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Research report

Reduced spontaneous neuronal activity in the insular cortex and thalamus in healthy adults with insomnia symptoms

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ABSTRACT

Poor sleep and insomnia have been recognized to be strongly correlated with the development of depression. The exploration of the basic mechanism of sleep disturbance could provide the basis for improved understanding and treatment of insomnia and prevention of depression. In this study, 31 subjects with insomnia symptoms as measured by the Hamilton Rating Scale for Depression (HAMD-17) and 71 age- and gender-matched subjects without insomnia symptoms were recruited to participate in a clinical trial. Using resting-state functional magnetic resonance imaging (rs-fMRI), we examined the alterations in spontaneous brain activity between the two groups. Correlations between the fractional amplitude of low frequency fluctuations (fALFF) and clinical measurements (e.g., insomnia severity and Hamilton Depression Rating Scale [HAMD] scores) were also tested in all subjects. Compared to healthy participants without insomnia symptoms, participants with insomnia symptoms showed a decreased fALFF in the left ventral anterior insula, bilateral posterior insula, left thalamus, and pons but an increased fALFF in the bilateral middle occipital gyrus and right precentral gyrus. More specifically, a significant, negative correlation of fALFF in the left thalamus with early morning awakening scores and HAMD scores in the overall sample was identified. These results suggest that insomnia symptoms are associated with altered spontaneous activity in the brain regions of several important functional networks, including the insular cortex of the salience and the thalamus of the hyperarousal network. The altered fALFF in the left thalamus supports the "hyperarousal theory" of insomnia symptoms, which could serve as a biomarker for insomnia.

1. Introduction

Insomnia is the most common sleep disorder, with considerable persistence and incidence rates in the general population (Moore, 2012; Zhang et al., 2011). Longitudinal studies have shown that insomnia is often chronic; in particular, persistent insomnia represents between 28% and 74% of all insomnia cases (Morin et al., 2009; Zhang et al., 2012). In addition, previous work also indicated that approximately 15% of individuals without insomnia symptoms at baseline reported insomnia symptoms at a 12-month follow-up study (Morphy et al., 2007). More importantly, 35–77% of insomnia patients are also diagnosed with major depressive disorder (MDD), according to both cross-sectional and longitudinal studies (Coleman et al., 1982; Tan et al., 1984), and insomnia could be a major contributor to MDD recurrence (Baglioni et al., 2011; Katz and McHorney, 2002). Interestingly, approximately 80% of patients with MDD have concurrent symptoms of insomnia (Sunderajan et al., 2010). Insomnia symptoms have been associated with an increased rate of MDD relapse, longer duration of symptoms, poor response to antidepressant medication, poor quality of life, and increased risk of suicidal behavior (Chellappa and Araujo, 2007; McCall, 2001; Sunderajan et al., 2010). A bidirectional association between insomnia symptoms and depressive symptoms was recently proposed (Luo et al., 2013). As such, the high risk of MDD among individuals with insomnia necessitates the early and adequate treatment of insomnia symptoms. In addition to MDD,

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insomnia symptoms have also been associated with adverse medical outcomes (Zhang et al., 2011), an increased public health burden (Daley et al., 2009), and poor quality of life (Kyle et al., 2010). Consequently, there is a compelling need to identify the neural mechanisms underlying insomnia to better treat insomnia symptoms and to prevent their numerous possible consequences.

Symptoms of insomnia include difficulty falling asleep, staying asleep, and obtaining refreshing sleep (Ohayon, 2002). These symptoms are also assessed by the Hamilton Depression Rating Scale (HAMD) (Hamilton, 1967), which reveals the association between insomnia and MDD. Recent evidence has suggested that neural systems (e.g., general arousal system, emotion and reward system, and prefrontal cognitive control system) are dysfunctional in the case of insomnia (Spiegelhalder et al., 2015). These systems can be conceptualized as subcortical systems, including the amygdala and ventral striatum, which are involved in emotion and reward processing, and cortical regions, including the medial prefrontal cortex (mPFC), anterior cingulate cortex (ACC), ventrolateral prefrontal cortex (vlPFC), and dorsolateral prefrontal cortex (dlPFC), which are involved in cognitive control and voluntary regulation of emotion (Phillips et al., 2008). Based on the hyperarousal theory of insomnia (e.g., the ascending reticular activating system and thalamus), which characterizes the thalamus as a hub of sleep-related activity (Colavito et al., 2014; Saalmann, 2014; Sakurai, 2014), hyperarousal in patients with insomnia might be related to intrinsically altered thalamic activity.

In recent years, resting-state functional magnetic resonance imaging (rs-fMRI) has been used to explore dynamic brain function in the absence of a specific task or in non-alert participants (Barkhof et al., 2014). Among various rs-fMRI data analysis methods, the fractional amplitude of low-frequency fluctuations (fALFF) is an advanced technique to measure local fluctuations in neuronal activity, rather than generalized neuronal activity. Compared to the traditional measurement of the amplitude of low-frequency fluctuations (ALFF), fALFF measurements have shown increased sensitivity and reduced bias from nonspecific physiological signal components (Yan et al., 2013a; Zou et al., 2008). Using rs-fMRI combined with the fALFF method, we aimed to examine and compare individuals with and without insomnia symptoms to explore the relationships among neural activation, insomnia symptom severity, and HAMD scores.

2. Results

2.1. Demographic, HAMD, and HAMA comparisons between the two groups

The demographic and behavioral data are provided in Table 1, in which we discovered that there were no significant differences in age (t [1,100]= 0.94, p = 0.35), gender (x^2 [1]=0.23, p =0.63) or educational level (t [1,100]= −2.74, p = 0.01) between the healthy participants with insomnia symptoms and healthy participants without insomnia symptoms. In particular, it was observed from Table 1 that the HAMD scores were higher for the insomnia symptoms group than for the without insomnia symptoms group (t [1,100]=14.63, p < 0.001). In accordance with Kennedy's work (Kennedy, 2008), we categorized sleep disturbances (consisting of early insomnia items, middle insomnia items, and late insomnia items) using the HAMD-17 items. The sleep disturbance scores indicate the sum of three items from HAMD-17, including early insomnia, middle insomnia, and late insomnia.

2.2. fALFF comparison between healthy adults with insomnia symptoms and healthy adults without insomnia symptoms

Compared to the healthy participants without insomnia symptoms, the subjects with the insomnia symptom group were identified as having significantly increased fALFF in the bilateral middle occipital gyrus and right precentral gyrus and the decreased fALFF in the left ventral anterior insula, bilateral posterior insula, left thalamus, and pons (Fig. 1 and Table 2).

2.3. Voxel-wise correlation between fALFF and HAMD scores in healthy participants

Voxel-wise correlation analysis was conducted, and the results showed that decreased fALFF in the left thalamus (peak coordinate: −15, −24, 3) was significantly correlated with total HAMD score (r= −0.404, p < 0.01, Fig. 2). The findings from voxel-wise correlation analysis also revealed that decreased fALFF in the left thalamus (peak coordinate: −15, −24, 9) was significantly correlated with the late insomnia (early morning awakening) scores (r= −0.408, p < 0.01, Fig. 3). No brain loci showed significant correlations with insomnia symptoms or HAMA scores.

3. Discussion

In this study, we comprehensively evaluated the resting-state fALFF in healthy individuals experiencing insomnia symptoms who are at an increased risk for developing depression. More importantly, we discovered that, compared to healthy participants without insomnia symptoms, healthy participants with insomnia symptoms showed significantly decreased fALFF within the thalamocortical circuits, especially in the thalamus and insula. Notably, decreased fALFF in the left thalamus during the resting state was significantly correlated with HAMD scores and late insomnia

Table 1
Group demographics and clinical measures.

Measure (mean ± SD)	Healthy participants with insomnia symptoms (n=31)	Healthy participants without insomnia symptoms (n=71)	Value	p Value
Age, years	38.58 ± 12.09	36.07 ± 12.49	0.94	0.35[#]
Years of education	14.00 ± 3.31	15.14 ± 2.47	−1.93	0.06[#]
Sex(male/female)	16/15	33/38	0.23	0.63[△]
HAMD	2.97 ± 1.45	0.17 ± 0.48	14.63	< 0.001[#]
HAMA	3.32 ± 2.20	0.30 ± 0.74	10.38	< 0.001#
Sleep disturbance	1.74 ± 0.93	0.00 ± 0.00	15.89	< 0.001#
Early insomnia	0.71 ± 0.74	0.00 ± 0.00	8.14	< 0.001#
Middle insomnia	0.71 ± 0.74	0.00 ± 0.00	8.14	< 0.001#
Late insomnia	0.32 ± 0.54	0.00 ± 0.00	5.06	< 0.001#

Abbreviations: SD: standard deviation; HAMD: Hamilton Depression Rating Scale; HAMA: Hamilton Anxiety Scale.

[#] Indicates p values for two-sample t-tests.

[△] Indicates p values for chi-square test.