의학박사 학위논문

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

불면증의 기능적 뇌 연결성에 대한

인지행동치료의 효과 분석

2018년 2월

서울대학교 대학원

의학과 정신과학 전공

이 유 진

불면증의 기능적 뇌 연결성에 대한 인지행동치료의 효과 분석

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

지도교수 이 유 진

이 논문을 의학박사 학위논문으로 제출함

2017년 10월

서울대학교 대학원

의학과 정신과학 전공

이 유 진

이유진의 박사학위논문을 인준함.

2017 년 12 월

위 원 장 _____ **(인)**

부위원장 _____ **(인)**

위 원 _____ **(인)**

위 원 _____ **(인)**

위 원 _____ **(인)**

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

by

Yu-Jin Lee, M.D.

A Thesis Submitted to the Department of Medicine in

Partial Fulfillment of the Requirements for

the Degree of Doctor of Philosophy in Medicine (Psychiatry) at

Seoul National University College of Medicine

December 2017

Approved by Thesis Committee:

Professor _____ **(인) Chairman**

Professor _____ **(인) Vice Chairman**

Professor _____ **(인)**

Professor _____ **(인)**

Professor _____ **(인)**

Abstract

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

Yu-Jin Lee

College of Medicine

The Graduate School

Seoul National University

Psychophysiological insomnia (PI) is characterized by cognitive, emotional, and physiological hyperarousals. The effectiveness of cognitive–behavioral therapy for insomnia (CBTi) has supported the concept of PI as a psychological disorder. However, the recent expansion in neuroimaging techniques has identified cortical, emotional, and sensory arousal in insomnia patients by demonstrating functional changes as well as structural changes in the brains these patients. Taken together with the psychological (cognitive-behavioral) aspects of insomnia, the neurobiological hyperarousal motivates the hyperarousal theory of insomnia. Functional connectivity (FC) changes in the default mode network (DMN) and in emotional, limbic, and somatosensory areas are being revealed and provide substantial evidence for hyperarousal in insomnia patients. However, despite the clinical effectiveness

of CBTi in insomnia patients, resting-state FC changes after CBTi have not been identified. The purpose of the present study was to compare the resting-state FC between PI patients and good sleepers (GS) and to investigate resting-state FC changes after CBTi in PI patients.

The present study included 13 patients in the PI group (mean age: 51.0 ± 10.2 years) and 18 controls in the GS group (mean age: 42.7 ± 12.3 years). The FC between subcortical seed regions (caudate, putamen, pallidum, amygdala, thalamus, and hippocampus) and DMN regions (anterior cingulate cortex, posterior cingulate cortex, paracingulate cortex, inferior parietal cortex) were analyzed in relation to the voxels of the whole brain. The FC between DMN regions were also examined by region-to-region analysis. Next, FC was compared in the PI group before and after 5 weeks of CBTi. The results were thresholded at a false discovery rate (FDR)-corrected cluster level of $q < 0.05$; k_e indicates the cluster size in voxels.

In the subcortical seed region analyses, compared to the GS group, the PI group exhibited stronger FC between the thalamus and prefrontal cortex ($q = 0.031$, $k_e = 101$ for right frontal gyrus and $q = 0.041$, $k_e = 78$ for bilateral frontal poles) and between the pallidum and precuneus ($q = 0.009$, $k_e = 118$), but weaker FC between the pallidum and angular gyrus ($q = 0.006$, $k_e = 113$), the caudate and orbitofrontal cortex ($q = 0.040$, $k_e = 86$), and the hippocampus and fusiform gyrus ($q = 0.029$, $k_e = 100$). In the DMN seed region analyses, compared to the GS group, the PI group exhibited stronger FC between the paracingulate gyrus and fusiform gyrus ($q = 0.006$, $k_e = 130$),

lingual gyrus (q = 0.006, k_e = 121), and the left amygdala (q = 0.028, k_e = 79), and stronger FC between the anterior cingulate cortex and the lingual gyrus (q = 0.045, k_e = 88). However, ROI-to-ROI analysis between DMN structures showed no significant difference in FC in the PI group compared to the GS group.

After CBTi, in the subcortical seed region analyses, the PI group exhibited decreased FC between the thalamus and parietal cortex (q = 0.022, k_e = 61), the putamen and motor cortices (q = 0.034, k_e = 56 for the right superior frontal gyrus and q = 0.034, k_e = 54 for the left supplementary motor area), and the amygdala and lingual gyrus (q = 0.028, k_e = 61), but increased FC between the caudate and supramarginal gyrus (q = 0.038, k_e = 58), the pallidum and orbitofrontal cortex (q < 0.001, k_e = 146), and the hippocampus and frontal/parietal gyri (q =0.002, k_e = 113 for the frontal pole, q =0.047, k_e = 51 for the left supramarginal gyrus, and q =0.047, k_e = 50 for the right paracingulate gyrus). In the DMN seed region analyses, the PI group exhibited decreased FC between the posterior cingulate cortex and occipital cortex (q = 0.033, k_e = 70), between the paracingulate gyrus and occipital cortex (q = 0.022, k_e = 74), between the angular gyrus and fusiform gyrus (q = 0.013, k_e = 76), and between the anterior cingulate cortex and pericentral cortex level (q = 0.034, k_e = 55 for the left precentral gyrus and q = 0.034, k_e = 54 for the left postcentral gyrus), but increased FC between the supramarginal gyrus and precuneus (q = 0.001, k_e = 129). ROI-to-ROI analysis between

DMN structures showed no significant difference in FC after CBTi in the PI group.

The present study found significant FC changes in the subcortical and DMN regions in relation to the whole brain. After CBTi, significant FC changes were observed in the PI group. These findings demonstrate the existence of hyperarousal in PI and the therapeutic effect of CBTi on this, and may provide insight into the neurobiological mechanisms of CBTi.

Keywords: psychophysiological insomnia, insomnia, resting state, functional magnetic resonance imaging, cognitive–behavioral therapy, functional connectivity, subcortical structures, default mode network.

Student Number: 2015-30574

CONTENTS

Abstract ----------i

Contents ----------v

List of Tables ----------vi

List of Figures ----------vii

List of Abbreviations ----------xii

I. Introduction ----------1

II. Methods ----------11

III. Results ----------21

IV. Discussion ----------56

V. Conclusion ----------69

VI. References ----------70

Abstract in Korean----------75

LIST OF TABLES

Table 1. Comparisons of the demographic and clinical variables between the PI and GS groups ----------22

Table 2. Changes in clinical parameters after CBTi in the PI group----------23

Table 3. Significant differences in subcortical FC in the PI group compared to the GS group ----------28

Table 4. Significant differences in DMN FC in the PI group compared to the GS group ----------33

Table 5. Significant differences in subcortical FC in the PI group after CBTi compared to baseline ----------40

Table 6. Significant differences in DMN FC in the PI group after CBTi compared to baseline ----------47

Table 7 Changes in post-CBTi FC of the PI group and comparisons with baseline GS ----------54

LIST OF FIGURES

Figure 1. The subcortical and DMN structures used as seed regions in the present study were predefined by the Harvard-Oxford Atlas ----------19

Figure 2. Compared to GS, stronger FC of the PI group between the right thalamus (seed) and the right frontal gyrus (left) and bilateral frontal poles (right), respectively are shown in coronal, sagittal, and transverse views ----25

Figure 3. Compared to GS, stronger FC of the PI group between the right pallidum (seed) and bilateral precuneus (A) and weaker FC between the right pallidum (seed) and the left angular gyrus (B) are shown in coronal, sagittal, and transverse views ----------26

Figure 4. Compared to GS, weaker FC of the PI group between the right caudate (seed) and right orbitofrontal cortex are shown in coronal, sagittal, and transverse views ----------27

Figure 5. Compared to GS, weaker FC of the PI group between the left hippocampus (seed) and left fusiform gyrus are shown in coronal, sagittal, and transverse views ----------27

Figure 6. Differences in subcortical FC in the PI group compared to the GS group ----------29

Figure 7. Compared to GS, stronger FC of the PI group between the left paracingulate gyrus (seed) and right fusiform gyrus (left), both lingual gyri (right), and left amygdala (below), respectively, are shown in sagittal, coronal, and transverse views ----------31

Figure 8. Compared to GS, stronger FC of the PI group between the anterior cingulate cortex (seed) and right lingual gyrus are shown in coronal, sagittal, and transverse views----------32

Figure 9. Differences in DMN FC in the PI group compared to th GS group -- ----------34

Figure 10. Compared to pre-CBTi, post-CBTi FC of the PI group was increased between the left caudate (seed) and left supramarginal gyrus and shown in coronal, sagittal, and transverse views----------36

Figure 11. Compared to pre-CBTi, post-CBTi FC of the PI group was increased between the left pallidum (seed) and left orbitofrontal cortex and shown in coronal, sagittal, and transverse views----------36

Figure 12. Compared to pre-CBTi, post-CBTi FC of the PI group was increased between the left hippocampus (seed) and left frontal pole (left), left supramarginal gyrus (right), and right paracingulate gyrus (below), respectively, and shown in coronal, sagittal, and transverse views ----------37

Figure 13. Compared to pre-CBTi, post-CBTi FC of the PI group was decreased between the right thalamus (seed) and right superior parietal gyrus and shown in coronal, sagittal, and transverse views----------38

Figure 14. Compared to pre-CBTi, post-CBTi FC of the PI group was decreased between the left amygdala (seed) and left lingual gyrus and shown in coronal, sagittal and transverse views ----------38

Figure 15. Compared to pre-CBTi, post-CBTi FC of the PI group was decreased between the left putamen (seed) and right superior frontal gyrus (left) and left supplementary motor area (right) and shown in coronal, sagittal, and transverse views ----------39

Figure 16. Changes in subcortical post-CBTi FC relative to pre-CBTi FC in the PI group.

a) Areas of significant decreases in post-CBTi FC compared to pre-CBTi FC in the PI group b) Areas of significant increases in post-CBTi FC compared to pre-CBTi FC in the PI group ----------41

Figure 17. Compared to pre-CBTi, post-CBTi FC of the PI group was decreased between the posterior cingulate cortex (seed) and right occipital pole and shown in coronal, sagittal and transverse views ----------43

Figure 18. Compared to pre-CBTi, post-CBTi FC of the PI group was decreased between the left angular gyrus (seed) and right fusiform gyrus and shown in coronal, sagittal and transverse views ----------43

Figure 19. Compared to pre-CBTi, post-CBTi FC of the PI group was decreased between the left paracingulate gyrus (seed) and right lateral occipital gyrus and shown in coronal, sagittal and transverse views----------44

Figure 20. Compared to pre-CBTi, post-CBTi FC of the PI group was decreased between the anterior cingulate gyrus and left precentral gyrus (left) and left postcentral gyrus (right) and shown in coronal, sagittal and transverse views----------45

Figure 21. Compared to pre-CBTi, post-CBTi FC of the PI group was increased between the right anterior supramarginal gyrus and precuneus and shown in coronal, sagittal and transverse views ----------46

Figure 22. Changes in DMN post-CBTi FC relative to pre-CBTi FC in the PI group. a) Areas of significant decreases in post-CBTi FC compared to pre-CBTi FC in the PI group. b) Areas of significant increases in post-CBTi FC compared to pre-CBTi FC in the PI group ----------48

Figure 23. The FC between the left hippocampus and left fusiform gyrus significantly correlated with the pre-CBTi ISI score in the PI group ----------50

Figure 24. The FC between the right pallidum and precuneus significantly correlated with the pre-CBTi PSQI score in the PI group ----------50

Figure 25. The Δ FC between the right thalamus and right superior parietal gyrus significantly correlated with the Δ sleep efficiency (upper) and Δ sleep latency (below), respectively in the PI group ----------52

Figure 26. Changes in the functional connectivity of the pre-CBTi, Post-CBTi, and baseline GS groups are shown. ----------55

Figure 27. A hypothetical illustration of altered subcortical FC (left) and DMN FC (right) with the cortex and the changes after CBTi in patients with PI ----------66

LIST OF ABBREVIATIONS

ACC: anterior cingulate cortex

BDI: Beck Depression Inventory

BG: basal ganglia

BOLD: blood oxygenation level-dependent

CBTi: cognitive–behavioral therapy for insomnia

CNS: central nervous system

DBAS-16: Dysfunctional Beliefs and Attitudes about Sleep scale

DMN: default mode network

EEG: electroencephalography

FC: functional connectivity

FDR: false discovery rate

fMRI: functional magnetic resonance imaging

GABA: γ-aminobutyric acid

GS: good sleepers

IPC: inferior parietal cortex

ICSD-2: International Classification of Sleep Disorders, version 2

ISI: Insomnia Severity Index

MNI: Montreal Neurological Institute

MRI: magnetic resonance imaging

MRS: magnetic resonance spectroscopy

SCID-IV: Structural and Clinical Interview for the DSM-IV

SPECT: single-photon emission computed tomography

PCC: posterior cingulate cortex

PCG: paracingulate cortex

PI: psychophysiological insomnia

PET: position emission tomography

PSG: polysomnography

PSQI: Pittsburgh Sleep Quality Index

ROI: region of interest

SE: sleep efficiency

SL: sleep latency

TIB: time in bed

TST: total sleep time

WASO: wake time after sleep onset

I. INTRODUCTION

1. Insomnia

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 involves 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 (DSM, 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, from ICSD-3 (AASM, 2014), the term PI is notable for encompassing diverse aspects of insomnia pathogenesis.

2. Hyperarousal theory of insomnia

2.1. Spielman's 3-P model for insomnia

Spielman's 3-P model of insomnia uses 3 types of factors comprising psychological and biological aspects—the predisposing, precipitating, and perpetuating factors—to describe the evolution of acute insomnia into chronic insomnia. Predisposing factors are psychological or biological characteristics that increase vulnerability to insomnia, such as female sex and increased level of cortisol, but that are not direct causes of insomnia. Precipitating factors, such as stressful life events, are medical or psychological factors that trigger the development of insomnia. Perpetuating factors are elements that maintain or exacerbate insomnia by producing cognitive distortions (excessive worries, fear of sleeplessness) and maladaptive behaviors (excessive time in bed, napping), which cause insomnia to persist even after the acute precipitating factors have disappeared (Spielman, Yang, & Glovinsky, 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).

2.2. Hyperarousal theory of insomnia

The hyperarousal theory is currently the most widely accepted integrative model of the pathophysiology of PI, based on the Spielman 3-P model (Riemann et al., 2010). The hyperarousal theory postulates that difficulties with initiating or maintaining sleep are due to global increases in cortical, physiological, somatic or emotional arousals across the sleep–wake cycle (Perlis, Giles, Mendelson, Bootzin, & Wyatt, 1997). Increased cognitive or cortical activity is hypothesized to promote enhanced sensory and cognitive information processing, including memory formation during sleep or at sleep onset (Riemann et al., 2010).

2.3. Neurobiological evidence for hyperarousal in insomnia

Recent studies have attempted to clarify the neurobiological basis of insomnia disorder with regard to hyperarousal. The biological evidence for hyperarousal has been studied in terms of numerous physiological markers associated with the peripheral nervous system. Studies of body temperature (Lushington, Dawson, & Lack, 2000), circadian variations in metabolic rate, heart rate (Bonnet & Arand, 1995), and low-frequency power in heart rate variability during sleep (Bonnet & Arand, 1998) have shown differences in

patients with insomnia, which is taken as supportive evidence for physiological hyperarousal.

More direct evidence for hyperarousals has been developed by central nervous system (CNS) studies based on electroencephalography (EEG), magnetic resonance spectroscopy (MRS), and functional imaging modalities such as position emission tomography (PET), single-photon emission computed tomography (SPECT), and functional magnetic resonance imaging (fMRI). In EEG power spectral analysis, higher frequency EEG power, which is a manifestation of brain activation, has been demonstrated during both wake and sleep stages (Freedman, 1986). During the eyes-closed resting-state, higher beta activity has been observed, particularly in the prefrontal, frontal, central, right temporal, and bilateral posterior regions (Colombo et al., 2016). Also, greater alpha and theta waves during deep sleep were demonstrated in insomnia patients suggesting that wakefulness-like brain activity persists even in the deepest sleep stage (Riedner et al., 2016). MRS studies in insomnia patients have focused on γ-aminobutyric acid (GABA), the primary inhibitory neurotransmitter in the CNS, which is crucial in regulating sleep. Positive allosteric modulators of $GABA_A$ receptors, such as benzodiazepine drugs, are effective in increasing sleep. MRS studies have consistently shown lower GABA levels in the parieto-occipital cortex (Morgan et al., 2012) or anterior cingulate cortex (ACC) (Plante, Jensen, Schoerning, & Winkelman, 2012) in insomnia patients. .

Rapidly accumulating neuroimaging studies are producing more

substantial evidence concerning the neurobiological bases of insomnia disorder. One 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 in has been localized in patients with primary insomnia to areas related to cognition and to the default mode network (DMN) (Kay et al., 2016). Structural MRI studies have identified volume changes in the frontal cortex (Altena, Vrenken, Van Der Werf, van den Heuvel, & Van Someren, 2010; Joo et al., 2013; Stoffers et al., 2012; Winkelman et al., 2013) and the hippocampus (Joo, Kim, Suh, & Hong, 2014; Riemann et al., 2007). 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).

2.4. The functional connectivity changes in insomnia

Fuctional connectivity (FC) is the temporal dependence of fluctuations of neuronal activity in anatomically separate brain regions. Insomnia patients have been shown to exhibit alterations in FC during specific cognitive tasks (Altena et al., 2008; Drummond et al., 2013; 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 DMN, that are activated during a resting state (Buckner, Andrews-Hanna, & Schacter, 2008). Resting-state studies may contribute significantly to the field of insomnia research, because the neurophysiology 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 (Y. Li et al., 2014; Nie et al., 2015), sensorimotor functions, and limbic regions (Chen, Chang, Glover, & Gotlib, 2014; Huang et al., 2012; Killgore, Schwab, Kipman, Deldonno, & Weber, 2013), complementing previous physiological and emotional arousal findings in insomnia patients. A recent study found the resting-state FC between the amygdala and rostral ACC 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).

2.5. DMN

The DMN is of particular interest in functional brain studies, because of its implications for internal modes of cognition such as mind wandering, recovery of past memories, planning or projection of future events, and

consideration of the perspectives of other individuals, all of which occur in the absence of external tasks during rest (Buckner et al., 2008). The DMN includes the medial prefrontal cortex, ACC, posterior cingulate cortex, (PCC), paracingulate cortex (PCG), precuneus, inferior parietal cortex (IPC), and hippocampus. The IPC is a multimodal complex that receives somatosensory, visual, and auditory inputs, and is comprised of the angular gyrus and the supramarginal gyrus.

The DMN is suggested to be involved in worry and rumination, which are common symptoms in depressive disorder, and extensive studies of disruptions in the DMN have been conducted in depressive patients. Though both stronger and weaker FC have been found, the majority of studies have demonstrated stronger FC between the DMN structures to be related to higher rumination (Hamilton et al., 2011).

Insomnia patients also worry and ruminate about sleep (cognitive distortions), and altered DMN function is hypothesized to be related to the hyperarousal symptoms of these patients. Activation of the DMN specifically prior to bedtime is thought to contribute to increased rumination and worries concerning sleep, which in turn may hinder the progression from wakefulness to sleep (Marques, Gomes, Clemente, Moutinho dos Santos, & Castelo-Branco, 2015). Insomnia patients also evidence higher levels of activity in the DMN during several sleep stages (Marques et al., 2015). Two prior studies that specifically investigated DMN region-to-region FC in insomnia patients produced conflicting results, however (Nie et al., 2015; Regen et al., 2016).

2.6. Subcortical structures

Recently, the involvement of the BG in emotional and cognitive functioning through its connections with the frontal cortex and thalamus has been highlighted (Arsalidou, Duerden, & Taylor, 2013). In particular, the striatum and pallidum play important roles in emotional processing via input from the amygdala and hippocampus, which produce signals that are then relayed to the thalamus. Interconnected with the prefrontal cortex, the cortico-striato-thalamo-cortical circuit regulates cortical arousal by filtering sensory input from the thalamus (Alexander & Crutcher, 1990). Marked hypoperfusion in the BG was demonstrated by earlier SPECT studies in insomnia patients (M. T. Smith, Perlis, Chengazi, Soeffing, & McCann, 2005) and a recent whole-brain FC analysis showed increased FC among several regions, including the putamen and amygdala (C. 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 have been limited.

2.7. Cognitive-behavioral therapy for insomnia

CBTi aims to reduce the hyperarousal caused by the cognitive distortions and maladaptive behaviors of insomnia patients, which run in a

vicious cycle. Cognitive distortions include unrealistic expectations about sleep and catastrophic thinking about the outcomes of sleepless nights. Maladaptive behaviors such as taking naps to compensate for the sleepless nights or staying in bed excessively are common features of insomnia patients. CBTi targets cognitive distortions and behavioral problems, and effectively reduces insomnia symptoms with long-term results (Morin, Hauri, et al., 1999). The mechanisms by which CBTi works remain unclear but considering that the treatment components consist of enhancing relaxation, removing stimuli from the sleep environment, and aligning the sleep drive for the circadian phase to its lowest wake drive, reductions in hyperarousal appear to be significant in the therapeutic process (Kay & Buysse, 2017). 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). However, to date, no studies have explored the effects of CBTi on the intrinsic resting-state FC of insomnia patients.

3. Study objectives

The hyperarousal theory of insomnia encompasses many structures in various overlapping networks. It is the most widely accepted model of pathophysiology for PI, which is a specific subtype of insomnia characterized by heightened physiological, emotional, cognitive arousals in association with

distorted cognition and maladaptive behavioral problems that feedback in a vicious cycle. According to the definition of PI, patients with PI can be regarded as a homogeneous group, with hyperarousal being the main factor in the pathogenesis of their insomnia symptoms. The present study aimed to reveal the neurobiological correlates of hyperarousal as a cause of insomnia.

Specifically, the present study sought to verify the hypothesis that patients with PI would exhibit altered FC in subcortical structures in relation to the cortex and other subcortical regions implicated in the cortico-striato-thalamo-cortical circuit and the limbic system, which are known to be associated with sensory, emotional, cortical, and cognitive arousal and regulation. In addition, the DMN FC in PI patients was explored based on the hypothesis that increased DMN FC is associated with rumination, a cardinal feature of cognitive distortions in PI. Furthermore, the present study hypothesized the effectiveness of CBTi to be related to the recovery of the altered FC associated with hyperarousal.

The primary aim of the present study was to determine whether patients with PI would exhibit different resting-state FC in subcortical structures and the DMN and among DMN regions. The secondary purpose of the present study was to evaluate the therapeutic effects of CBTi on resting-state FC in insomnia patients. 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.

II. METHODS

1. Participants

This study was conducted from May 2014 to November 2015, and 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, in the same study period, 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 less than 6 months, 6) shift-work employment, 7) borderline or antisocial personality disorder, 8) any contraindications for MRI scans, or 9) 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, nocturnal polysomnography (PSG; Profusion PSG3; Compumedics, Abbotsford, VIC Australia) was performed in the laboratory. The 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), 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. Baseline clinical assessments of sleep

All participants completed several sleep-related questionnaires, including the Pittsburgh Sleep Quality Index (PSQI), Dysfunctional Beliefs and Attitudes about Sleep Scale (DBAS-16), and the Beck Depression Inventory (BDI). The PI group also completed the Insomnia Severity Index (ISI). The PSQI is a self-report questionnaire assessing overall sleep quality including, but not limited to, insomnia (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). The ISI is a self-report questionnaire that rates distress related to insomnia and sleep quality (Bastien, Vallieres, & Morin, 2001). The DBAS-16 is a self-report questionnaire that assesses sleep-related cognitive dysfunction, such as unrealistic expectations, faulty beliefs, and excessive worry regarding sleep (Morin, Vallieres, & Ivers, 2007). The BDI (Beck, Steer, & Brown, 1996) was administered to control for and exclude the risk of depressive symptoms, which may independently affect imaging findings.

3. CBTi

Five sessions of individual CBTi were delivered face-to-face by two certified psychologists. The sessions were approximately 90 min long and were conducted weekly. Any medications that could potentially affect sleep were prohibited during the entire study procedure. A modified CBTi protocol (Edinger & Carney, 2007) that included behavioral, cognitive, and educational interventions was used in the present study. Patients were asked to go to bed only when sleepy, to get out of bed whenever they were unable to fall asleep, to wake up at the same time every morning, and to limit naps. They were also asked to restrict their sleep time according to their individual time-in-bed (TIB) window, which was prescribed based on the sleep efficiency (SE) during the previous week. Initially, the TIB window was 30 minutes more than total sleep time (TST). In the next session, the TIB window was titrated based on the SE of the previous week. If the SE in the sleep diary (described below) was <85%, the prescribed TIB was decreased by 15 minutes. If the SE was over 90%, TIB was increased by 15 minutes. The sleep diary was collected for at least 7 days to provide baseline data before CBTi was initiated. Sleep diaries were collected continuously for each CBTi. Additionally, cognitive interventions were performed to address dysfunctional thoughts and beliefs.

To track changes in sleep over time, the participants kept a sleep

diary that recorded actual TIB, sleep latency (SL), TST, wake time after sleep onset (WASO), and SE. In the PI group, the ISI, PSQI, DBAS-16, and BDI were also administered after the 5-week CBTi period (post-CBTi). For each questionnaire and for the sleep parameters assessed using the sleep diaries, the post-CBTi sleep scores were subtracted from the pre-CBTi scores (Δ ISI, Δ PSQI, Δ DBAS-16, Δ BDI, Δ TST, Δ SL, Δ WASO, and Δ SE, respectively).

4. MRI data acquisition

Resting-state fMRI data were acquired with a 3T whole-body Siemens Tim Trio scanner (Siemens AG; Erlangen, Germany) using a 12-channel birdcage head coil and interleaved T2*- weighted echo-planar imaging with the following characteristics: TR = 3500 ms, TE = 30 ms, flip angle = 90°, slice thickness = 3.5 mm, in-plane resolution = 1.9 × 1.9 mm, no gap, 35 axial slices, FOV = 240 mm, 116 volumes, and a scan duration of 6 min and 58 sec for each subject. Following the fMRI scanning, high-resolution structural images were acquired with a T1-weighted 3D gradient echo pulse sequence with magnetization-prepared rapid gradient-echo sequencing using the following characteristics: TR = 1,670 ms, TE = 1.89 ms, flip angle = 9°, slice thickness = 1.0 mm, in-plane resolution = 1.0 × 1.0 mm, and FOV = 250 mm).

4.1. Data pre-processing

Pre-processing of the resting-state fMRI data was done using SPM12 (Wellcome Trust Centre for Neuroimaging; London, UK), and all images were checked to ensure that the data were not corrupted by artifacts. The DICOM data was converted to the NIfTi format, head motion was corrected by realigning the data to the first image, and differences in slice timing were corrected. The functional images were co-registered with anatomical images and then spatially normalized to the Montreal Neurological Institute (MNI) space using a transformation matrix derived from the T1 anatomical image segmentation. The resulting data were then resliced to 3 × 3 × 3 mm. Finally, the data were spatially smoothed using a Gaussian kernel with full-width at half-maximum of 6 mm.

4.2. FC analysis

Resting-state FC analyses were performed using CONN functional connectivity toolbox v16b (http://www.nitrc.org/projects/conn) (Whitfield-Gabrieli & Nieto-Castanon, 2012). All data were band-pass filtered (0.008–0.09 Hz), and physiological and other spurious noise sources in the blood oxygenation level-dependent (BOLD) signal were removed using the anatomical component-based noise correction (CompCor) strategy

implemented in CONN (Behzadi, Restom, Liau, & Liu, 2007). White matter signals, cerebrospinal fluid signals, and six motion-correction parameters obtained from the pre-processing procedure were also removed. The seed-to-voxel analysis was performed with 12 subcortical seed regions (the thalamus, caudate, putamen, pallidum, amygdala, and hippocampus for both hemispheres) and 14 DMN seed regions (ACC, PCC, PCG, precuneus, anterior supramarginal gyrus, posterior supramarginal gyrus, angular gyrus for both hemispheres) that were predefined by the Harvard-Oxford atlas (FSL, [fMRIB, Oxford, UK]) (S. M. Smith et al., 2004) (Fig. 1). The mean time series for each seed region was calculated and then correlated with the time courses of all other voxels in the brain for each participant. Using the DMN seed regions, region of interest (ROI)-to-ROI analyses were also performed among the 7 DMN substructures for each hemisphere for every participant, and pairwise correlation coefficients were extracted between the mean time series of the 14 DMN ROIs. Pearson's correlation coefficients were converted to normally distributed scores using the Fisher *r*-to-*z* transformation. Group-level analyses for a second-level general linear model were carried out using independent-sample *t*-tests between the *z*–scores of the PI and GS groups and paired *t*-tests between the pre-and post-CBTi groups. The reported results of the seed-to-voxel correlation analyses were thresholded at a false discovery rate (FDR)-corrected cluster level of $q < 0.05$ and an uncorrected peak level of $P < 0.001$ to correct for false positives. The reported results of the ROI-to-ROI analyses in DMN substructures were thresholded at a false discovery rate

(FDR)-corrected cluster level of $q < 0.05$.

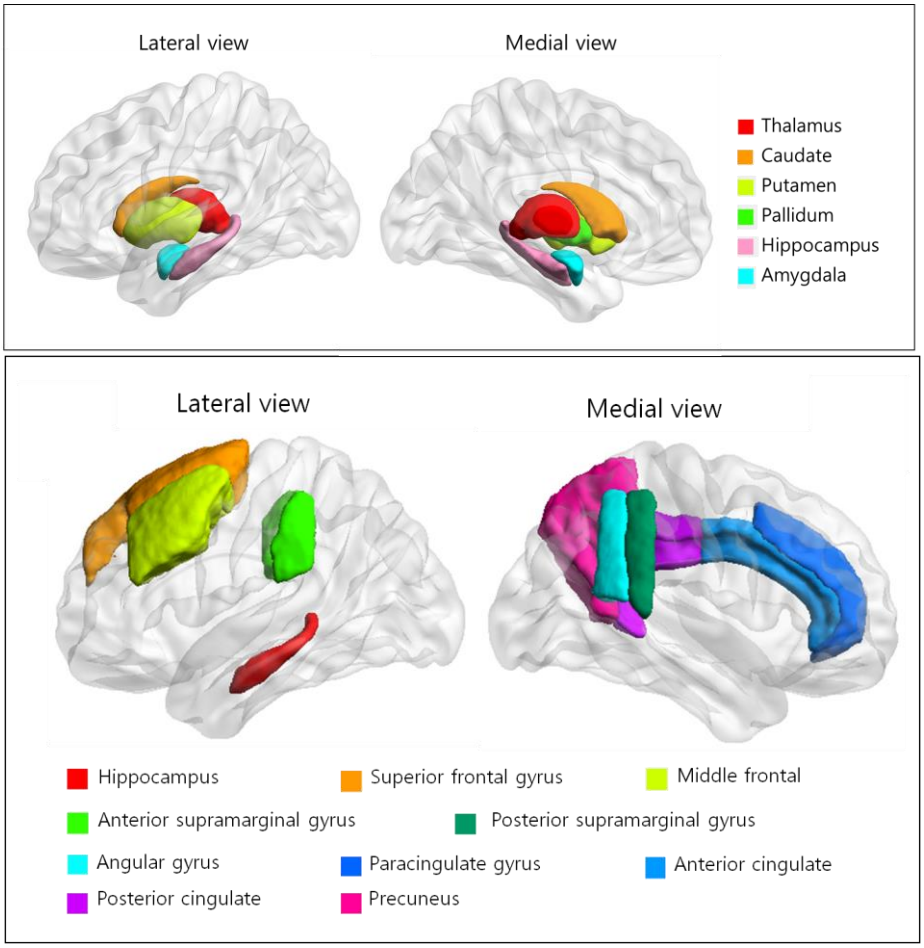

Figure 1. The subcortical (upper) and DMN structures (below) seed regions in the present study were predefined by the Harvard-Oxford Atlas. DMN, default mode network.

5. Statistical analyses

First, the baseline demographic and clinical data were compared using independent *t*-tests for continuous values and Fisher's exact test for categorical values. The pre-CBTi and post-CBTi clinical data were compared using paired *t*-tests. Next, the *z*-scores of the baseline FC maps for the PI and GS groups were compared using independent *t*-tests, with age, sex, and BDI scores with the insomnia-related items excluded ([insomnia excluded]-BDI) as nuisance covariates. Additionally, the *z*-scores of the FC maps from the PI group before and after CBTi were compared using paired *t*-tests with Δ (insomnia excluded)-BDI score as a nuisance covariate. Third, correlations of baseline sleep questionnaire scores and PSG parameters with the pre-CBTi *z*-scores, and the correlations of Δ sleep questionnaire scores with the post-CBTi *z*-scores subtracted from the pre-CBTi *z*-scores (i.e., Δ *z*-scores) in the PI group were examined using Pearson's correlation analyses. Fourth, the mean *z*-scores of the areas that had shown significant FC differences between the baseline GS and PI groups were compared between the post-CBTi PI group and baseline GS group using independent *t*-tests, and compared between the pre- and post-CBTi PI groups using paired *t*-tests. The data were analyzed using SPSS for Windows software (v21; SPSS, Inc., Chicago, IL, USA), and *P*-values <0.05 were considered to indicate statistical significance. For multiple comparisons, *P*-values <0.016 were considered significant.

III. RESULTS

1. Demographic and clinical data

Table 1 shows the demographic characteristics and PSG sleep parameters of the PI and GS groups. The two groups did not significantly differ in terms of age, sex distribution, or BDI scores. Compared to the GS group, the PI group had significantly higher scores on PSQI and DBAS, shorter TST, and greater WASO. In the PI group, scores on all post-CBTi sleep questionnaires were significantly lower than the pre-CBTi scores. Additionally, the post-CBTi sleep parameters assessed by sleep diaries showed significant improvement in WASO and SL compared to pre-CBTi levels (Table 2).

Table 1. Comparisons of the demographic and clinical variables between the PI and GS groups.

	PI (n = 13)	GS (n = 18)	*P*
Age	51.0 ± 10.2	42.7 ± 12.3	0.056
Sex[a]	3M, 10F	4M, 14F	0.642
PSQI[†,b]			
Median (25–75 percentile)	13 (10-16)	4 (3-6)	< 0.001
Cutoff value ≥ 5, n	13 (100%)	8 (44.6%)	
DBAS[†,b]			
Median (25–75 percentile)	98 (77.5-98.0)	62.5 (45.5-70.25)	0.001
BDI[b,c]			
Median (25–75 percentile)	5 (2-10)	3.5 (0.75-8.25)	0.440
Cutoff value ≥ 14, n	2 (15.4%)	2 (11.2%)	
Nocturnal PSG			
TIB (min)	477.9 ± 25.3	486.1 ± 11.9	0.110
TST (min)[*]	407.1 ± 49.7	443.7 ± 19.1	0.024
SE (%)	85.8 ± 9.0	91.3 ± 3.9	0.054
SL (min)	11.8 ± 12.2	11.5 ± 10.3	0.932
WASO (min)[*]	55.8 ± 38.0	31.2 ± 16.9	0.044
REML (min)	90.5 ± 40.9	92.8 ± 25.0	0.851
N1 (%)	13.8 ± 5.3	10.3 ± 5.5	0.082
N2 (%)	58.1 ± 9.4	61.0 ± 7.0	0.325
N3 (%)	5.0 ± 4.7	6.5 ± 5.8	0.435
REM (%)	23.1 ± 7.4	21.8 ± 3.8	0.516

Mean ± standard deviation; Independent *t*-test; [a] Fisher's exact test; [b]Mann-Whitney test; [c]Insomnia-excluded BDI scores; [*] $P < 0.05$; [†]$P < 0.001$. Abbreviations: PI, psychophysiological insomnia; GS, good sleepers; PSQI, Pittsburgh Sleep Quality Index; DBAS, Dysfunctional Beliefs and Attitudes about Sleep; BDI, Beck Depression Inventory; PSG, polysomnography; TIB, time in bed, TST, total sleep time; SE, sleep efficiency; SL, sleep latency; WASO, wake after sleep onset; REM, rapid eye movement sleep; REML, REM latency

Table 2. Changes in clinical parameters after CBTi in the PI group (n = 13).

	Pre-CBTi	Post-CBTi	*P*
ISI[*]			
Median (25–75 percentile)	14 (10.5-17.5)	7 (1.5-12.0)	0.005
Cutoff value ≥ 8, n	13 (100%)	6 (46.2%)	
Cutoff value ≥ 15, n	6 (46.2)	1 (7.7%)	
PSQI[†,a]			
Median (25–75 percentile)	13 (10-16)	6 (5-9)	< 0.001
Cutoff value ≥ 5, n	13 (100%)	12 (92.3%)	
DBAS[†,a]			
Median (25–75 percentile)	98 (77.5-98.0)	34 (27.0-73.5)	< 0.001
BDI[a,b]			
Median (25–75 percentile)	5 (2-10)	4 (0.5-8.0)	0.178
Cutoff value ≥ 14, n	2 (15.4%)	2 (15.4%)	
Sleep diary			
TST (hr)	5.6 ± 1.2	5.9 ± 1.9	0.666
SL (min)[*]	39.3 ± 34.7	14.0 ± 16.2	0.003
WASO (min)[*]	68.2 ± 50.8	30.8 ± 33.9	0.008
SE (%)	75.7 ± 13.8	82.1 ± 26.5	0.436

Mean ± standard deviation; Paired *t*-test; [a]Wilcoxon's signed-ranks test; [b]Insomnia-excluded BDI scores; [*] $P < 0.05$; [†]$P < 0.001$. Abbreviations: PI, psychophysiological insomnia; GS, good sleepers; ISI, Insomnia Severity Index; PSQI, Pittsburgh Sleep Quality Index; DBAS, Dysfunctional Beliefs and Attitudes about Sleep; BDI, Beck Depression Inventory; TST, total sleep time; SL, sleep latency; SE, sleep efficiency; WASO, wake after sleep onset.

2. Between-group FC findings

2.1. Subcortical seed regions in relation to the whole brain voxels

Compared to the GS group, the PI group exhibited stronger FC between the right thalamus and right superior frontal gyrus and bilateral frontal poles (Fig. 2) and between the right pallidum and bilateral precuneus (Fig. 3). FC was significantly weaker between the right caudate and right orbitofrontal cortex (OFC) (Fig. 4), the right pallidum and left angular gyrus (Fig. 3), and the left hippocampus and left fusiform gyrus (Fig. 5). FC between the putamen and amygdala and other brain regions was not significantly different. Subcortical FC comparisons between the GS and the PI groups are summarized in table 3 and figure 6.

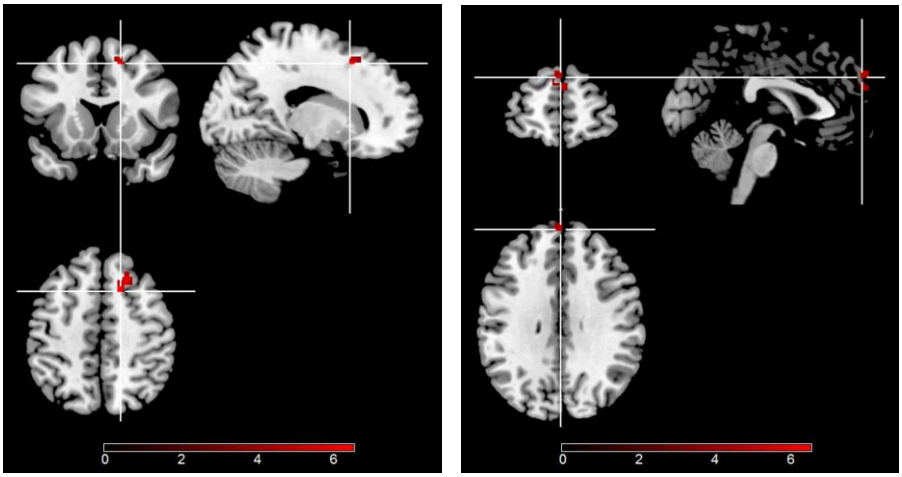

Figure 2. Compared to GS, stronger FC of the PI group between the right thalamus (seed) and the right frontal gyrus (left) and bilateral frontal poles (right), respectively are shown in coronal, sagittal, and transverse views.

(Left) Red areas represent (16, 16, 50) in MNI coordinates (x, y, z), FDR-corrected cluster-level q = 0.031, *ke* = 101, uncorrected peak-level P <0.001, T = 5.44. (Right) Red areas represent (0, 58, 32) in MNI coordinates (x, y, z), FDR-corrected cluster-level q = 0.041, *ke* = 78, uncorrected peak-level P <0.001, T = 4.23. GS, good sleepers; PI, psychophysiological insomnia; FC, functional connectivity; MNI, Montreal Neurological Institute; FDR, false discovery rate; *ke* indicates the cluster size in voxels.

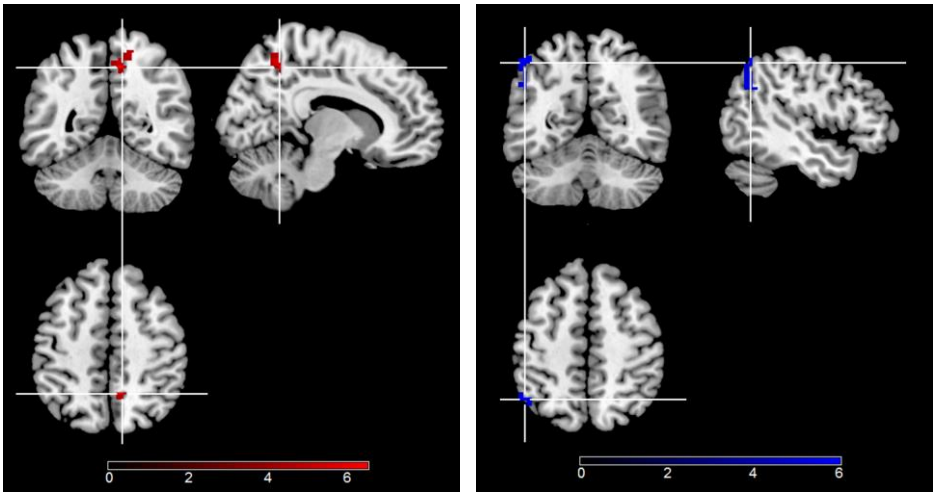

Figure 3. Compared to GS, stronger FC of the PI group between the right pallidum (seed) and bilateral precuneus (left) and weaker FC between the right pallidum (seed) and the left angular gyrus (right) are shown in coronal, sagittal, and transverse views.

(Left) Red areas represent (10, -52, 50) in MNI coordinates (x, y, z), FDR-corrected cluster-level q = 0.009, *ke* = 118, uncorrected peak-level P <0.001, T = 5.52. (Right) Blue areas represent (-48, -58, 52) in MNI coordinates (x, y, z), FDR-corrected cluster-level q = 0.006, *ke* = 113, uncorrected peak-level P <0.001, T = 4.54. GS, good sleepers; PI, psychophysiological insomnia; FC, functional connectivity; MNI, Montreal Neurological Institute; FDR, false discovery rate; *ke* indicates the cluster size in voxels.

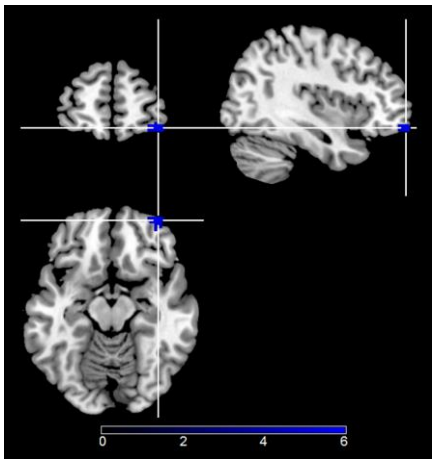

Figure 4. Compared to GS, weaker FC of the PI group between the right caudate (seed) and right orbitofrontal cortex are shown in coronal, sagittal, and transverse views.

Blue areas represent (42, 58, -16) in MNI coordinates (x, y, z), FDR-corrected cluster-level q = 0.040, *ke* = 86, uncorrected peak-level P <0.001, T = 4.84. GS, good sleepers; PI, psychophysiological insomnia; FC, functional connectivity; MNI, Montreal Neurological Institute; FDR, false discovery rate; *ke* indicates the cluster size in voxels.

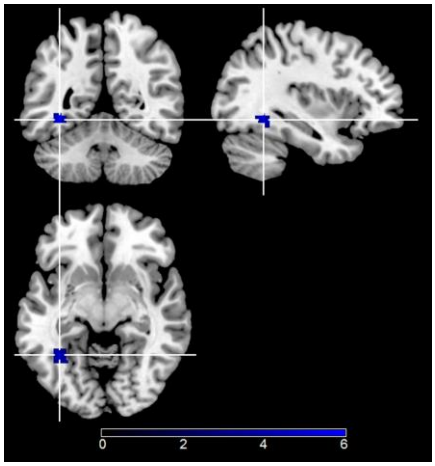

Figure 5. Compared to GS, weaker FC of the PI group between the left hippocampus (seed) and left fusiform gyrus are shown in coronal, sagittal, and transverse views.

Blue areas represent (-36, -52, -8) in MNI coordinates (x, y, z), FDR-corrected cluster-level q = 0.029, *ke* = 100, uncorrected peak-level P <0.001, T = 6.47. GS, good sleepers; PI, psychophysiological insomnia; FC, functional connectivity; MNI, Montreal Neurological Institute; FDR, false discovery rate; *ke* indicates the cluster size in voxels.

Table 3. Significant differences in subcortical FC in the PI group compared to the GS group.

Seed	Brain region	FC increased Vs. decreased	MNI coordinate (x, y, z)	k_e
Rt. thalamus	Rt. superior frontal gyrus	Increased	16, 16, 50	101
	Bilateral frontal poles	Increased	0, 58, 32	73
Rt. caudate	Rt. orbitofrontal cortex	Decreased	42, 58, -16	86
Rt. pallidum	Bilateral precuneus	Increased	10, -52, 50	118
	Lt. angular gyrus	Decreased	-48, -58, 52	113
Lt. hippocampus	Lt. fusiform gyrus	Decreased	-36, -52, -8	100

The threshold was set at an uncorrected peak-level of $P < 0.001$ and a whole-brain, false discovery rate-corrected cluster level of $q < 0.05$. FC, functional connectivity; MNI, Montreal Neurological Institute; Rt., right; Lt., left. k_e indicates the cluster size in voxels.

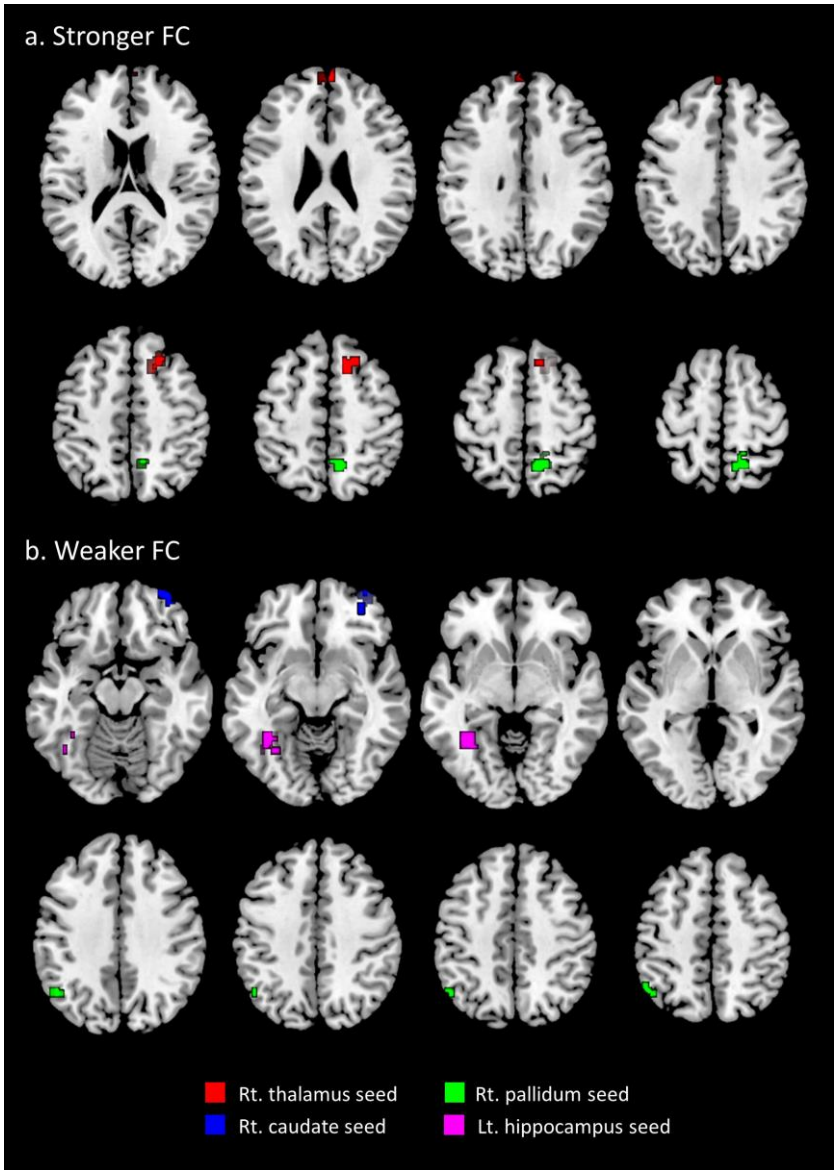

Figure 6. Differences in subcortical FC in the PI group compared to the GS group. a) Areas where FC was stronger in the PI group compared to the GS group. Red areas: right superior frontal gyrus and frontal poles; green area: precuneus. b) Areas where FC was weaker in the PI group compared to the GS group. Blue areas: right orbitofrontal cortex; green area: left angular gyrus; pink area: left fusiform. The colored areas indicate differences in FC in relation to the same-colored seed region. Abbreviations: FC, functional connectivity; PI, psychophysiological insomnia; GS, good sleepers; Rt., right; Lt., left. Thresholded at a whole-brain false discovery rate-corrected cluster level of $q < 0.05$ and an uncorrected peak level of $P < 0.001$.

2.2. DMN seed regions in relation to the whole brain voxels and ROI to ROI analysis

Compared to the GS group, the PI group exhibited stronger FC between the left PCG and right fusiform gyrus, both lingual gyri, and left amygdala, respectively (Fig. 7). Also, the PI group exhibited stronger FC between the ACC and right lingual gyrus compared to the GS group (Fig. 8). The precuneus, PCC, IPL cortical seed regions did not show FC differences in relation to the whole brain voxel between the PI and GS groups. As stated earlier, the HC had weaker FC with the fusiform gyrus in the PI group compared to the GS group. DMN FC comparisons between the GS and the PI groups are summarized in table 4 and figure 9. ROI-to-ROI analysis among DMN substructures did not show significant results between the GS and PI groups.

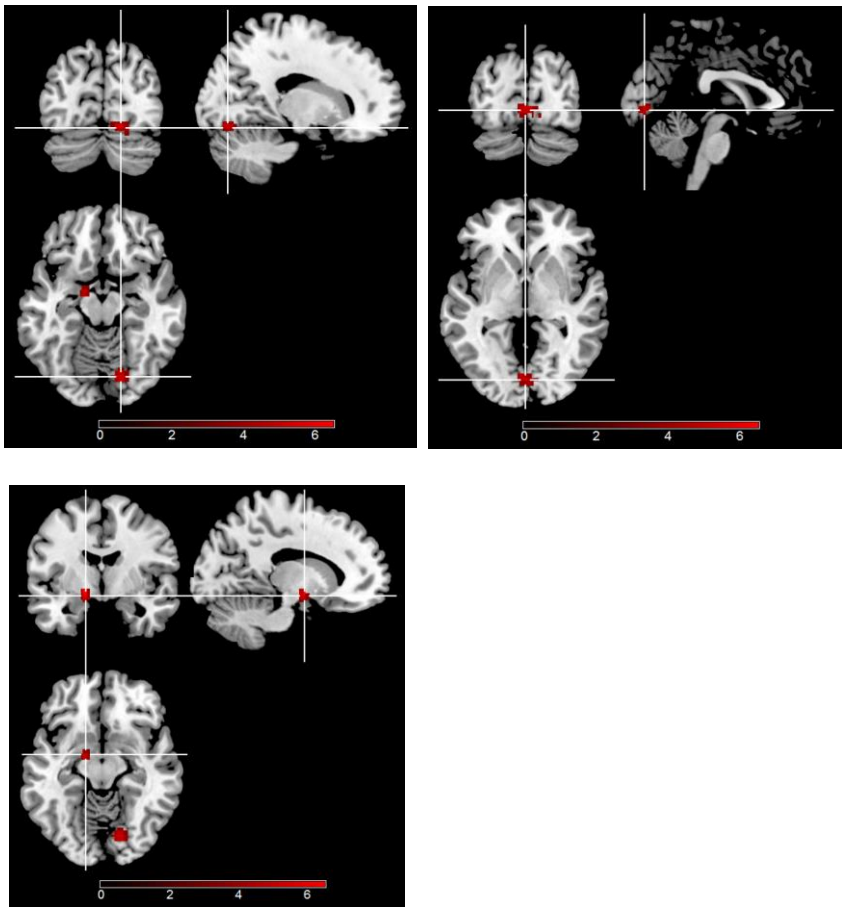

Figure 7. Compared to GS, stronger FC of the PI group between the left paracingulate gyrus (seed) and right fusiform gyrus (left), both lingual gyri (right), and left amygdala (below), respectively, are shown in sagittal, coronal, and transverse views.

(Left) Red areas represent (16, -76, -14) in MNI coordinates (x, y, z), FDR-corrected cluster-level q = 0.006, *ke* = 130, uncorrected peak-level P <0.001, T = 5.85. (Right) Red areas represent (0, -82, -2) in MNI coordinates (x, y, z), FDR-corrected cluster-level q = 0.006, *ke* = 121, uncorrected peak-level P <0.001, T = 4.42. (Below) Red areas represent (-14, -4, -8) in MNI coordinates (x, y, z), FDR-corrected cluster-level q = 0.028, *ke* = 79, uncorrected peak-level P <0.001, T = 6.91. GS, good sleepers; PI, psychophysiological insomnia; FC, functional connectivity; MNI, Montreal Neurological Institute, FDR, false discovery rate; *ke* indicates the cluster size in voxels.

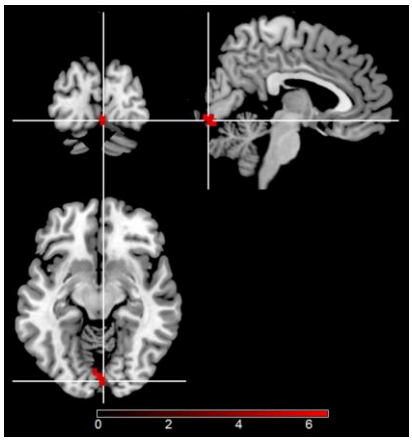

Figure 8. Compared to GS, stronger FC of the PI group between the anterior cingulate cortex (seed) and right lingual gyrus are shown in coronal, sagittal, and transverse views.

Red areas represent (4, -88, -10) in MNI coordinates (x, y, z), FDR-corrected cluster-level q = 0.045, *ke* = 88, uncorrected peak-level P <0.001, T = 4.55. GS, good sleepers; PI, psychophysiological insomnia; FC, functional connectivity; MNI, Montreal Neurological Institute, FDR, false discovery rate; *ke* indicates the cluster size in voxels.

Table 4. Significant differences in DMN FC in the PI group compared to the GS group.

Seed	Brain region	FC increased Vs. decreased	MNI coordinate (x, y, z)	k_e
Lt. paracingulate gyrus	Rt. fusiform gyrus	Increased	16, -76, -14	130
	Both lingual gyri	Increased	0, -82, -2	121
	Lt. Amygdala	Increased	-14, -4, -8	79
Anterior cingulate cortex	Rt. lingual gyrus	Increased	4, -88, -10	88

The threshold was set at an uncorrected peak-level of $P < 0.001$ and a whole-brain, false discovery rate-corrected cluster level of $q < 0.05$. DMN: default mode network, FC: functional connectivity; MNI: Montreal Neurological Institute; Rt.: right, Lt.: left; k_e indicates the cluster size in voxels.

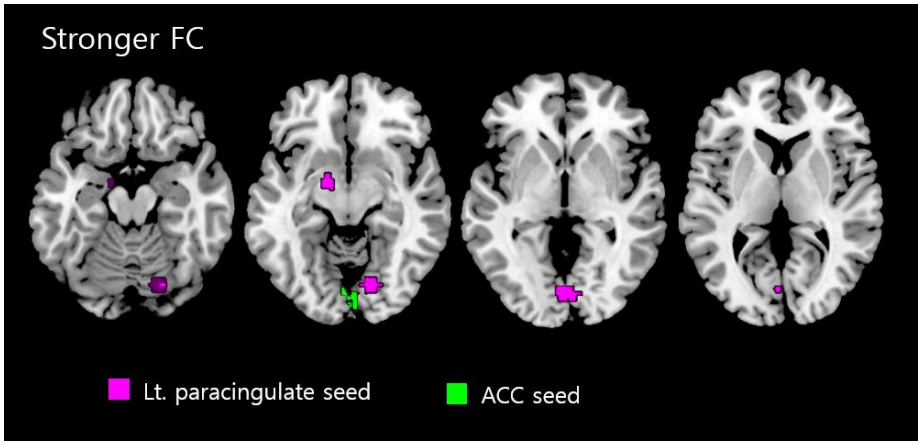

Figure 9. Differences in DMN FC in the PI group compared to the GS group. Areas where FC was stronger in the PI group compared to the GS group.

Pink areas: right fusiform gyrus, both lingyri, left amygdala; green areas: right lingual gyrus. The colored areas indicate differences in FC in relation to the same-colored seed region. Abbreviations: DMN, default mode network; FC, functional connectivity; PI, psychophysiological insomnia; GS, good sleepers; Lt., left. Thresholded at a whole-brain false discovery rate-corrected cluster level of $q < 0.05$ and an uncorrected peak level of $P < 0.001$.

3. FC in the PI group before and after CBTi

3.1. Subcortical seed regions in relation to the whole brain voxels

Compared to pre-CBTi FC, post-CBTi FC significantly increased between the left caudate and left supramarginal gyrus (Fig. 10), between the left pallidum and left OFC (Fig. 11), and between the left hippocampus and the left frontal pole, left supramarginal gyrus, and right paracingulate gyrus (Fig. 12). FC significantly decreased between the right thalamus and right superior parietal gyrus (Fig. 13), between the left amygdala and left lingual gyrus (Fig. 14), and between the left putamen and the right superior frontal gyrus and left supplementary motor area (Fig. 15). The changes in subcortical FC after CBTi of the PI group are summarized in table 5 and figure 16.

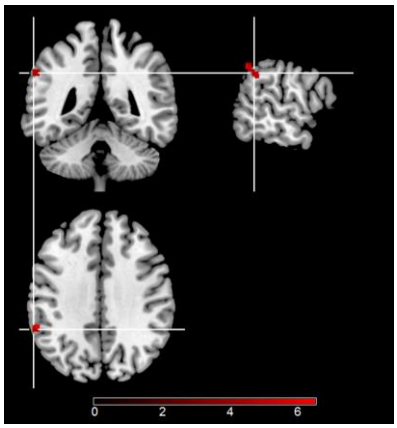

Figure 10. Compared to pre-CBTi, post-CBTi FC of the PI group was increased between the left caudate (seed) and left supramarginal gyrus and shown in coronal, sagittal, and transverse views.

Red areas represent (-60, -52, 40) in MNI coordinates (x, y, z), FDR-corrected cluster-level q = 0.038, *ke* = 58, uncorrected peak-level P =0.001, T = 6.33. CBTi, cognitive-behavioral therapy for insomnia; PI, psychophysiological insomnia; FC, functional connectivity; MNI, Montreal Neurological Institute, FDR, false discovery rate; *ke* indicates the cluster size in voxels.

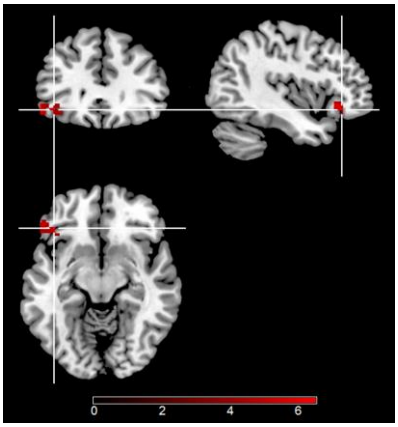

Figure 11. Compared to pre-CBTi, post-CBTi FC of the PI group was increased between the left pallidum (seed) and left orbitofrontal cortex and shown in coronal, sagittal, and transverse views.

Red areas represent (-42, 32, -10) in MNI coordinates (x, y, z), FDR-corrected cluster-level q < 0.001, *ke* = 146, uncorrected peak-level P =0.001, T = 6.67. CBTi, cognitive-behavioral therapy for insomnia; PI, psychophysiological insomnia; FC, functional connectivity; MNI, Montreal Neurological Institute, FDR, false discovery rate; *ke* indicates the cluster size in voxels.

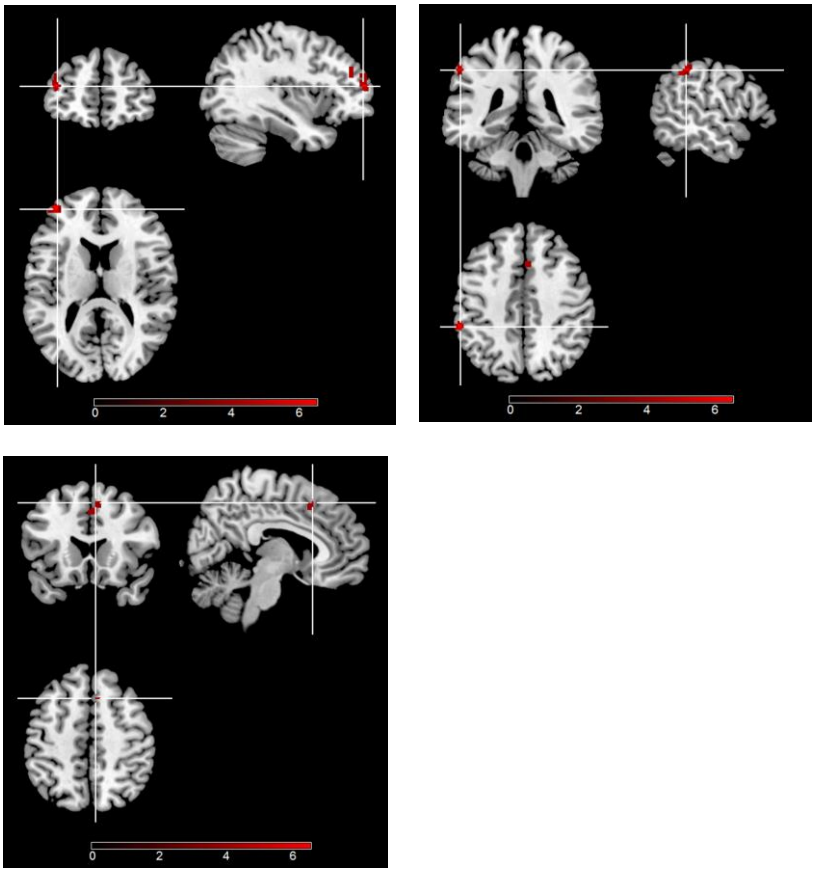

Figure 12. Compared to pre-CBTi, post-CBTi FC of the PI group was increased between the left hippocampus (seed) and left frontal pole (left), left supramarginal gyrus (right), and right paracingulate gyrus (below), respectively, and shown in coronal, sagittal, and transverse views. (Left) Red areas represent (-38, 52, 14) in MNI coordinates (x, y, z), FDR-corrected cluster-level q =0.002, *ke* = 113, uncorrected peak-level P <0.001, T = 7.01. (Right) Red areas represent (-56, -38, 44) in MNI coordinates (x, y, z), FDR-corrected cluster-level q =0.047, *ke* = 51, uncorrected peak-level P <0.001, T = 6.77. (Below) Red areas represent (6, 20, 50) in MNI coordinates (x, y, z), FDR-corrected cluster-level q =0.047, *ke* = 50, uncorrected peak-level P <0.001, T = 4.83. CBTi, cognitive-behavioral therapy for insomnia; PI, psychophysiological insomnia; FC, functional connectivity; MNI, Montreal Neurological Institute, FDR, false discovery rate; *ke* indicates the cluster size in voxels.

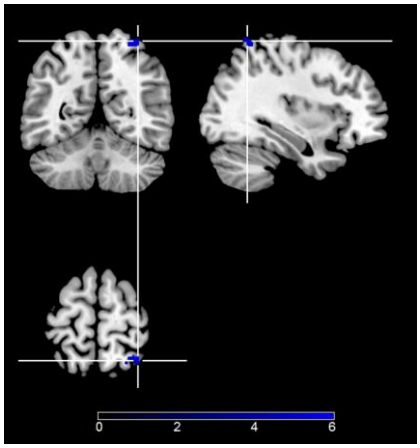

Figure 13. Compared to pre-CBTi, post-CBTi FC of the PI group was decreased between the right thalamus (seed) and right superior parietal gyrus and shown in coronal, sagittal, and transverse views.

Blue areas represent (34, -56, 68) in MNI coordinates (x, y, z), FDR-corrected cluster-level q = 0.022, *ke* = 61, uncorrected peak-level P <0.001, T = 5.44. CBTi, cognitive-behavioral therapy for insomnia; PI, psychophysiological insomnia; FC, functional connectivity; MNI, Montreal Neurological Institute, FDR, false discovery rate; *ke* indicates the cluster size in voxels.

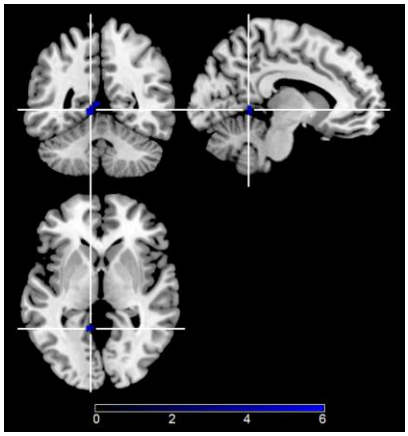

Figure 14. Compared to pre-CBTi, post-CBTi FC of the PI group was decreased between the left amygdala (seed) and left lingual gyrus and shown in coronal, sagittal and transverse views.

Blue areas represent (-12, -50, -4) by the MNI coordinate (x, y, z), FDR-corrected cluster-level q = 0.028, *ke* = 61, uncorrected peak-level P <0.001, T = 5.83. CBTi, cognitive-behavioral therapy for insomnia; PI, psychophysiological insomnia; FC, functional connectivity; MNI, Montreal Neurological Institute, FDR, false discovery rate; *ke* indicates the cluster size in voxels

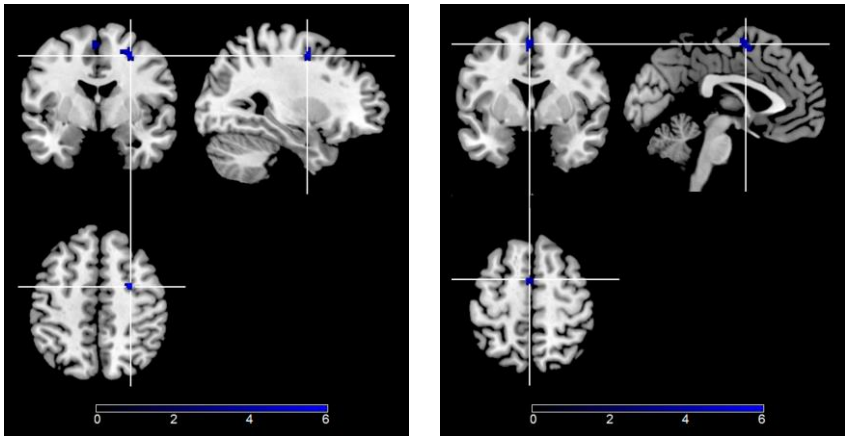

Figure 15. Compared to pre-CBTi, post-CBTi FC of the PI group was decreased between the left putamen (seed) and right superior frontal gyrus (left) and left supplementary motor area (right) and shown in coronal, sagittal, and transverse views.

(Left) Blue areas represent (-28, -2, 50) in MNI coordinates (x, y, z), FDR-corrected cluster-level q = 0.034, *ke* = 56, uncorrected peak-level P <0.001, T = 7.54. (Right) Blue areas represent (-2, 2, 58) in MNI coordinates (x, y, z), FDR-corrected cluster-level q = 0.034, *ke* = 54, uncorrected peak-level P <0.001, T = 6.18. CBTi, cognitive-behavioral therapy for insomnia; PI, psychophysiological insomnia; FC, functional connectivity; MNI, Montreal Neurological Institute, FDR, false discovery rate; *ke* indicates the cluster size in voxels.

Table 5. Significant differences in subcortical FC in the PI group after CBTi compared to baseline.

Seed	Brain region	FC increased or decreased	MNI coordinate (x, y, z)	k_e
Rt. thalamus	Rt. superior parietal gyrus	Decreased	34, -56, 68	61
Lt. caudate	Lt. supramarginal gyrus	Increased	-60, -52, 40	58
Lt. putamen	Rt. superior frontal gyrus	Decreased	28, -2, 50	56
	Lt. supplementary motor area	Decreased	-2, 2, 58	54
Lt. pallidum	Lt. orbitofrontal cortex	Increased	-42, 32, -10	146
Lt. hippocampus	Lt. frontal pole	Increased	-38, 52, 14	113
	Lt. supramarginal gyrus	Increased	-56, -38, 44	51
	Rt. Paracingulate	Increased	6, 20, 50	50
Lt. amygdala	Lt. lingual gyrus	Decreased	-12, -50, -4	61

The threshold was set at an uncorrected peak-level of $P < 0.001$ and a whole-brain, false discovery rate-corrected cluster level of $q < 0.05$. CBTi, cognitive behavioral therapy for insomnia; FC, functional connectivity; MNI, Montreal Neurological Institute; Rt., right; Lt., left; k_e indicates the cluster size in voxels.

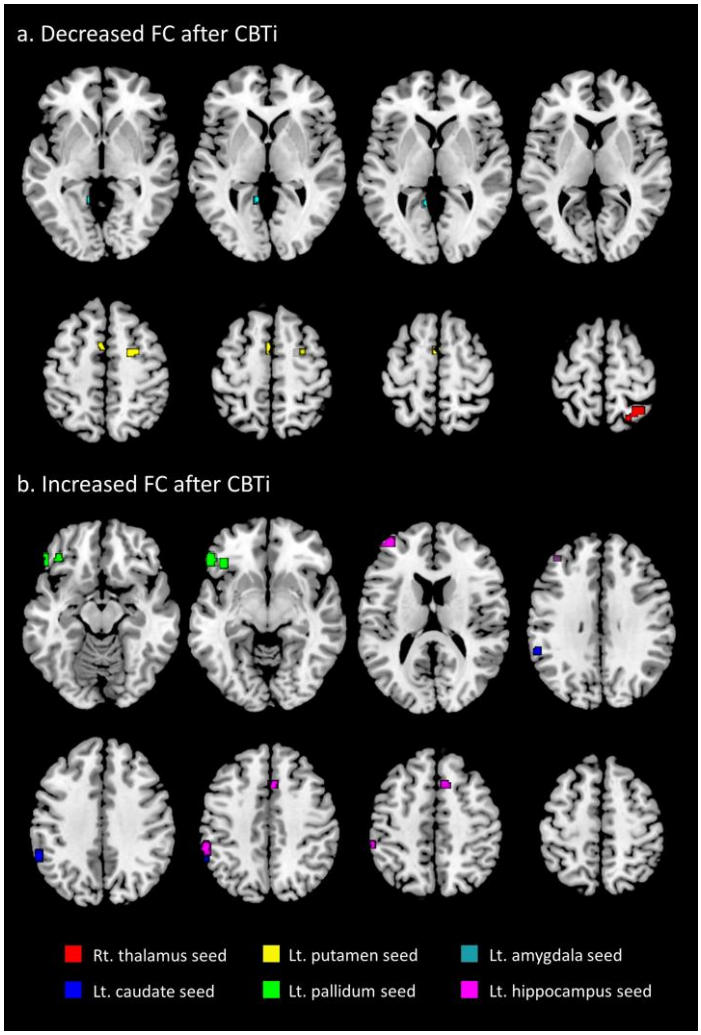

Figure 16. Changes in subcortical post-CBTi FC relative to pre-CBTi FC in the PI group. a) Areas of significant decreases in post-CBTi FC compared to pre-CBTi FC in the PI group. Red area: right superior parietal gyrus; yellow areas: right superior frontal gyrus and left supplementary motor cortex; blue area: left lingual gyrus. b) Areas of significant increases in post-CBTi FC compared to pre-CBTi FC in the PI group. Blue areas: left supramarginal gyrus; green areas: left orbitofrontal cortex; pink areas: left frontal pole, left supramarginal gyrus, and right paracingulate gyrus. The colored areas indicate altered FC in relation to the same-colored seed region. Abbreviations: FC, functional connectivity; CBTi, cognitive-behavioral therapy for insomnia; PI, psychophysiological insomnia; rt., right; lt., left. Thresholded at a whole brain false discovery rate-corrected cluster-level of $q < 0.05$ and an uncorrected peak-level of $P < 0.001$.

3.2. DMN seed regions in relation to whole brain voxels and ROI to ROI analysis

Compared to pre-CBTi FC, post-CBTi FC significantly decreased between the PCC and right occipital pole (Fig. 17); the left angular gyrus and right fusiform gyrus (Fig. 18); the PCG and right occipital cortex (Fig. 19); and the ACC and left precentral and postcentral cortex (Fig. 20). FC significantly increased between the right anterior supramarginal gyrus and precuneus (Fig. 21). Changes in FC after CBTi of the PI group are summarized in table 6 and figure 22. ROI-to-ROI analysis among DMN substructures did not show significant differences between the pre- and post-CBTi PI groups.

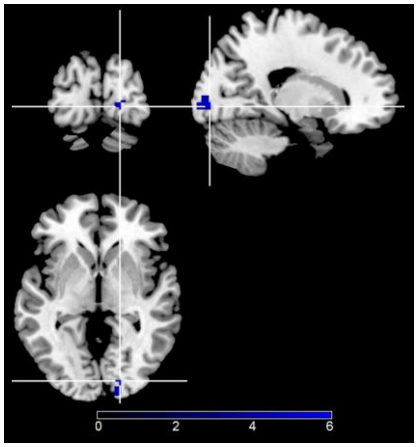

Figure 17. Compared to pre-CBTi, post-CBTi FC of the PI group was decreased between the posterior cingulate cortex (seed) and right occipital pole and shown in coronal, sagittal and transverse views.

Blue areas represent (18, -88, -2) in MNI coordinates (x, y, z), FDR-corrected cluster-level q = 0.033, *ke* = 70, uncorrected peak-level P <0.001, T = 7.05. CBTi, cognitive-behavioral therapy for insomnia; PI, psychophysiological insomnia; FC, functional connectivity; MNI, Montreal Neurological Institute; FDR, false discovery rate; *ke* indicates the cluster size in voxels.

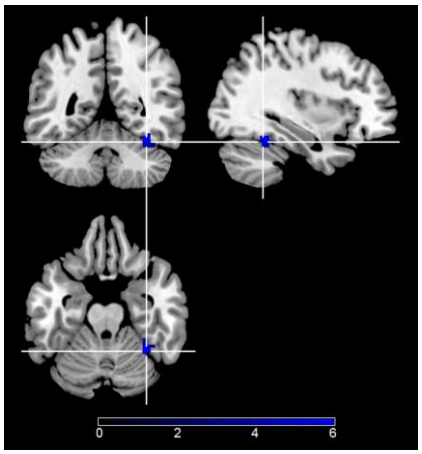

Figure 18. Compared to pre-CBTi, post-CBTi FC of the PI group was decreased between the left angular gyrus (seed) and right fusiform gyrus and shown in coronal, sagittal and transverse views.

Blue areas represent (34, -50, -22) in MNI coordinates (x, y, z), FDR-corrected cluster-level q = 0.013, *ke* = 76, uncorrected peak-level P <0.001, T = 6.79. CBTi, cognitive-behavioral therapy for insomnia; PI, psychophysiological insomnia; FC, functional connectivity; MNI, Montreal Neurological Institute; FDR, false discovery rate; *ke* indicates the cluster size in voxels.

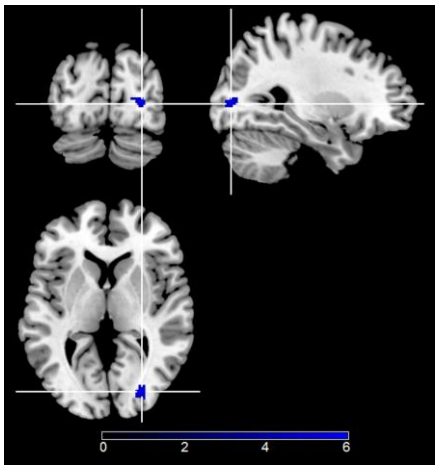

Figure 19. Compared to pre-CBTi, post-CBTi FC of the PI group was decreased between the left paracingulate gyrus (seed) and right lateral occipital gyrus and shown in coronal, sagittal and transverse views.

Blue areas represent (28, -82, 4) in MNI coordinates (x, y, z), FDR-corrected cluster-level q = 0.022, *ke* = 74, uncorrected peak-level P <0.001, T = 6.58. CBTi, cognitive-behavioral therapy for insomnia; PI, psychophysiological insomnia; FC, functional connectivity; MNI, Montreal Neurological Institute; FDR, false discovery rate; *ke* indicates the cluster size in voxels.

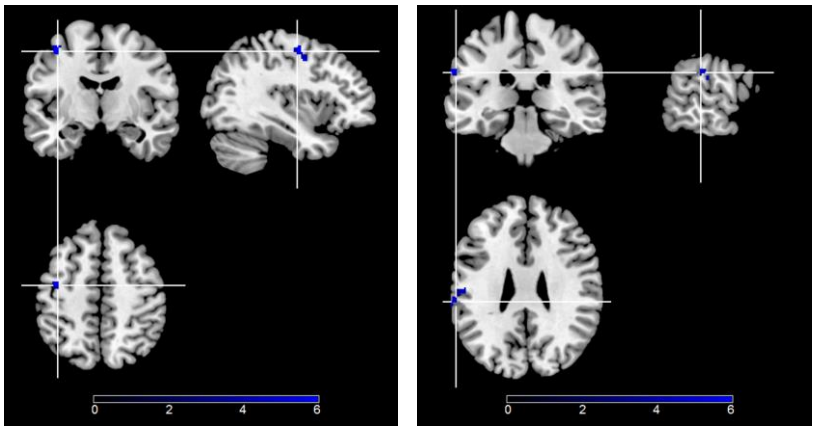

Figure 20. Compared to pre-CBTi, post-CBTi FC of the PI group was decreased between the anterior cingulate gyrus and left precentral gyrus (left) and left postcentral gyrus (right) and shown in coronal, sagittal and transverse views.

(Left) Blue areas represent (-38, -8, 52) in MNI coordinates (x, y, z), FDR-corrected cluster-level q = 0.034, *ke* = 55, uncorrected peak-level P <0.001, T = 6.40. (Right) Blue areas represent (-62, -28, 28) in MNI coordinates (x, y, z), FDR-corrected cluster-level q = 0.034, *ke* = 54, uncorrected peak-level P <0.001, T = 6.21. CBTi, cognitive-behavioral therapy for insomnia; PI, psychophysiological insomnia; FC, functional connectivity; MNI, Montreal Neurological Institute; FDR, false discovery rate; *ke* indicates the cluster size in voxels.

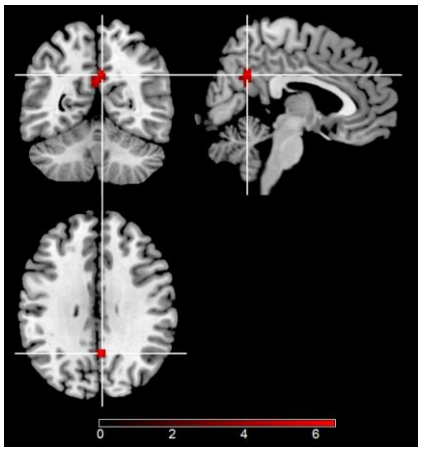

Figure 21. Compared to pre-CBTi, post-CBTi FC of the PI group was increased between the right anterior supramarginal gyrus and precuneus and shown in coronal, sagittal and transverse views.

Red areas represent (4, -56, 32) in MNI coordinates (x, y, z), FDR-corrected cluster-level q = 0.001, *ke* = 129, uncorrected peak-level P <0.001, T = 7.38 CBTi, cognitive-behavioral therapy for insomnia; PI, psychophysiological insomnia; FC, functional connectivity; MNI, Montreal Neurological Institute; FDR, false discovery rate; *ke* indicates the cluster size in voxels.

Table 6. Significant differences in DMN FC in the PI group after CBTi compared to baseline.

Seed	Brain region	FC increased or decreased	MNI coordinate (x, y, z)	k_e
Posteror cingulate cortex	Rt. occipital pole	Decreased	18, -88, -2	70
Rt. supramarginal gyrus	Precuneus	Increased	4, -56, 32	129
Lt. angular gyrus	Rt. fusiform gyrus	Decreased	34, -50, -22	76
Lt. paracingulate gyrus	Rt. lateral occipital gyrus	Decreased	28, -82, 4	74
Anterior cingulate cortex	Lt. precentral gyrus	Decreased	-38, -8, 52	55
	Lt. postcentral gyrus	Decreased	-62, -28, 28	54

The threshold was set at an uncorrected peak-level of $P < 0.001$ and a whole-brain, false discovery rate-corrected cluster level of $q < 0.05$. CBTi: cognitive behavioral therapy for insomnia; FC: functional connectivity; MNI: Montreal Neurological Institute; Rt.: right, Lt.: left; *ke* indicates the cluster size in voxels.

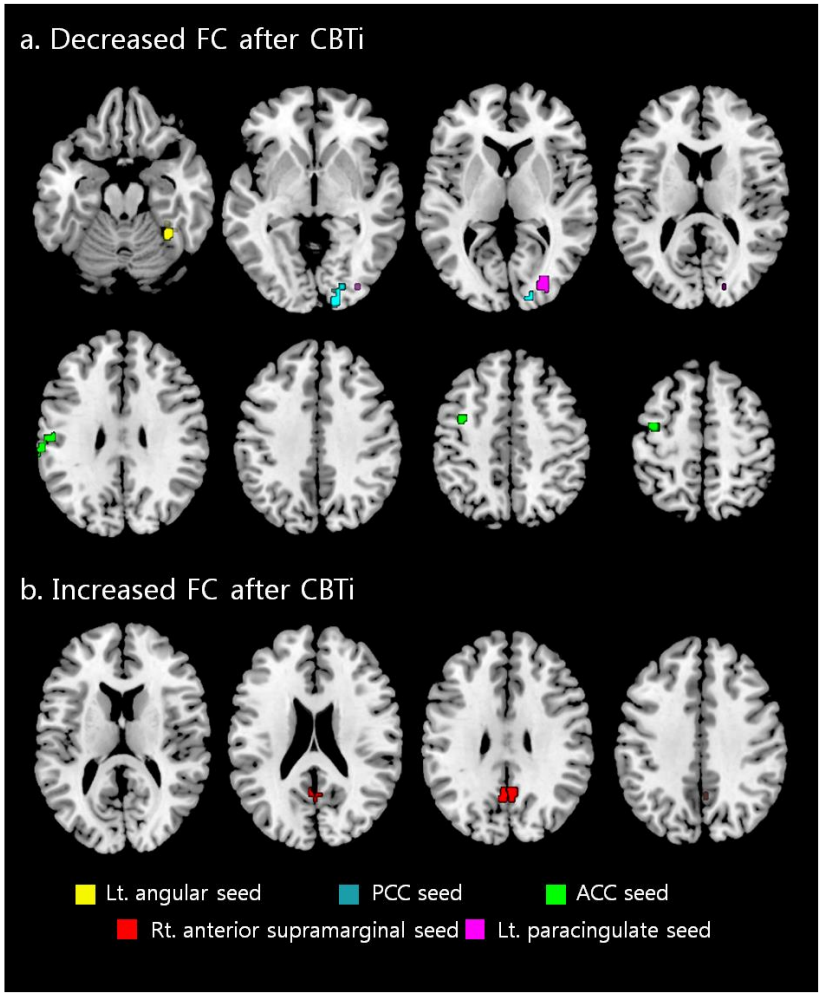

Figure 22. Changes in DMN post-CBTi FC relative to pre-CBTi FC in the PI group.

a) Areas of significant decreases in post-CBTi FC compared to pre-CBTi FC in the PI group. Yellow areas: right fusiform gyrus; blue area: right occipital pole; pink areas: right lateral occipital gyrus; green areas: precentral and postcentral gyri b) Areas of significant increases in post-CBTi FC compared to pre-CBTi FC in the PI group. Red areas: precuneus. The colored areas indicate altered FC in relation to the same-colored seed region. Abbreviations: DMN: default mode network; FC, functional connectivity; CBTi, cognitive-behavioral therapy for insomnia; PI, psychophysiological insomnia; PCC: posterior cingulate cortex; ACC: anterior cingulate cortex; Rt., right; Lt., left. Thresholded at a whole brain false discovery rate-corrected cluster-level of $q < 0.05$ and an uncorrected peak-level of $P < 0.001$.

4. Correlations between FC and sleep parameters

4.1. Correlations between FC and pre-CBTi sleep parameters

In the PI group, ISI score was correlated with FC between the left hippocampus and left fusiform gyrus (r = -0.770, P = 0.009; Fig. 23), and the FC between the right pallidum and precuneus was significantly correlated with the pre-CBTi PSQI score (r = 0.673, P = 0.033; Fig. 24) and reached near significance with WASO (r = 0.620, P = 0.056) and SE (r = -0.592, P = 0.071) assessed by sleep diaries. Apart from the hippocampus, the DMN structures did not significantly correlate with FC in the PI group.

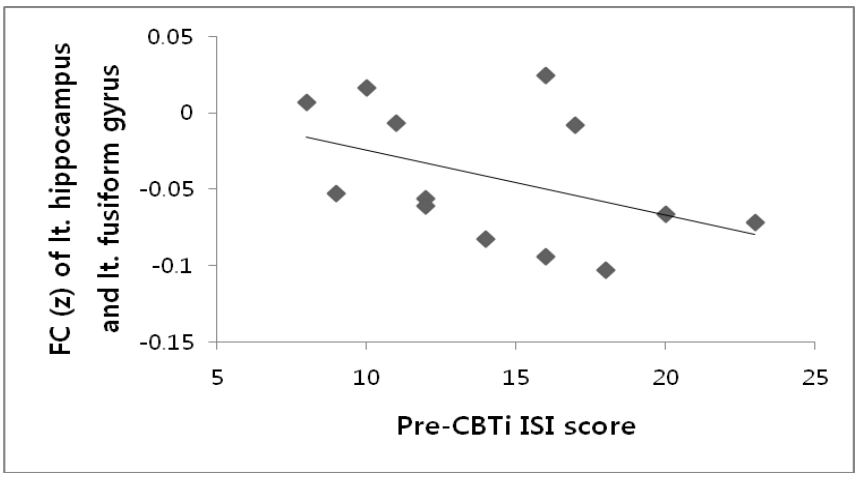

Figure 23. The FC between the left hippocampus and left fusiform gyrus significantly correlated with the pre-CBTi ISI score in the PI group.

Pearson's correlation analysis was conducted with age, gender, and (insomnia-excluded)-BDI scores controlled. FC, functional connectivity; lt., left; CBTi, cognitive behavioral therapy for insomnia; ISI, insomnia severity index.

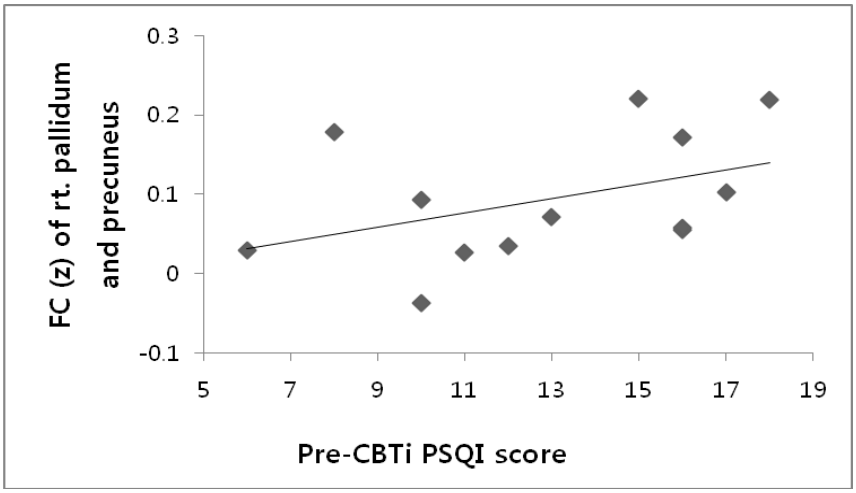

Figure 24. The FC between the right pallidum and precuneus significantly correlated with the pre-CBTi PSQI score in the PI group.

Pearson's correlation analysis was conducted with age, sex, and (insomnia-excluded)-BDI scores controlled. FC, functional connectivity; rt., right; CBTi, cognitive behavioral therapy for insomnia; PSQI, Pittsburgh sleep quality index.

4.2. Correlations between Δ FC and Δ post-pre CBTi sleep parameters

After the CBTi sessions, the Δ FC between the right thalamus and right superior parietal gyrus was significantly correlated with the Δ SE (r = -0.671, P = 0.034) and with the Δ SL (r = 0.640, P = 0.046) (Fig. 25). Δ Sleep questionnaires and the DMN structures did not significantly correlate with the Δ FC.

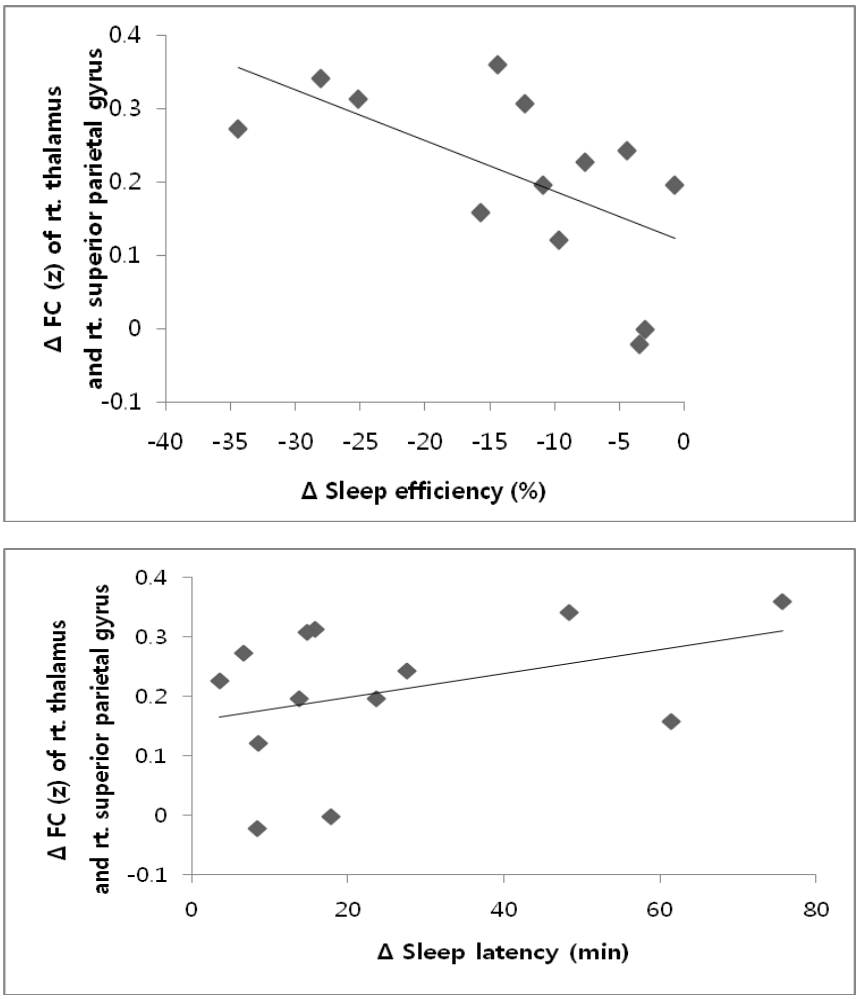

Figure 25. The Δ FC between the right thalamus and right superior parietal gyrus significantly correlated with the Δ sleep efficiency (upper) and Δ sleep latency (below), respectively in the PI group.

Pearson's correlation analysis was conducted with age, sex, and (insomnia-excluded)-BDI scores controlled. FC, functional connectivity; rt., right.

5. Comparisons between post-CBTi FC of the PI group and baseline FC of the GS group

For the FC values that showed significant differences between the GS and PI groups, the pre-CBTi and post-CBTi changes were compared in the PI group, and the post-CBTi values for the PI group were compared with the baseline FC of the GS group (Table 7 and Fig. 26). In pre- and post-CBTi comparisons, the FC between the right thalamus and frontal poles, the right pallidum and both precuneus and left angular gyrus, the left hippocampus and left fusiform gyrus, and the left PCG and right fusiform gyrus were significantly different after correcting for multiple comparisons. In post-CBTi and GS comparisons, no significant differences in FC were seen after correcting for multiple comparisons. All the FC values shown were significantly different between the baseline GS and pre-CBTi groups.

Table 7.Changes in post-CBTi FC of the PI group and comparisons with baseline GS.

Seed	Brain region	PI group		GS group (z,n=18)	Comparisons between	
		Pre-CBTi (*z*, n=13)	Post-CBTi (*z*, n=13)		Pre- & Post-CBTi P^{*}	Post-CBTi & GS $P^{\dagger}$
Rt. thalamus	Rt. superior frontal gyrus	0.1169	0.0492	-0.2197	0.030	0.036
	Bilateral frontal poles	0.1259	-0.0117	-0.0418	0.003	0.593
Rt. caudate	Rt. orbitofrontal cortex	-0.0118	0.0626	0.1425	0.144	0.080
Rt. pallidum	Bilateral precuneus	0.0941	-0.1406	-0.0495	0.010	0.379
	Lt. angular gyrus	-0.1033	-0.0148	0.0725	0.012	0.031
Lt. hippo-campus	Lt. fusiform gyrus	-0.0426	0.1128	0.1227	0.001	0.804
Lt. para-cingulate gyrus	Rt. fusiform gyrus	0.0947	-0.1099	-0.1304	<0.001	0.551
	Both lingual gyri	0.1080	-0.0447	-0.0666	0.064	0.696
	amygdala	0.2103	0.1247	0.0294	0.117	0.044
Anterior cingulate cortex	Rt. lingual gyrus	0.0174	-0.1266	-0.1472	0.021	0.677

*Paired *t*-test between pre-and post-CBTi FC of the PI group, † Independent *t*-test between post-CBTi FC of the PI group and baseline FC of the GS group. FC, functional connectivity; CBTi, cognitive-behavioral therapy for insomnia; PI, psychophysiological insomnia; GS, good sleeper; Rt., right; Lt., left, P <0.016 considered significant

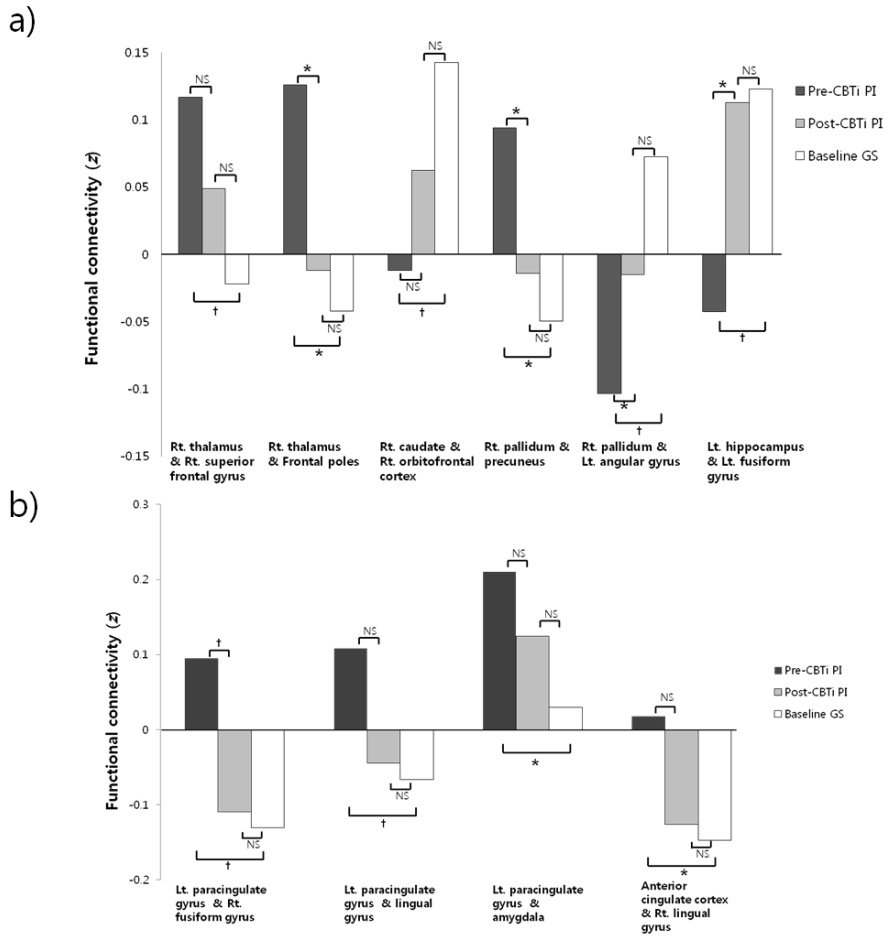

Figure 26. Changes in the functional connectivity of the pre-CBTi, post-CBTi, and baseline GS groups are shown.

a) FC of the subcortical seed regions that showed significant differences between the baseline GS and PI groups b) FC of the DMN seed regions that showed significant differences between the baseline GS and PI groups. Independent *t*-test for comparisons between pre-CBTi PI and baseline GS groups and between post-CBTi PI and baseline GS groups. Paired *t*-test for comparisons between pre- and post-CBTi PI groups. * $P < 0.016$, † $P < 0.001$. CBTi, cognitive behavioral therapy for insomnia; PI, psychological insomnia; GS, good sleeper; Rt., right; Lt. left.

IV. DISCUSSION

The present study investigated resting-state FC with subcortical seed regions, including the BG, thalamus, amygdala, hippocampus; and the DMN regions, including the ACC, PCC, PCG, IPC, and precuneus, in relation to whole brain voxels. The study also examined resting-state FC between the DMN regions by ROI-to-ROI analysis. The present study was the first to evaluate the effects of CBTi on intrinsic resting-state FC in PI patients. The results showed significantly altered FC of the subcortical and DMN structures with various cortical regions in patients with PI. Additionally, the intrinsic FC of the insomnia patients exhibited significant changes after a 5-week CBTi treatment program. The results support the hyperarousal theory of insomnia, which includes aspects of cognitive, emotional, and physiological hyperarousal, and provide neurobiological evidence for the widely-accepted Spielman's 3-P model, the diathesis-stress model of insomnia. Though the functions of the subcortical nuclei and DMN examined in the present study have yet to be fully understood, efforts to discern and describe their roles in the pathogenesis of insomnia have yielded important results.

1. Thalamus and prefrontal cortex

In the present study, the PI group exhibited stronger FC between the thalamus and prefrontal cortex than the control group. The thalamus and cortex are strongly connected by neuronal fibers radiating from the thalamus to the cortex. The thalamus has multiple functions, including relaying sensory signals between subcortical nuclei and the associated primary cortical areas, regulating sleep and wakefulness via thalamo-cortico-thalamic circuits, memory functions, emotion processing, and motor control, involving relationships with the hippocampus, amygdala, and BG mediated by cortico-striato-thalamo-cortical loops (Sherman, 2016). Accordingly, the present results provide a neural basis for sensory-related hyperarousal based on the observed hyperactivity of the thalamus in relation to cortical excitability. After CBTi, there was a decrease in connectivity between the thalamus and parietal cortex, rather than the frontal cortex, and this change was correlated with an increase in SE, and nearly-significantly correlated with a decrease in WASO, as assessed by the sleep diaries of the participants. Patients with insomnia are reported to show weaker FC between the parietal and frontal cortices (Y. Li et al., 2014). It is possible that after CBTi, FC in the frontoparietal network improved, and hyperarousal was reduced by the decrease in thalamus activity.

2. BG and OFC

The striatum, which consists of the caudate and putamen, is innervated by the OFC, dorsolateral prefrontal cortex, and posterior (inferior) parietal cortex. Previous findings consistently report that the caudate is more likely to receive input from the OFC and parietal cortex and modulate sleep through inhibition of cortical excitability, while the putamen receives input from the somatosensory, primary motor, and premotor cortices in parallel circuits (Arsalidou et al., 2013). Reductions in orbitofrontal volume have been identified in several studies of insomnia patients (Altena et al., 2010; Joo et al., 2013; Stoffers et al., 2012), and more recently Stoffers et al. (Stoffers et al., 2014) observed a smaller BOLD response in the left caudate during executive tasks in insomnia patients compared to controls. Through additional analyses, the investigators interpreted the findings to be unrelated to increased baseline perfusion and possibly due to decreased FC from the OFC. These authors also emphasized the role that aberrant caudate activation plays in cortical activity and hyperarousal and showed that the reduced caudate activity did not recover after CBTi with light therapy; thus, it was suggested that this pattern of activity may be an endophenotype for insomnia.

The present findings, showing weaker FC between the caudate and OFC during the resting state, strengthen prior claims that attenuated inhibition from the OFC may account for weaker caudate activity (Stoffers et al., 2014).

The cortico-striato-thalamo-cortical circuit has multiple neurocognitive functions, including regulating arousal along with cognitive and affective functions. The cortex connects to the striatum (caudate and putamen) and then (via the pallidum) to the thalamus, which connects back to the cortex (Alexander & Crutcher, 1990). After CBTi, the caudate did not show changes in FC. This may be interpreted as supporting the notion that weak caudate activity is a trait-like marker of insomnia, persisting despite therapy (Stoffers et al., 2014).

3. BG and DMN

The present results revealed altered resting-state FC between the pallidum and various DMN regions, particularly the inferior parietal cortex (IPC) and precuneus, in the PI group compared to the GS group. FC was weaker between the right pallidum and left angular gyrus, but stronger between the right pallidum and precuneus. After CBTi, the FC between the left caudate and left supramarginal gyrus increased. Despite the disparity in altered FC of the BG substructures (pallidum and caudate) with the associated gyri of the IPC (angular gyrus and supramarginal gyrus) before and after CBTi, it is important to mention the effect of CBTi on the weaker FC between the BG and the IPC, which resulted in an increase in FC afterwards. Recently, a role of the DMN in maintaining cognitive flexibility has been suggested,

and the angular gyrus (associated with the precuneus) also has executive and working memory functions (Vatansever, Manktelow, Sahakian, Menon, & Stamatakis, 2016). Considering the extensive links between cognitive functions and corticostriatal pathways, the present results suggest that cognitive dysfunction in insomnia patients may be influenced by altered FC between the BG and DMN, and support the effect of CBTi on cognitive recovery, which was demonstrated by FC enhancement in the associated regions. However, as the functions of the DMN are ubiquitous and its substructures also have roles apart from the DMN, the complex interaction with BG needs to be clarified further by future research.

4. DMN

In ROI-to-ROI analysis between DMN regions, no significant findings were obtained from PI and GS comparisons, or between the pre- and post-CBTi PI groups. However, the present study obtained significant findings regarding stronger FC between the DMN and cortical regions, in particular the occipital cortex, for which the FC was decreased after CBTi. Compared to the GS group, the PI group showed stronger FC between the PCG and occipital cortex (fusiform and lingual gyrus), which decreased after CBTi. Also, the PI group showed stronger FC between the ACC and lingual gyrus compared to the GS group. The FC between the ACC and precentral cortex and postcentral

cortex were both decreased after CBTi. Though the FC in the precuneus, PCC, or IPL were not significantly different between the PI and GS groups, after CBTi, significant decreases in FC between the PCC or IPL and the occipital cortex, were noted. These findings suggest implications of the DMN for visual-stimulus related hyperarousal and the therapeutic effect of CBTi on this. A previous study demonstrated increased FC between the amygdala and occipital regions (Huang et al., 2012) and more recent studies of sleep-related pictorial stimuli are lending evidence for hyper-visual sensory processing in insomnia patients (Kim et al., 2017). Also, the decrease in FC between the ACC and somatomotor cortex after CBTi are indicative of a decrease in somatosensory arousal caused by therapeutic effects.

The present study demonstrated an increase in FC between the right supramarginal gyrus and precuneus after CBTi. This was the only significant finding regarding FC changes between the DMN structures in the seed-to-voxel analysis. Nie et al. showed decreased FC between the medial prefrontal cortex and medial temporal lobe, and between the medial temporal lobe and inferior parietal cortex (Nie et al., 2015), whereas Regen et al. reported greater waking connectivity between the retrosplenial cortex/hippocampus and other nodes of the DMN to be associated with lower sleep efficiency (Regen et al., 2016).

5. BG and motor cortex

After the PI group underwent CBTi, FC between the left putamen and the supplementary motor area (SMA) decreased. The putamen is involved in motor regulation via connections with the primary motor cortex/premotor area (Arsalidou et al., 2013). Specifically, complex and voluntary movements, in contrast to automated and well-learned movements, are suggested to be lateralized in the left hemisphere, and to be more strongly related to the putamen (Arsalidou et al., 2013). If abnormal FC between the putamen and motor cortex is related to motor restlessness, a manifestation of physiological arousal, then the present findings imply that CBTi may be an effective therapy for physiological arousal.

5. Hippocampus, amygdala, and fronto–parietal cortex

The PI group exhibited weaker FC between the left hippocampus and left fusiform gyrus compared to the GS group. After CBTi, FC between the left hippocampus and the frontal cortex and left supramarginal gyrus increased. Previous studies have also reported decreased hippocampal volume and abnormal FC between the hippocampus and other DMN regions in patients with insomnia disorders (Joo et al., 2014; Regen et al., 2016; Riemann et al., 2007).

The hippocampus, a component of both the limbic system and the DMN, plays an important role in memory. In conjunction with the amygdala (another part of the limbic system), the hippocampus sends signals to the striatum via cortico–striato–thalamic and limbic circuits. The present results, showing increased FC between the hippocampus and fronto-parietal regions after CBTi, suggest that this may be a neurobiological basis for the recovery of reduced cognitive functioning, which is a common finding in insomnia patients (Nissen et al., 2011). After CBTi, we observed increased FC between the hippocampus and fronto-parietal regions, areas known to be linked to executive functions. Other recent research shows the parietal cortex to function in memory retrieval in concert with the hippocampus (Alexander & Crutcher, 1990). Though more evidence is required to elucidate the direction of causality, successful therapy of insomnia is associated with changes in the FC of hippocampus. When interpreted in the light of previous studies, the present results are encouraging in suggesting that adequate treatment for insomnia may reverse the memory decline of insomnia patients.

The amygdala is a central aspect of the emotional circuit, and has bidirectional connections with the prefrontal cortex and limbic structures (Roy et al., 2009). An amygdala seed-based study in insomnia patients suggested the existence of a compensatory response to disrupted emotional functioning, in which decreased FC between the amygdala and other subcortical regions was observed, but increased FC with the sensorimotor cortices, including the occipital cortex (Huang et al., 2012). However, findings regarding the

relationship of sleep-related stimuli with emotional circuits, including the amygdala, have been inconsistent (Spiegelhalder et al., 2016). The present study did not identify significant FC changes in the PI group with the amygdala as seed region, but the FC between the PCG and amygdala was stronger. After CBTi, there was a significant decrease in FC between the amygdala and the lingual gyrus, which is linked to visual processing. This suggests that there may be disrupted FC within the emotional circuit which is related to sensory hyperarousal.

The present study examined the FC of subcortical structures and the DMN structures with all parts of the brain, and arrived at several findings related to the hyperarousal and disrupted cognition seen in chronic insomnia (Fig. 27). Though differences in FC between the PI and GS groups were not reflected consistently in post-CBTi changes in the PI group, the post-CBTi FC values for the PI group were comparable to those for the baseline GS group after correcting for multiple comparisons, which lends support to the idea that post-CBTi changes manifest a trend toward normalization of the altered FC in the PI group. In the post-CBTi and GS comparisons, the FC between the right thalamus and right superior frontal gyrus, between the right pallidum and left angular gyrus, and between the left paracingulate gyrus and amygdala all showed differences when *P* values were not adjusted for multiple comparisons. The degree of recovery of FC in the post-CBTi PI group may have been limited due to the short period of CBTi conducted in the study, which would result in partial responses to therapy or (despite our efforts to control for

them) to unrecognized comorbidity with various conditions and disorders, which are frequently comorbid with insomnia.

The significant FC findings from the subcortical seed region-to-voxel analysis were not consistent with the DMN seed regions analysis; i.e., the decreased FC of the PI group between the right pallidum (seed) and left angular gyrus was not apparent in the angular gyrus (seed) analysis with the pallidum. After CBTi, the increase in FC between the left caudate(seed) and left supramarginal gyrus was not matched by significance in the supramarginal gyrus (seed) analysis with the caudate. However, altered FC between a seed and a significant area should not be interpreted to concern the same region as the seed or ROI region which was predefined by the Harvard-Oxford atlas; rather it should be interpreted as involving a part of that region.

Overall, the regions related to cognitive, emotional, and sensory arousal are interrelated and have overlapping functions in the salience, somatosensory motor, DMN, and limbic networks. Other compensatory networks are yet to be revealed. With limited knowledge of the complexity of brain functioning, the present findings are insufficient to demonstrate an integrative explanation of the pathogenesis of insomnia, and our attempts to link the significant changes in FC after CBTi with differences between the PI and GS at baseline are, at this point, speculative.

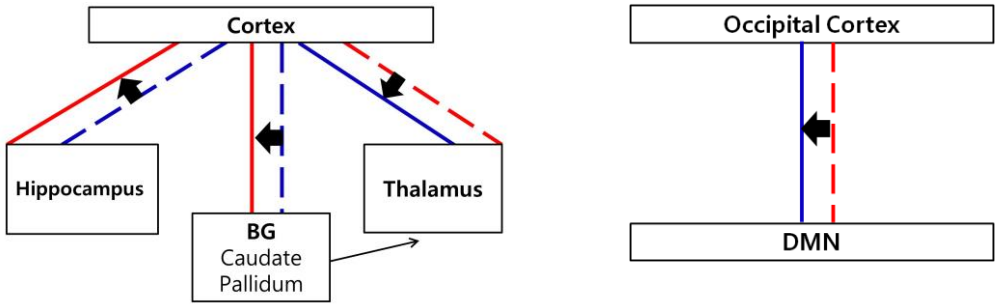

Figure 27. A hypothetical illustration of altered subcortical FC (left) and DMN FC (right) with the cortex and the changes after CBTi in patients with PI.

The connection between the BG and the thalamus was not explored in the present study, but presented in the illustration based on the cortico-striato-thalamo-cortical circuit. Broken lines represent pre-CBTi FC. Solid lines represent post-CBTi FC. Red lines represent stronger or increased FC compared to GS or pre-CBTi, respectively. Blue lines represent weaker or decreased FC compared to GS or pre-CBTi, respectively. Abbrevations: FC, functional connectivity; CBTi, cognitive-behavioral therapy for insomnia; BG, basal ganglia; GS, good sleepers; DMN, default mode network.

6. Limitations

The present study has several limitations. First, the sample size of the PI group was small. Second, a wait list comparison was not possible due to the lack of a second fMRI scan and the absence of follow-up in the GS group after 5 weeks; thus, time or placebo effects on the FC changes between pre- and post-CBTi cannot be excluded. However, the FC of the post-CBTi PI group was compared with the GS and yielded no significant differences. Also, correlations between changes in clinical sleep measurements and changes in FC after CBTi support an association of CBTi results with FC changes. The PI group showed a reduction in the ISI score of more than 7 points, which is considered to represent modest improvement, and they subsequently reached a score of below 8 points, which is the cutoff score for absence of insomnia (Morin, Belleville, Belanger, & Ivers, 2011). These findings cannot be explained by time or placebo effects alone. Third, follow-up PSG analyses were not conducted after the CBTi sessions, and no objective clinical measures related to the alterations in FC were administered to the PI group. However, an attempt was made to link the observed neural mechanisms with the clinical features using data from the sleep questionnaires and sleep diaries, which were comparable to objective PSG measures (Morin, Colecchi, Stone, Sood, & Brink, 1999). Fourth, non-significant difference in the ages of the PI and GS groups were noted, but controlled for in the between-group

comparisons.

V. CONCLUSIONS

In conclusion, the present study found significant differences in the resting-state FC of subcortical structures and DMN structures with various cortical regions in insomnia patients compared to good sleepers. A 5-week CBTi program without medication modified the resting-state FC of these patients comparable to that of glood sleepers. These findings clarify the neural correlates of hyperarousal in insomnia disorder and provide insights into the neurobiological basis for the effectiveness of CBTi.

VI. REFERENCES

AASM. (2005). *International Classification of Sleep Disorders: Diagnostic and Coding Manual, 2nd ed* (A. A. o. S. Medicine Ed. 2nd ed.). Westches ter, IL: American Academy of Sleep Medicine.

AASM. (2014). *The International Classification of Sleep Disorders, 3rd ed*. Da rien, IL: American Academy of Sleep Medicine.

Alexander, G. E., & Crutcher, M. D. (1990). Functional architecture of basal g anglia circuits: neural substrates of parallel processing. *Trends Neurosci, 13*(7), 266-271.

Altena, E., Van Der Werf, Y. D., Sanz-Arigita, E. J., Voorn, T. A., Rombouts, S. A., Kuijer, J. P., & Van Someren, E. J. (2008). Prefrontal hypoact ivation and recovery in insomnia. *Sleep, 31*(9), 1271-1276.

Altena, E., Vrenken, H., Van Der Werf, Y. D., van den Heuvel, O. A., & Va n Someren, E. J. (2010). Reduced orbitofrontal and parietal gray matte r in chronic insomnia: a voxel-based morphometric study. *Biol Psychia try, 67*(2), 182-185. doi: 10.1016/j.biopsych.2009.08.003

Arsalidou, M., Duerden, E. G., & Taylor, M. J. (2013). The centre of the brai n: topographical model of motor, cognitive, affective, and somatosensor y functions of the basal ganglia. *Hum Brain Mapp, 34*(11), 3031-3054. doi: 10.1002/hbm.22124

Bastien, C. H., Vallieres, A., & Morin, C. M. (2001). Validation of the Insom nia Severity Index as an outcome measure for insomnia research. *Sleep Med, 2*(4), 297-307.

Beck, A. T., Steer, R. A., & Brown, G. K. (1996). *Beck Depression Inventory, Manual* (Vol. 2nd ed). San Antonio, Texas: Psychological Corp.

Behzadi, Y., Restom, K., Liau, J., & Liu, T. T. (2007). A component based n oise correction method (CompCor) for BOLD and perfusion based fM RI. *Neuroimage, 37*(1), 90-101. doi: 10.1016/j.neuroimage.2007.04.042

Bonnet, M. H., & Arand, D. L. (1995). 24-Hour metabolic rate in insomniacs and matched normal sleepers. *Sleep, 18*(7), 581-588.

Bonnet, M. H., & Arand, D. L. (1998). Heart rate variability in insomniacs an d matched normal sleepers. *Psychosom Med, 60*(5), 610-615.

Buckner, R. L., Andrews-Hanna, J. R., & Schacter, D. L. (2008). The brain's default network: anatomy, function, and relevance to disease. *Ann N Y Acad Sci, 1124*, 1-38. doi: 10.1196/annals.1440.011

Buysse, D. J., Reynolds, C. F., 3rd, Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The Pittsburgh Sleep Quality Index: a new instrument fo r psychiatric practice and research. *Psychiatry Res, 28*(2), 193-213.

Chen, M. C., Chang, C., Glover, G. H., & Gotlib, I. H. (2014). Increased insu la coactivation with salience networks in insomnia. *Biol Psychol, 97*, 1 -8. doi: 10.1016/j.biopsycho.2013.12.016

Colombo, M. A., Ramautar, J. R., Wei, Y., Gomez-Herrero, G., Stoffers, D., Wassing, R., . . . Van Someren, E. J. (2016). Wake high-density elect roencephalographic spatiospectral signatures of insomnia. *Sleep, 39*(5), 1015-1027. doi: 10.5665/sleep.5744

Dai, X. J., Peng, D. C., Gong, H. H., Wan, A. L., Nie, X., Li, H. J., & Wan g, Y. X. (2014). Altered intrinsic regional brain spontaneous activity a

nd subjective sleep quality in patients with chronic primary insomnia: a resting-state fMRI study. *Neuropsychiatr Dis Treat, 10*, 2163-2175. doi: 10.2147/ndt.s69681

Drummond, S. P., Walker, M., Almklov, E., Campos, M., Anderson, D. E., & Straus, L. D. (2013). Neural correlates of working memory performance in primary insomnia. *Sleep, 36*(9), 1307-1316. doi: 10.5665/sleep.2952

DSM. (2013). *Diagnostic and Statistical Manual of Mental Disorders, 5th* (5th ed.). Arlington, VA: American Psychiatric Association.

Edinger, J. D., & Carney, C. E. (2007). *A Cognitive-Behavioral Therapy Approach*: Oxford University Press.

Freedman, R. R. (1986). EEG power spectra in sleep-onset insomnia. *Electroencephalogr Clin Neurophysiol, 63*(5), 408-413.

Hamilton, J. P., Furman, D. J., Chang, C., Thomason, M. E., Dennis, E., & Gotlib, I. H. (2011). Default-mode and task-positive network activity in major depressive disorder: implications for adaptive and maladaptive rumination. *Biol Psychiatry, 70*(4), 327-333. doi: 10.1016/j.biopsych.2011.02.003

Huang, Z., Liang, P., Jia, X., Zhan, S., Li, N., Ding, Y., . . . Li, K. (2012). Abnormal amygdala connectivity in patients with primary insomnia: evidence from resting state fMRI. *Eur J Radiol, 81*(6), 1288-1295. doi: 10.1016/j.ejrad.2011.03.029

Joo, E. Y., Kim, H., Suh, S., & Hong, S. B. (2014). Hippocampal substructural vulnerability to sleep disturbance and cognitive impairment in patients with chronic primary insomnia: magnetic resonance imaging morphometry. *Sleep, 37*(7), 1189-1198. doi: 10.5665/sleep.3836

Joo, E. Y., Noh, H. J., Kim, J. S., Koo, D. L., Kim, D., Hwang, K. J., . . . Hong, S. B. (2013). Brain Gray Matter Deficits in Patients with Chronic Primary Insomnia. *Sleep, 36*(7), 999-1007. doi: 10.5665/sleep.2796

Kay, D. B., & Buysse, D. J. (2017). Hyperarousal and Beyond: New Insights to the Pathophysiology of Insomnia Disorder through Functional Neuroimaging Studies. *Brain Sci, 7*(3). doi: 10.3390/brainsci7030023

Kay, D. B., Karim, H. T., Soehner, A. M., Hasler, B. P., Wilckens, K. A., James, J. A., . . . Buysse, D. J. (2016). Sleep-sake differences in relative regional cerebral metabolic rate for glucose among patients with insomnia compared with good sleepers. *Sleep, 39*(10), 1779-1794. doi: 10.5665/sleep.6154

Killgore, W. D., Schwab, Z. J., Kipman, M., Deldonno, S. R., & Weber, M. (2013). Insomnia-related complaints correlate with functional connectivity between sensory-motor regions. *Neuroreport, 24*(5), 233-240. doi: 10.1097/WNR.0b013e32835edbdd

Kim, S. J., Lee, Y. J., Kim, N., Kim, S., Choi, J. W., Park, J., . . . Jeong, D. U. (2017). Exploration of changes in the brain response to sleep-related pictures after cognitive-behavioral therapy for psychophysiological insomnia. *Sci Rep, 7*(1), 12528. doi: 10.1038/s41598-017-13065-0

Li, C., Dong, M., Yin, Y., Hua, K., Fu, S., & Jiang, G. (2017). Abnormal whole-brain functional connectivity in patients with primary insomnia. *Neuropsychiatr Dis Treat, 13*, 427-435. doi: 10.2147/NDT.S128811

Li, Y., Wang, E., Zhang, H., Dou, S., Liu, L., Tong, L., . . . Zhang, Q. (201

4). Functional connectivity changes between parietal and prefrontal cort ices in primary insomnia patients: evidence from resting-state fMRI. *E ur J Med Res, 19*, 32. doi: 10.1186/2047-783x-19-32

Lushington, K., Dawson, D., & Lack, L. (2000). Core body temperature is ele vated during constant wakefulness in elderly poor sleepers. *Sleep, 23* (4), 504-510.

Marques, D. R., Gomes, A. A., Clemente, V., Moutinho dos Santos, J., & Cas telo-Branco, M. (2015). Default-mode network activity and its role in comprehension and management of psychophysiological insomnia: A ne w perspective. *New Ideas in Psychology, 36*, 30-37. doi: http://dx.doi.o rg/10.1016/j.newideapsych.2014.08.001

Morgan, P. T., Pace-Schott, E. F., Mason, G. F., Forselius, E., Fasula, M., Val entine, G. W., & Sanacora, G. (2012). Cortical GABA levels in prima ry insomnia. *Sleep, 35*(6), 807-814. doi: 10.5665/sleep.1880

Morin, C. M., Belleville, G., Belanger, L., & Ivers, H. (2011). The Insomnia Severity Index: psychometric indicators to detect insomnia cases and e valuate treatment response. *Sleep, 34*(5), 601-608.

Morin, C. M., Colecchi, C., Stone, J., Sood, R., & Brink, D. (1999). Behavior al and pharmacological therapies for late-life insomnia: a randomized c ontrolled trial. *JAMA, 281*(11), 991-999.

Morin, C. M., Hauri, P. J., Espie, C. A., Spielman, A. J., Buysse, D. J., & B ootzin, R. R. (1999). Nonpharmacologic treatment of chronic insomnia. An American Academy of Sleep Medicine review. *Sleep, 22*(8), 1134-1156.

Morin, C. M., Vallieres, A., & Ivers, H. (2007). Dysfunctional beliefs and attit udes about sleep (DBAS): validation of a brief version (DBAS-16). *Sle ep, 30*(11), 1547-1554.

Nie, X., Shao, Y., Liu, S. Y., Li, H. J., Wan, A. L., Nie, S., . . . Dai, X. J. (2015). Functional connectivity of paired default mode network subregi ons in primary insomnia. *Neuropsychiatr Dis Treat, 11*, 3085-3093. do i: 10.2147/ndt.s95224

Nissen, C., Kloepfer, C., Feige, B., Piosczyk, H., Spiegelhalder, K., Voderholze r, U., & Riemann, D. (2011). Sleep-related memory consolidation in pr imary insomnia. *J Sleep Res, 20*(1 Pt 2), 129-136. doi: 10.1111/j.1365-2869.2010.00872.x

Nofzinger, E. A., Buysse, D. J., Germain, A., Price, J. C., Miewald, J. M., & Kupfer, D. J. (2004). Functional neuroimaging evidence for hyperarous al in insomnia. *Am J Psychiatry, 161*(11), 2126-2128. doi: 10.1176/app i.ajp.161.11.2126

Pace-Schott, E. F., Zimmerman, J. P., Bottary, R. M., Lee, E. G., Milad, M. R., & Camprodon, J. A. (2017). Resting state functional connectivity i n primary insomnia, generalized anxiety disorder and controls. *Psychiat ry Res, 265*, 26-34. doi: 10.1016/j.pscychresns.2017.05.003

Perlis, M. L., Giles, D. E., Mendelson, W. B., Bootzin, R. R., & Wyatt, J. K. (1997). Psychophysiological insomnia: the behavioural model and a ne urocognitive perspective. *J Sleep Res, 6*(3), 179-188.

Plante, D. T., Jensen, J. E., Schoerning, L., & Winkelman, J. W. (2012). Redu ced gamma-aminobutyric acid in occipital and anterior cingulate cortice s in primary insomnia: a link to major depressive disorder? *Neuropsyc*

hopharmacology, 37(6), 1548-1557. doi: 10.1038/npp.2012.4

Qaseem, A., Kansagara, D., Forciea, M. A., Cooke, M., Denberg, T. D., & Cli nical Guidelines Committee of the American College of, P. (2016). Ma nagement of chronic insomnia disorder in adults: A clinical practice gu ideline from the American College of Physicians. *Ann Intern Med, 165* (2), 125-133. doi: 10.7326/M15-2175

Regen, W., Kyle, S. D., Nissen, C., Feige, B., Baglioni, C., Hennig, J., . . . S piegelhalder, K. (2016). Objective sleep disturbances are associated wit h greater waking resting-state connectivity between the retrosplenial cor tex/ hippocampus and various nodes of the default mode network. *J P sychiatry Neurosci, 41*(5), 295-303. doi: 10.1503/jpn.140290

Riedner, B. A., Goldstein, M. R., Plante, D. T., Rumble, M. E., Ferrarelli, F., Tononi, G., & Benca, R. M. (2016). Regional patterns of elevated alp ha and high-frequency electroencephalographic activity during nonrapid eye movement sleep in chronic insomnia: A pilot study. *Sleep, 39*(4), 801-812. doi: 10.5665/sleep.5632

Riemann, D., Spiegelhalder, K., Feige, B., Voderholzer, U., Berger, M., Perlis, M., & Nissen, C. (2010). The hyperarousal model of insomnia: a revie w of the concept and its evidence. *Sleep Med Rev, 14*(1), 19-31. doi: 10.1016/j.smrv.2009.04.002

Riemann, D., Voderholzer, U., Spiegelhalder, K., Hornyak, M., Buysse, D. J., Nissen, C., . . . Feige, B. (2007). Chronic insomnia and MRI-measure d hippocampal volumes: a pilot study. *Sleep, 30*(8), 955-958.

Roy, A. K., Shehzad, Z., Margulies, D. S., Kelly, A. M., Uddin, L. Q., Gotim er, K., . . . Milham, M. P. (2009). Functional connectivity of the hum an amygdala using resting state fMRI. *Neuroimage, 45*(2), 614-626. do i: 10.1016/j.neuroimage.2008.11.030

Sherman, S. M. (2016). Thalamus plays a central role in ongoing cortical funct ioning. *Nat Neurosci, 19*(4), 533-541. doi: 10.1038/nn.4269

Smith, M. T., Perlis, M. L., Chengazi, V. U., Soeffing, J., & McCann, U. (20 05). NREM sleep cerebral blood flow before and after behavior therap y for chronic primary insomnia: preliminary single photon emission co mputed tomography (SPECT) data. *Sleep Med, 6*(1), 93-94. doi: 10.101 6/j.sleep.2004.10.003

Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E., Johansen-Berg, H., . . . Matthews, P. M. (2004). Advances in func tional and structural MR image analysis and implementation as FSL. *N euroimage, 23 Suppl 1*, S208-219. doi: 10.1016/j.neuroimage.2004.07.05 1

Spiegelhalder, K., Baglioni, C., Regen, W., Kyle, S. D., Nissen, C., Hennig, J., . . . Riemann, D. (2016). Brain reactivity and selective attention to sl eep-related words in patients with chronic insomnia. *Behav Sleep Med*, 1-15. doi: 10.1080/15402002.2016.1253014

Spielman, A., Yang, C. M., & Glovinsky, P. B. (2011). *Assessment techniques for insomnia* (K. M, R. T & D. WC Eds. Principles and practice of sleep medicine, 5th ed.). Philadelphia: WB Saunders.

Stoffers, D., Altena, E., van der Werf, Y. D., Sanz-Arigita, E. J., Voorn, T. A., Astill, R. G., . . . Van Someren, E. J. (2014). The caudate: a key node in the neuronal network imbalance of insomnia? *Brain, 137*(Pt

2), 610-620. doi: 10.1093/brain/awt329

Stoffers, D., Moens, S., Benjamins, J., van Tol, M. J., Penninx, B. W., Veltman, D. J., . . . Van Someren, E. J. (2012). Orbitofrontal gray matter relates to early morning awakening: a neural correlate of insomnia complaints? *Front Neurol, 3*, 105. doi: 10.3389/fneur.2012.00105

Vatansever, D., Manktelow, A. E., Sahakian, B. J., Menon, D. K., & Stamatakis, E. A. (2016). Cognitive Flexibility: A Default Network and Basal Ganglia Connectivity Perspective. *Brain Connect, 6*(3), 201-207. doi: 10.1089/brain.2015.0388

Whitfield-Gabrieli, S., & Nieto-Castanon, A. (2012). Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. *Brain Connect, 2*(3), 125-141. doi: 10.1089/brain.2012.0073

Winkelman, J. W., Plante, D. T., Schoerning, L., Benson, K., Buxton, O. M., O'Connor, S. P., . . . Gonenc, A. (2013). Increased rostral anterior cingulate cortex volume in chronic primary insomnia. *Sleep, 36*(7), 991-998. doi: 10.5665/sleep.2794

Zhou, F., Huang, S., Gao, L., Zhuang, Y., Ding, S., & Gong, H. (2016). Temporal regularity of intrinsic cerebral activity in patients with chronic primary insomnia: a brain entropy study using resting-state fMRI. *Brain Behav, 6*(10), e00529. doi: 10.1002/brb3.529

국문 초록

정신생리성 불면증은 인지적, 정서적, 생리적 과각성을 동반하는 질환으로서, 인지행동치료가 일차적인 치료법이다. 뇌영상 연구 기법의 발달로 과각성과 관련된 뇌영역의 기능적 및 구조적 변화가 발견되고 있으며, 이로 인하여 불면증의 과각성 이론이 대두되고 있다. 특히 불면증 환자의 뇌 연결성의 의 기능적 변화에 관한 연구들이 디폴트 모드 네트워크(DMN), 감각 영역, 변연계 중심으로 활발히 진행되면서 불면증 환자의 뇌연결성의 기능적 변화가 확인되고 있다. 그러나 인지행동치료는 불면증의 치료로 그 임상적 효과 및 장기 효과까지 입증되었음에도 불구하고, 인지행동치료 전후의 뇌연결성의 변화를 본 연구는 아직 없다. 따라서, 본 연구는 정신생리성 불면증환자와 정상 대조군의 안정기 상태의 뇌연결성을 비교하고, 정신생리성 불면증 환자군의 인지행동치료 전후의 안정기 상태의 뇌연결성의 변화를 보고자 하였다.

본 연구에는 13 명의 정신생리성 불면증 환자군과 18 명의 정상 대조군이 참여하였다. 모든 참여자는 기능적 뇌자기공명영상을 촬영하였고, 불면증 환자군은 5 주간의 인지행동치료 후에 추가로 두번째 기능적 뇌자기공명영상을 촬영하였다. 피질하 구조와 DMN 구조들이 뇌 전 영역과 갖는 뇌 연결성의 강도 및 DMN 구조간의

뇌연결성의 강도를 분석함으로써 불면증 환자군과 대조군 간에, 그리고 불면증 환자군의 인지행동치료 전후의 뇌 연결성을 비교 분석하였다.

불면증 환자군과 대조군간의 뇌 연결성의 차이는 두드러졌다. 특히, 불면증 환자군에서 피질하 구조들과 DMN 영역들이 피질의 과각성과 관련된 영역과 유의하게 연결성이 변화한 것을 확인하였고, 인지행동치료 후에는 호전하는 것을 볼 수 있었다. 본 연구 결과는 뇌연결성의 실질적인 변화가 있고, 인지행동치료 후에 유의한 호전이 있는 것을 증명함으로써 불면증의 과각성 이론과 인지행동치료의 신경학적인 근거가 마련될 기대한다.

핵심어: 정신생리성 불면증, 불면증, 안정기 상태, 뇌자기공명영상, 뇌 연결성, 피질하 구조, 디폴트 모드 네트워크

학번: 2015-30574