

Review

Neurophysiology and Molecular Basis of Cognitive Behavioral Therapy for Patients with Insomnia: Implications for Non-Pharmacological Approaches

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Abstract

Cognitive behavioral therapy for insomnia (CBT-I) is a widely used psychological intervention known for its effectiveness in improving insomnia symptoms. However, the neurophysiological mechanisms underlying the cognitive-behavioral treatment of insomnia remain unclear. This narrative review aimed to elucidate the neurophysiological and molecular mechanisms of CBT-I, focusing on the fields of psychology, neurophysiology, neuroendocrinology, immunology, medical microbiology, epigenetics, neuroimaging and brain function. A comprehensive search was conducted using databases including: PubMed, Embase, PsycINFO and Web of Science, with customized search strategies tailored to each database that included controlled vocabulary and alternative synonyms. It revealed that CBT-I may have a beneficial effect on the central nervous system, boost the immune system, upregulate genes involved in interferon and antibody responses, enhance functional connectivity between the hippocampus and frontoparietal areas and increase cortical gray matter thickness. In conclusion, an integrated model is proposed that elucidates the mechanisms of CBT-I and offers a new direction for investigations into its neurophysiological mechanisms.

Keywords: insomnia disorder; cognitive behavioral therapy for insomnia; brain function; neurophysiology; neuroendocrine

1. Introduction

Sleep is a complex neurobiological phenomenon that involves multiple molecular pathways, neurotransmitter release, synaptic activity and factors modulating neuronal networks [1]. The synaptic homeostasis hypothesis suggests that sleep promotes global synaptic weakening, which offsets the global synaptic strengthening that occurs during wakefulness [2]. This reflects the bidirectional relationship between sleep–wake cycles and neuronal plasticity [1], highlighting that the regulation of sleep is a complex process involving numerous molecular interactions [3,4]. Insomnia disorder, a common and often unavoidable sleep disorder, has become a major public health concern that has gradually attracted recent societal attention [5,6].

Cognitive behavioral therapy for insomnia (CBT-I) is one of the most widely used psychological interventions owing to its efficacy [7]. Both the American Academy of Sleep Medicine [8] and the American College of Physicians [9] have recommended CBT-I as a preferred modality for the treatment of insomnia. This therapy significantly improves the symptoms of insomnia by shortening sleep latency and nighttime awakenings, increasing total sleep time and sleep efficiency and correcting irrational sleep beliefs. Additionally, CBT-I enhances sleep quality and reduce daytime dysfunction resulting from impaired sleep [7], with the added benefits of sustained efficacy and minimal side

effects [10,11]. CBT-I has also demonstrated efficacy as an intervention for various psychiatric disorders, including depressive disorders [12], bipolar disorder [13], post-traumatic stress disorder [14] and generalized anxiety disorder [15]. Furthermore, CBT-I has been shown to be an effective treatment for comorbid insomnia associated with somatic disorders, such as cancer [16], heart failure [17], chronic pain [18], Alzheimer's disease [19] and Parkinson's disease [20]. For example, among cancer survivors, CBT-I has shown improvements in sleep efficiency, wake after sleep onset and sleep latency [21].

Studies suggest that while the efficacy of CBT-I is well documented, a small number of patients do not respond to this therapy, and their symptoms do not improve in clinical practice. The effectiveness of CBT-I is typically assessed clinically using scales [22,23]; however, the subjective nature of these tools limits understanding of the biological mechanisms of CBT-I. Interestingly, research has shown that structural and functional changes in the brain occur during learning and this capacity persists throughout an organism's lifespan [24]. Psychotherapy, such as CBT-I, involves learning and practicing new skills until they become habitual and integrate into an individual's personality [25]. In this narrative review, the aim is to explore the biological mechanisms of CBT-I from various perspectives by systematically analyzing the existing literature. Two researchers independently searched PubMed, Embase, PsycINFO and



Table 1. Research agenda.

A more comprehensive neuroanatomical framework is required to facilitate the investigation of the biological mechanisms underlying cognitive behavioral therapy for insomnia (CBT-I).
To gain a deeper understanding of the biological parameters that change during the different phases of CBT-I, including the follow-up phase, conducting a more detailed and larger sample size experimental design is necessary. Furthermore, identifying the specific biological mechanisms involved is essential.
The biological mechanisms of CBT-I are complex and multifaceted; this study aims to provide a more comprehensive understanding of these mechanisms and their underlying implications.
Research should focus on utilizing diverse biological indicators to determine the suitability of CBT-I for different individuals and to accurately assist its clinical efficacy.

Web of Science, tailoring search strategies for each database that incorporated controlled vocabulary and alternative synonyms, including: (1) insomnia; (2) concepts of cognitive behavioral therapy, including individual intervention components (e.g., stimulation control); and (3) factors related to psychology, neurophysiology, neuroendocrinology, immunology, medical microbiology, epigenetics, neuroimaging and brain function. To identify additional articles, the researchers manually examined each reference including those cited in each study and related meta-analyses. The search dates covered from the inception of each database to September 2023. Subsequently, two investigators independently reviewed all the retrieved articles. Specifically, the study aimed to determine the impact of CBT-I (intervention) on the physiological functions of individuals with insomnia. By integrating the potential mechanisms through which CBT-I operates, it was aimed to develop a more comprehensive research agenda (Table 1) that would enhance the utility of this focused review for clinicians and researchers engaged in the non-pharmacological treatment of insomnia.

2. Psychology

CBT-I is rooted in cognitive and behavioral theories that emphasize the significance of thoughts and feelings. It examines how an individuals' perceptions and interpretation of life events influence their behavior. From a cognitive perspective, negative cognition, negative affect and insomnia are interrelated, with cognitive factors mediating emotional and behavioral responses [26]. For example, patients are encouraged to modify negative thoughts about sleep, including techniques such as 'de-catastrophizing', which addresses exaggerated perceptions of the consequences of sleep deprivation [27,28]. Cognitive enhancements, such as sleep hygiene education, can improve sleep quality by controlling attention and bolstering compliance [29]. Cognitive changes are crucial mechanisms for alleviating the severity of insomnia. These changes reduce wakefulness after sleep onset (WASO), enhance sleep efficiency (SE) [30], improve mood and relieve fatigue and stress [26,31,32]. Moreover, pre-therapy cognitive dispositions, such as a sense of sleep-related helplessness, can be a positive indicator of CBT-I outcomes [33]. Behavioral

techniques, such as sleep restriction and stimulus control, can reduce sleep latency and time awake after sleep onset, increase sleep efficiency and mitigate the overall severity of insomnia [34,35].

3. Neurophysiology

CBT-I may exert a beneficial effect on the central nervous system (CNS). Following CBT-I, reductions in cortical hyperarousal were observed near bedtime and during sleep onset [36], along with improvement in sleep fragmentation parameters. Additionally, the duration of rapid eye movement (REM) sleep and slow wave activity significantly increased, while delta waves increased and high-frequency electroencephalogram (EEG) β and sigma activity decreased [36,37], this effectively reduced sleep latency [36] and WASO [38,39]. Moreover, individuals with insomnia who underwent behavioral therapy showed a decrease in 13- to 31-Hz relative power in their pre-sleep EEG [35]. CBT-I may enhance daytime wakefulness, nighttime sleep drive, improve sleep structure and increase the speed of decline in EEG delta power [37]. A previous sleep microarchitecture study suggested that a relatively low peak EEG delta power in the first non-rapid eye movement (NREM) period and a slow decline in peak EEG delta power during the pre-treatment NREM period predicted a better response to CBT-I [40]. Further research suggested that lower spindle density may be a susceptibility factor for stress-related sleep problems [41]. Lower spindle density at pre-treatment predicted a poorer response to CBT-I, as reflected by a smaller reduction in the Pittsburgh Sleep Quality Index (PSQI) over time [42]. Similarly, studies have confirmed that some alterations in brain function are reversible in patients with insomnia; for instance, hypoactivation of the medial and inferior prefrontal cortical areas, common in insomnia, was found to be reduced. Altena *et al.* [43] reported that CBT-I can reverse this change in brain function. This was observed through changes in prefrontal blood oxygen level-dependent responses during verbal fluency task. Additionally, patients with insomnia showed a relative decrease in regional glucose metabolism in the prefrontal areas [44]. In another study, activation of the basal ganglia was observed after behavioral therapy [45].

One study investigated brain function during cognitive tasks and changes in brain activity before and after six weeks of CBT-I in elderly patients with chronic insomnia. The study found that insomniacs reduced hypoactivation in the medial and inferior prefrontal cortical areas, but this hypoactivation was reversed after receiving CBT-I [43], suggesting that CBT-I improves hyperarousal in insomnia. However, no significant differences were found in a Stroop task and task-related brain activation between individuals with insomnia and controls. Although behavioral performance or brain activation did not change after CBT-I, improvements in an Insomnia Severity Index scores were significantly correlated with changes in the left supramarginal gyrus during the Stroop task [46]. This suggests that improvement in insomnia is associated with task-related cerebral function.

While previous studies have mostly used cognitive tasks to explore brain function in insomnia, more recent studies have focused on brain activity in response to sleep-related stimuli. Baglioni *et al.* [47] found that amygdala activation was significantly higher when patients with insomnia processed sleep-related picture stimuli and that this activation was negatively correlated with total sleep time, SE, slow wave activity and REM sleep and positively correlated with sleep onset latency. In 2019, Kim *et al.* [48] investigated changes in brain activity during the processing of sleep-related sounds in patients with unmedicated insomnia after CBT-I and found reduced functional activity in the left middle temporal gyrus and middle occipital gyrus post-treatment compared to pre-treatment. Correlation analyses showed that post-treatment scores on the Dysfunctional Beliefs and Attitudes Scale were associated with task-state thalamic activities and the degree of decrease in activity was also correlated. Recent studies using functional magnetic resonance imaging (fMRI) have explored the neural mechanisms underlying CBT-I and have found reduced functional thalamic-prefrontal connectivity and enhanced resting-state brain connectivity between the default network and the premotor/dorsolateral prefrontal cortex following treatment [49,50]. A study has examined structural and functional brain changes in CBT-I-treated patients with fibromyalgia and insomnia, revealing that this treatment improved brain atrophy and increased gray matter volume in brain regions, such as the orbitofrontal cortex and posterior cingulate [51]. Additionally, the degree of functional brain improvement was more pronounced after the use of CBT-I [52].

4. Neuroendocrinology and Immunology

Several studies have shown that the immune system is involved in various central nervous system disorders, including anxiety, depression, schizophrenia, stroke and autoimmune and neurodegenerative diseases [53–56]. Studies on psychosocial interventions to enhance and improve immunity suggest that the immune system is influenced by

social, neurocognitive and behavioral factors [57,58]. Additionally, psychosocial factors such as life stress, negative emotions and social support significantly affect immune function [59,60]. Chronic stress has been reported to suppress cellular and humoral immunity and increase non-specific inflammation; for example, psychosocial resilience factors such as social support reduces the negative impact of life stress on immune function and health [61].

CBT-I has been shown to alleviate insomnia severity while significantly reducing the inflammatory marker C-reactive protein (CRP) by more than 50% [62]. This reduction corresponds with a decrease in the systemic inflammatory response, which can remain low for extended periods. Improving insomnia has been shown to play a key role in reducing CRP levels [62]. CBT-I reverses the activation of molecular inflammatory signaling pathways and reduces the expression of pro-inflammatory mediator genes. Additionally, functional secretion levels of interferon- γ and interleukin-1 β (IL-1 β) significantly increase during CBT-I treatment, potentially associated with the relief of symptoms such as psychological distress and fatigue. Furthermore, leukocyte and lymphocyte counts tend to increase significantly from the end of treatment to the follow-up period, reflecting a delayed effect; these increases correlate with improvements in insomnia and fatigue [63]. CBT-I also decreases the cytokines interleukin-6 and tumour necrosis factor- α (TNF- α), which may relieve somatic pain [64]. Overall, CBT-I improves insomnia by modulating inflammatory cytokines and enhancing immune functions [63]. Previous studies have shown that sleep and cytokine expression interact and influence each other [64].

5. Microbiology-Gut Brain Axis

The gastrointestinal tract plays a key role in the functioning of the body as it is constantly in contact with dietary elements and diverse gut microorganisms [65,66]. A previous study has found significant alterations in the gut microbiota of individuals with insomnia compared to that of a healthy population, including differences in composition, diversity and metabolic function [67]. Gut microbiota is essential for maintaining overall health and an imbalance in gut flora leads to various neuropsychiatric disorders through the neuroimmune system, microbial metabolites and other substances. Although there is limited research on the effects of CBT-I on gut flora, CBT is known to be effective in the treatment of neuropsychiatric disorders. A significant interaction exists between gut microbiota biorhythms and sleep [68]. Additionally, changes in sleep architecture affect the rhythmic characteristics of flora and several studies have found that sleep deprivation affects the expression of biological clock genes and the composition of gut flora [69–71]. In previous clinical studies, CBT treatment was found to significantly alter the composition and metabolites of the intestinal flora in patients. Lactobacillus levels increased and anaphylactic bacteria levels

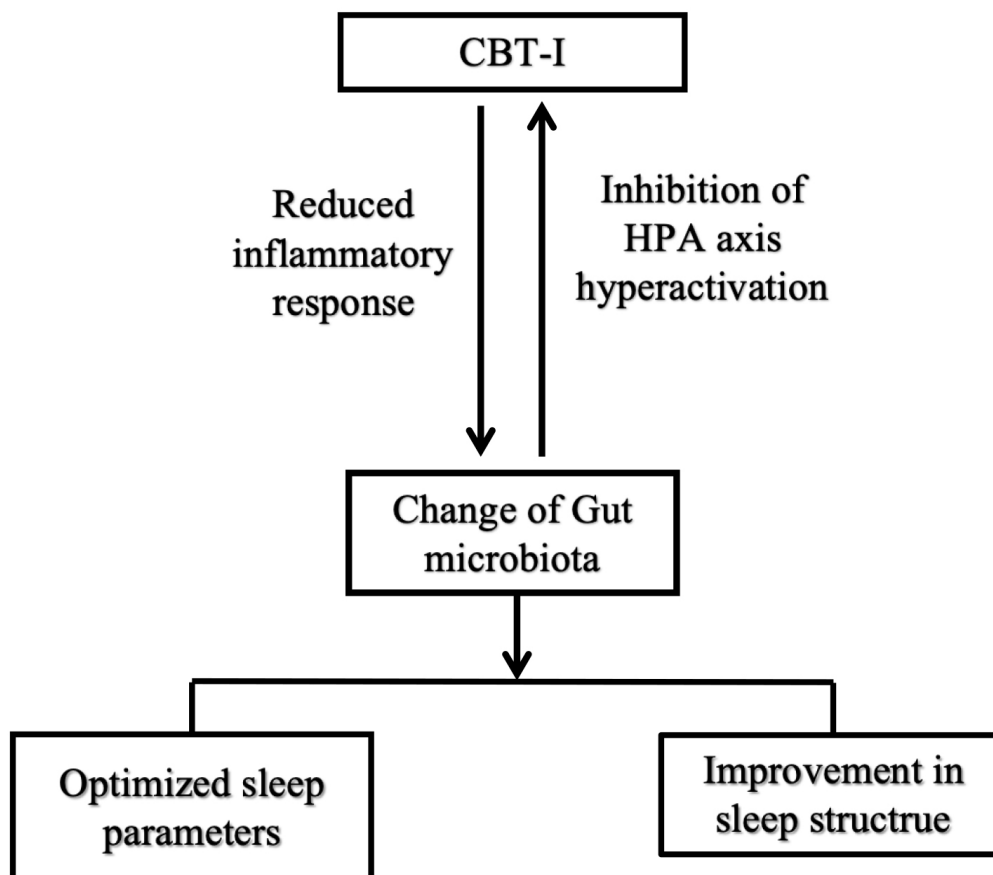


Fig. 1. The influence of CBT-I-Gut microbiome on insomnia. CBT-I, cognitive behavioral therapy for insomnia; HPA, hypothalamic–pituitary–adrenal.

decreased after CBT treatment [7,72]. Restoring intestinal flora improves the metabolism of monoamine neurotransmitters, such as 5-hydroxytryptamine (5-HT) [73], which plays an important role in melatonin synthesis due to the excessive activation of the hypothalamic–pituitary–adrenal (HPA) axis [74]. An unexplored hypothesis suggests that sleep disturbances may induce anal sphincter dysfunction and enhance pelvic floor muscle tone, thereby aggravating constipation [75]. Additionally, mechanisms involving inflammatory cytokines and gut microbiota should be noted. Studies have revealed that sleep in mice alters the immune response [76] and the variety of the gut microbiota [77]. For example, sleep deprivation leads to an increased secretion of pro-inflammatory cytokines, activation of inflammatory-related signaling pathways [78] and reduced diversity of gut bacteria [68]. These immune changes resulting from insufficient sleep may increase the susceptibility to infection. CBT significantly inhibits the HPA axis. Two randomized, clinically controlled studies found reduced blood cortisol levels after CBT treatment compared to a waiting group [79,80]; however, it has also been shown that cortisol increases in the early morning, core body temperature decreases [81] and brain-derived neurotrophic factor rises by 2.9 ng/mL after CBT-I treatment [82] (Fig. 1).

6. Epigenetics

Irwin *et al.* [83] found that gene transcripts after CBT-I treatment included downregulated genes involved in inflammation (e.g., Toll-like receptor-1 and TNF) and upregulated genes involved in interferon and antibody responses (e.g., *CD19*, *MX1* and *ISG15*). The effect on the expression of pro-inflammatory genes in the basal leukocyte transcriptome suggests modulation of properties and potential therapeutic value [83]. An exploratory study investigating the relationship between genetic inheritance and intervention outcomes using CBT-I for cancer survivors found that specific gene variants were not significantly associated with CBT-I treatment outcomes [84].

7. Neuroimaging and Brain Function

Insomnia symptoms, including unpleasant intrusive thoughts, excessive and uncontrollable worry before bed, anxiety, neuroticism, dysphoria, hypervigilance and tension during the daytime [85], activate the sympathetic nervous system [86]. Neuroimaging techniques have been used to detect sleep-related cerebral activity and changes, such as functional connectivity (FCs) strength, density and volume, within different brain areas, though consistent con-

clusions have not been reached. From a neurobiological perspective, reduced FCs suggest the impairment of intrinsic pathways in insomniacs. The perception and regulation of emotion and cognition require cortical–subcortical interactions [87,88]. One previous study has suggested that poor sleep quality can impair FCs within the brain, particularly between the amygdala and insula, striatum and thalamus [89], as well as in the right dorsolateral prefrontal cortex, right medial prefrontal cortex (mPFC), left basal ganglia/insula and right cerebellum anterior lobe [90].

Subcortical areas, including the amygdala—a central part of cognitive and emotional circuits with bidirectional connections to the prefrontal cortex and limbic structures [91]—are functionally altered in individuals with insomnia. Psychologically, the amygdala plays many roles, such as processing both fear-related [92] and disgust-related stimuli [93], evaluating affective significance [94], mediating emotional memory [95,96] and increasing attention to stimuli of unknown or uncertain predictive value [97]. Recent research has demonstrated an increase in amygdala reactivity in insomniacs, particularly on the left side when exposed to negative emotional stimuli related to the experience of insomnia [47]. Disgust was the emotion category that consistently enhanced the activation of voxels in the amygdala, rather than fear or anger, compared to other emotion categories reported in other brain regions [98]. Additionally, the amygdala and right hippocampus are functionally connected during the encoding of salient stimuli, leading to increased activity in the right hippocampus when participants witness an instance of emotional expression in the face, body, or voice [99]. The hippocampus, a component of the limbic system and the default mode network, is crucial for memory. The hippocampus communicates with the striatum through the cortico-striato-thalamic and limbic circuits in collaboration with the amygdala via the limbic system. FCs connectivity between the hippocampus and frontoparietal areas is increased by CBT-I, which may explain the improvement in cognitive function observed in individuals with insomnia.

Recent neuroimaging studies have highlighted fronto-amygdala interactions, especially the role of the mPFC in regulating amygdalar responses to negative stimuli. Both animal and human neuroimaging studies have shown that the mPFC is critical for fear extinction and the modulation of learned fear responses via the amygdala [100,101]. Hypoactivation of the medial and inferior prefrontal cortical areas is reduced in individuals with insomnia; however, Altena *et al.* [43] found that CBT-I reversed this change, as evidenced by prefrontal blood oxygen level-dependent data. The prefrontal cortex is a crucial region involved in executive function, decision-making, working memory and social cognition [102,103]. Changes in FCs between the amygdala and other areas of the brain indicate existing cognitive and emotional impairments within different cerebral regions. The present study shows that CBT-I has no signif-

icant influence on the FCs between the amygdala and other subcortical areas, except for the lingual gyrus, which is associated with visual processing. This indirectly suggests that CBT-I may help reduce stimuli within the emotional circuit related to sensory hyperarousal [50]. Furthermore, the middle temporal lobe, responsible for auditory processing; the left middle occipital area, which is associated with the interpretation of visual stimuli; and the thalamus, which regulates sleep and alertness by transmitting sensory and motor signals [104], have been shown to play a role in insomnia [44,105]. The response to sleep-related sounds in cortical activity, middle occipital activity, middle temporal activity and thalamic activity decreased after the use of CBT-I. This suggests a decrease in the nighttime activity of the brain areas responsible for processing hearing, vision and vigilance. It was observed that the degree of WASO and sleep onset latency were associated with a decrease in arousal and the cerebral changes correlated with cognition and emotion veridically, according to Dysfunctional Beliefs and Attitudes Scale evaluation [48]. Similarly, a previous neuroimaging study in patients with specific phobias have also revealed a reduction in thalamic activation following successful CBT [106].

The thalamus and cortex are virtually connected by neuronal fibers that extend from the thalamus [107]. In individuals with insomnia, stronger FCs have been observed between the thalamus and prefrontal cortex [50] and weaker FCs between the parietal and frontal cortices [108], which provides a neural basis for sensory-related hyperarousal. High EEG frequencies (beta and gamma) are elevated during sleep onset and polysomnographic sleep, suggesting ‘hyperarousal’ in the CNS [109–111]. Following CBT-I, FCs decreased in the thalamus-parietal cortex region, potentially due to improved FCs in the frontoparietal network and reduced hyperarousal caused by a decline in thalamic activity. The reduction of beta activity during NREM sleep after CBT-I also indicates that CBT-I alleviates CNS hyperarousal [16]. A message is actually sent from the cortex to a brainstem or spinal motor region to change or initiate some behavior after information first enters the cortex via thalamic relay and is processed through a hierarchical series of sensory, sensorimotor and finally, motor areas until the top level is reached. The processing and transmission in the aforementioned circuit result in a behavioral outcome; therefore, it can be inferred that CBT-I reduces extraneous information processing in the brain.

The caudate nucleus, a major receptive component of the basal ganglia, is implicated in various functions, such as reward processing, sensory processing, motivation, learning and memory and regulation of cortical excitability. They are more likely to receive input from the orbitofrontal cortex (OFC) and parietal cortices [112]. The cortex connects to the striatum (caudate and putamen), the pallidum to the thalamus and back to the cortex [113]. Studies on both humans and animals have shown that stimulation of the cau-

date reduces cortical excitability and reticular firing in the thalamus and hypothalamus [114,115] and improves sleep [116], whereas caudate injuries may result in a failure of the inhibitory regulation of sensory information [117] and affect sleep [118,119]. The attenuated recruitment of the left caudate head did not recover in patients with insomnia after CBT-I; the activation of a portion of the left caudate head that includes zones innervated by the medial and dorsolateral prefrontal cortical areas, as well as portions that receive efferent input from the OFC, appears to be attenuated by insomnia and hyperarousal [120]. Low gray matter densities (GMs) in the OFC, possibly resulting in restriction of its excitatory efferent, might contribute to insufficient recruitment of the caudate [121]. These findings suggest that one endophenotype associated with the precipitating factors of insomnia includes decreased orbitofrontal GMs and diminished recruitment of the head of the caudate nucleus [122], while lower GMs in the left OFC and hyporecruitment of the caudate are related to sleep vulnerability [123,124].

Additionally, structural neuroimaging studies have indicated decreased grey matter volumes in the medial frontal and middle temporal gyri, which have been associated with cognitive deficits. Moreover, decreased grey GMs in the dorsolateral prefrontal and pericentral cortices, superior temporal gyrus and cerebellum [123,124], have been linked to shifting attention and working memory [111]. Approaches such as sleep restriction, relaxation, cognitive therapy, behavioral strategies and stimulus management of CBT-I all share mechanisms targeting cognition, affect and arousal. Improvements in WASO, SE and sleep quality are particularly noticeable after CBT-I and reduced WASO is a hallmark symptom, which is particularly important as an indicator of increased arousal or central sensitization. Hence, reduced arousal is likely the mechanism causing increased cortical gray matter thickness [51], particularly in the left lateral orbitofrontal cortex, which correlates significantly with the perceived severity of insomnia [123]. Changes in capillaries, dendritic spines, axon terminals and glial hyperplasia may contribute to these macrostructural alterations.

8. Discussion

Patients with insomnia require a combination of pharmacological and non-pharmacological therapies when non-pharmacological treatments prove ineffective or are not recommended due to side effects [125]. For patients with chronic insomnia, the preferred treatment involves a combination of CBT-I alongside non-benzodiazepine hypnotics or orexin receptor antagonists; if short-term symptom relief is achieved with these hypnotics, gradual tapering is recommended. Otherwise, regular monthly assessments of clinical symptoms and comprehensive sleep assessments at six-month intervals are required to determine whether to continue with the CBT-I intervention [126,127]. While the differences in brain regions of patients with insomnia were not reflected consistently in the change after CBT-I, it is true

that after CBT-I, people with insomnia change beliefs and attitudes toward sleep [26,27]. This may help in improving hyperarousal symptoms of insomnia by controlling the processing of external sensory stimuli in temporal, occipital and thalamic activity and changing abnormal FCs and hyperactivation of different cerebral regions [87,88,90]. Many cortical and subcortical regions are activated during emotional and cognitive states and cerebral regions associated with cognitive, emotional and sensory arousal are interconnected with overlapping functions [87,88,90]. Positive improvements during CBT-I show that some of the functional brain abnormalities observed in individuals with insomnia are reversible [43].

Functional neuroimaging studies in humans have mapped specific neural circuits associated with cytokine-induced sickness. Researchers have observed altered connections between the anterior cingulate cortex, amygdala and mPFC [128,129] as well as a diminished ventral striatum response to reward stimuli [130]. Pro-inflammatory cytokines, entering the brain through various molecular signaling pathways, can alter emotions (anhedonia, tiredness and dysphoria), cognitive and motor performance, sleep and social and reproductive drives [131,132]. The hypothalamus and hippocampal interleukin-1 receptors are partially responsible for these actions [131,132]. CBT-I has been shown to modulate cognitive and emotional processes, improve insomnia symptoms, regulate abnormal neuroendocrine functions and reduce the concentration of pro-inflammatory cytokines in the peripheral blood of patients. Increased levels of pro-inflammatory cytokines in the immune system are associated with psychological stress and negative emotions in patients, whereas immune cells in the central nervous system also play a regulatory role in brain function and behavior [133]. A study has shown that CBT-I significantly enhances immune system function, lower levels of pro-inflammatory cytokines or markers [54], increases immune cell counts and enhances natural killer cell activity. Furthermore, the benefits of CBT-I treatment were consistent regardless of basal or stimulated levels of immune markers, disease status, or the reason for treatment.

Specific patterns of neural and endocrine activity are associated with distinct social or ecological conditions that affect the nature of injuries experienced by people. Thus, immune response genes are under natural selective pressure to become sensitive to neuronal and endocrine signaling. Individuals with insomnia typically experience nocturnal sympathetic hyperactivation [134], resulting in higher levels of sympathetic catecholamines [135]. Additionally, nuclear factor (NF)- κ B, activated by β -adrenergic signaling, upregulates the transcription of pro-inflammatory cytokine genes, resulting in an increased production of interleukin-6, which raises CRP levels [136]. Consequently, CBT-I may reduce sympathetic nervous system activity, potentially reducing CRP levels [62]. In turn, inflammatory cy-

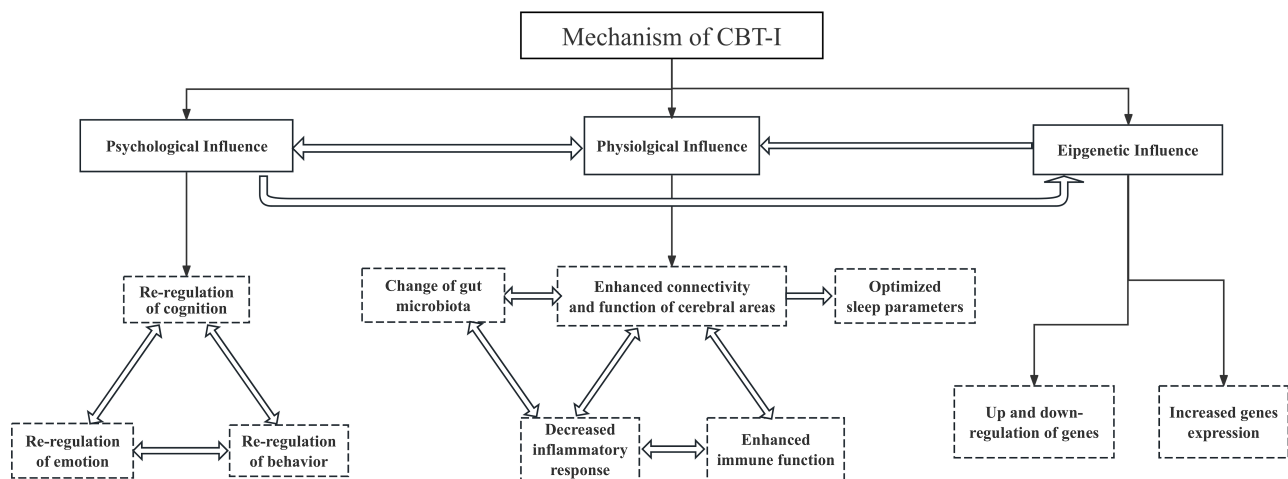


Fig. 2. CBT-I integrated mechanism model. CBT-I, cognitive behavioral therapy for insomnia.

tokines signal to the CNS and alter the symptoms of fatigue [62] and depression [136], suggesting that reducing pro-inflammatory activity may have beneficial effects on these insomnia-related symptoms. Similarly, TNF production may be affected if insomnia relief reduces sympathetic arousal and related pathways and blockade of cytokine TNF can virtually reduce fatigue, depression and altered sleep [137,138]; TNF blockade can also normalize REM sleep levels [139]. Moreover, serum levels of brain-derived neurotrophic factor increased after CBT-I, although it did not significantly correlate with sleep outcomes; this underscores the strong connection between sleep-related cognition, the HPA axis and autonomic function [82].

Gut bacteria play a significant role in insomnia via their interaction with the neuroimmune system, microbial metabolites and other substances. Recent studies have established a significant reciprocal relationship between gut flora and insomnia [140,141]. In previous study by the authors, it was revealed that individuals with insomnia exhibited a drastically changed composition and diversity of gut microbiota, while Bacteroidetes were the dominant taxa in individuals with insomnia [67]. Imbalances in the intestinal flora can affect the central nervous system via metabolites, such as short-chain fatty acids [142] and neurotransmitters, such as 5-HT [143], via the periphery, which in turn affects sleep [144]. Laboratory studies have shown that sleep deprivation-induced alterations in gut flora can increase levels of glucocorticoids [77,145] and inflammatory factors such as IL-1 β and TNF- α [140]. This alteration activates the HPA axis, which results in the hypersecretion of cortisol and exerts inhibitory effects on the immune system by suppressing the cellular immune response and increasing inflammatory cytokines. These effects further exacerbate insomnia. By regulating the HPA axis activation via the composition of the gut flora, the levels of inflammatory factors in the body can be reduced, potentially improving sleep quality.

The efficacy of CBT-I has been significantly linked to enhanced immune function even six months post-treatment, despite variations in immune function strength [54], suggesting that the long-term biological effects of CBT-I may begin in the gene transcription process. Behavioral interventions may benefit from the regulation of leukocytes by the CNS; for example, CNS-mediated reductions in peripheral inflammation feedback can reciprocally reduce various symptoms. Research has shown that behavioral interventions can reverse the anxiety-related upregulation of pro-inflammatory gene expression in circulating leukocytes, potentially influencing emotional and cognitive processes in the brain and thereby impacting physical health [146]. CBT-I influences epigenetic changes in genes, regulating gene expression and function, as well as modulating levels of inflammatory and antibody genes [83]. Innate immune responses may be partially regulated by the CNS anticipation of future environmental conditions. Through hormones and neurotransmitters, the CNS integrates information regarding general physiological conditions and the extra-organism-perceived environment to regulate immune response gene expression programs [136]. CBT-I modifies the patient's cognitive assessment of life events, enhancing mood and behavior and changing a negative coping pattern toward a more positive one, improving adaptation to the current environment. Thus, the activation of cytokine receptors in the hypothalamus triggers the HPA axis and sympathetic nervous system, both of which show CNS-mediated anticipatory activation [136] through the blood to regulate gene expression in the cells of the body. Previous research suggests that changes in epigenetic factors may reflect the interaction between an individual's genetic predisposition and environmental exposure [147]. CBT-I alters the levels of gene regulation and expression of specific genes, ultimately affecting the release of hormones in the neuroendocrine system and the production of pro-inflammatory cytokines, forming a direct connection be-

tween genetic and physiological levels. Individuals who receive CBT-I gradually move away from dysfunctional coping patterns, becoming more adaptable to their environment [148].

9. Conclusions

Integrating findings from psychological, physiological and genetic studies, it is proposed here that the biological mechanisms of CBT-I involve a multidisciplinary integration across micro, meso and macro levels. These mechanisms are associated with the interaction of the “gene-protein-molecule-brain-behavior-environment”, which reflects how individuals undergo psychological transformation influenced by their environment. By superimposing the ‘extrinsic’ positive cognitional and emotional modification on an ‘intrinsic’ CNS-mediated anticipatory activation, the organism gains a reversible opportunity to recover from insomnia within broader microbiological conditions that affect overall survival and natural selection. As individuals adapt to their environment using CBT-I principles and techniques, their internal biological indicators change, forming an integrated model of mutually interacting mechanisms (Fig. 2). However, the majority of research is still at a phenomenological stage; therefore, the biological mechanisms of CBT-I necessitate a comprehensive understanding of the multidimensional and multifaceted biological mechanisms of CBT-I, as these mechanisms cannot be completely explained at a single level. Moreover, in experimental design, there is a paucity of studies that have established a control group for intervention. Consequently, it remains unclear whether the therapeutic effect of CBT-I is related to CBT-I itself or to the natural progression of the disease. Furthermore, the sample sizes of the existing studies are relatively small, necessitating an increase in sample size in future studies to replicate and validate these findings. Research should aim to better explain the observed phenomena and delve into their underlying implications.

Abbreviations

CBT-I, cognitive behavioral therapy for insomnia; WASO, wakefulness after sleeping onset; SE, sleep efficiency; EEG, electroencephalogram; CNS, central nervous system; REM, rapid eye movements; mPFC, medial prefrontal cortex; 5-HT, 5-hydroxytryptamine; CRP, C-reactive protein; TNF, tumor necrosis factor; HPA, hypothalamic–pituitary–adrenal axis; OFC, orbitofrontal cortex; FCs, functional connectivity strength; NF- κ B, nuclear factor- κ B; GMs, gray matter densities.

Author Contributions

GZ, SW and PM proposed the theme of this study, performed investigation, completed the writing of the original draft, JP proposed the conception and design of the work. All authors contributed to editorial changes in

the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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