Original Article

Elucidating the Effects of Sleep Deprivation: Exploring fMRI Imaging Biomarkers to Analyze Brain Functions Related to Insomnia

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Abstract

Background: This study aimed to propose functional magnetic resonance imaging (fMRI) imaging biomarkers for the diagnosis of insomnia by examining the brain maps of young and old people during sleep deprivation (SD).

Materials and Methods: A total of 50 healthy individuals were selected in two groups, including the young group: 17 people (20 to 30 years) and the elderly group: 23 people (65 to 75 years), who were involved in a 1-month period of SD, so that during the experiment they woke up 3 hours earlier than usual. Insomnia and sleepiness questionnaires were collected from these individuals (OpenfMRI website). Independent component analysis (ICA) processing was performed using the Generalized Intelligent Framework for Tutoring (GIFT) toolbox on old and young people's data. Correlations between clinical variables and imaging were performed to extract insomnia biomarkers with a significance level of $P = 0.05$.

Results: In the dynamic range variable, the difference in the effect of insomnia between the two groups was significant in areas such as the inferior occipital gyrus (IOG), superior temporal gyrus (STG), and posterior cingulate (PC). The fractional amplitude of low-frequency fluctuation (fALFF) variable in the anterior cingulate and precuneus areas, as well as the spatial map variable in areas such as the inferior semilunar lobule, anterior cingulate, subcallosal gyrus, and middle temporal gyrus (MTG) between the two groups, was significantly different ($P = 0.05$).

Conclusion: Based on the results of this study, brain activity map in sleep-deprived people has a significant change in some brain areas and this effect is different in old and young adults.

Keywords: Biomarkers, computer-assisted, image processing, magnetic resonance imaging, sleep deprivation

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Introduction

Today, health experts emphasize the importance of getting 7 to 9 hours of sleep at night.[1] However, people in modern societies suffer from insufficient sleep.[2] Sleep deprivation (SD) is the most common and recognized sleep disorder. SD refers to the feeling of not getting enough sleep in terms of quantity or quality and is usually not associated with daytime sleepiness. This issue has led to various health problems in modern societies, as it is necessary for maintaining and preserving energy, physical appearance, and well-being. During sleep, hormones such as epinephrine, serotonin, and growth hormone are released, leading to cellular nourishment

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and chemical changes that allow the body to recover for the next day's activities.[3]

SD can have a significant impact on the central nervous system and may be associated with various psychiatric disorders, such as depression.[4,5] However, the mechanisms of sleep are not yet well understood and continue to be a challenging subject for researchers in this field.[6] Functional magnetic resonance imaging (fMRI) studies have shown changes in the activity levels of brain regions as a result of SD.[1] Other findings, such as those obtained from positron emission tomography (PET) imaging, have indicated increased activity in the thalamus and insula during SD.[7,8] With advances in research, credible studies have been conducted to evaluate the brain function of individuals who have experienced sleeplessness or SD.[9,10] For example, increased activity in the default mode network (DMN) and reduced connectivity between different brain regions have been reported in resting-state fMRI studies during periods of SD.[11]

Resting-state fMRI is a highly regarded method in neuroimaging that can provide new insights into the pathophysiology of diseases. It benefits from high spatial localization accuracy (due to the ease of combining functional imaging with structural imaging) and has the additional advantage of not requiring the patient to be exposed to radioactive tracers.[12] The fractional amplitude of low-frequency fluctuations (fALFF) is an index that can identify which brain regions have intrinsic neural activity in the abnormal range of blood oxygen-level-dependent (BOLD) signals and has been shown to have excellent reliability in this regard.[12-14] Previous studies conducted in this field have demonstrated that the fALFF method exhibits high sensitivity and specificity, making it a potentially useful noninvasive imaging tool and an initial biomarker for detecting brain changes in patients with sleep disorders.[15]

In general, the wide range of influential factors such as imaging techniques, statistical methods, cognitive tasks, and heterogeneous small sample sizes in previous studies has presented an ambiguous picture of brain abnormalities during periods of SD. None of the previous studies have specifically investigated the pattern of brain activity in individuals with insomnia during resting states. Therefore, further studies and research are needed to shed more light on this topic.[16]

In a previous study,[17] the investigation focused on brain region interactions during periods of SD. This study not only depends on the selected region of interest but is also model based, and it is essential to have knowledge of how the brain regions function to obtain additional information. To address these challenges, this study employed the use of independent component analysis (ICA) to examine brain activity and functional connectivity (unlike model-based approaches, which do not require *a priori* determination of regions of interest). Ultimately, this study aimed to provide a cognitive science perspective on examining brain regions and extracting brain maps in normal sleep-deprived individuals, as well as the impact of SD on brain regions in young and elderly individuals during periods of SD, with the goal of proposing imaging biomarkers.

Materials and Methods

Participants

In this study, 25 young individuals (aged 20 to 30) and 25 elderly individuals (aged 65 to 75) underwent 1 month of SD, with a nightly reduction of 3 hours of sleep. Data analysis was conducted on information from 17 young participants and 23 elderly participants due to motion artifacts and noise. Resting-state fMRI images were obtained at two time points, 1 month apart, with permission from the OpenNeuro website. Exclusion criteria included psychiatric disorders, tobacco use, excessive nicotine consumption, and low image quality. The study utilized the Epworth Sleepiness Scale (ESS) questionnaire and the Insomnia Severity Index (ISI) to assess sleepiness and insomnia severity, respectively.

fMRI protocol

MRI Data Acquisition: In this study, a General Electric Discovery 3 Tesla MRI scanner was utilized, and echo-planar imaging (EPI) was employed to obtain the following settings: flip angle of 75 degrees, echo time (TE) of 30 ms, repetition time (TR) of 2.5 ms, a field of view of 28 cm^2, and a slice thickness of 3 mm. Additionally, anatomical or structural scans with T1-weighted images using the BRAVO(Brain Volume imaging) sequence were acquired. The three-dimensional T1-weighted gradient-echo sequences (e.g., BRAVO) are widely utilized because they produce T1-weighted images with high-resolution differentiation between gray matter and white matter. The parameters for the anatomical scans included a field of view of 24 cm^2 and a slice thickness of 1 mm.

Analysis of fMRI images

After collecting fMRI data, determining activated brain regions and revealing the resulting connections in the brain regions following a specific task require analyzing the acquired data. In this analysis, the images are processed using the Generalized Intelligent Framework for Tutoring (GIFT) toolbox to generate a parametric image. For this purpose, the SPM12 software was utilized.

Preprocessing of fMRI images

In the initial stage of preprocessing, the first five scans from each imaging session were discarded to establish magnetic field equilibrium. Then, a series of necessary preprocessing steps were applied to the fMRI data for analysis. These steps included image realignment to correct motion artifacts, temporal slice correction, head motion correction, image segmentation, registration of structural and functional images, normalization, and smoothing using a 6-millimeter Gaussian filter. It is important to note that all preprocessing steps were performed using the SPM12 toolbox integrated with MATrix LABoratory (MATLAB) software.

Processing using ICA

In this study, the ICA method was employed to analyze the fMRI data. This method allows for the extraction of both sustained activities and temporally transient experimental activities related to physiologically unrelated signals in fMRI experiments without requiring specific knowledge about the experimental design. Using the GIFT toolbox, which utilizes the ICA method for data processing, the signals present in the fMRI data were extracted, and the number of components was estimated. The regions associated with each component are presented in Table 1. It is important to note that the optimal number of components was determined by the GIFT software using the maximum variance and discriminability between different categories to calculate the optimal number of essential components. After selecting the essential components, brain activity maps and corresponding time series were extracted, and dynamic range values, fALFF, and spatial maps were obtained for each component.

Statistical analysis

The obtained results were subjected to statistical analysis using the Statistical Package for Social Sciences (SPSS) statistical software. To examine the effects of insomnia on the two groups (elderly and young) for variables with a normal distribution, a repeated-measures analysis was conducted. For variables with a nonnormal distribution, the Friedman test was utilized. In the next stage, to identify the differences in the effects of insomnia between the elderly and young groups, output parameters of neuroimaging such as dynamic range, spatial map, and fALFF obtained from the second session of the experiment were analyzed. Independent-samples t-tests were performed for variables with a normal distribution, while the Mann-Whitney U-test was used for variables with a nonnormal distribution. Furthermore, the correlation between clinical parameters such as ISI and ESS with dynamic range, spatial map, and fALFF was calculated using the Pearson correlation coefficient.

Table 1: Brain regions associated with each component

Component	Brain regions
1	Inferior occipital gyrus (IOG), superior temporal gyrus (STG), tuber, posterior cingulate (PC)
2	Superior frontal gyrus (SFG), inferior frontal gyrus (IFG), fusiform gyrus (FG), lingual gyrus (LING)
3	Supramarginal gyrus (SMG), third ventricle, transverse temporal gyrus (transverse TG), postcentral gyrus (PoCG)
4	Middle occipital gyrus (MOG), cerebellar tonsil (CR tonsil), inferior temporal gyrus (ITG), thalamus (THL)
5	Extranuclear, culmen, medial frontal gyrus (MFG), pyramis
6	Angular gyrus
7	Claustrum, insula, cingulate gyrus (CG)
8	Superior parietal lobule (SPL)
9	Precentral gyrus (PrCG)
10	Orbital gyrus, superior occipital gyrus (SOG)
11	Inferior semilunar lobule
12	Anterior cingulate
13	Uncus, declive of vermis
14	Subcallosal Gyrus
15	Middle temporal gyrus (MTG), lateral ventricle
16	Sub-gyral
17	Precuneus, declive, culmen of vermis
18	Inferior parietal lobule
19	Paracentral lobule (PCL)
20	Parahippocampal gyrus (PHG), uvula, fourth ventricle

Results

In this study, after preprocessing using the Statistical Parametric Mapping (SPM) toolbox, the final analysis was conducted using the GIFT toolbox, and the data were analyzed in a group-wise manner. In Figure 1, the red color spectrum indicates an increase in activity compared with the basic state and the blue color spectrum indicates a decrease in activity compared with the basic state in the young group: a) before the period of insomnia and b) after the period of insomnia, and in the elder group: c) before the period of insomnia and d) after the period of insomnia.

The effects of insomnia on elderly and young individuals

Quantitative results examining the differences in the effects of insomnia on each group of elderly and young individuals (with a significance threshold of $P = 0.05$) are presented in Tables 2 and 3 (significantly meaningful results are indicated by the green color in the tables).

Investigating the effect of insomnia on elderly and young individuals

In this stage of data analysis, the difference in the effect of insomnia between the elderly and young groups was examined based on the parameters obtained from the second session of the experiment. Significant changes were observed in the dynamic range variable of component 1, fALFF variables of components 12 and 17, and the spatial map variables of components 18, 17, 16, 14, 13, 12, 11, 9, and 2 at a significance level of $P = 0.05$ in these tests.

The results of the independent-samples *t*-test showed that there were significant changes in the dynamic range variable of component 18, which includes the inferior parietal lobule region. The Mann-Whitney U-test results indicated significant changes in the dynamic range variable of component 1, which includes the posterior cingulate (PC), inferior occipital gyrus (IOG), and superior temporal gyrus (STG) regions. Furthermore, the results of this test revealed significant changes in the fALFF variable of component 12, which includes the anterior cingulate cortex (ACC), and component 17, which includes the precuneus, vermis culmen, and declive regions ($P < 0.05$) [see complete results in Tables 2 and 3].

Calculation of the correlation between clinical parameters and imaging parameters

The relationship between the ISI and ESS peripheral parameters and all imaging parameters was examined by calculating the Pearson correlation coefficient. The Pearson correlation coefficient test showed a significant correlation

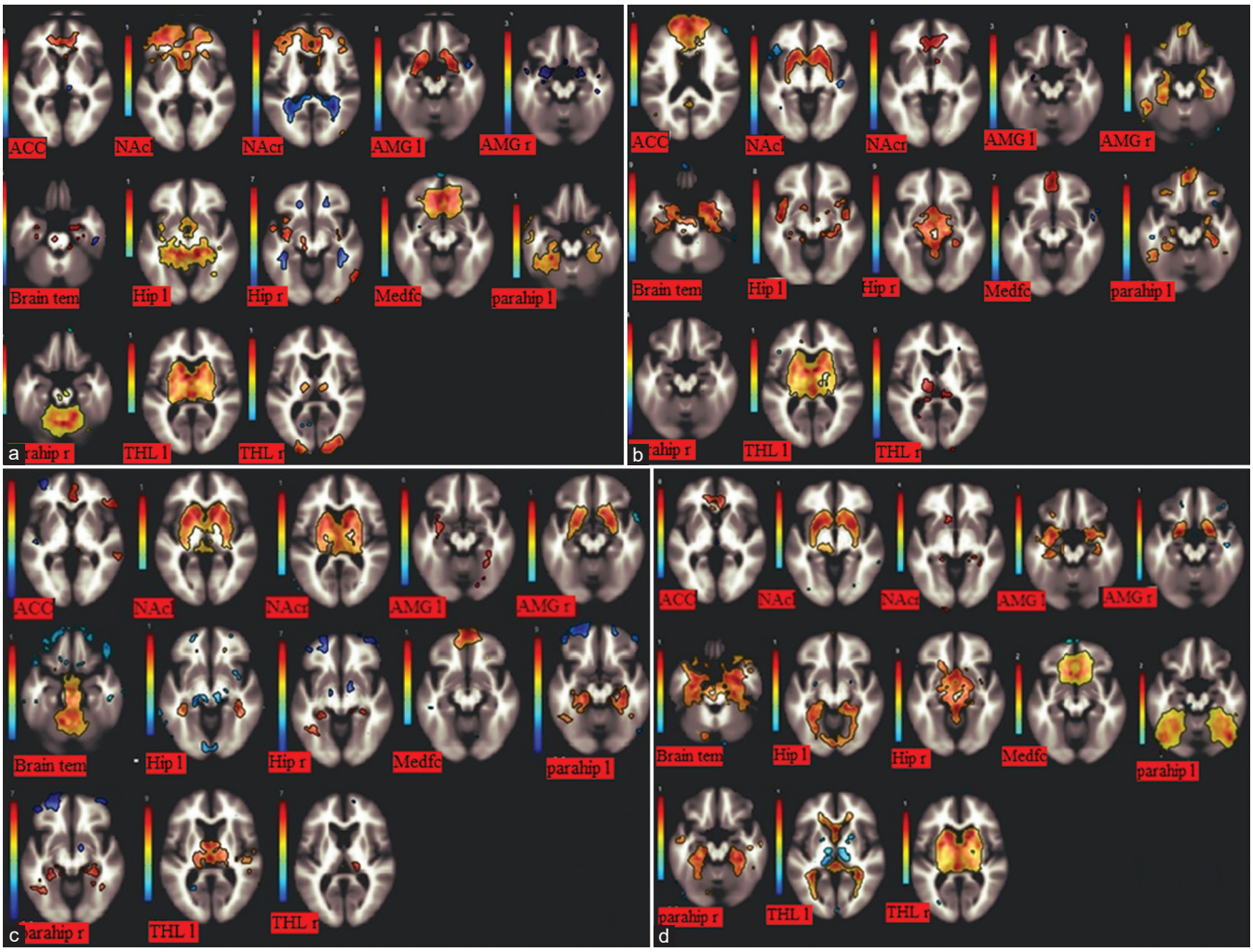

Figure 1: Red color spectrum indicates an increase in activity compared with the basic state, and the blue color spectrum indicates a decrease in activity compared with the basic state in the young group: (a) before the period of insomnia and (b) after the period of insomnia, and in the elder group: (c) before the period of insomnia and (d) after the period of insomnia

between ISI and spatial maps in components 19, 18, 17, 15, 14, 6, 5, 4, 3, and 2 [see complete results in Table 4].

Discussion

Previous studies have indicated that SD has a negative impact on the brain and health.[18,19] Therefore, investigating the physiological and psychophysiological factors that contribute to SD and aid in disease treatment has received significant attention in recent years.[20,21] Understanding the central mechanisms related to SD and its effects on the brain is crucial for the recognition and improvement of therapeutic approaches.[22]

In a study conducted by Benedict *et al*.,[23] investigating the effect of SD on the brain's response to food stimuli, it was found that the activity of the ACC region increases. Similarly, in the present study, a similar result regarding this region was obtained.

In a study conducted by Gao *et al*.,[24] they investigated the effect of SD on the brain's activity in response to acupuncture. Based on their findings, SD has a significant impact on the activity of brain regions, and in young individuals (similar to the young group in this study), the results indicated increased brain activity in regions including the ACC, thalamus, middle frontal gyrus (MFG), middle temporal gyrus (MTG), STG, postcentral gyrus (PoCG), and fusiform gyrus under SD conditions. As mentioned in the Results section, these regions showed increased activity in the sleep-deprived state compared with the well-rested state in the young group, which is consistent with the study by Gao *et al*.[24] In a study conducted by Tamm *et al*.,[25] titled "The Effect of Sleep Restriction on Pain Perception in Elderly and Young Individuals," the fusiform gyrus region showed increased activity in the elderly group compared with the young group, which is contrary to the results obtained in the present study. This difference in the direction of activity in this region is likely related to the intensity of pain, as Rathleff *et al*.[26] found in their study on knee pain intensity in elderly and young individuals that older individuals experience greater pain intensity. The results of a study titled "The Impact of Sleep Deprivation on Delayed Brain Function" conducted by Habec *et al*.[27] revealed that brain

regions that are simultaneously activated in most individuals as a result of SD are primarily located in the posterior regions of the brain, especially areas related to vision and attention. In their study, they reported regions such as the anterior cingulate gyrus, thalamus, and basal ganglia, as well as the prefrontal cortex. The Habec study confirms the findings of the present research in most cases. However, regarding the basal ganglia region, no significant change in activity was observed in the present study. It is likely that the role of the basal ganglia in sleep-wake control mechanisms contributes to this difference in activity levels.[28,29] In a meta-analysis study titled "Functional Brain Changes in Chronic Sleep Deprivation" conducted by Javaheri Pour *et al*.,[30] they reported the disruption of brain function in visual perception, memory, and reasoning in cases of SD, based on the analysis of previous studies. Additionally, the results indicated functional connectivity between regions such as the superior parietal lobule, insula, inferior frontal gyrus, occipital cortex, and cerebellum during the resting state of sleep-deprived individuals. These findings align with the results of the present study.

The variable fALFF was statistically analyzed in this study to examine the differential effects of SD on young and elderly individuals across all components. A significant difference was observed in components 12 and 17, which include the anterior cingulate gyrus, precuneus regions, prominent piece, and sloping piece of the cerebellum. In the study by Nechifor *et al*.[31] titled "Altered Activity in Reward-Related Brain Regions with Sleep Deprivation," the precuneus region exhibited significantly higher activity in the sleep-deprived group.

Luber *et al*.,[32] in a study titled "Sleep Deprivation-Induced Memory Enhancement Using fMRI," reported increased activity in the inferior parietal, STG, hippocampus, thalamus, and PoCG regions as a result of SD. The results of this study are consistent with the present study in this regard. In this study, the Pearson correlation coefficient test showed a correlation between ISI and the spatial map in components 19, 18, 17, 14, 6, 6, 5, 4, 3, and 2, except for component 19, which exhibited a positive correlation. As the spatial map variable reflects the volume of active regions in the components, the significant positive correlation between the ISI parameter and this variable is likely due to increased activity in these regions. According to the results, the spatial map variable in component 19, which includes the paracentral lobule, exhibited a negative correlation with the ISI parameter. This region likely has lower activity during sleepiness compared with the non-sleepy state. This finding is consistent with a study conducted by Wu *et al*., titled "Activation of Alpha Band in Resting State and Functional Connectivity after Sleep Deprivation."[33]

Conclusion

The results of this study demonstrated that the impact of SD differs between elderly and young individuals, and there are significant changes in brain activity maps in sleep-deprived individuals in certain brain regions. The effects of SD also differ between elderly and young individuals. Considering that fMRI during the resting state was utilized in this study, future research can focus on fMRI imaging with task performance and analyze and interpret its results accordingly.

Table 2: Results of the Friedman test on dynamic range parameters in all components

Dynamic range	Areas	Young	Old
Co7	Claustrum, insula, cingulate gyrus	.025	.180
Co19	Paracentral lobule	.045	1.000
Co20	Parahippocampal gyrus, uvula, fourth ventricle	.045	1.000

Table 3: Results of the Friedman test on spatial map parameters

Spatial maps	Areas	Young	Old
Co1	Inferior occipital gyrus (IOG), superior temporal gyrus (STG), tuber, posterior cingulate (PC)	.000	.007
Co2	Superior frontal gyrus (SFG), inferior frontal gyrus (IFG), fusiform gyrus, lingual gyrus	.000	.002
Co3	Supramarginal gyrus, third ventricle, transverse temporal gyrus, postcentral gyrus	.007	.002
Co5	Extranuclear, culmen, medial frontal gyrus, pyramis	.074	.025
Co7	Claustrum, insula, cingulate gyrus	.655	.025
Co8	Superior parietal lobule	.025	.074
Co9	Precentral gyrus	.007	.025
Co10	Orbital gyrus, superior occipital gyrus	.002	.371
Co11	Inferior semilunar lobule	.025	.002
Co12	Anterior cingulate	.025	.371
Co13	Uncus, declive of vermis	.180	.025
Co14	Subcallosal gyrus	.371	.007
Co15	Middle temporal gyrus, lateral ventricle	.007	.007
Co16	Sub-gyral	.002	.025
Co17	Precuneus, declive, culmen of vermis	.007	.000
Co18	Inferior parietal lobule	.000	.000
Co19	Paracentral lobule	.015	.009

Table 4: Results of the Pearson correlation test on variable spatial map components

Spatial maps	Areas	ISI
Co2	Superior frontal gyrus (SFG), inferior frontal gyrus (IFG), fusiform gyrus, lingual gyrus	.025
Co3	Supramarginal gyrus, third ventricle, transverse temporal gyrus, postcentral gyrus	.045
Co4	Middle occipital gyrus, cerebellar tonsil, inferior temporal gyrus, thalamus	.045
Co5	Extranuclear, culmen, medial frontal gyrus, pyramis	.022
Co6	Angular gyrus	.032
Co14	Subcallosal gyrus	.012
Co15	Middle temporal gyrus, lateral ventricle	.043
Co17	Precuneus, declive, culmen of vermis	.045
Co18	Inferior parietal lobule	.003
Co19	Paracentral lobule	.032

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Declarations

All authors hereby declare that all the above information is correct and accurate.

Ethics approval and consent to participate

This study has been approved by the ethics committee of Kermanshah University of Medical Science with a reference number of IR.KUMS.MED.REC.1400.003.

Consent for publication

There are no personal data for publication.

Availability of data and materials

The data presented in this study are available on request from the corresponding authors.

Authors' contributions

Meysam SiyahMansoory and Hamid Sharini conceptualized the study, designed the methodology, and provided software. Yazdan Choghazardi, Korosh Saber, and Fatemeh Sabzevarian curated the data, wrote the original manuscript, and prepared the draft. Mehdi Khodamoradi visualized the data and investigated the study.

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Conflicts of interest

There are no conflicts of interest.

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