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Changes in subcortical resting-state functional connectivity in patients with psychophysiological insomnia after cognitive–behavioral therapy Changes in resting-state FC after CBT for insomnia patients

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ABSTRACT

Study objectives: To examine the resting-state functional connectivity (FC) between subcortical regions in relation to whole-brain activity in patients with psychophysiological insomnia (PI) and changes following cognitive–behavioral therapy for insomnia (CBTi).

Methods: The FC between subcortical seed regions (caudate, putamen, pallidum, amygdala, thalamus, and hippocampus) and whole-brain voxels were compared between the PI group (n = 13, mean age: 51.0 ± 10.2 years) and good sleepers (GS, n = 18, mean age: 42.7 ± 12.3 years). Also, in the PI group, FC was compared before and after 5 weeks of CBTi.

Results: Compared to the GS group, the PI group exhibited stronger FC between the thalamus and prefrontal cortex and between the pallidum and precuneus but weaker FC between the pallidum and angular gyrus, the caudate and orbitofrontal cortex, and the hippocampus and fusiform gyrus. After CBTi, the PI group exhibited decreased FC between the thalamus and parietal cortex, the putamen and motor cortices, and the amygdala and lingual gyrus, but increased FC between the caudate and supramarginal gyrus, the pallidum and orbitofrontal cortex, and the hippocampus and frontal/parietal gyri.

Conclusions: The present findings demonstrate different FC in PI patients compared to GS and provide insight into the neurobiological rationale for CBTi.

1. Introduction

Almost half of the general population has reported experiencing insomnia, making it one of the most common sleep disorders (Riemann et al., 2010). Insomnia is diagnosed based on subjective clinical features because its pathogenesis is a complex interplay of psychological, behavioral, and physiological elements. As insomnia symptoms warrant independent attention along with the associated mental or physical condition, primary insomnia has been removed from the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (Association AP, 2013), and the condition has been incorporated into insomnia disorder, which is now specified by comorbidity with other mental, medical, and sleep disorders. The International Classification of Sleep Disorders (ICSD-2) defines psychophysiological insomnia (PI) as a state of "heightened arousal and learned sleep-preventing associations that result in a complaint of insomnia and associated decreased function during wakefulness" (AASM, 2005). Despite the removal of various insomnia subdiagnoses, including PI in ICSD-3 (AASM, 2014), the term PI is notable for encompassing the diverse aspects of pathogenesis in insomnia.

The most widely accepted model of the pathophysiology of PI is the hyperarousal theory, which states that difficulties with initiating and/or maintaining sleep are due to global increases in cortical and physiological arousal across the sleep–wake cycle (Perlis et al., 1997). Spielman's 3-P model encompasses the hyperarousal theory by

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describing an individual's hyper-arousability with regard to constitutional predisposing factors or to perpetuating factors such as cognitive distortions and maladaptive behaviors, which cause insomnia to persist even after the acute precipitating factors (such as stressful life events) have disappeared (Spielman et al., 2011). However, the identification of trait-like neurobiological factors that act as predisposing factors in patients with insomnia has proven elusive (Spielman et al., 2011). Thus, cognitive–behavioral therapy for insomnia (CBTi), which addresses the maladaptive behaviors and cognitive distortions of insomnia patients, is considered the first-line treatment for this chronic disorder (Qaseem et al., 2016).

There has been a recent increase in neuroimaging studies attempting to reveal the underlying neurobiological bases of insomnia disorder. A previous report supporting hyperarousal was a PET study showing altered brain metabolism in patients with insomnia (Nofzinger et al., 2004). More recently, altered glucose metabolism has been localized to areas related to cognition and the DMN, which affect patients with primary insomnia (Kay et al., 2016). Structural magnetic resonance imaging (MRI) studies have identified volume changes in the frontal cortex (Joo et al., 2013; Altena et al., 2010; Stoffers et al., 2012; Winkelman et al., 2013) and the hippocampus (Riemann et al., 2007; Joo et al., 2014). Another measure of brain activity, functional connectivity (FC), is the temporal dependence of neuronal activity across anatomically separate brain regions. Insomnia patients have been shown to exhibit alterations in FC during specific cognitive tasks (Drummond et al., 2013; Altena et al., 2008; Stoffers et al., 2014), and two previous studies investigated the effects of non-pharmacological therapies for insomnia (CBTi and/or light therapy) on altered FC during specific tasks (Altena et al., 2008; Stoffers et al., 2014).

More recently, technical improvements in studying FC have allowed whole-brain analyses to identify networks of highly correlated regions, such as the default-mode network (DMN), that are exclusively activated during a resting state (Buckner et al., 2008). Resting-state studies may be able to significantly contribute to the field of insomnia research because the neurobiology of this disorder is becoming increasingly recognized as a 24-hour process that continues throughout the sleep-wake cycle. Previous studies observed disruptions in FC within the DMN and in regions associated with executive function (Li et al., 2014; Nie et al., 2015), sensorimotor functions, and limbic regions (Chen et al., 2014; Killgore et al., 2013; Huang et al., 2012), supporting previous physiological and emotional arousal findings associated with insomnia patients. A recent study found the resting-state FC between the amygdala and rostral anterior cingulate cortex to be intermediate in patients with primary insomnia compared to those with generalized anxiety disorder and controls, indicating that the emotional circuit is disrupted by insomnia (Pace-Schott et al., 2017). Intrinsic resting-state activity, identified by brain entropy or regional homogeneity analyses, has also been introduced as a variable in insomnia studies, resulting in consistent evidence for hyperarousal in related structures such as the hippocampus, DMN, basal ganglia (BG) (Zhou et al., 2016), and temporal cortex (Dai et al., 2014). If the therapeutic effects of CBTi are, in fact, related to the recovery of intrinsic FC, then the current understanding of the neurobiology of insomnia will be broadened. However, to date, no studies have explored the effects of CBTi on the intrinsic resting-state FC of insomnia patients.

Recently, the involvement of the BG in emotional and cognitive functioning through connections with the frontal cortex and thalamus has been highlighted (Arsalidou et al., 2013). In particular, the striatum and pallidum play important roles in emotional processing via input from the amygdala and hippocampus, which then relay signals to the thalamus. Interconnected with the prefrontal cortex, the cortico-striato-thalamo-cortical circuit regulates cortical arousal by filtering sensory input of the thalamus (Alexander and Crutcher, 1990). Marked hypoperfusion in the BG was demonstrated earlier by single-photon emission computed tomography (SPECT) in insomnia patients (Smith et al., 2002), and a recent whole-brain FC analysis showed increased FC among regions including the putamen and amygdala (Li et al., 2017). However, because the traditional view of the BG is limited to motor processing functions, studies focusing on BG-related resting-state networks in insomnia patients are limited.

The primary aim of the present study was to determine whether patients with PI would exhibit different resting-state FC, using the caudate, putamen, pallidum, thalamus, amygdala, and hippocampus as seed regions in relation to whole-brain neural activity. The secondary purpose of the present study was to evaluate the therapeutic effects of CBTi on resting-state FC in insomnia patients.

2. Methods

2.1. Participants

This study included 25 patients recruited from the Center for Sleep and Chronobiology at Seoul National University Hospital who were diagnosed with PI based on the criteria of the International Classification of Sleep Disorders, version 2 (ICSD-2). Additionally, 23 good sleepers (GS) were enrolled in the study via advertisements. The study protocol was approved by the Institutional Review Board of Seoul National University Hospital, and written informed consent was obtained from the participants after a complete description of the study was given. Individuals who had 1) a past history of serious medical or neurological illness, 2) a current medical or neurological illness, 3) an Axis I psychiatric disorder other than primary insomnia based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV), 4) a sleep disorder other than PI (based on ICSD-2 criteria), 5) insomnia duration < 6 months, 6) shift-work employment, 7) borderline or antisocial personality disorder, or 9) any contraindications for magnetic resonance imaging (MRI) scans, and 10) those who were pregnant were not eligible for enrollment.

To screen out those with psychiatric disorders, the Structural and Clinical Interview for the DSM-IV (SCID-IV) was administered to all participants by trained psychologists. To screen out participants with common sleep disorders such as obstructive sleep apnea, in lab nocturnal polysomnography (PSG; Profusion PSG3; Compumedics, Abbotsford, VIC Australia) was performed. Additionally, participants were asked not to take any medications that could potentially affect sleep, including hypnotics, sedatives, antipsychotics, antidepressants, and mood stabilizers.

PSG and functional MRI (fMRI) were conducted 15.8 ± 12.4 and 6.9 ± 4.5 days before the first CBTi session, respectively. Of the 25 PI patients, six were excluded prior to the initiation of CBTi due to brain lesions identified on the MRI scan (n = 2), the presence of obstructive sleep apnea on the nocturnal PSG (n = 1), the inability to discontinue hypnotics (n = 2), or withdrawal of consent during screening (n = 1). Of the 19 remaining PI patients, six who began CBTi withdrew from the study due to refusal to undergo a second fMRI scan after the CBTi sessions (n = 2), missing fMRI data (n = 1), and incomplete CBTi sessions (n = 3). Of the 23 GS, five were excluded at screening due to the presence of obstructive sleep apnea on the nocturnal PSG (n = 2) or withdrawal of consent during screening (n = 3). Thus, 13 PI patients and 18 GS were included in the final analyses of the present study. Among the 13 patients with PI, four were taking zolpidem at the time of recruitment. No patient was taking any other psychotropic medication. Those taking zolpidem participated in the study after a washout period ranging from 7 to 30 days. The included and excluded participants did not significantly differ in terms of their demographic and clinical characteristics. The PI group underwent a second fMRI scan after five sessions of CBTi were completed.

2.2. Baseline clinical assessments of sleep

All participants completed several sleep-related questionnaires, including the Pittsburgh Sleep Quality Index (PSQI), Dysfunctional Beliefs