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Published in:
Journal of Cognitive Psychotherapy: an international quarterly

DOI:
10.1891/JCPSY-D-21-00006

Neuroimaging correlates of Cognitive Behavioral Therapy for Insomnia: A Systematic Literature Review

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Abstract

Cognitive behavioral therapy for insomnia (CBT-I) is the gold-standard non-pharmacological treatment for insomnia, a complex disorder that comprises psychological, behavioral, and physiological components. This systematic literature review aimed to evaluate a growing body of exploratory studies that have examined CBT-I treatment effects using neuroimaging assessment. Nine studies met current review selection criteria, of which six studies compared insomnia groups with good sleepers, waitlist, and/or control groups. CBT-I administration varied in treatment length and duration across the studies, as did neuroimaging assessment, which included task-based and resting-state fMRI, and structural MRI. Functional connectivity abnormalities were observed in participants, including reduced engagement in task-related brain regions and apparent difficulties in regulating default mode brain areas that appeared to reverse following CBT-I treatment. Taken together, the neuroimaging results complement behavioral measures of treatment efficacy, indicating support for the effectiveness of CBT-I treatment in the recovery of brain function and structure.

Keywords: insomnia disorder, cognitive behavioral therapy for insomnia, functional magnetic resonance imaging, treatment, neuroimaging, hyperarousal

Introduction

Insomnia is a complex disorder comprising psychological, behavioral, and physiological components (Lee et al., 2018). Symptoms of insomnia include persistent difficulties in falling asleep, maintaining sleep, or early morning awakenings, which are associated with significant daytime impairments, such as attention deficits, fatigue, and mood instability (American Psychiatric Association [APA], 2013). An estimated 10%–20% of the worldwide adult population meets diagnostic criteria for insomnia disorder (Buysse, 2013; Morin & Benca, 2012). While insomnia is comorbid with affective disorders such as depression (Baglioni et al., 2011; Leerssen et al., 2020), it is also considered a primary condition in the *Diagnostic and Statistical Manual of Mental Disorders–Fifth Edition* (DSM-5; APA, 2013). Insomnia increases the risk of cardiovascular disease, diabetes, and suicide (Anothaisintawee et al., 2016; Cunnington et al., 2013; Javaheri & Redline, 2017); therefore, a greater understanding of insomnia should be a critical focus of research (Herbert et al., 2018). Traditional models of insomnia are based on behavioral and psychological constructs (Perlis et al., 2011). For instance, the behavioral stimulus-control model (Bootzin, 1972) is based on the notion that in insomnia patients, the cues associated with sleep (e.g., bed, bedroom, bedtime) are paired with other activities (e.g., working or watching television). In contrast, the psychobiological inhibition model focuses on the physiological construct of arousal (caused by psychological stress), which interferes with normal homeostatic and circadian regulation of sleep (Borbély, 1982). However, neuroimaging techniques, such as magnetic resonance imaging (MRI), have begun to contribute pathophysiological understanding of insomnia (Herbert et al., 2018; Kay & Buysse, 2017; Riemann et al., 2011), revealing abnormal task-related activation patterns, especially in fronto-striatal networks (Altena et al., 2008; Drummond et al., 2013; Stoffers et al., 2014). thCognitive behavioral therapy for insomnia (CBT-I) is the recommended non-pharmacological treatment for

insomnia disorder (Qaseem et al., 2016; Riemann et al., 2009; Sateia et al., 2017; Schutte-Rodin et al., 2008; Trauer et al., 2015). Standard CBT-I consists of five techniques: stimulus control, sleep restriction, sleep hygiene, relaxation training, and cognitive reframing. Through a combination of cognitive, behavioral, and psychoeducational approaches, the goal of CBT-I is to modify maladaptive thoughts and behaviors associated with sleep difficulties (Edinger & Carney, 2014; Morin & Espie, 2007) by reducing sleep-related hyperarousal and decreasing responses to sleep-related stimuli (Morin, Mimeault et al., 1999).

The efficacy of CBT-I treatment is typically measured using questionnaires, actigraphy, and polysomnography (PSG; Anderson & Kim, 2003). Such measures provide useful clinical and functional insights; however, they lack neuroanatomical precision that can be provided by neuroimaging methods (Buysse et al., 2011). While CBT-I is associated with robust and long-term improvements in self-reported and behavioral correlates of daytime performance (Fortier-Brochu et al., 2012), objective and detailed measures of neurocognitive functioning following CBT-I treatment are needed (Herbert et al., 2018). Neuroimaging assessment of CBT-I may help delineate the mechanisms of CBT-I treatment, including the responsiveness of specific brain regions. In this paper, we focus on the opportunities arising from the most popular neuroimaging method, magnetic resonance imaging (MRI), which allows researchers to measure whole brain activity non-invasively, with a high degree of spatial precision (~ up to 1 mm in fMRI; e.g., Suthana et al., 2014) and reasonable temporal resolution (up to 10Hz; LeVan et al., 2018).

To date there has been no systematic literature review of studies that have examined the specific impact of CBT-I as an insomnia intervention using magnetic resonance imaging outcomes. Therefore, the current review aimed to evaluate studies that have provided a neuroimaging assessment of CBT-I treatment in individuals with insomnia. Findings will complement existing psychological and behavioral knowledge of the multidimensional

experience of insomnia by furthering neurocognitive understanding of the impact of CBT-I treatment.

Method

The current systematic literature review followed the general reporting principles for the preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P; Moher et al., 2015).

Search Strategy and Selection Criteria

Online databases Google Scholar, PubMed Central (PMC), PsycINFO, and Scopus were searched from their inception to 16th December 2020. Due to the limited research in the field, no time parameters were set. A title and word search strategy was conducted using the terms: "cognitive behav* therapy for insomnia" or "CBT-I" or "CBTi" or "insomnia-related CBT" AND "objective measures" or "functional resonance imaging" or "fMRI" or "MRI" or "neuroimag*". A flow chart of the search process is displayed in Figure 1 [*Figure 1 near here*].

The first and second review authors independently assessed all reviewed studies regarding their internal and statistical validity and have reported any identified issues in the manuscript (e.g., small sample sizes). This individual assessment of study quality was employed since standard clinical trial ratings cannot be readily applied to experimental neuroimaging studies – particularly task-based studies – due to their complex and idiosyncratic nature. Given the fact-based focus of data extraction and the relatively low number of studies involved, there was no disagreement between authors regarding eligible studies. Additionally, the authors qualitatively identified similarities and dissimilarities between the studies based on the extracted criteria (i.e., study design and outcomes). Included studies met the following selection criteria: (a) published empirical research; (b) recruited human adult participants (minimum 18 years of age); (c) administered a form of

CBT-I treatment; and (d) provided pretest and posttest measures using MRI or fMRI (task-based performance or resting-state) data. Non-English literature was excluded from the review. See Table 1 for a detailed summary of the eligible studies.

Figure 1

Flow Chart of Included Studies

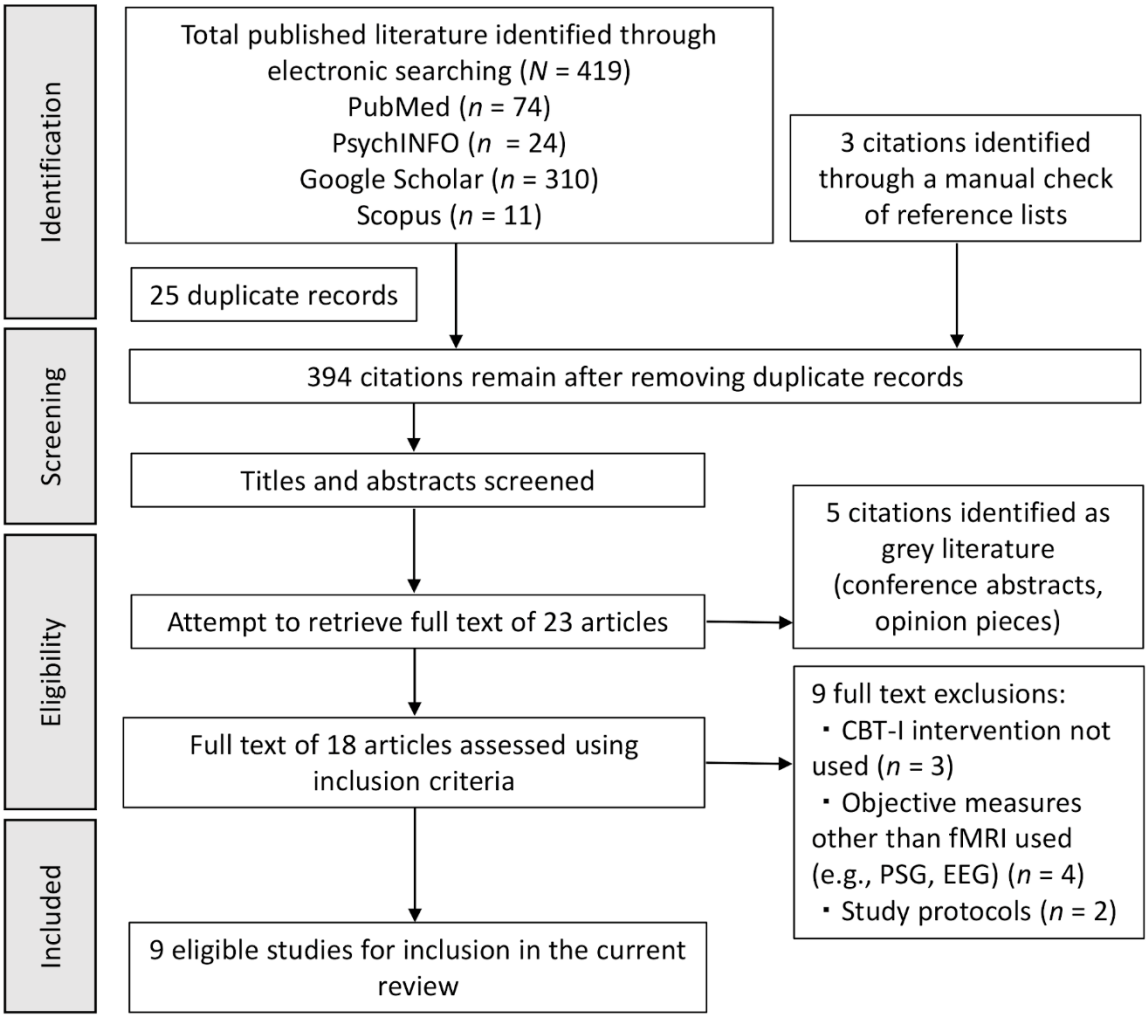

Table 1

Characteristics of Included Studies in the Systematic Literature Review

First author and date	Sample, Age (*M* ± *SD*), Recruitment Population	Study Design	Insomnia Diagnostic Criteria	Treatment Group(s)	CBT-I Treatment	Medication status	Method and Measures
Altena et al., 2008	Chronic insomnia group = 21 (60 years ± 8.2; 4 women); matched wait-list control group = 12 (61 years ± 6.2; 3 women).	Quasi-experimental	Chronic insomnia (CI), lasting for at least 2.5 years based on established qualitative and quantitative insomnia diagnostic criteria.	Exclusion criteria: sleep apnoea, severe restless legs or periodic leg movement syndrome, and somatic disorders that effect sleep.	Six weeks of CBT-I together with sleep restriction, morning and late afternoon bright light exposure, and body temperature manipulations. Weekly telephone-follow-ups treatment on the basis of patients' reports.	Medication-free for 2-month minimum.	fMRI scanning during category and letter fluency blocked design tasks. Participants pressed a button when a covertly generated word was presented that either belonged to a category or started with a letter displayed on screen.
Hwang et al., 2019	Chronic Insomnia Disorder (CID) = 21 (46.9 years ± 11.9; 16 women); GS = 25 (39.1 years ± 13.2; 19 women); recruited from psychiatry outpatient clinic at Seoul National University Hospital.	Quasi-experimental	Chronic Insomnia Disorder (CID) criteria of DSM-IV (APA, 1994).	Screened for comorbid psychiatric disorders, sleep apnoea, shift work.	Five weeks of 90-minute CBT-I with a certified psychologist that addressed cognitive strategies to reduce psychological distress, alter dysfunctional sleep beliefs, stimulus control, sleep restriction, sleep hygiene education.	Five-day minimum wash-out period for medication that influences sleep (e.g., hypnotics, sedatives).	Colour–word Stroop task with block design consisting of congruent (e.g., "red" displayed in red ink) and incongruent (e.g., "red" displayed in blue ink) trials were randomly intermixed.

Kim et al., 2017	Psychophysiological insomnia (PI) group = 14 (49.0 years ± 12.3 years; 10 women); Good Sleepers (GS) group = 18 (42.7 years ± 12.3 years; 14 women); Center for Sleep and Chronobiology, Seoul National University Hospital and community advertisements.	Quasi-experimental	PI criteria of ICSD-2 (AASM, 2005).	One-on-one physician assessment for medical problems; no comorbid psychiatric disorders assessed using DSM-IV (SCID-IV); screened for brain lesions and other sleep disorders (e.g., obstructive sleep apnoea) using PSG, no use of psychotropic medication.	Five sessions of CBT-I delivered face-to-face by two psychologists.	Drug-free state.	Brain response to visual sleep-related stimuli (SS) and neutral stimuli (NS) pre and post-CBT-I treatment assessed. fMRI experiment used a block design. Presentation of 28 sleep-related and neutral stimuli consisting of pictures taken by researchers and selected Internet images.
Kim et al., 2019	Psychophysiological insomnia (PI) group = 14 (10 women), 49.0 ± 12.3 years, recruited from Center for Sleep and Chronobiology, Seoul National University Hospital.	Quasi-experimental	PI criteria of ICSD-2 (AASM, 2005).	No comorbid psychiatric disorders assessed using DSM-IV (SCID-IV); screened for brain lesions and other sleep disorders (e.g., obstructive sleep apnoea) using PSG, no use of psychotropic medication.	Five weekly sessions (each 90-minutes in duration) individual CBT-I were delivered by two psychologists. A modified CBT-I protocol focused on sleep time restriction and stimulus control therapy.	5-day drug washout period.	Block design featuring auditory SS (e.g., alarms sounds, ticking clock, heartbeat sound) and white noise (NS) sound trials were randomly intermixed; SS and NS trials were each presented four times. Participants were asked to rate whether the sounds were related to sleep or insomnia.

Lee et al., 2018	Psychophysiological insomnia (PI) group = 13 (51.0 ± 10.2 years; 10 women) recruited from Center for Sleep and Chronobiology, Seoul National University Hospital; Good Sleepers (GS) group = 18 (42.7 ± 12.3 years; 14 women) were recruited via community advertisements.	Quasi-experimental	PI criteria of ICSD-2 (AASM, 2005).	No comorbid psychiatric disorders assessed using DSM-IV (SCID-IV); screened for brain lesions and other sleep disorders (e.g., obstructive sleep apnoea) using PSG; no use of psychotropic medication.	5 x 90 minute face-to-face sessions of individual CBT-I delivered across 5 weeks. Include a modified CBT-I protocol (Edinger & Carney, 2008).	Four PI participants were taking the hypnotic zolpidem had a wash-out period of 7 - 30 prior to trial commencement.	Resting-state functional connectivity (FC) analyses were performed.
Marques et al., 2020	Two male participants (aged 43 and 53 years); Sleep Medicine Centre of Coimbra University Hospital Centre, Portugal	Single-group	Chronic Insomnia Disorder (CID) criteria of ICSD-3 (AASM, 2014)	No other sleep or psychiatric disorders.	Ten psychotherapy sessions on a monthly-basis across 12-months; first two sessions comprised structured psychological and clinical assessment.	Non-medicated.	Resting-state fMRI (rs-fMRI) period of 12-minutes, in which eyes were open and closed in two-minute intervals. Recorded instructions were administered through headphones, and participants alternated between fixating on a central point on the screen or closed their eyes.
McCrae et al., 2018	All participants diagnosed with fibromyalgia (FM) and comorbid insomnia. RCT treatment groups: CBT-I = 14 (59.5 ± 9.9 years; 14 women); CBT-Pain = 16 (50.8 ± 14.4 years; 14 women); and, 7 wait-list control (60.3 ± 7.18 years; 7 women); community recruitment.	Randomized control trial (RCT)	Insomnia diagnosis based on ICSD-2 (AASM, 2005) and research criteria.	Non-blinded treatment groups.	8 weekly 50-minute individualised sessions administered by doctoral clinical psychology students. CBT-I intervention consisted of sleep education and training on sleep hygiene, stimulus control, autogenic relaxation, sleep restriction, cognitive therapy, long-term maintenance.	Prescription and over-the-counter sleep medications were permitted.	Structural MRI data.

Park et al., 2020	17 adults with insomnia (*M* age not specified; 13 women) undergoing haemodialysis (n = 5) or peritoneal dialysis (n = 12).	Quasi-experimental	Primary Insomnia criteria of DSM-IV (APA, 1994).	Screened for comorbid psychiatric disorders, sleep apnoea, other active medical conditions, severe vision or hearing impairment.	Nine sessions of self-directed computerised CBT-I. Sessions were 30-minutes tri-weekly administered either in the dialysis unit during treatment or at home. Treatment was a modified CBT-I protocol that included hygiene education, sleep restriction, and stimulus control, and challenging sleep misconceptions.	Maintenance dialysis.	Resting-state fMRI. During the scans, participants were instructed to keep their eyes open and fixate on a white cross at the centre of a screen.
Stoffers et al., 2014	Primary insomnia = 24 (60.3 years ± 6.0 years; 17 females) and 13 control subjects (60.1 years ± 8.3 years; 9 women) and 14 good sleepers (control) matched for age, gender, and education; recruited using community advertisements and invitations from a sleep disorders outpatient clinic.	Quasi-experimental	Chronic Insomnia Disorder (CID) diagnosed according to DSM-IV-TR criteria (APA, 2000).	Screened for sleep disorders, cognitive functioning impairments, and (comorbid) disorders.	Replicated 6-week period of intense non-pharmacological multi-modal insomnia treatment that included CBT-I and chronotherapeutic intervention.	Minimum abstinence from hypnotic medication for at least 2 months.	Participants performed Tower of London task trials with four difficulty levels.

Results

Study Components

Participant Characteristics

Samples across the studies had group sizes ranging between 2 and 25 participants. Six of the nine studies that compared insomnia groups with good sleepers, waitlist, and/or control groups had similar sample sizes and age statistics. The insomnia samples ranged between 13 and 24 participants (M_{age} = 54.5 years; SD_{age} = 6.2 years); whereas, the waitlist or control groups ranged from 12 to 25 participants (M_{age} = 51.0 years; SD_{age} = 10.5 years).

Insomnia diagnostic criteria were based on the APA's *DSM-IV* (4th ed.; 1994), the *DSM-IV-TR* (4th ed., text rev.; APA; 2000), the American Academy of Sleep Medicine's (AASM) *International Classification of Sleep Disorders: Diagnostic and Coding Manual* (2nd ed.; ICSD-2; 2005), or the *ICSD-3* (3rd ed.; AASM, 2014) in all but one study (Lee et al., 2018), which based insomnia diagnosis on established qualitative and quantitative benchmarks (see Buysse et al., 2006; Edinger et al., 2004; Lichstein et al., 2003). Screening for comorbid disorders and medical conditions (e.g., depression, obstructive sleep apnoea) was consistent across the studies. Two-thirds of the studies noted that participants were screened for brain lesions. Participants were otherwise medically healthy, except for McCrae et al.'s (2018) participants, who had comorbid fibromyalgia, and Park et al.'s (2020) participants, who were undergoing haemodialysis or peritoneal dialysis. Hypnotic medication and sedative wash-out periods ranged from 5 days to 2 months, although McCrae et al. (2018) permitted prescriptions and over-the-counter sleep medications.

Cognitive Behavioral Therapy for Insomnia (CBT-I) Intervention

CBT-I administration ranged from five 90-minute weekly sessions in the studies conducted by Hwang et al. (2019), Kim et al. (2017), Kim et al. (2019), and Lee et al. (2018) to eight sessions across 12 months in Marques et al.'s (2020) study. Therapy was

administered in-person by trained personnel, except for Park et al.'s (2020) study, which used self-directed computerised CBT-I (cCBT-I) delivered across 3 weeks.

Neuroimaging Assessment

Participants performed task-based activities during fMRI scans in five studies, of which four used visual block design tasks. In particular, Altena et al. (2008) assessed letter and category word fluency, while Hwang et al. (2019), Kim et al. (2017), and Stoffers et al. (2014) administered the colour–word Stroop task, sleep stimuli imagery, and Tower of London task, respectively, during scans. The fifth study by Kim et al. (2019) randomly presented auditory sleep stimuli (e.g., alarm sounds, ticking clock, heartbeat) and white noise. Kim et al.'s (2019) participants rated whether the sounds related to sleep or insomnia. Of the four remaining studies, three used resting-state fMRI (rs-fMRI), during which participants were instructed via headphone voice recordings to keep their eyes open and fixate on a central point or to close their eyes. The one remaining study examined CBT-I effects on cortical thickness using pretest and posttest structural MRI data (McCrae et al., 2018).

Discussion

The present review aimed to evaluate studies that had examined the impact of CBT-I on individuals with insomnia using neuroimaging measures. Nine studies met current review selection criteria. Overall, cognitive function differences were observed in MRI and fMRI data of participants with insomnia following CBT-I treatment.

Support for Theoretical Models of Insomnia

Across five studies that used task stimuli during fMRI scans, participants with insomnia showed abnormal patterns of brain activity compared to baseline measures or controls. Altena et al. (2008) observed hypoactivation of the medial and inferior prefrontal cortical areas in individuals with insomnia compared to controls, during performance of executive function tasks that involved letter and category fluency measures. The hypoactivation in the frontal cortex was accompanied by reduced performance in their tasks,

indicating the abnormally reduced patterns of brain activity were related to functional impairments caused by insomnia. Importantly, following CBT-I intervention, sleep patterns, cognitive-behavioral deficits, and the brain activity patterns normalised, indicating treatment success. It should be noted, however, that the sample of treated patients was quite small (i.e., $n = 10$), which required the authors to rely on a relatively lenient statistical significance threshold. Stoffers and colleagues (2014) also identified hypoactivation in insomnia patients, but those were located in the striatum (i.e., caudate nucleus) rather than the frontal areas identified by Altena et al. (2008). Notably, while the CBT-I treatment in this study appeared effective in ameliorating the insomnia symptoms, the striatal hypoactivation did not subside. Furthermore, the striatal hypoactivation was also not correlated with behavioral performance in the executive tasks employed in the study (i.e., Tower of London Test), suggesting that the abnormal pattern of brain activity is more indicative of a general risk factor for insomnia rather than being causally related to cognitive effects of the insomnia.

In contrast to the two aforementioned studies, Hwang et al. (2019) did not observe altered cognitive performance and related brain activity using a colour-word Stroop task following CBT. It is important to note, however, that only 14 participants were used for the pre- vs. post- CBT-I comparison, and considering a quite conservative statical threshold was employed, it is not entirely surprising that no differences in brain activity were detected.

Kim and colleagues (2017) took a different approach; instead of focussing on cognitive performance measures and related-brain activation, they sort to capture brain activity in response to sleep-related visual stimuli (e.g., bed, moon) as a biomarker for insomnia. Firstly, higher activity in response to sleep-related images was observed in Kim et al.'s (2017) patients compared to control; and those activations were located in well-known visual attention-related areas (e.g., fusiform gyrus, posterior-parietal cortex, cingulate cortex). More importantly, they found that the strength of the increased differential response to sleep-related images was reduced after CBT-I. Kim and colleagues (2019) corroborated these

results in a follow-up study using auditory sleep-related stimuli (i.e., snoring, alarm clocks), which also suggested that the brain activity in response to sleep-related sounds decreased after CBT-I treatment. In terms of behavioral outcomes, Kim et al. (2019) found that reductions in response to sleep stimuli appeared to be associated with decreases in wake time after sleep onset (WASO; total minutes awake between sleep onset and final awakening) recorded using sleep diaries. The results by Kim and colleagues are consistent with the cognitive model of psychophysiological insomnia (Espie et al., 2006). This paradigm, known as the attention-intention-effort pathway model, suggests that selective attention to sleep stimuli reinforces a preoccupation with sleep, which in turn increases sleep-related anxiety and maintains insomnia.

In contrast to the task-based fMRI activity approach employed by the previous five studies in this review, resting-state fMRI has been used to investigate potential abnormal brain activation patterns due to insomnia. Two prior resting-state studies explored the homogeneity (Dai et al., 2014) and regularity (Zhou et al., 2016) of spontaneous brain activity in individuals with insomnia compared to controls and found that the task-less approach provided a reliable biomarker. Two further studies focused on the diagnostic potential and suitability of resting-state fMRI to evaluate treatment efficacy (Lee et al., 2018; Marques et al., 2020). Marques et al. (2020) observed differences between pre- and post- CBT-I intrinsic brain connectivity contrasts in the anterior default-mode, visual, and auditory resting-state networks. Notwithstanding their small sample (n = 2), which has limited their findings' generalisability, Marques et al.'s results are consistent with the hyperarousal model of insomnia (Perlis et al., 1997). In this model, insomnia is considered the combined effect of genetic vulnerabilities in sleep-inducing brain activity, psychosocial stressors, and behavioral factors that are influenced by dysfunctional sleep beliefs, learned sleep associations, and anxiety (Riemann et al., 2010). Similarly, Lee et al. (2018) observed significant differences between insomnia participants and good sleepers in the resting-state

functional connectivity of the basal ganglia, amygdala, hippocampus, and thalamus. Furthermore, consistent with Kim et al.'s (2019), Kim et al.'s (2017), and Altena et al.'s (2008) findings, Lee et al. (2018) also observed altered brain responses in individuals with insomnia following 5-weeks of CBT-I treatment, suggesting that CBT-I improves the functional connectivity in the frontoparietal network while reducing hyperarousal through decreases in thalamus activity. The changes in functional connectivity observed by Lee et al., (2018) were found to significantly correlate with increased sleep efficiency (i.e., percentage of total time in bed spent sleeping) based on patient's sleep diary records.

The advantage of using a task-free approach is that it requires minimal patient compliance and can be easily standardised across laboratories. On the downside, the analytical approaches for resting-state data vary considerably, so that it is not straightforward to compare the outcomes among different studies in terms of the specific connectivity profiles.

Complementing the functional imaging approaches, also the use of structural imaging has revealed promising outcomes for assessing the effectiveness of CBT-I. Specifically, McCrae et al.'s (2018) structural MRI data revealed cortical thickness increases in participants with insomnia following CBT-I, suggesting that CBT-I may reverse cortical gray matter atrophy due to sleep deprivation. These changes observed in an extensive network, incorporating areas in the frontal, temporal, and cingulate cortex, were found to be associated with reductions in WASO assessed using sleep diary records. However, McCrae et al.'s results have limited generalisability as all participants had comorbid fibromyalgia. Further, the authors did not provide a long-term assessment of apparent treatment effects, which highlights an opportunity for future longitudinal research designs. Collectively, present studies offer preliminary support that CBT-I treatment effects are related to the recovery of regional task-related activity, resting-state intrinsic activity and connectivity, and brain morphology.

Inconsistencies in CBT-I

Across all studies, CBT-I was guided by established protocols (Edinger & Carney, 2014; Morin, Hauri et al., 1999) comprising behavioral, cognitive, and educational components. While the recommended delivery of CBT-I remains between six and eight weekly or fortnightly sessions (Jansson-Fröjmark & Norell-Clarke, 2016), four studies administered only five sessions – one session less than the minimum recommended therapeutic duration – and one study administered eight treatment sessions across 12 months. Since only two-thirds of the studies met recommended CBT-I treatment guidelines, neuroimaging data may not reflect full CBT-I treatment effects. Additionally, details on between-session communication with participants were omitted by all studies but one, which reported weekly telephone calls to participants to follow-up treatment progress (Altena et al., 2008). Since motivational support has been found to improve insomnia treatment outcomes (Lancee et al., 2013), observed improvements may be attributable to maturation effects. Further, Altena et al. (2008) and Stoffers et al. (2014) supplemented the CBT-I intervention with light therapy. However, due to the combination of therapeutic interventions, CBT-I treatment efficacy in their studies was confounded.

We considered expanding the review search criteria to include neurocognitive studies that had examined particular components of CBT-I (e.g., relaxation training, cognitive reframing). While this may have increased the number of studies included in the review, it was decided to retain a strong focus on CBT-I to enable better comparability of the outcomes. Notwithstanding, the homogenous administration of CBT-I intervention and detailed intervention reporting is recommended for future study designs.

Study Design and Participant Disparities

Differences in functional brain activity between individuals with insomnia and good sleepers can contribute a pathophysiological understanding of insomnia disorder and help guide direction for treatment (Riemann et al., 2011). Since one-third of studies lacked a

waitlist or control group, it is not possible to determine whether observed changes in brain activity were due to the CBT-I intervention. Trials with controls will increase the internal validity of future study designs. It is also important to recognise that the experience of insomnia has significant variability because the disorder comprises multiple dimensions, including dysfunctional sleep beliefs, selective attention biases, coping strategies, which occur in unique combinations (Morin et al., 2011). Treatment effects are likely to vary even within insomnia samples. Therefore, larger samples are needed to increase statistical power to detect differences in baseline and posttest CBT-I treatment outcomes. Such insights will add to the existing behavioral and psychological understanding of insomnia.

The studies in the present review had several strengths. Each study used stringent exclusion criteria based on commonly occurring comorbid disorders to reduce the risk of confounding factors in observed treatment effects. However, the strict criteria contributed to the small sample sizes. In terms of participant demographics, the mean age was largely consistent across treatment groups and controls. This presented another strength of the studies in the current review, since sleep architecture changes with age; that is, older adults (≥ 65 years) tend to experience reduced sleep efficiency and more strongly endorse dysfunctional beliefs about sleep than middle adults (Neikrug & Ancoli-Israel, 2010). Two studies also matched controls using age, gender, and education demographics. This is an important study design feature since education can significantly influence neuroimaging measures of task-based cognitive function (Lezak et al., 2004).

Notwithstanding the current strengths, the studies had limitations. All studies but one had a higher representation of female participants. This gender imbalance is problematic since biological influences have been linked to differences in sleep quality, sleep-onset latency, and sleep efficiency experienced by women compared to men (Krishnan & Collop, 2006). Separate assessment of men and women may help to identify potential sex-based differences in CBT-I treatment effects. This is a central consideration for future research

since approximately 20% of insomnia patients within clinical trials do not respond to CBT-I (Morin, 2002). Studies that compare specific participant characteristics can help to build a profile of CBT-I responders. In particular, future neuroimaging research may be able to determine whether there is a distinct neural pattern between CBT-I responders and non-responders (Marques et al., 2016), of which larger and more homogenous samples will assist. An additional study weakness was the significant disparity in medication usage, with some studies permitting a minimum 5-day wash-out for participants. It is possible this minimum period was insufficient to ensure results were not confounded by medication effects (Vignola et al., 2000).

Limitations of the Current Review

Of the nine studies that met current inclusion criteria, one study appeared to be a data subset of another study, and one had only two participants, which has limited the generalisability of the results summarised in the present review. Quasi-experiemental studies without waitlist or control groups were also included in the review. Gender-balanced waitlists or healthy controls would be a preferable study design for future testing to eliminate confounding factors. In addition, the present review lacked a quality assessment that addressed whether each study employed appropriate image processing and thresholding method. It is also important to note that fMRI data does not lend itself to classical effect size measures; instead, it focuses on identifying specific patterns of activity associated with the disorder and the treatment. So, while fMRI analysis involves statistical testing across thousands of brain voxels, the outputs are essentially treated qualitatively. That is, the outputs identify the areas that are activated and the usual function of those areas. Accordingly, a qualitative systematic review style was selected for the current review as opposed to a quantitative meta-analytic approach.

Conclusion

The present systematic literature review identified nine studies that examined the efficacy of CBT-I for individuals with insomnia using magnetic resonance imaging measures. The reviewed research provides evidence for abnormal brain activity patterns in individuals with insomnia. More specifically, altered patterns of brain activity included reduced task-related engagement of frontal and striatal brain regions and apparent dysregulation in default-mode brain connectivity patterns. Most importantly, those abnormal patterns of brain activity, connectivity, and even morphology appeared to reverse following CBT-I treatment.

The evidence summarised in the current systematic review suggests that distinct neurocognitive changes may be associated with CBT-I treatment. Specifically, the neuroimaging findings indicate that CBT-I reverses neurofunctional abnormalities associated

with sleeping disorders, and therefore complements behavioral measures of CBT-I efficacy. In the future, neuroimaging could have utility in clinical practice, not only as a measure of overall CBT-I treatment efficacy but as a guide for psychological treatment strategies that target specific activation specific areas of the brain. Future studies could assess how altered brain activity relates to other sleep outcomes measures of CBT-I, such as sleep quality. In particular, future studies could look to provide greater detail of the CBT-I treatment administered to participants. This would facilitate an opportunity to examine correlations between treatment modules and their neurocognitive findings.While larger trials with controls are desirable, the reviewed studies offer evidence for CBT-I efficacy at a neuronal level. This initial body of work complements evidence from sleep physiology, cognitive-behavioral performance, and self-reports that supports CBT-I as an effective non-pharmacological treatment for insomnia.

Acknowledgements

No financial support was provided for the conduct of the research and/or preparation of the article.

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