investigate the relationship between baseline cerebral blood flow (or oxygen metabolism) and the blood oxygenation level dependent (BOLD) signal in insomnia [8, 9]. Assessing the baseline arterial spin labeling-fMRI data would be a good method to achieve this [29].

In our regression analysis, brain activation in the right middle temporal cortex was negatively correlated with insomnia severity. However, the TST of PSG did not show a significant correlation with any brain regions and selected VOIs. The sleep duration of insomnia patients changes every night, and severity of insomnia is not determined as TST. Therefore, it is important to analyze the correlation between brain activation and sleep duration over a longer time (e.g., 1–2 weeks).

The limitations of our study should be acknowledged. First, we used liberal cluster-based correction for statistical threshold, therefore, the probability of a false positive might be increased with this threshold. Second, insomnia patients using hypnotic pharmacotherapies are commonly excluded from studies to eliminate the effects of medication on cognitive function. As a result, the majority of insomnia patients assessed in this type of study are not classified with severe insomnia.

In summary, the present fMRI findings showed more activation in several of the brain regions of the insomnia patients relative to those of the good sleepers during a working memory task. These findings elucidate the neuroscientific mechanism underlying cognitive function of the insomnia disorder. Future studies utilizing other cognitive tasks and larger study cohorts will likely provide more evidence regarding the clinical implications of this relationship.

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Compliance with ethical standards

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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