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ORIGINAL RESEARCH

Common Neural Correlates for Subjective and Objective Sleepiness Indices: A Functional Connectivity Study

Yuki Motomura[1,2], Shingo Kitamura[1], Kentaro Oba[1,3], Ruri Katsunuma[1], Yuri Terasawa[1,4], Akiko Hida[1], Yoshiya Moriguchi[1,5], Kazuo Mishima[1,6]

[1]Department of Sleep-Wake Disorders, National Institute of Mental Health, National Center of Neurology and Psychiatry Tokyo Japan; [2]Department of Human Life Design and Science, Faculty of Design, Kyushu University, Fukuoka, Japan; [3]Smart Aging Research Center, Tohoku University, Miyagi, Japan; [4]Department of Psychology, Keio University, Kanagawa, Japan; [5]Development Center, Lundbeck, Japan, Tokyo, Japan; [6]Department of Neuropsychiatry, Akita University Graduate School of Medicine, Akita, Japan

Correspondence: Yuki Motomura, Faculty of Design, Kyushu University, 4-9-1 Shiobaru, Minami-ku, Fukuoka, 815-8540, Japan, Email motomura@design.kyushu-u.ac.jp; Kazuo Mishima, Department of Neuropsychiatry, Akita University Graduate School of Medicine, 1-1 Tegatagakuen-machi, Akita-shi, Akita, Japan, Email clocksclub@gmail.com

Purpose: This study examined the neural correlates in functional brain connectivity common to subjective and objective sleepiness. Because functional connectivity can be measured at rest and during tasks, it is well suited for exploring the commonalities between sleepiness during psychomotor vigilance task (PVT) and at rest with measurement of The Karolinska Sleepiness Scale (KSS). Serial resting and task-based fMRI measurements across various states of arousal may reveal a common neural substrate that does not vary with task demands. The neural basis shared by the PVT, an objective measure highly sensitive to sleep debt, and subjective reports of sleepiness may be robust markers for sleepiness and contribute to an improved understanding of the brain mechanisms underlying sleepiness.

Participants and Methods: The participants were 16 healthy right-handed (self-reported) adult men who, after a 2-week home examination, participated in a 14-day/13-night experiment that included 9 days of extended sleep (12 h per night), followed by one night of total sleep deprivation (0 h), and recovery sleep. KSS and the PVT were used as subjective and objective measures of sleepiness, respectively. Functional connectivity in the brain during each condition were measured using fMRI. In particular, the association between the inverse of the reaction time to the PVT task and resting-state functional connectivity was analyzed using a general linear mixed model.

Results: Functional connectivity in six pairs of regions commonly associated with the KSS and PVT were identified. These included the anterior cingulate cortex-posterior cingulate cortex (part of the default mode network) and thalamus-middle temporal cortex, indicating that connectivity in these brain regions were strongly associated with sleepiness.

Conclusion: These results suggest a common neural substrate for subjective and objective sleepiness, which may be an important indicator of sleepiness. In addition, the functional connectivity between the thalamus and the middle temporal cortex may be a new network that deserves further attention in sleep research. The results of this study provide valuable insights into the effects of sleep deprivation and total sleep deprivation experienced in daily life on the brain and offer a new perspective on the expression of sleepiness in the brain.

Keywords: functional connectivity, sleepiness, psychomotor vigilance task, default mode network, middle temporal cortex, thalamus

Introduction

Modern society is often referred to as a "24-hour society", characterized by lifestyle factors that disrupt sleep and circadian rhythms, including shift work, jet lag, nocturnal living, short sleep durations, and irregular mealtimes. Consequently, an increasing number of individuals experience sleep-related issues such as insomnia, hypersomnia, and irregular sleep rhythms.[1–6] Surveys in developed countries indicate that >30% of the population receives <6 h of sleep per night.[4,7–9]

Sleep deprivation and circadian rhythm disruption lead to pronounced sleepiness, resulting in a decline in various mental functions. After one night of total sleep deprivation, several crucial cognitive functions, including working memory and sustained attention, along with the corresponding brain activity, show marked declines. A review by Durmer et al[10] and

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a meta-analysis by Lim et al[11] demonstrated increased microsleep and errors in attention tasks, reduced psychomotor performance, impaired learning ability, and difficulties maintaining prolonged concentration during sleep deprivation.

Although many studies have compared sleep-deprived and well-rested states, sleepiness exhibits inter-individual and diurnal variability, even during sleep deprivation. In some cases, sleepiness measured during tasks may better reflect the brain's state than sleep conditions alone.[12] The various methods used to assess sleepiness associated with sleep deprivation can be broadly categorized into subjective and objective sleepiness measures. Subjective indices, such as self-reported sleepiness, are often perceived as less reliable owing to their susceptibility to environmental factors and motivation. However, when environmental factors are controlled, subjective measures can be highly sensitive and useful.[13] Objective measures include electroencephalography (EEG) assessments, the multiple sleep latency test (MSLT),[14] and the psychomotor vigilance task (PVT).[15] Of these, the PVT, which assesses sustained attention and deteriorates linearly with accumulating sleep debt,[16,17] has been widely used as a reliable indicator of sleep deprivation.[18–20]

Van Dongen et al[16] demonstrated that PVT performance continued to worsen in proportion to the degree of sleep loss, while subjective sleepiness plateaued after approximately one week after two weeks of restricted sleep. This created a situation in which individuals did not feel subjectively sleepy but performed poorly on objective measures. This discrepancy between subjective and objective sleepiness has been observed not only in behavioral performance such as in the PVT but also in studies using the MSLT,[21] posing a significant challenge in accurately assessing sleepiness.

To better understand sleepiness, functional MRI (fMRI) has been used to examine brain states associated with sleepiness. Past fMRI studies have reported changes in brain activity corresponding to performance decline during sleep deprivation. Studies on networks of attention, including the thalamus, parietal cortex, and frontal cortex, have reported activity changes in these regions during sleep deprivation.[22] For instance, studies using fMRI to measure brain activity during attentional tasks reported decreased activity in frontoparietal regions when stimuli were missed, although participants who tolerated sleep deprivation exhibited increased compensatory activity in the parietal regions.[23,24] Additionally, impaired working memory during sleep deprivation has been linked to reduced attentional function, which mediates decreased task performance.[24–26]

In recent years, functional connectivity measured using time-series correlations between different brain regions has been examined using fMRI during sleep deprivation. For example, studies measuring fMRI during PVT have reported that the changes in functional connectivity in the anterior cingulate and insular cortex due to 36 h of sleep deprivation showed a significant positive correlation with reaction time in the PVT.[27] Additionally, it has been reported that the functional connectivity of the whole brain, such as the salience and default mode networks, is strongly associated with subjective sleepiness.[28] Moreover, altered mood during sleep deprivation has been linked to functional connectivity between the amygdala and the anterior cingulate cortex.[29]

Previous studies using EEG functional connectivity have reported that, after 24 or 36 h of sleep deprivation, the functional connectivity of the default mode network, precuneus, and inferior parietal lobule is impaired.[30]

Because functional connectivity can be measured at rest and during tasks, it is well suited for exploring the commonalities between sleepiness during PVT tasks and at rest. Serial resting-state and task-based fMRI measurements across various states of arousal may reveal a common neural substrate that does not vary according to task demands. This study examined the neural correlates, in terms of functional brain connectivity, common to subjective and objective sleepiness. The neural basis shared by the PVT, an objective measure highly sensitive to sleep debt, and subjective reports of sleepiness may be robust markers of sleepiness and contribute to an improved understanding of the brain mechanisms underlying sleepiness.

Materials and Methods

Participants

This study recruited 16 healthy right-handed (self-reported) adult men (mean age 23.4 ± 2.4 years), who provided written informed consent before their study participation. To confirm their health status, all participants visited the laboratory once before the experiment and underwent an overnight clinical polysomnogram (PSG), structural MRI imaging, questionnaires, a physician interview, and blood tests. The exclusion criteria were: individuals with any sleep disorders

or serious medical conditions; those taking medications or substances that could affect the study outcome (eg, sleeping pills, antihistamines, or steroids); individuals with psychiatric disorders, metal implants such as cardiac pacemakers, visual impairments including color blindness; individuals working in rotating shifts; those who had traveled across time zones >6 h within the past three months; and smokers. One of the 16 participants dropped out of the study.

The participants were originally recruited for a study investigating individual sleep debt potential[31] and had participated in a similar intervention study. However, the current study focused on a different aspect of the data (specifically exploring brain functions related to both subjective and objective sleepiness); thus, the data in the present study do not overlap with that published previously.

Experimental Protocol

All participants took part in a 14-day, 13-night sleep study, which included two nights of baseline sleep (8 h), nine nights of sleep extension (12 h), followed by one night of total sleep deprivation (0 h), and subsequent recovery sleep at the sleep laboratory of the National Institute of Mental Health, National Center of Neurology and Psychiatry, after a two-week home sleep monitoring period.

During the two weeks before the laboratory experiment, the habitual sleep time of all participants was measured using a sleep diary and a wristwatch activity meter worn on the non-dominant hand, with sleep duration calculated using Sadeh's algorithm.[32] Nighttime and daytime sleep during the observation period were calculated and summed to determine each participant's habitual sleep time.

After completing the home recordings, all participants entered the 14-day laboratory experiment. The sleep schedule during the experiment was based on the average sleep and waking times recorded during the home period. On nights 1 and 2, the participants slept for 8 h to obtain baseline sleep data. On nights 3–11, the time spent in bed was extended to 12 h by shifting the baseline sleep time 2 h earlier and the wake time 2 h later. After waking on night 11, the participants underwent 39 h of total sleep deprivation, followed by 12 h of recovery sleep starting 1 h after the habitual sleep time.

During the experimental period, the participants lived exclusively in the laboratory. Use of the Internet and cellular phones was prohibited to prevent access to external information. During the waking period, the participants were instructed to remain in an environment with 100 lx brightness and were not allowed to sleep. During the sleep period, they were instructed to sleep in bed with the lights off (0 lx). The participants were continuously monitored by the experimenter or an assistant during the awake periods, and if they appeared to be falling asleep, they were verbally awakened. The participants were allowed to move around the laboratory, read, write, listen to music, watch videos, play video games, and converse with the experimenter. Physical exercise, eating, and drinking outside of scheduled times were restricted. The laboratory environment was maintained at a temperature of 25 ± 0.5°C and a relative humidity of 50 ± 5%.

The participants also underwent other fMRI studies on days 1, 12, and 13 between 18:00 and 20:00. Additionally, at 19:00 each day, they underwent maintenance wakefulness tests (MWT), respiratory metabolism measurements, and blood sampling upon waking. These data have been reported previously.[31,33,34]

PVT Task in fMRI Scanner

Within the experimental protocol described above, imaging was performed while the participants completed a PVT task on nights 1 (baseline: BL), 6 (sleep extension day 4: SE4), 11 (sleep extension day 9: SE9), and 12 (total sleep deprivation: TSD), 9 h after the midpoint of sleep (baseline, 5 h after awakening; sleep extension, 3 h after awakening; and total sleep deprivation, 27 h after sleep onset). fMRI data from the resting state and PVT under these four conditions were used in this study.

In the PVT, the participants observed the monitor of the MRI machine. Figure 1 shows a schematic of the task. First, participants were asked to observe the fixation cross. After the task started, a number counter appeared at the position of the fixation cross, and the participants were asked to press the button in front of them as quickly as possible to stop the counter. Immediately after pressing the button, the number in milliseconds was recorded as the reaction time. The interval at which the counter started to count was set randomly between 2 and 10s; therefore participants were required to be ready to respond at any time. This task can measure sustained attention. There are various indicators in the PVT; however, we used 1/RT averages in this study. 1/RT is the reciprocal of reaction time. Decline of sustainable attention causes a delay in normal reaction times and an increase in missed trials; however, if the reaction times are averaged as

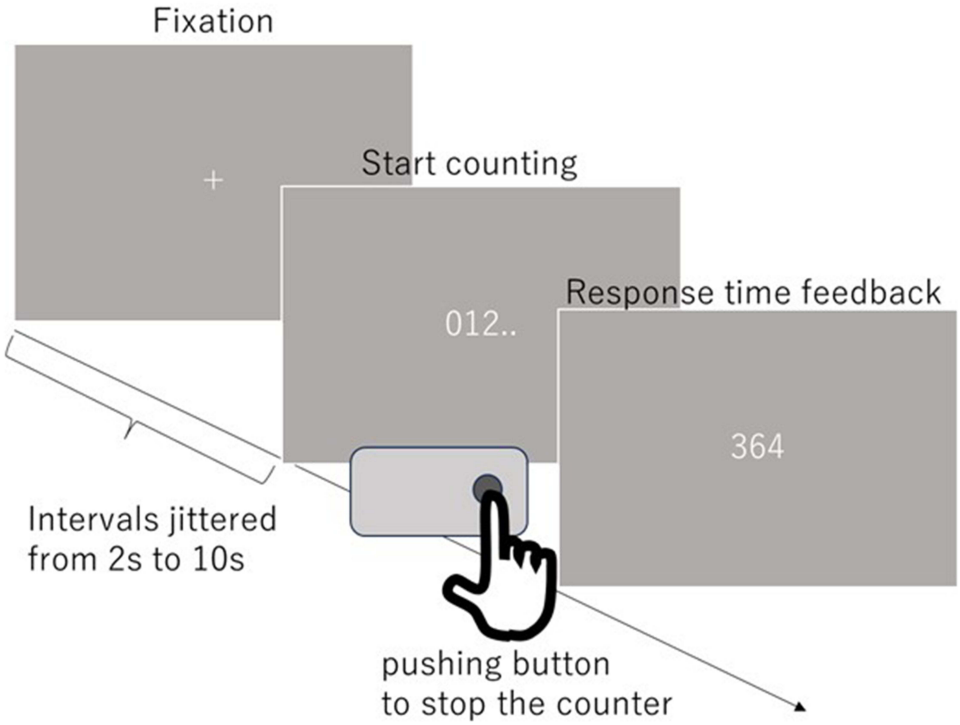

Figure 1 Task protocol. The participants were instructed to press a button as quickly as possible in response to a signal presented at random intervals of 2–10 s. The task lasted 10 min and the reaction time from the signal onset to the button press was recorded.

they are, the delay in reaction times due to missed trials of 500 ms or more will be overestimated compared to the delay in reaction times of approximately 300 ms. To reduce the variation in the weight of this evaluation, the average of 1/RT is recommended as an indicator. The sensitivity of the average of 1/RT has been shown to be high, reflecting acute and chronic sleep deprivation.[35] A general linear mixed model was used to evaluate the relationship between the mean of the inverse reaction time (1/RT) and functional connectivity.

Resting-State fMRI with Subjective Sleepiness Measurement

After completing the PVT task, two types of resting-state MRI scans (arterial spin labeling [ASL] and resting fMRI) were conducted, followed by the administration of a questionnaire measuring subjective mood (State-Trait Anxiety Inventory [STAI], Positive and Negative Affect Schedule [PANAS]). The ASL, STAI and PANAS results have been previously reported and are not described in the present study.[33]

The participants underwent a 6-min resting-state fMRI scan, completed a questionnaire, and then underwent a 4-min ASL scan. All resting imaging was performed while the participants remained at rest with their eyes open. They were instructed to keep their eyes open and look straight ahead with minimal eye movements to prevent falling asleep during the scans. The Karolinska Sleepiness Scale (KSS) was used to measure subjective sleepiness during rest. This questionnaire asks participants to select their current state from a nine-point scale ranging from "very clearly awake" to "fighting sleepiness", allowing for the assessment of a wide range of alertness and sleepiness levels.

Structural MRI Acquisition

A Siemens 3T MRI Verio scanner was used to perform MRI. Structural images for reference in the analyses were obtained during the screening phase. The parameters were as follows: (T1-weighted magnetization-prepared rapid gradient-echo [MPRAGE]) repetition time/echo time (TR/TE)=1900 ms/2.52 ms, voxel size=1 mm×1 mm×1 mm, flip angle = 9°, and field of view=256 mm×192 mm.

fMRI Data Acquisition and Preprocessing

Single-shot echo-planar imaging (EPI) was used to capture functional images during PVT [TR/TE=3000ms/40ms, 25 axial slices, voxel size=3 mm×3 mm×4 mm, flip angle 90°, matrix size=64×64, and field of view=960 mm×960 mm]. A total of 207 scans were obtained; the first five were excluded from the analysis.

Single-shot EPI was also used to capture resting-state functional images [TR/TE=2500ms/25ms, 30 axial slices, voxel size=6 mm×6 mm×4 mm, flip angle 90°, matrix size=64×64, field of view=384 mm ×384 mm]. A total of 150 scans were performed per session, with the first five scans excluded from the analysis.

SPM12 (Wellcome Department of Imaging Neuroscience, http://www.fil.ion.ucl.ac.uk/spm/software/spm8/) and SPM toolbox CONN (Alfonso Nieto-Castanon, http://www.alfnie.com/software/conn) were used for preprocessing and functional connectivity analyses. Each functional image was corrected for motion, ART-based outlier scrubbing (eliminating the influence of scan volumes with large motion >95% of all scans),[36] slice-timing correction, co-registration to MPRAGE structural images, spatial normalization using the Montreal Neurological Institute template, and smoothing with an 8 mm full width at half maximum (FWHM) Gaussian kernel.

Functional Connectivity Analysis

The three-dimensional brain image was divided into 116 regions based on the automated anatomical labeling (AAL) template and the functional connectivity between each region was calculated. Blood-oxygen-level-dependent (BOLD) signals and movement parameters in the white matter and cerebrospinal fluid (CSF) regions without neural activity were regressed out using the aCompCor method.[37] In the PVT analysis, stimulus presentation and button-press response events were also regressed. After applying a bandpass filter of 0.008 hz–0.16 hz, functional connectivity was calculated across the 116 regions (116 regions × 115 regions/2 = 6670 connectivity).

Statistical Analysis with Linear Mixed Model

Individual differences exist in the amount of sleep required and tolerance to sleep deprivation. Therefore, even if the same intervention is used, the degree of sleepiness and performance decline varies greatly from person to person. Our research group has repeatedly shown that actual sleepiness at a particular time explains brain activity measured by fMRI more strongly than do comparisons between conditions.[12,28] Because the data in this study involved multiple repeated measurements per participant (15 participants × 4 conditions = 60), a multilevel analysis was conducted using a linear mixed model (random intercept model), with participant factors entered as random effects to examine the direct relationship between functional connectivity and sleepiness or PVT performance.

Behavioral Data

To confirm that the intervention in this experiment was effective in dispersing drowsiness from high-to-low-vigilance conditions, we created scatter plots of 1/RT and the KSS and jitter plots for each condition. We also analyzed the relationship between 1/RT and the KSS using a linear mixed model. The lmerTest package in R 4.4.2 was used to create a model predicting the KSS as the dependent variable and 1/RT of PVT as a fixed effect, assuming a random effect on the intercept for each participant. The t- and p-values for the fixed effects were calculated based on Satterthwaite's degrees of freedom, using the default settings for the lmerTest function. When the variance estimate for the random intercept approaches zero, the t- and p-values for fixed effects in the linear model showed. The significance level was set at $p < 0.05$. We also calculated the fixed-effect determination coefficient using the MuMIn package in R (https://cran.rproject.org/web/packages/MuMIn/MuMIn.pdf).

Functional Connectivity Data

The lmerTest package in R 4.4.2 was used to create a model predicting the value of functional connectivity, with functional connectivity as the dependent variable and 1/RT of PVT as a fixed effect, assuming a random effect on the intercept for each participant. To validate the analysis, residuals were tested for normality using the Shapiro–Wilk test. Results with distributions significantly deviating from normal were categorized as "model validation failure." The t- and p-values for fixed effects were calculated based on Satterthwaite's degrees of freedom using the default settings for the lmerTest function. When the variance estimate for the random intercept approached zero, the t- and p-values for fixed

effects in the linear model. The significance level was set at $p < 0.05$, and Bonferroni correction was applied for multiple comparisons. The false discovery rate (FDR) method (Benjamini & Hochberg[38]) was used as a reference, and the results are presented in Supplementary Table 1. All subsequent statistical analyses were performed using R 4.4.2 and Microsoft Excel 2016. Brainnet viewer[39] was used to create brain maps of significant connectivity.

Functional connectivity analysis was also performed using a linear mixed model with the KSS during resting state fMRI as a fixed effect, following the same analysis steps as for the PVT task. Scatter plots were generated for these regions using raw data from Conn.

Conjunction Analysis

We performed conjunction analysis to identify pairs of brain regions in which resting-state connectivity was commonly associated with the KSS and PVT task 1/RT and the pairs of brain regions were mapped using the BrainNet viewer. Because the relationship between the size of the values and level of arousal was reversed in the KSS and 1/RT, we searched for connectivity with interpreting reversely KSS value. We calculated the fixed-effects determination coefficient using the MuMIn package in R for the six pairs of regions in which functional connectivity was significantly related to PVT 1/RT and KSS.

Results

Behavioral Data

Figure 2 presents the behavioral data. It can be observed that the values of the KSS and PVT 1/RT changed according to sleep conditions, but in particular, it was observed that the variation within the conditions was large for the KSS.

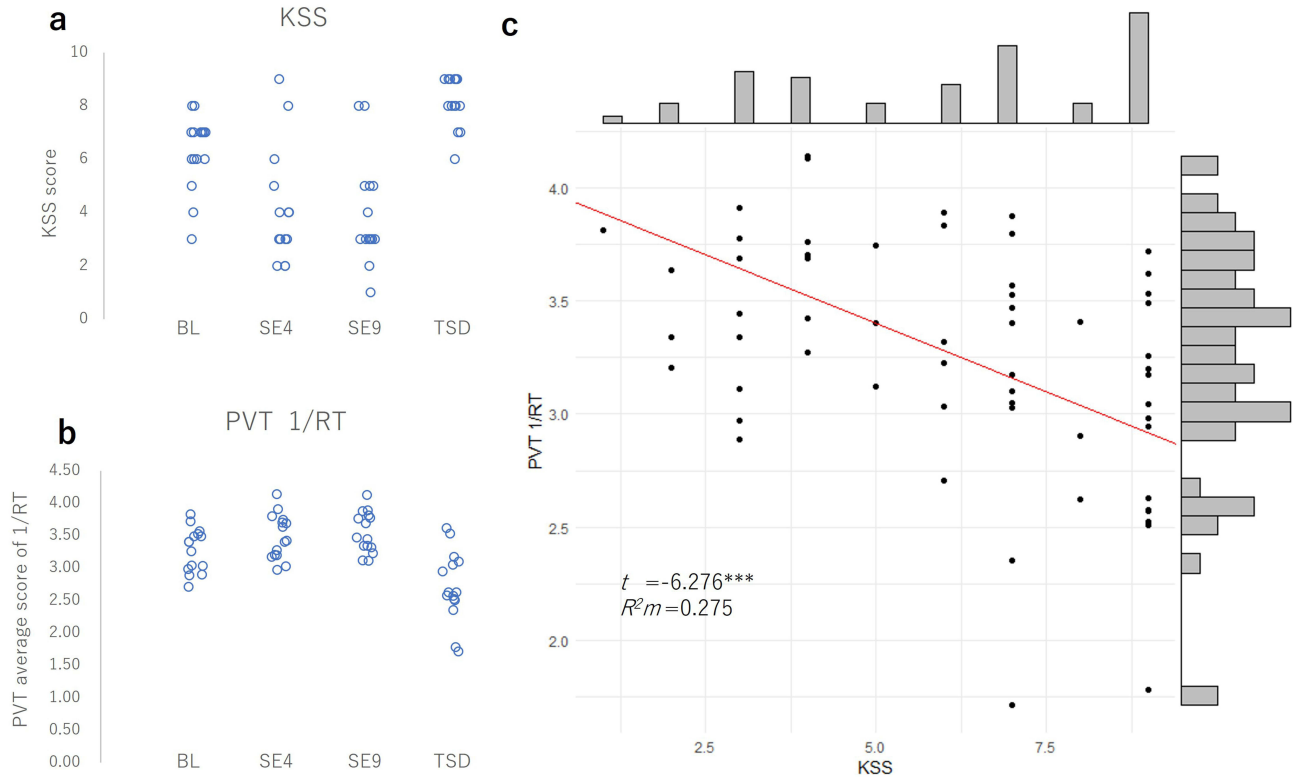

Figure 2 Behavioral data. (**a**) Jitter plot of the KSS for each condition. (**b**) Jitter plot of PVT 1/RT for each condition. (**c**) Scatter plot of PVT 1/RT and the KSS with histograms for all conditions. Red line: regression line corresponding to the linear mixed model.
Note: ***p<0.001 R^2m shows coefficient of determination of fixed effect in linear mixed model.
Abbreviations: KSS, Karolinska Sleepiness Scale; PVT, psychomotor vigilance test; RT, reaction time; BL, baseline; SE4, sleep extension day 4; SE9, sleep extension day 9; TSD, total sleep deprivation.

The linear mixed model analysis results showed a significant relationship between KSS and PVT 1/RT (t=−6.276, p<0.001, R2m=0.275). Although there was a significant relationship, the determination coefficient was 0.275, and the explanatory rate was less than 30%.

Functional Connectivity Analysis with Linear Mixed Model

The results of the mixed model analysis are presented in Table 1 and Figures 3–5.

Table 1 Functional Binding Significantly Correlated with PVT Performance (1/RT) (Bonferroni Corrected)

ROI Name from aal	Satterthwaite-df	t	Bonferroni Corrected p value*[a]	Model Validation
Postcentral R - Thalamus L	56.62	6.77	0.000	
Putamen R - Precentral R	56.05	6.32	0.000	
Thalamus L - Thalamus R	57.14	−6.29	0.000	
Temporal Mid R - Thalamus R*[b]	54.14	6.32	0.000	
Parietal Sup L - Angular R	51.81	−6.36	0.000	
Cingulum Ant R - Angular L	49.34	6.39	0.000	
Thalamus L - Temporal Mid R*[b]	55.18	6.24	0.000	
Cingulum Ant R - Cingulum Post L*[b]	51.80	6.29	0.000	Failed
Precentral R - Insula L	55.83	5.93	0.001	
Occipital Inf L - Vermis 8	57.80	5.87	0.001	
Precentral R - Putamen L	52.39	5.85	0.002	
Thalamus R - Temporal Inf L	53.69	5.81	0.002	
Thalamus R - Postcentral R	56.98	5.76	0.002	
Temporal Mid L - Frontal Sup Med L	52.18	5.75	0.003	
Temporal Mid L - Cingulum Ant L	52.44	5.69	0.004	
Insula L - Postcentral R	57.94	5.57	0.005	
Fusiform L - Thalamus R	54.73	5.59	0.005	
Precentral L - Vermis 8	49.95	5.61	0.006	
Thalamus L - Precentral L	53.49	5.56	0.006	
Angular L - Frontal Med Orb L	51.59	5.53	0.007	
Cingulum Post L - Cingulum Ant L*[b]	50.54	5.46	0.010	
Precentral R - Thalamus L	55.94	5.40	0.010	
Cingulum Post R - Cingulum Ant R*[b]	55.28	5.38	0.010	
Temporal Pol Mid L - Thalamus L	54.63	5.21	0.020	
Angular L - Cingulum Ant L	49.18	5.24	0.022	

(*Continued*)

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Table 1 (Continued).

ROI Name from aal	Satterthwaite-df	t	Bonferroni Corrected p value*[a]	Model Validation
Vermis 8 - Occipital Inf R	53.89	5.18	0.023	
Vermis 7 - Occipital Inf L	55.04	5.09	0.030	
Paracentral Lob R - Cingulum Mid R	50.87	5.13	0.030	
Parietal Inf L - Temporal Mid R	55.67	−5.08	0.030	Failed
Postcentral R - SupraMarginal L	51.53	5.06	0.038	
Cingulum Ant R - Temporal Mid L	51.56	5.03	0.041	
Frontal Med Orb R - Angular L	49.64	5.06	0.041	
Insula R - Precentral R	56.31	4.97	0.043	
Temporal Mid L - Thalamus L*[b]	57.85	4.95	0.045	
Frontal Sup Med R - Temporal Mid L	51.78	5.00	0.046	

Notes: *[a]The corrected p-value, which is 6670 times the number of tests is displayed. *[b]Significant functional connectivity in common with KSS.
Abbreviations: R, right; L, left; df, degree of freedom.

Regarding PVT 1/RT, the mixed model analysis results showed a significant association of PVT performance with the connectivity in many pairs of brain regions, and even after Bonferroni correction for 6,670 tests, the connectivity in 35 pairs of brain regions were significant (Table 1 and Figure 3). The results of FDR correction are presented in Supplementary Table 1.

Similarly, for the KSS, 28 pairs of brain regions with significant connectivity were found after Bonferroni correction (Figure 3). For details of the KSS results, please refer to other reports.[28]

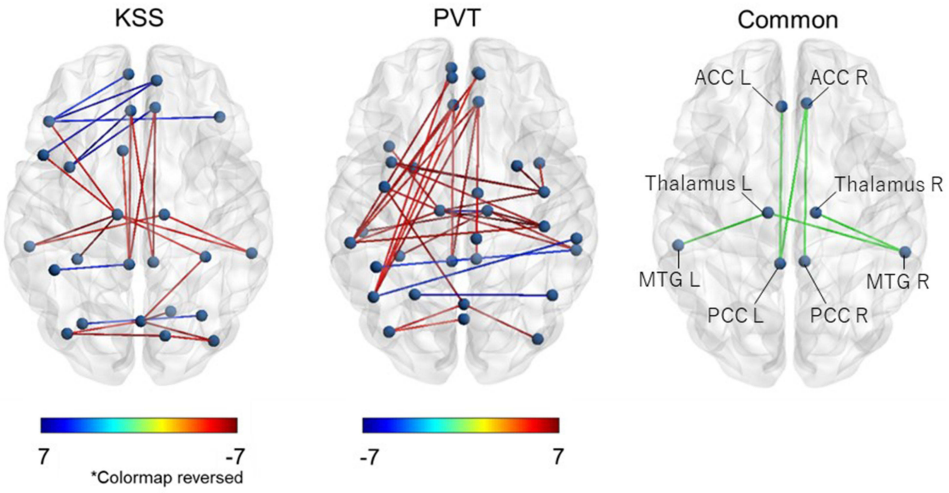

Figure 3 Map of regions in which functional connectivity is associated with the KSS and PVT ($p < 0.05$) with Bonferroni correction. All figures are axial views from the top to the bottom. The colors of the edges reflect the t-values. Because the relationship between numerical values and arousal is reversed in the KSS and PVT 1/RT, the scale of KSS has been reversed to show the relationship in the same direction.
Abbreviations: KSS, Karolinska Sleepiness Scale; PVT, psychomotor vigilance test; ACC, anterior cingulate cortex; PCC, posterior cingulate cortex; MTG; middle temporal gyrus; L, left; R, right. RT: reaction time.

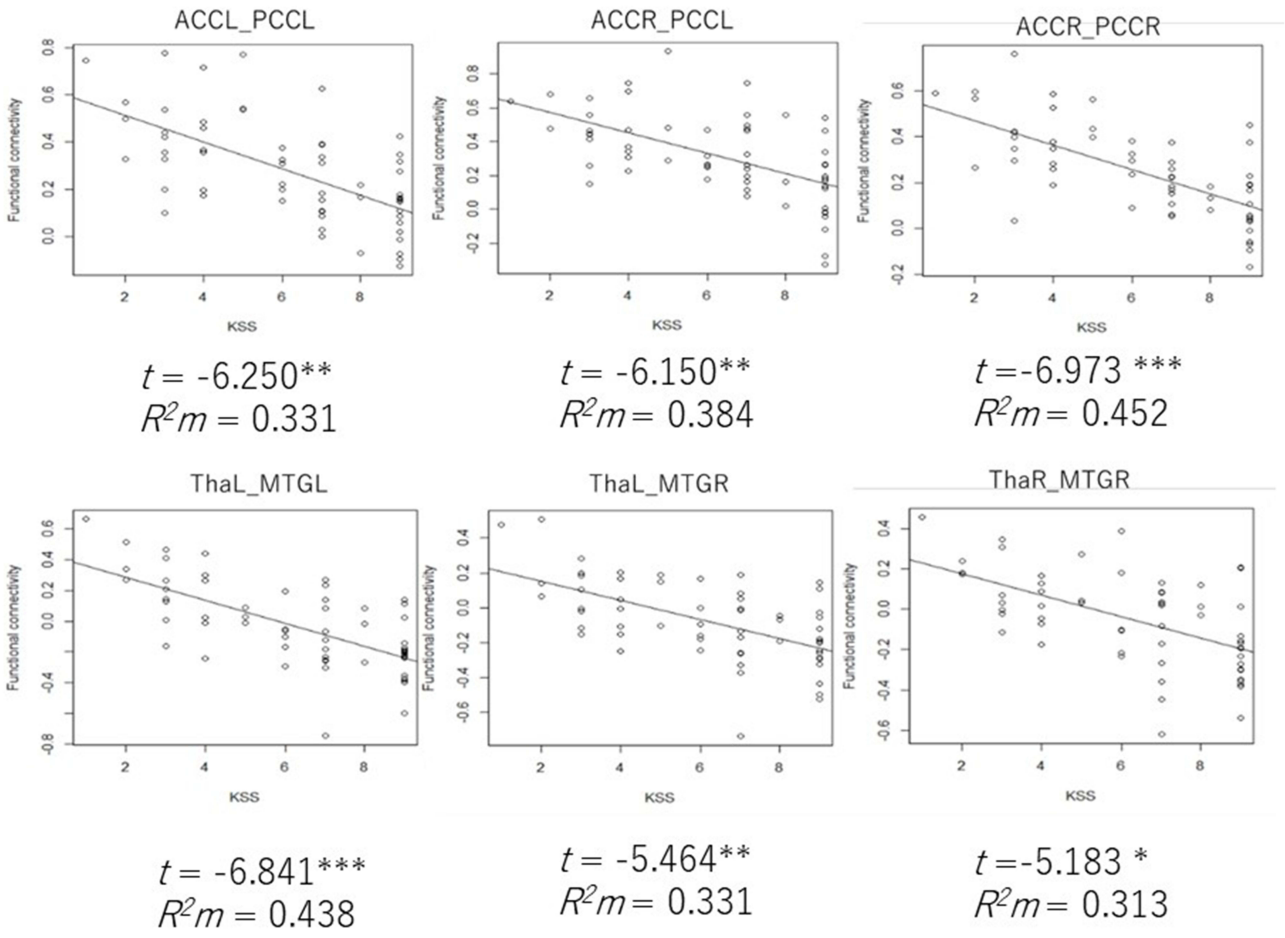

Figure 4 Scatterplot of KSS and functional connectivity Functional connectivity was associated with subjective sleepiness, which accounted for the random effect of each participant. Grey line: regression line corresponding to the linear mixed model.
Notes: ***p<0.001, **p<0.01, *p<0.05 (Bonferroni corrected). R^2m denotes the coefficient of determination of the fixed effect in the linear mixed model.
Abbreviations: KSS, Karolinska Sleepiness Scale; ACC, anterior cingulate cortex; PCC, posterior cingulate cortex; Thal, thalamus; MTG; middle temporal gyrus; L, left; R, right.

Conjunction Analysis

Connectivity in six pairs of brain regions were identified by searching for areas significantly related to the KSS and PVT 1/RT. Table 2 lists the statistical values of each connectivity measure. Model validation was not possible for the right anterior cingulate cortex–left posterior cingulate cortex because the residuals did not show a normal distribution. Scatter plots for PVT 1/RT and the KSS are shown in Figures 4 and 5, respectively.

Discussion

This study explored the functional connectivity related to both subjective and objective sleepiness during the execution of the PVT task and resting states. The KSS and the PVT were used as subjective and objective measures of sleepiness. Despite employing a conservative analysis, six functional connectivity commonly associated with both the KSS and PVT were identified, including functional connectivity between the anterior and posterior cingulate cortex pair and the thalamus and middle temporal cortex.

During the 9-day sleep extension period, the total sleep time decreased continuously, and a decrease in subjective sleepiness was observed following sleep extension.[31] These results suggest that the sleep debt accumulated in daily life can be recovered or reduced by extended sleep. However, sleep deprivation thereafter resulted in increased sleepiness. The experimental protocol allowed for a wide range of variations in conditions, from intense sleepiness to high arousal. Similarly, during the PVT, 1/RT values were widely distributed from low to high arousal. Although a significant

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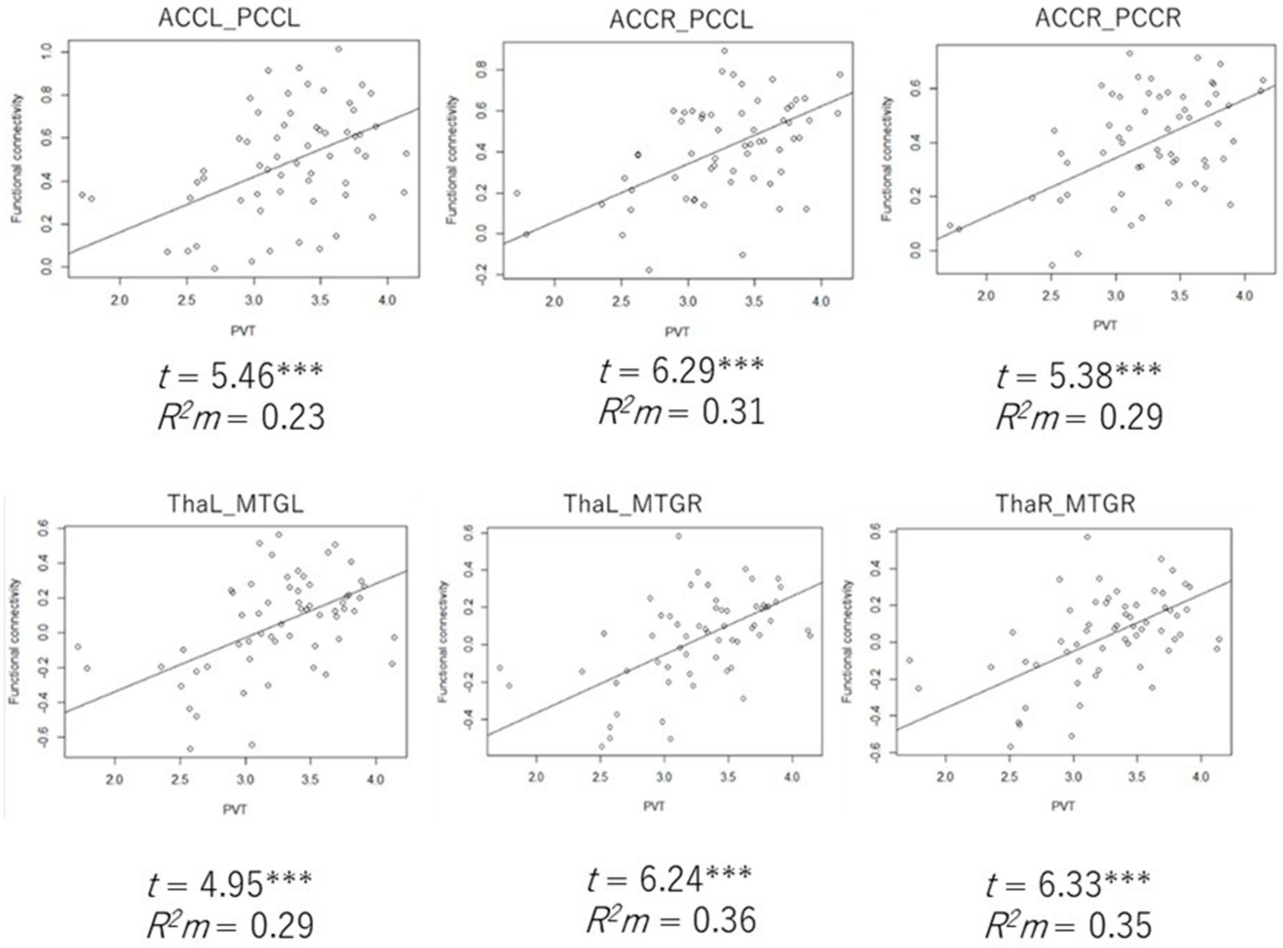

Figure 5 Scatterplot of PVT performance and functional connectivity.Functional connectivity was associated with objective sleepiness, which accounted for the random effects of each participant. Grey line: regression line corresponding to the linear mixed model.
Notes: ***p<0.001 (Bonferroni corrected). R^2m denotes the coefficient of determination of the fixed effect in the linear mixed model.
Abbreviations: PVT, psychomotor vigilance test; ACC, anterior cingulate cortex; PCC, posterior cingulate cortex; Thal, thalamus; MTG; middle temporal gyrus; L, left; R, right.

relationship between the KSS and 1/RT was observed, the explanatory rate was approximately 0.28; therefore, more than 70% of variance is not explained. For example, even if the KSS is 2 or 3, there are cases where the 1/RT value is the same as when the KSS is 8 or 9. The participant feels high subjective sleepiness, showing cases where subjective sleepiness and objective sleepiness do not match.

Regarding the functional connectivity of the anterior-posterior cingulate cortex, the posterior and anterior cingulate cortices are the core regions of the default mode network (DMN). Horovitz et al[40] reported a loss of frontal-occipital connectivity in the DMN during sleep stage 2, suggesting its possible association with reduced levels of consciousness. Several subsequent studies[41–43] supported these findings; however, later studies demonstrated that functional connectivity in the DMN are retained even during deep non-rapid eye movement (REM) sleep.[44–49] However, some results remain inconclusive. In contrast, a study investigating functional connectivity during wakefulness reported that increased daytime sleepiness, as measured by the Epworth Sleepiness Scale (ESS), was associated with decreased functional connectivity in the DMN.[44] Other studies have also suggested a link between subjective sleepiness and functional connectivity in the DMN.[45,46] As the DMN is deactivated during tasks,[47] the consistent results during both task performance and rest were surprising, indicating that the strength of functional connectivity in the DMN may be linked to sleepiness even when external attention is focused and activity is reduced.

Few studies have examined functional connectivity during the PVT. Mai et al[48] analyzed brain function during the PVT and observed a link between dynamic functional connectivity in the thalamo-frontal network-default mode network

Table 2 Brain Regions in Which Functional Connectivity Showed Associations with Both the Karolinska Sleepiness Scale and Psychomotor Vigilance Task

	ROI Name from aal	Region Name	Satterthwaite-df	Fixed Effect	se of Fixed Effect	t value	Bonferroni Corrected p value*[a]	R^2m
KSS	Cingulum Post L – Cingulum Ant L	Left anterior cingulate cortex - left posterior cingulate cortex	49.836	−0.060	0.010	−6.250	0.001	0.331
	Cingulum Post L – Cingulum Ant R	Right anterior cingulate cortex - left posterior cingulate cortex	55.473	−0.056	0.009	−6.150	0.001	0.384
	Cingulum Post R – Cingulum Ant R	Right anterior cingulate cortex - right posterior cingulate cortex	58.000	−0.053	0.008	−6.973	0.000	0.452
	Temporal Mid L – Thalamus L	Right middle temporal gyrus - right thalamus	55.880	−0.075	0.011	−6.841	0.000	0.438
	Thalamus L – Temporal Mid R	Right middle temporal gyrus - left thalamus	55.752	−0.055	0.010	−5.461	0.008	0.331
	Temporal Mid R – Thalamus R	Left middle temporal gyrus - left thalamus	58.000	−0.053	0.010	−5.183	0.019	0.313
PVT	Cingulum Post L – Cingulum Ant L	Left anterior cingulate cortex - left posterior cingulate cortex	50.539	0.258	0.047	5.464	0.010	0.232
	Cingulum Post L – Cingulum Ant R	Right anterior cingulate cortex - left posterior cingulate cortex	51.805	0.281	0.045	6.290*[b]	0.000	0.311
	Cingulum Post R – Cingulum Ant R	Right anterior cingulate cortex - right posterior cingulate cortex	55.284	0.217	0.040	5.383	0.010	0.294
	Temporal Mid L – Thalamus L	Right middle temporal gyrus - right thalamus	57.849	0.311	0.063	4.948	0.045	0.288
	Thalamus L – Temporal Mid R	Right middle temporal gyrus - left thalamus	55.175	0.313	0.050	6.238	0.000	0.359
	Temporal Mid R – Thalamus R	Left middle temporal gyrus - left thalamus	54.141	0.309	0.049	6.324	0.000	0.355

Notes: *[a]The corrected p-value, which is 6670 times the number of tests is displayed. *[b]Model validation failed.
Abbreviations: ROI, region of interest; AAL, automated anatomical labeling; R, right; L, left; KSS, Karolinska Sleepiness Scale; PVT, psychomotor vigilance task; df, degree of freedom; se. standard error;

and wakefulness during the task. Although comparisons are difficult owing to differences in analysis methods, the results of the present study are consistent with the brain regions reported previously.

In the present study, the functional connectivity between the anterior and posterior cingulate cortices was consistently positively associated with sleepiness during both subjective sleepiness measurements and PVT tasks. The decrease in positive functional connectivity between the anterior cingulate cortex-posterior cingulate cortex and increased sleepiness suggests that this may be related to a decrease in consciousness levels and vigilance maintenance.

Moreover, functional connectivity between the thalamus and middle temporal cortex were significantly associated with both subjective and objective sleepiness, with connectivity in three pairs of regions consistently observed across the left and right hemispheres. Previous studies have implicated the thalamus in sleepiness,[29,50,51] and the middle temporal cortex has been linked to semantic processing, language, memory,[52,53] and face recognition.[54] Shao et al[51] compared functional connectivity in the resting state during sleep deprivation and normal sleep and reported reduced functional connectivity between the right thalamus and right middle temporal cortex, consistent with the present results. Similarly, Li et al[55] observed decreased connectivity between the left thalamus and left middle temporal cortex during total sleep deprivation. Lei et al[56] reported reduced activation in the middle temporal gyrus during deprivation after financial loss, further supporting the link between deprivation and functional decline. The strong association between the thalamus-

middle temporal cortex functional connectivity and sleepiness observed in the present study highlights this connection as a focus for future research.

The thalamus-middle temporal cortex functional connectivity showed positive connectivity at high arousal levels and negative connectivity at low arousal levels, consistent with the findings of previous study.[28] Positive functional connectivity is associated with excitatory projection,[57] possibly reflecting thalamocortical projection loops that promote high arousal levels. However, the biological significance of negative functional connectivity remains unclear. Some researchers argue that negative connectivity is an artifact of analysis,[58–60] but animal studies have confirmed that negative connectivity reflects inhibitory projections.[61,62] Subsequent studies have supported the physiological relevance of negative connectivity using graph-theoretic approaches.[62] If negative functional connectivity reflects inhibitory projections, it suggests a shift from excitatory to inhibitory signals as the brain transitions to sleep. Previous reports[28] noted that functional connectivity in several cortical regions transitions from positive to negative as subjective sleepiness increases and proposed that TRN activity may be linked to these changes. In contrast, animal EEG studies have reported that inhibitory neural activity contributes to gamma wave synchronization,[63,64] which contradict the results of this study. Further investigation is required to clarify the detailed mechanism. The results of the present study suggest that functional connectivity between the thalamus and middle temporal cortex may be a robust marker of sleepiness during both subjective and objective measurements.

However, this study has several limitations. Although a linear mixed model was applied, the residuals in the functional combination of the Cingulum Ant R - Cingulum Post L connection did not follow a normal distribution, thus limiting the validity of the statistical methods used. Additionally, owing to equipment limitations, whether the participants kept their eyes open during imaging could not be confirmed. Moreover, because the PVT task was performed during fMRI, it was not used in its original form.[15] Furthermore, the study included only male participants, which may have affected the generalizability of the findings. Another limitation was the relatively small sample size. Owing to equipment limitations, confirming whether the participants were awake with their eyes open during resting state was not possible. In addition, it may have been possible to investigate the level of arousal in more detail by combining it with other measurements of arousal levels, such as EEG.

Conclusion

The results of this study revealed the association of functional brain connectivity with both subjective and objective sleepiness. Anterior-posterior cingulate and thalamus-middle temporal cortex connectivity was strongly linked to sleepiness, particularly the novel finding of positive connectivity during high arousal and negative connectivity during low arousal in the thalamus-middle temporal cortex. This functional connectivity may be a robust biomarker of sleepiness and a common neural basis for both resting and task-based conditions. Therefore, the thalamus-middle temporal cortex network, which has received little attention in previous studies, could become a new focus for future sleep research.

Abbreviations

AAL, automated anatomical labeling; ASL, arterial spin labeling; BOLD, blood-oxygen-level-dependent; CSF, cerebrospinal fluid; DMN, default mode network; EEG, electroencephalography; EPI, echo-planar imaging; ESS, Epworth Sleepiness Scale; FDR, false discovery rate; fMRI, functional magnetic resonance imaging; FWHM, full width at half maximum; KSS, Karolinska Sleepiness Scale; MPRAGE, magnetization-prepared rapid gradient-echo; MSLT, multiple sleep latency test; MWT, maintenance wakefulness tests; PANAS, Positive and Negative Affect Schedule; PSG, polysomnogram; PVT, psychomotor vigilance task; REM, rapid eye movement; RT, reaction time; STAI, State-Trait Anxiety Inventory; TE, echo time; TR, repetition time; TSD, total sleep deprivation.

Data Sharing Statement

The data is unavailable for sharing, since the consent for sharing of the data was not obtained from the participants.

Ethics Approval and Informed Consent

All subjects provided written informed consent, and the study was conducted in accordance with the Declaration of Helsinki. The protocol was approved by the Ethics Committee of the National Center of Neurology and Psychiatry (approval number: A2011-071).

Author Contributions

Conceptualization: YM, SK, AH, YoM, KM; **Methodology**: YM, SK, AH, YoM, KM; **Project administration**: AH, YoM, KM; **Investigation**: YM, SK, KO, RK, YT, AH; **Formal Analysis**: YM, SK; **Funding acquisition**: KM; **Writing – original draft**: YM, KM; **Writing – review & editing**: All authors.

All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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