Altered Regional Homogeneity in Chronic Insomnia Disorder with or without Cognitive Impairment

X. R. Pang, X. R. Guo, X. Wu, F. Hu, M. Liu, L. Zhang, Z. Wang, and K. Li

ABSTRACT

BACKGROUND AND PURPOSE: Many studies have shown that insomnia is an independent factor in cognitive impairment, but the involved neurobiological mechanisms remain unclear. We used regional homogeneity to explore the specific neurobiologic indicators of chronic insomnia disorder with mild cognitive impairment.

MATERIALS AND METHODS: Thirty-nine patients with insomnia were divided into a group with and without cognitive impairment; we also included a control group (n = 28). Abnormalities in brain functional activity were identified by comparing the regional homogeneity values for each brain region among the groups.

RESULTS: Subjective insomnia scores were negatively correlated with cognitive impairment after controlling for age, sex, and educational effects. Regions with significant differences in regional homogeneity values in the 3 groups were concentrated in the right medial prefrontal cortex, the right superior frontal gyrus, and the left superior occipital gyrus. Meanwhile, subjective insomnia scores were negatively correlated with the strength of the decreased regional homogeneity in the right medial prefrontal cortex. The increased regional homogeneity value in the right superior frontal gyrus was positively correlated with the Montreal Cognitive Assessment score in patients.

CONCLUSIONS: Our results indicate that decreased regional homogeneity values in the medial prefrontal cortex and increased regional homogeneity values in the cuneus may be important neurobiologic indicators of chronic insomnia disorder and accompanying cognitive impairment. Overall, our study described the regional homogeneity of the whole brain in chronic insomnia disorder with mild cognitive impairment and could be the basis for future studies.

ABBREVIATIONS: BA = Brodmann area; CID = chronic insomnia disorder; MCI = mild cognitive impairment; mPFC = medial prefrontal cortex; NC = healthy control; NI = no impairment; ReHo = regional homogeneity; SFG = superior frontal gyrus

The relationship between insomnia and cognitive function has attracted considerable attention in recent years. Large-sample meta-analyses have shown that patients with insomnia have mild or moderate dysfunction in attention, episodic memory, working memory, and executive function compared with healthy controls. A number of neuropsychological studies have found that older patients with chronic insomnia disorder (CID) have significant deficits in cognitive function compared with individuals of the same age without insomnia symptoms. Although some scholars have proposed that insomnia is associated with normal aging or neurodegenerative changes, recent research indicates that insomnia is an independent factor in cognitive impairment.

Using [18F] FDG-PET, the earliest study found that the interacting neural networks of patients with insomnia were mainly distributed in the awakening, affective control, and cognitive systems. The observed abnormalities in the hippocampus and medial prefrontal cortex (mPFC) were consistent with the clinical features of cognitive impairment in patients with insomnia and the results of neurophysiology and neuroendocrine studies, indicating that memory integration is impaired in insomnia. Considering similarities in neuromodulatory factors and their...
Mechanisms of action sites in insomnia and Alzheimer disease, a possibility that has attracted much attention from neurologists, neuroscientists, and neuroradiologists is whether insomnia and Alzheimer disease share the same pathogenesis.16,17

fMRI provides a primary method of mechanism detection in insomnia. Some researchers have explored network mechanisms underlying decreased working memory and executive dysfunction in insomnia using task-state fMRI.18-20 They have found decreased activity in the frontoparietal cortex18 and an abnormal fronto-striatal network during task-state in patients with insomnia.19 Furthermore, the activity of the medial prefrontal lobe could be recovered following insomnia improvement.20 Behavioral and fMRI studies have shown that the impairment of the executive control network in patients with CID is associated with reduced nocturnal slow-wave sleep time,21 which is consistent with the impairments in the prefrontal and thalamus attention networks during sleep deprivation.3,22,23 Moreover, PET and fMRI studies have yielded similar results.24,25 Although the above studies suggest that insomnia may be the potential reason for cognitive impairment, the involved mechanisms in patients with insomnia remain unclear.

Compared with task-state fMRI, resting-state fMRI can be used to disregard differences in brain activation caused by inconsistencies in task performance and may be used as a reflection of the real changes within inherent brain activity and/or the endogenous neurophysiologic process of the patients’ brains under the awake state. The regional homogeneity (ReHo) method can effectively evaluate resting-state brain activity across the whole brain of an individual and has good reproducibility.26,27 The method has been widely used in the study of resting-state brain functional imaging for neurodegenerative diseases, emotional diseases, and cognitive function.

Several previous studies have investigated the regional spontaneous activity patterns in patients with insomnia. These studies have found that patients with insomnia have abnormal spontaneous activity in specific regions, including the insula, cingulate gyrus, fusiform gyrus, and cerebellum.28,29 In addition, these altered ReHo values are associated with sleep quality and psychological scores30; these findings suggest that the abnormal ReHo values of specific regions could reflect the brain mechanism of emotional disorders in patients with insomnia. Moreover, neuro-imaging studies have shown that abnormal brain regional homogeneity is an important marker of cognitive impairment in patients with Alzheimer disease31,32 and could accurately reflect the severity of cognitive impairment.33

We diagnosed mild cognitive impairment (MCI) according to the Peterson MCI standard, and patients with insomnia were divided into the cognitive impairment (CID-MCI) group or the group without cognitive impairment (CID-NI). Then, we used the ReHo method to explore differences in regional spontaneous activity in the whole brain between the healthy control (NC), CID-NI, and CID-MCI groups. We hypothesized that the ReHo index would differ among the NC, CID-NI, and CID-MCI groups and that the differences in ReHo would be associated with differences in cognitive ability. A post hoc analysis was then performed to compare the ReHo index between each pair of groups. Finally, a correlation analysis was performed between the ReHo index of the identified regions and various clinical variables in the CID-NI and CID-MCI groups to evaluate the relationship between the ReHo scores and the cognitive abilities of the CID-NI and CID-MCI groups.

Materials and Methods
The participants in the present study also composed the sample in a previous study of spontaneous activity measured by whole-brain functional connectivity.34 All subjects met identical methodologic stringency criteria; comprehensive clinical details can be found in the prior work.34

Participants
Patients with insomnia and volunteers were enrolled from a neurology clinic. The participants underwent a series of examinations, including a clinical interview, laboratory blood tests, and neuropsychological assessment. Consent forms were signed by the participants before the study, and the study protocol was approved by the ethics committee.

All participants underwent a complete physical and neuropsychological examination, standard laboratory tests, and an extensive battery of neuropsychological assessments, which included the Pittsburgh Sleep Quality Index, Insomnia Severity Index, Hamilton Anxiety Scale, Hamilton Depression Rating Scale, Mini-Mental State Examination, Montreal Cognitive Assessment, and Clinical Dementia Rating. Patients with CID also underwent polysomnography.

The diagnosis of CID met the criteria of the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders and the third edition of the International Classification of Sleep Disorders.35 Although chronic insomnia is not exactly equal to primary insomnia, we did not find severe anxiety and depression disorders in the included patients.

The On-line Table presents the demographic, neuropsychological, and sleep characteristics of the enrolled participants.

Study Method
The patients with CID completed subjective and objective sleep-quality assessments (Pittsburgh Sleep Quality Index and Insomnia Severity Index scales and Polysomnography monitoring). Sleep time data were analyzed and calculated by an experienced technician and were reviewed by a neurologist. These data included total sleep time, sleep-onset latency, wake time, nonrapid eye movement slow-wave activity (S3 + S4) time and latency, and rapid eye movement sleep time and latency. The details of the neuropsychological assessments are provided in the On-line Table.

MR Imaging Acquisition
Briefly, MR imaging was performed using a 1.5T superconducting MR imaging scanner (Intera Achieva; Philips Healthcare, Best, the Netherlands). The parameters and scanning mode of the MR imaging in this study can be found in the previously published study.34

MR Imaging Data Preprocessing
The fMRI data were preprocessed with a method consistent with protocols in previously published studies using the BRainNetome fMRI Toolkit (Brant; http://brant.brainnetome.org). The prepro-
cessing steps included the following: 1) slice-timing, 2) realignment to reduce head motion, 3) normalization to a standard EPI template and reslicing to 2 mm cubic voxels, 4) denoising by regressing out several effects (6 motion parameters, linear drift, and the mean time-series of all voxels within the white matter and CSF), and 5) temporal filtering (0.01–0.08 Hz) to reduce noise.

**Estimation of Interregional Functional Connectivity—ReHo Index**

ReHo provides a fast mapping of the regional activity across the whole brain. For each subject, the ReHo map was normalized by dividing it by the mean ReHo of the whole brain for each subject to reduce the effect of individual variability, for each voxel: ReHo_normalized = ReHo (x, y, z) / Mean (ReHo).

**Statistical Analysis**

A 1-way ANOVA with age and sex as covariances was performed to identify the differences among the CID-MCI, CID-NI, and NC groups. The resultant F value map was then thresholded using P < .001 (F = 7.76, two df, 60 df for each voxel and a cluster size of at least 60 voxels, uncorrected). Subsequently, the regions that showed significant differences were extracted as ROIs, and the mean ReHo values were used for a post hoc analysis. Statistical comparisons of the mean ReHo values between each pair of groups were performed using a 2-sample 2-tailed t test at a threshold of P < .05.

To determine whether the ReHo index varied with disease progression in the CID-MCI and CID-NI groups, we performed correlation analyses between the ReHo index and each of the clinical variables (Mini-Mental State Examination, Pittsburgh Sleep Quality Index, and Hamilton Anxiety Scale scores). Because these analyses were exploratory in nature, we used a statistical significance level of P < .05 (uncorrected).

**RESULTS**

**Group Differences**

A 1-way ANOVA was used to determine the regions in which the ReHo index was significantly altered among the CID-NI, CID-MCI, and NC groups. We found that the ReHo index was significantly different in the following regions: the right mPFC (inferior frontal gyrus, orbital middle frontal gyrus, and Brodmann areas [BAs] 47 and 11), the right superior frontal gyrus (SFG; BA 11), the left cuneus (BA 18), and the left superior occipital gyrus (BAs 31 and 18) among the CID-NI, CID-MCI, and NC groups (Table and Fig 1).

As Fig 2 shows, the mean ReHo values in the mPFC decreased significantly (P < .05) in the CID-NI and CID-MCI groups compared with the NC group, while the mean ReHo values in the cuneus increased significantly (P < .05) in the CID-NI and CID-MCI groups compared with the NC group. In addition, the mean ReHo value in the right SFG significantly increased (P < .05) in the CID-NI group compared with the CID-MCI and the NC groups.

**Relationship between ReHo and Clinical Variables**

As Fig 3 shows, the strength of the ReHo score was negatively correlated with the Pittsburgh Sleep Quality Index ratings (r = −0.35, P = .03) in the right inferior frontal gyrus in patients with CID. The strength of the ReHo index was positively correlated with the Montreal Cognitive Assessment ratings in the right superior frontal gyrus (r = 0.40, P = .01).

**DISCUSSION**

To the best of our knowledge, this is the first study to investigate the ReHo index of brain spontaneous activity in patients with both CID-MCI and CID-NI as well as to compare them with NCs. Significant differences were found in the ReHo scores in various brain regions—that is, the right mPFC (inferior frontal gyrus, orbital middle frontal gyrus, and Brodmann areas [BAs] 47 and 11), the right superior frontal gyrus (SFG; BA 11), the left cuneus (BA 18), and the left superior occipital gyrus (BAs 31 and 18) among the CID-NI, CID-MCI, and NC groups (Table and Fig 1).

As Fig 2 shows, the mean ReHo values in the mPFC decreased significantly (P < .05) in the CID-NI and CID-MCI groups compared with the NC group, while the mean ReHo values in the cuneus increased significantly (P < .05) in the CID-NI and CID-MCI groups compared with the NC group. In addition, the mean ReHo value in the right SFG significantly increased (P < .05) in the CID-NI group compared with the CID-MCI and the NC groups.
Fig 2. Plot of the regional homogeneity index among the CID-NI, CID-MCI, and NC groups in the identified brain regions (voxels at least 60, $P < .001$). a, The ReHo index is significantly different between the NC and CID-MCI groups. b, The ReHo index is significantly different between the NC and CID-NI groups. c, The ReHo index is significantly different between the CID-MCI and CID-NI groups. R indicates right; L, left; IFG, inferior frontal gyrus; MFG, middle frontal gyrus; SOG, superior occipital gyrus.

Fig 3. Correlations between altered regional homogeneity patterns and subjective sleep scores and cognitive scores in the chronic insomnia disorder group ($P < .05$). A, Right inferior frontal gyrus. B, Right SFG. Although the 2 points in the figure (B) look like outliers, the high correlation was also obtained without them ($r = 0.36$, $P = .03$). PSQI indicates the Pittsburgh Sleep Quality Index; MoCA, the Montreal Cognitive Assessment.

We observed that regions with decreased ReHo were located in the right mPFC (inferior frontal gyrus, orbital middle frontal gyrus) in the CID-MCI and CID-NI groups compared with the NC group. Many studies have demonstrated that the mPFC plays a pivotal role in mediating sleep and generating nonrapid eye movement slow-wave oscillations. Recent electroencephalography and fMRI studies have shown that the waking metabolism rate and reduced gray matter volumes in the medial frontal gyrus of humans are both related to aging and closely related to nighttime slow-sleep intensity. Previous morphometry studies have found that patients with chronic insomnia displayed significantly reduced gray matter volumes in the orbitofrontal cortex (BAs 10 and 11) and medial frontal lobe, and that the gray matter volumes in the orbitofrontal cortex are positively correlated with the severity of insomnia in patients with chronic insomnia. Furthermore, an fMRI study found that the activity of the medial prefrontal lobe could be recovered after the insomnia improved. All these results strengthen the evidence for insomnia-related changes in the mPFC in this study. Moreover, this correlation was supported by the negative relationship between the ReHo index values in the right inferior frontal gyrus and scores on the Pittsburgh Sleep Quality Index (Fig 3).

Considering that the mPFC is a key region in the default mode network that characterizes autobiographic memory retrieval, our results further suggest that ReHo values in the mPFC can reflect disrupted global cognitive function in patients with CID-MCI. Consistent with our findings, several previous studies have found decreased connectivity in the prefrontal cortex, internal default network, and between the default network and its negative feedback network after short-term sleep deprivation in healthy individuals. In recent years, impaired connectivity in the default mode network has been found to be common in patients with insomnia. Moreover, slow-wave sleep plays an important role in memory integration and storage. Some studies have reported that structural and functional destruction in the mPFC, which is known as the major region generating slow-wave sleep oscillations, could destroy the memory systems. In this study, the ReHo values in the right orbital middle frontal gyrus were lower in the CID-MCI than in the CID-NI group (Fig 2). This finding indicates that the coherence in the regional activity of the mPFC gives an expression of affected memory systems induced by CID. Moreover, the patients in the CID-MCI group had lower nonrapid eye movement slow-wave activity ($S_3 + S_4$) (%) and were older than the patients in the CID-NI group (On-line Table). Combined with previous experimental results, our observations suggest that the disruption of spontaneous brain activity in the mPFC due to insomnia may be accelerated with aging, or shortened nonrapid eye movement slow-wave activity (slow wave activity) and aging may synergistically disrupt certain cognitive abilities. Taken together, the decreased homogeneity in the mPFC may be a characteristic alteration in the patients with CID-MCI.

We also found an increased ReHo in the left cuneus in the CID-NI and the CID-MCI groups compared with the NC group (Fig 2). Several neuroimaging studies have found abnormal metabolism and dysfunction in the occipital lobe in patients with insomnia. Although these results are inconsistent, both studies reported a negative correlation between gammabutyric acid content in the occipital lobe and sleep-onset latency, which suggests that the occipital lobe plays an important role in sleep-awakening mediation. In addition, previous studies have shown that patients with insomnia displayed significantly increased ReHo in the left cuneus compared with NCs. This conclusion is consistent with the results of our study, wherein we found that the ReHo of the left cuneus was increased in all patients with CID.

In the present study, the right SFG was the only region that could be used to distinguish the 3 groups. We found that the right SFG exhibited a significantly increased ReHo in both the CID-MCI and CID-NI groups compared with the NC group (Fig 2).
and the ReHo index values in the SFG positively correlated with Montreal Cognitive Assessment ratings. In a recent study, patients with CID showed an increased positive correlation between the left SFG and ipsilateral parahippocampal gyrus, and the connectivity strength was positively correlated with the Mini-Mental State Examination scores. This result suggests that increased functional connectivity of the SFG could contribute to the cognitive impairment after prefrontal disconnection. In addition, 2 studies using the ReHo method have observed that patients with insomnia showed altered spontaneous activity in extensive emotional brain regions (including the insula, cingulate gyrus, fusiform gyrus, temporal lobe, cerebellum, and frontal lobe). Wang et al found that altered ReHo values (the left insula, the right middle cingulated cortex, and the right precentral gyrus) are associated with psychological scores, while Dai et al considered the decreased ReHo values in the SFG to be a marker for cognitive and emotional dysfunction in insomnia. Moreover, the patients in the CID-NI group had both the highest ReHo values in the SFG and the most severe clinical manifestations of difficulty with sleep onset and abnormal emotions compared with the CID-MCI and NC groups; this finding is consistent with the cortical hyperarousal and emotional disorders hypothesis. Taken together, our results further indicate that ReHo values in the right SFG can reflect the degree of difficulty with sleep onset or the hyperarousal state in patients with CID.

Some limitations should be borne in mind when interpreting the results. No regions showed significantly decreased ReHo scores in the CID-MCI group compared with the CID-NI group, while the right orbital middle frontal gyrus had a significantly more destructive tendency in the CID-MCI than in the CID-NI and NC groups (Fig 2). In addition, more data from sleep-monitoring indicators, such as nonrapid eye movement slow-wave activity and rapid eye movement sleep duration, sleep latency, and band characteristics, as well as analysis of correlations between electrophysiology and fMRI measures and cognitive ability, are required for further studies. The present study showed the brain functional changes and clinical indices of CID-MCI and CID-NI in the 2 insomnia subgroups, but not in patients with pure MCI. Further studies could consider including patients with amnesic MCI to better explain the sleep and cognitive decline effect and may help us understand the pathogenetic process that leads from insomnia to Alzheimer disease or of the aggravation of insomnia, which could explain the phenomenon of patients with insomnia having an increased incidence rate of Alzheimer disease compared with individuals without insomnia.

CONCLUSIONS
This study is the first to examine the spontaneous brain activity of patients with CID-MCI, to our knowledge. Our results indicate that the decreased ReHo values observed in the mPFC of patients may be an important neurobiologic indicator of CID and accompanying cognitive impairment and that the enhanced local homogeneity observed in the right SFG may act as a predictor of both destruction in emotional moderation and the degree of hyperarousal state. Overall, our study describes the regional homogeneity of the whole brain in patients with CID-MCI and provides a foundation for future related studies.

Ethical Approval and Informed Consent
This experiment was conducted on humans.

Approval: All experimental protocols were approved by the Clinical Research Ethics Committee of Dongfang Hospital of Beijing University of Chinese Medicine.

Accordance: The methods were carried out in accordance with the approved guidelines.

Informed consent: Informed consent was obtained from all participants before participation.

ACKNOWLEDGMENTS
We thank all authors of the included studies. We especially thank Dr Yunling Zhang for his kind help and suggestions. Moreover, we would like to thank Editage (www.editage.com) for English language editing.

REFERENCES
1. Fortier-Brochu E, Beaulieu-Bonneau S, Ivers H, et al. Insomnia and daytime cognitive performance: a meta-analysis. Sleep Med Rev 2012;16:83–94 CrossRef Medline
2. Naismith SL, Lewis SJ, Rogers NL. Sleep-wake changes and cognition in neurodegenerative disease. Prog Brain Res 2011;190:21–52 CrossRef Medline
3. Blackwell T, Yaffe K, Laffan A, et al; Osteoporotic Fractures in Men (MrOS) Study Group. Associations of objectively and subjectively measured sleep quality with subsequent cognitive decline in older community-dwelling men: the MrOS sleep study. Sleep 2014;37:655–63 CrossRef Medline
4. Lim AS, Kowgier M, Yu L, et al. Sleep fragmentation and the risk of incident Alzheimer’s disease and cognitive decline in older persons. Sleep 2013;36:1027–32 CrossRef Medline
5. Wolkow N, Elkholy O, Baltzan M, et al. Sleep and aging, 1: sleep disorders commonly found in older people. CMAJ 2007;176:1299–304 CrossRef Medline
6. Pace-Schott EF, Spencer RM. Age-related changes in the cognitive function of sleep. Prog Brain Res 2011;191:75–89 CrossRef Medline
7. Hauw JJ, Hauser-Hauw C, Hasboun D, et al. The neuropathology of sleep in human neurodegenerative diseases (in French). Rev Neurol (Paris) 2008;164:669–82 CrossRef Medline
8. Yaffe K, Falvey CM, Hoang T. Connections between sleep and cognition in older adults. Lancet Neurol 2014;13:1017–28 CrossRef Medline
9. Potvin O, Lorrain D, Forget H, et al. Sleep quality and 1-year incident cognitive impairment in community-dwelling older adults. Sleep 2012;35:491–99 CrossRef Medline
10. Branger P, Arenaza-Urgoqui EM, Tomadesso C, et al. Relationships between sleep quality and brain volume, metabolism, and amyloid deposition in late adulthood. Neurobiol Aging 2016;41:107–14 CrossRef Medline
11. Lucey BP, Holtzman DM. How amyloid, sleep and memory connect. Nat Neurosci 2015;18:933–34 CrossRef Medline
12. Nozinger EA. What can neuroimaging findings tell us about sleep disorders? Sleep Med 2004;3(5 Suppl 1):S16–22 Medline
13. Muto V, Shaffii-Le Bourdiec AN, Matarazzo L, et al. Influence of acute sleep loss on the neural correlates of alerting, orientating and executive attention components. J Sleep Res 2012;21:648–58 CrossRef Medline
14. Morin CM, Benca R. Chronic insomnia. Lancet 2012;379:1129–41 CrossRef Medline
15. van Marle HJ, Hermans EJ, Qin S, et al. The effect of exogenous cortisol during sleep on the behavioral and neural correlates of emotional memory consolidation in humans. Psychoneuroendocrinology 2013;38:1639–49 CrossRef Medline
16. Monti JM. The neurotransmitters of sleep and wake, a physiological reviews series. Sleep Med Rev 2013;17:313–15 CrossRef Medline

AJNR Am J Neuroradiol ●● 2018 www.ajnr.org
17. Spira AP, Gamaldo AA, An Y, et al. Self-reported sleep and β-amyloid deposition in community-dwelling older adults. JAMA Neurol 2013;70:1537–43 CrossRef Medline
18. Drummond SP, Walker M, Almklov E, et al. Neural correlates of working memory performance in primary insomnia. Sleep 2013;36: 1307–16 CrossRef Medline
19. Stoffers D, Altena E, van der Werf, et al. The caudate: a key node in the neural network imbalance of insomnia? Brain 2014;137: 610–20 CrossRef Medline
20. Altena E, Van Der Werf YD, Sanz-Arigita EJ, et al. Prefrontal hypo-activation and recovery in insomnia. Sleep 2008;31:1271–76 Medline
21. Li Y, Liu H, Weed JG, et al. Deficits in attention performance are associated with insufficiency of slow-wave sleep in insomnia. Sleep Med 2016;24:124–30 CrossRef Medline
22. Verweij IM, Romeijn N, Smit DJ, et al. Sleep deprivation leads to a loss of functional connectivity in frontal brain regions. BMC Neurosci 2014;15:88 CrossRef Medline
23. Tomasi D, Wang RL, Telang F, et al. Impairment of attentional networks after 1 night of sleep deprivation. Cereb Cortex 2009;19:233–40 CrossRef Medline
24. Thomas M, Sing H, Belenky G, et al. Neural basis of alertness and cognitive performance impairments during sleepiness, I: effects of 24 h of sleep deprivation on waking human regional brain activity. J Sleep Res 2009;9:335–52 CrossRef Medline
25. Chee MW, Chuah LY, Venkatraman V, et al. Functional imaging of working memory following normal sleep and after 24 and 35 h of sleep deprivation: correlations of fronto-parietal activation with performance. Neuroimage 2006;31:419–28 CrossRef Medline
26. Zang Y, Jiang T, Lu Y, et al. Regional homogeneity approach to fMRI data analysis. Neuroimage 2004;22:394–400 CrossRef Medline
27. Kiviniemi V. Endogenous brain fluctuations and diagnostic imaging. Hum Brain Mapp 2008;29:810–17 CrossRef Medline
28. Dai XJ, Peng DC, Gong HH, et al. Altered intrinsic regional brain spontaneous activity and subjective sleep quality in patients with chronic primary insomnia: preliminary data from 4T proton magnetic resonance spectroscopy (1H-MRS). Sleep 2008;31:1271–76 Medline
29. Wang T, Li S, Jiang G, et al. Regional homogeneity changes in patients with primary insomnia. Eur Radiol 2016;26:1292–300 Medline
30. Dai XJ, Gong HH, Wang YX, et al. Gender differences in brain regional homogeneity of healthy subjects after normal sleep and after sleep deprivation: a resting-state fMRI study. Sleep Med 2012;13: 720–27 CrossRef Medline
31. Bai F, Zhang Z, Yu H. Default-mode network activity distinguishes amnestic type mild cognitive impairment from healthy aging: a combined structural and resting-state functional MRI study. Neurosci Lett 2008;438:111–15 CrossRef Medline
32. He Y, Wang L, Zang Y, et al. Regional coherence changes in the early stages of Alzheimer’s disease: a combined structural and resting-state functional MRI study. Neuroimage 2007;35:488–500 CrossRef Medline
33. Zhang Z, Liu Y, Jiang T, et al. Altered spontaneous activity in Alzheimer’s disease and mild cognitive impairment revealed by regional homogeneity. Neuroimage 2012;59:1429–40 CrossRef Medline
34. Pang R, Zhan Y, Zhang Y, et al. Aberrant functional connectivity architecture in participants with chronic insomnia disorder accompanying cognitive dysfunction: a whole-brain, data-driven analysis. Front Neurosci 2017;11:259 CrossRef Medline
35. Edinger JD, Bonnet MH, Bootzin RR, et al; American Academy of Sleep Medicine Work Group. Derivation of research diagnostic criteria for insomnia: report of an American Academy of Sleep Medicine Work Group. Sleep 2004;27:1567–96 CrossRef Medline
36. Wu T, Long X, Zang Y, et al. Regional homogeneity changes in patients with Parkinson’s disease. Hum Brain Mapp 2009;30:1502–10 CrossRef Medline
37. Liu C, Liu Y, Li W, et al. Increased regional homogeneity of blood oxygen level-dependent signals in occipital cortex of early blind individuals. Neuroreport 2011;22:190–94 CrossRef Medline
38. Mander BA, Rao V, Lu B, et al. Prefrontal atrophy, disrupted NREM slow waves and impaired hippocampal-dependent memory in aging. Nat Neurosci 2013;16:357–64 CrossRef Medline
39. Mander BA, Marks SM, Vogel JW, et al. β-amyloid disrupts human NREM slow waves and related hippocampus-dependent memory consolidation. Nat Neurosci 2015;18:1051–57 CrossRef Medline
40. Murphy M, Riedner BA, Huber R, et al. Source modeling sleep slow waves. Proc Natl Acad Sci U S A 2009;106:1608–13 CrossRef Medline
41. Mander BA, Rao V, Lu B, et al. Impaired prefrontal sleep spindle regulation of hippocampal-dependent learning in older adults. Cereb Cortex 2014;24:3301–09 CrossRef Medline
42. Wilckens KA, Aizenstein HJ, Nofzinger EA, et al. The role of non-rapid eye movement slow-wave activity in prefrontal metabolism across young and middle-aged adults. J Sleep Res 2016;25:296–306 CrossRef Medline
43. Joo EY, Noh HJ, Kim JS, et al. Brain gray matter deficits in patients with chronic primary insomnia. Sleep 2013;36:999–1007 CrossRef Medline
44. Altena E, Vrenken H, Van Der Werf YD, et al. Reduced orbitofrontal and parietal gray matter in chronic insomnia: a voxel-based morphometric study. Biol Psychiatry 2010;67:182–85 CrossRef Medline
45. Buckner RL, Andrews-Hanna JR, Schacter DL. The brain’s default network: anatomy, function, and relevance to disease. Ann N Y Acad Sci 2008;1124:1–38 CrossRef Medline
46. De Havas JA, Parimal S, Soon CS, et al. Sleep deprivation reduces default mode network connectivity and anti-correlation during rest and task performance. Neuroimage 2012;59:1745–51 CrossRef Medline
47. Khalsa S, Mayhew SD, Przedzinksi E, et al. Variability in cumulative habitual sleep duration predicts waking functional connectivity. Sleep 2016;39:87–95 CrossRef Medline
48. Suh S, Kim H, Dang-Vu TT. Cortical thinning and altered cortico-cortical structural covariance of the default mode network in patients with persistent insomnia symptoms. Sleep 2016;39:161–71 CrossRef Medline
49. Chauvette S, Seigneur J, Timofeev I. Sleep oscillations in the thalamocortical system induce long-term neuronal plasticity. Neuron 2012;75:1105–13 CrossRef Medline
50. Steriade M, Timofeev I. Neuronal plasticity in thalamocortical networks during sleep and waking oscillations. Neuron 2003;37:563–76 CrossRef Medline
51. Winkelmann JW, Buxton OM, Jensen JE, et al. Reduced brain GABA in primary insomnia: preliminary data from 4T proton magnetic resonance spectroscopy (1H-MRS). Sleep 2008;31:1499–506 CrossRef Medline
52. Morgan PT, Pace-Schott EF, Mason GF, et al. Cortical GABA levels in primary insomnia. Sleep 2012;35:807–14 CrossRef Medline
53. Killgore WD, Schwab ZJ, Kipman M, et al. Insomnia-related complaints correlate with functional connectivity between sensory-motor regions. Neuroreport 2013;24:233–40 CrossRef Medline