

Structural Brain Neuroimaging in Primary Insomnia

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Primary insomnia is a chronic disorder and characterized by inadequate sleep or poor sleep quality. The prevalence of insomnia is relatively high and daytime fatigue, mood disruption and cognitive impairments associated with insomnia negatively affect productivity and quality of life of patients. However, the neurobiological understanding of primary insomnia is still insufficient. Meanwhile, many neuroimaging studies have performed to investigate the structural or functional derangement in brains of patients with primary insomnia. There is no doubt that neuroimaging techniques can be useful in identifying the cerebral mechanisms of insomnia pathogenesis, and the neural correlates of insomnia symptoms. The current review focuses on structural neuroimaging findings in patients with primary insomnia.

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INTRODUCTION

Primary insomnia is a disorder whereby patients experience chronically disturbed sleep and sleep loss, non-refreshing sleep, and heightened arousal in bed; these conditions cannot be attributed to a comorbid medical or psychiatric disorder.¹ Symptoms during wakefulness accompany the sleep difficulties and result in the impairment of normal functioning. Common waking symptoms include fatigue, reduced motivation, reduced concentration, attention, and memory functioning, and irritability or reduced mood.

Complaints of subjective daytime sleepiness are also common, although, in contrast to patients with hypersomnolence conditions, many with this complaint are not able to nap in the daytime and few show unintentional sleep episodes. Patients complain about difficulty falling asleep, difficulty maintaining sleep and/or early awakenings.² Patients may accompany neurocognitive problems, and deficits in attention and working memory.³⁻⁷

Cognitive dysfunction in primary insomnia has been suggested, but few behavioral studies found abnormal performance in this condition, and no patterns of consistent results have emerged across studies.⁸ Studies of the pathophysiology of primary insomnia have revealed on one or more dimensions of physiological hyperarousal during sleep and wakefulness, however, the neurobiological understanding of primary insomnia is still insufficient. The current article reviews the findings that structural brain imaging techniques to explore the relevant neuroanatomical substrates associated with primary insomnia.

VOLUMETRY OF HIPPOCAMPUS

There have been several controversial findings concerning hippocampal volume in human insomnia studies. A pilot study by Riemann et al.⁵ reported that hippocampal volumes were significantly lower bilaterally in insomnia patients than in controls. In contrast, consecutive study by Winkelmann et al.⁶ did not find any objective differences in the hippocampal volumes

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of insomnia patients, even though some patients with sleep maintenance problems were shown to have smaller volumes, as determined by wrist actigraphy. However, there was a correlation between reduced volumes in the bilateral hippocampi and actigraphy-derived poor sleep efficiency and increased wakefulness after sleep onset in insomnia patients. These findings were later corroborated in a retrospective study by the same group of Winkelman et al.,⁹ examining two independent samples from previous studies.^{5,6} A later study by Noh et al.,¹⁰ obtained 1.5 Tesla MRI data from 20 physician-referred primary insomnia subjects (18 females; mean 50.8 ± 10.8 years) and 20 healthy controls. They compared hippocampal volume and cognitive function between patients and controls and investigated the correlation between hippocampal volumes and demographics and various factors measured from sleep studies and neuropsychological tests. The results showed that there were no definite differences in intracranial volumes and in absolute and intracranial volumes—normalized hippocampal volumes between patients and controls. However, the duration of insomnia and the arousal index in nighttime polysomnography exhibited significant negative correlations with hippocampal volumes in insomnia patients.¹⁰ Cognition—especially for attention and frontal lobe function—was significantly worse in insomnia patients than in controls and lower hippocampal volumes were associated with decreased cognitive performances.¹⁰ A subsequent study by Spiegelhalder et al.¹¹ investigated 28 patients with insomnia (18 females, mean 43.7 ± 14.2 years) and 38 controls. They revealed no statistically significant between-group differences in HV. Furthermore, no significant correlations were found between self-reported measure of insomnia severity or total sleep time and left or right hippocampal volumes.¹¹

Thus, there have been controversial findings concerning hippocampal volume in human insomnia studies. Several factors could have contributed to this discrepancy. First, the studies used different anatomical landmarks to delineate the boundary of the hippocampus. Riemann et al.⁵ included the fimbria, the alveus, and the hippocampus-amygdala transition area (HATA) when determining hippocampal volumes, but these regions were not included in the work of Winkelman et al.⁶ Noh et al.¹⁰ included the alveus but excluded the fimbria and the HATA because the fimbria is regarded as white matter and the HATA is not easy to delineate consistently between subjects. Second, the different subsets of patients examined in the studies may play a role. The mean duration of insomnia was longer of the study by Reimann et al.⁵ (11.6 years) than in Noh et al.¹⁰ (7.6 years) and that of Winkelman et al.⁶ A longer duration of insomnia might negatively influence hippocampal function and volumes. The more severe insomnia symptoms and a longer duration of disease might be attributable to the study involving physician-referred patients with chronic insomnia while the other study enrolling patients from community recruits who complained

of insomnia symptoms. Noh et al.¹⁰ observed that left and right hippocampal volumes in insomnia patients were significantly and negatively correlated with the duration of insomnia, which is remarkable. These methodological or demographics inconsistencies may be responsible for the discrepant findings about hippocampal volume in primary insomnia.

To overcome technical limitations of the low sensitivity of global hippocampal volumetry and the variability of the hippocampal segmentation, the automated subfield volumetry was adopted in the most recent study.¹² At a low resolution MRI (1 mm³) it may not have been sufficiently sensitive to visualize hippocampal subfields. Alternatively, vertex (= point)-wise morphometry based on a surface extracted from the manual segmentation of the whole hippocampus¹³⁻¹⁵ has been a surrogate to manual subfield volumetry, which can only be done on high-field (> 3 Tesla) and high-resolution MRI.^{16,17} As a result, hippocampal subfield atrophy in chronic insomnia suggests reduced neurogenesis in the dentate gyrus (DG) and neuronal loss in the cornu ammonis (CA) subfields in conditions of sleep fragmentation and related chronic stress condition. Atrophy in the CA3-4-DG region was associated with impaired cognitive functions in patients. These observations may provide insight into pathophysiological mechanisms that make patients with chronic sleep disturbance vulnerable to the cognitive impairment.¹²

VOXEL-BASED MORPHOMETRY

A number of morphometric studies were performed in insomnia using conventional high-resolution T1-weighted magnetic resonance images to quantify the size of specific brain structures. Voxel-based morphometry (VBM) is an automated technique that has grown in popularity since its introduction,^{18,19} reflecting the fact that it provides a comprehensive assessment of anatomical differences throughout the brain.¹⁹ An earlier optimized VBM study showed that patients with primary insomnia had gray matter deficits in the left orbitofrontal cortex and precuneus compared with controls.²⁰ However, optimized VBM has a significant circularity problem since the registration requires an initial tissue classification and vice versa.²¹ Statistical parametric mapping (SPM) 8-based VBM has been refined through the development of a registration method termed Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra (DARTEL), which is a more sensitive means of identifying differences of gray matter and white matter.²¹ Thus, SPM8-based VBM provides more accurate localization than optimized VBM in terms of supporting precise intersubject alignment and segmentation performance throughout the iterative unified model.^{21,22}

A first VBM study in insomnia patients by Altena et al.²⁰ reported smaller gray matter volumes in the left orbitofrontal

and parietal cortices in insomnia patients and the negative correlation between orbitofrontal gray matter and insomnia severity, without any correlation with mood ratings. Joo et al.²³ observed similar gray matter changes in the orbitofrontal gyrus, not in the precuneus. Orbitofrontal involvement in sleep vulnerability appears a robust finding.²⁴ The insomnia severity index of insomnia patients in the study of Joo et al.²³ were inversely correlated to GM in the dorsolateral prefrontal cortices. Several factors may be responsible for these partial discrepancies. The subject characteristics among the studies are different. Volume reduction in the orbitofrontal cortex has been related to major depression²⁵ and advanced age.²⁶ In the study of Altena et al.,²⁰ in only one patient the diagnosis of major depression with a prior history of antidepressant medication use was made. Joo et al.²³ excluded patients who had a history of any kind of psychiatric disease and use of antidepressants, hypnotic agents, or anxiolytic agents to avoid chronic mood or medication effects on the brain. Methodological differences might be responsible for the discrepancy. Altena et al.²⁰ used optimized VBM analysis, which is known to have a circularity problem.²² Instead, Joo et al.²³ adopted SPM8-based VBM embedded in a newly developed registration method (DARTEL), which is more sensitive to identify differences of gray matter and white matter.²¹ It is notable that different methodologies may lead to different results in neuroimaging studies.

Brain regions with GM deficit may suggest the relationship with clinical symptoms and cognitive dysfunctions in patients with insomnia. Joo et al.²³ found gray matter deficits in multiple brain regions including bilateral dorsolateral prefrontal area in patients with primary insomnia. Gray matter deficits in the dorsolateral prefrontal cortex may provide the anatomical substrates to be related to attention deficit, frontal lobe dysfunction, and nonverbal memory decline of patients with insomnia, which might be associated with poorer sleep.^{27,28} Gray matter deficit of the pericentral and lateral temporal areas may be associated with the difficulties in sleep initiation and maintenance.^{29,30} Winkelman et al.⁹ reported an increased volume of the rostral anterior cingulate cortex using FreeSurfer,³¹ an automated software for measuring the volume of brain structures. This result was, however, not corroborated by one study using both the same methodology and VBM¹¹ and by two other studies using VBM.^{20,23}

Although it is unclear whether gray matter reductions are a preexisting abnormality or a consequence of insomnia, gray matter reduction as well as a lack of sleep or poorer sleep quality in the patients with insomnia might be responsible for clinical features and cognitive dysfunction in chronic insomnia.

CONCLUSION

The computer-aided analysis of brain MRI in patients with primary insomnia revealed structural abnormalities located in

various brain structures, possibly in relation with the cognitive and mood disturbances observed in primary insomnia patients. Insomnia may be associated with abnormal brain structures in the frontal cortex, hippocampus and/or anterior cingulate cortex. In addition, structural volumetry studies provide the evidence that chronic sleep deprivation associated with insomnia impairs memory and frontal lobe function, and that insomnia duration and poor sleep quality. Higher tesla MRI scanners and further development of analysis software of brain MR images will be able to better characterize the structural changes in primary insomnia.

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Conflicts of Interest

The author has no financial conflicts of interest.

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