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REVIEW

Transcutaneous Auricular Vagus Nerve Stimulation (taVNS) for Insomnia Disorder: A Narrative Review of Effectiveness, Mechanisms and Recommendations for Clinical Practice

Chenshi Liu[1,2], Shiyin Chen[1,3], Yuwen Zhang[2,4], Xiao Wu[1,3], Jie Liu[1,2]

[1]Sichuan Provincial People's Hospital, School of Medicine, University of Electronic Science and Technology of China, Chengdu, People's Republic of China; [2]Department of Neurology, Sichuan Provincial People's Hospital, School of Medicine, University of Electronic Science and Technology of China, Chengdu, People's Republic of China; [3]Department of Chinese Medicine, Sichuan Provincial People's Hospital, School of Medicine, University of Electronic Science and Technology of China, Chengdu, People's Republic of China; [4]School of Clinical Medicine, Southwest Medical University, Luzhou, People's Republic of China

Correspondence: Jie Liu, Department of Neurology, Sichuan Provincial People's Hospital, School of Medicine, University of Electronic Science and Technology of China, Chengdu, People's Republic of China, Email liujiesyy@126.com; Xiao Wu, Department of Chinese Medicine, Sichuan Provincial People's Hospital, School of Medicine, University of Electronic Science and Technology of China, Chengdu, People's Republic of China, Email wuxiaozy@med.uestc.edu.cn

Abstract: Insomnia disorder is a very common disease that has received widespread attention in modern society, but the effects of current treatments for insomnia disorder are far from satisfactory. Transcutaneous auricular vagus nerve stimulation (taVNS) is a safe and highly tolerated method, and it might be an alternative therapy for patients with insomnia disorder. This narrative review synthesizes clinical and mechanistic evidence of taVNS for insomnia disorder, critically analyzing its multimodal therapeutic actions from the perspectives of brain networks modulation, neurotransmitter-hormone axis regulation, anti-inflammatory effects, and changes in autonomic nerve function. Existing studies have shown that taVNS can improve sleep quality, quality of life and the accompanying negative emotions. However, the deficiencies in the current trial methods may lead to a reduction in the quality of evidence. Although existing findings support taVNS as a promising strategy for treating insomnia, more high-quality trials are needed to verify its benefits and elucidate its mechanisms of action.

Keywords: insomnia disorders, transcutaneous auricular vagus nerve stimulation, vagus nerve, mechanism, brain network, autonomic nervous function

Introduction

Insomnia disorder is the most common type of sleep disorder, which is characterized by frequent and persistent difficulty falling asleep and/or staying sleep, and results in inadequate sleep.[1] Insomnia can be chronic (>3 months) or short-term (<3 months).[2] Epidemiological investigations have shown that insomnia affects up to 10% of adults globally[3] and 50% of primary care patients,[1] with higher prevalence observed in females,[4] and the prevalence of insomnia in China is 15%.[5] Insomnia significantly impacts the quality of life and working status of patients and is an especially important risk factor for cardiovascular diseases, diabetes and mental diseases,[6] which has a significant impact on social health and the economy. Therefore, timely and effective management of insomnia is needed. The current methods for the treatment of insomnia include drug therapy, cognitive-behavioral therapy for insomnia (CBT-I), physical therapy, and traditional Chinese medicine (TCM) therapy. There are many drugs for the treatment of insomnia with a fast onset of action, but long-term medication may be associated with drowsiness, drug dependence, cognitive and behavioral changes, and other risks.[7] The Guideline suggests that nonpharmacologic treatments are more effective than pharmacologic therapies in the treatment of chronic insomnia.[8] CBT-I is recommended as the first-line treatment for chronic insomnia in adults,[9,10] but it may be difficult to obtain, long duration, high costs and other shortcomings.[11] Therefore, it is very important to explore new, convenient, and safe nondrug therapies. Transcutaneous auricular vagus nerve stimulation (taVNS) is a non-invasive

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neuromodulation technique. Compared to repetitive transcranial magnetic stimulation (rTMS), which requires specialized equipment to operate, or transcranial direct current stimulation (tDCS), which carries the risk of skin irritation, taVNS demonstrates better ease of operation and tolerance through targeted modulation of the vagus nerve branches in the ear.[12] There has been increasing evidence to support that taVNS significantly reduced the severity of insomnia. However, as most of the available studies are limited to small-sample trials and short-term observations, there is still a lack of strong evidence elucidating the efficacy and mechanisms of taVNS for insomnia. In this review, we aim to provide clinical evidence for the efficacy and safety of taVNS, discuss its possible mechanisms for alleviating insomnia, and provide some suggestions for better application of taVNS in the future treatment of insomnia.

Common Pathogenesis of Insomnia

Chronic insomnia represents a dysregulation of the sleep-wake mechanism. The mutual inhibition system of sleep-induced and wake-induced brain pathways functions as a flip-flop switch, facilitating rapid and complete transitions between sleep and awake.[13,14] The sleep–wake cycle is primarily regulated by the ascending reticular activating system, the ventrolateral preoptic nucleus, the median preoptic nucleus and a cluster of orexinergic neurons in the lateral hypothalamus. The ascending reticular activating system includes cholinergic, monoaminergic, histaminergic, and glutamatergic neurons located in the brainstem, particularly within the pedunculopontine and laterodorsal tegmental nuclei, the locus coeruleus (LC), the nucleus tuberalis, and dorsal raphe nucleus. Importantly, these structures project to the thalamus, basal forebrain, and cerebral cortex and are associated with the generation of the wakeful state.[15]

There are many causes of insomnia, and its pathogenesis is complicated and not yet fully understood. Researchers have proposed a variety of pathogeneses and mechanisms of insomnia maintenance, including genetics, abnormalities in neuroendocrine-immune mechanisms (eg, abnormalities in the hypothalamic pituitary adrenal (HPA) axis), cognitive and psychological factors, and aging. However, in fact, hyperarousal is a general theme, the imbalance of the sleep–wake switch is caused mainly by various factors that cause the brain to exhibit a hyperarousal state.[15] This theory is one of the key models used to explain insomnia,[16] and now widely accepted and has improved our understanding of the pathophysiology of insomnia at all levels of analysis. Using positron emission tomography (PET), Nofzinger et al reported that subjective sleep disorders in patients with insomnia correlated with elevated brain metabolism.[17] The inability to initiate sleep may may be associated with a malfunction in the arousal mechanism. Specifically, the regions that promote wakefulness, including the ascending reticular activating system, hypothalamus, thalamus, insula, amygdala, and hippocampus, are related to failure to shift from wakefulness to sleep. In addition, patients with insomnia were also found to have greater cortical energy demands than normal sleepers.[18] These individuals are more likely to be disturbed during sleep and have higher levels of arousal,[19] all of which provide evidence for the hyperarousal hypothesis, indicating that the overexcitability but hypofunctionality of the cerebral cortex leads to nocturnal sleep disorders, daytime fatigue and low work efficiency.[20]

Interacting neural networks play a role in the neurobiology of insomnia, including the general arousal system (ascending reticular formation and hypothalamus), the emotion regulation system (hippocampus, amygdala and anterior cingulate cortex (ACC)), and the cognitive system (prefrontal cortex (PFC)).[17] From the perspective of the functional connectivity network, these regions belong mainly to the default mode network (DMN), affective network (AN), salience network (SN) and central executive network (CEN).[21] Insomnia symptoms are associated with changes in network connection. A functional magnetic resonance imaging (fMRI) study demonstrated that insomnia correlate with changes in network connectivity characteristics in the DMN, SN, and CEN.[22] A recent large cross-sectional study in the United Kingdom also revealed that frequent insomnia symptoms were associated with heightened internal connectivity between the DMN and frontoparietal network, increased negative connectivity between these network, and reduced connectivity between the SN and a node of the DMN.[23] Insomnia symptoms are associated with abnormal intra-hemispheric and inter-hemispheric interactions. These regions are involved in excessive arousal, sensorimotor, and cognitive processes, resulting in both subjective and objective impairments in sleep quality.

taVNS

Why Choose the Auricular Vagus Nerve?

The vagus nerve (VN) is the longest cranial nerve (from the brainstem to the abdomen); consists of myelinated A and B fibers and unmyelinated C fibers, including 80% afferent fibers and 20% efferent fibers, and is a major component of the parasympathetic fraction of autonomic nervous system.[24] The VN relays information between the brain and peripheral organs in a bidirectional manner. The majority the fibers are afferent fibers, primarily Aδ fibers and C fibers, which are responsible for transmitting sensory information from internal organs to the brain; the remaining fibers are efferent fibers, responsible for transmitting motor information to control the function of peripheral organs.[25]

Anatomy of the ear shows that the human external ear receives innervation from three sensory nerves: the auricular-temporal nerve, the greater auricular nerve and the auricular branch of the vagus nerve (ABVN).[26] While the ABVN is the only peripheral branch of the VN, it mainly innervates most areas around the auricular concha and external auditory canal (Figure 1). The cymba conchae and cavum concha have the highest projection density on the ABVN, of which the cymba conchae is innervated only by the ABVN.[26,27] These nerve branches form the cutaneous receptive field at the pinna to receive external stimuli (especially electrical stimulation) and thus directly transmit the stimulus to the brainstem through this external access.[28] The nucleus of the solitary tract (NTS) is the relay station of vagal afferent fibers, and it receives 95% of vagal fiber projections.[29] Stimulation of the parasympathetic nervous system can activate the NTS. Some cholinergic fibers sent by the NTS reach the parabrachial nucleus (PBN) and then project to the LC, raphe nucleus (RN), hypothalamus, and cerebral cortex. This process partially regulates the activities of the NTS through the autonomic feedback loop and partially projects ascending fibers directly to the ventrolateral preoptic area (VLPO) and the reticular

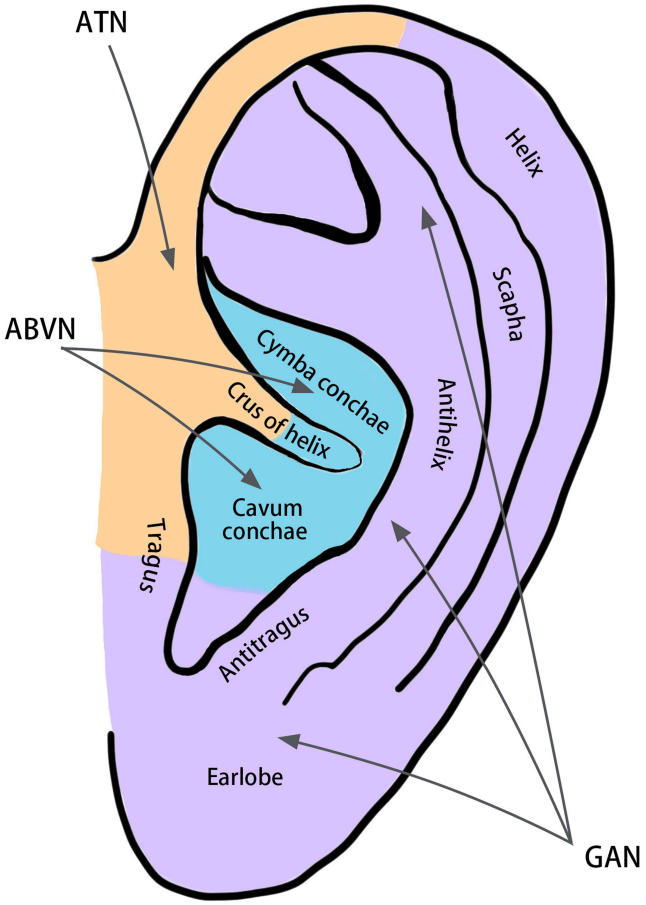

Figure 1 Diagram of the external ear and its possible innervation.
Abbreviations: ABVN, auricular branch of the vagal nerve; GAN, great auricular nerve; ATN, auriculotemporal nerve.

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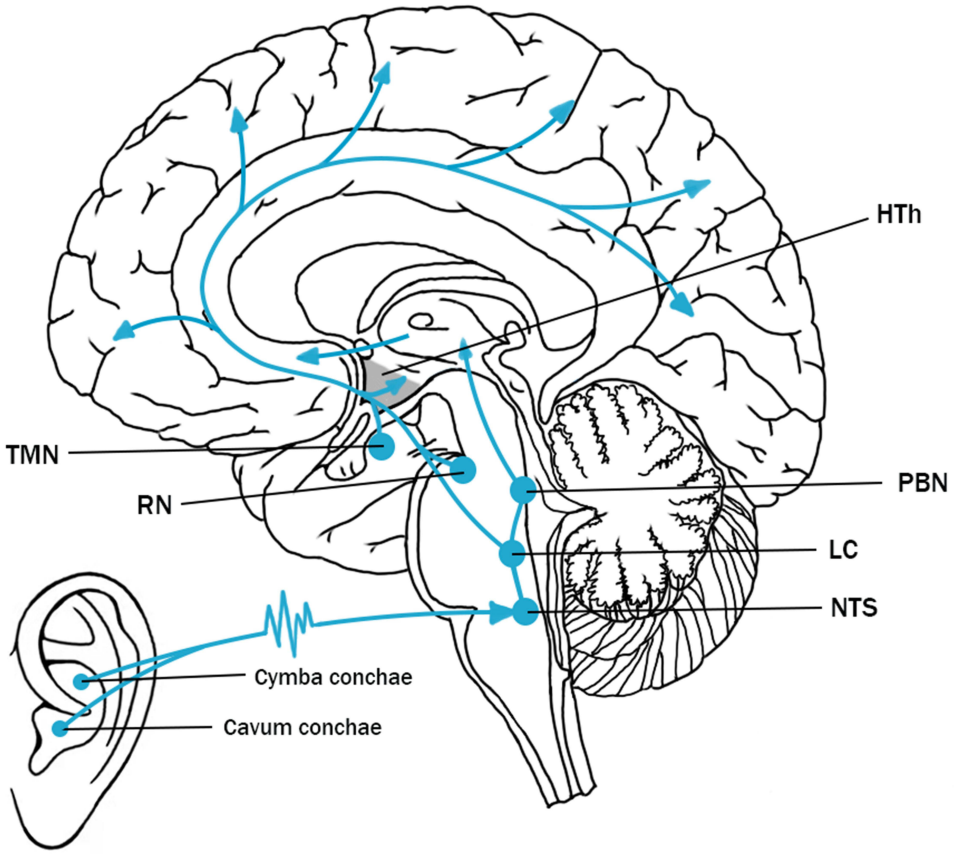

Figure 2 Transcutaneous auricular vagus nerve stimulation can modulate brain networks associated with insomnia neuropathology, and the ABVN projects to multiple brain regions through the NTS.
Abbreviations: HTh, hypothalamus; PBN, parabrachial nucleus; LC, locus coeruleus; NTS, nucleus of the solitary tract; RN, raphe nucleus; TMN, tuberomammillary nucleus.

formation of the hypothalamus.[30,31] These findings provide an anatomical basis for the therapeutic application of vagus nerve stimulation (VNS) (Figure 2).

Some scholars have reported that auricular acupuncture can induce vagal tone and have proposed the "auriculo-vagal afferent pathway (AVAP)"; that is, auricular VNS to the NTS through the ABVN can alter the autonomic nervous system and central nervous system.[32] To date, the AVAP has been explained as the only network for which the mechanism of action of ABVN stimulation of the pinna region activates brainstem nuclei (including the NTS, LC, trigeminal brainstem nuclei and nucleus cuneatus).[33]

Among the distribution and positioning of auricular points in TCM, the auricular concha is the distribution area for visceral auricular points in TCM; that is, the distribution area of the VN in the auricle overlaps with the representative area of auricular points in TCM viscera.[34] Many scholars have conducted systematic reviews and meta-analyses on auricular acupoint therapy for insomnia. These studies all showed that auricular acupoint therapy increased total sleep time and sleep efficiency (SE), decreased Pittsburgh Sleep Quality Index (PSQI) scores, shortened sleep latency (SL), and reduced the number of awakenings. In addition, auricular acupoint therapy is associated with a reduced incidence of adverse reactions compared with traditional drugs.[35,36] These findings provide an anatomical basis for the application of taVNS.

Development of taVNS

In the late 19th century, American neurologist J.L Corning was the first to use VNS to treat epilepsy.[37] Later, some animal studies began to elucidate the mechanism of action of VNS, which was subsequently used to treat diseases. VNS received approval from the Food and Drug Administration (FDA) in 1997 and 2005 for the management of drug-resistant

epilepsy and depression, respectively. To overcome the barrier to the application of invasive VNS (iVNS), Ventureyra et al introduced the concept of transcutaneous vagal nerve stimulation (tVNS) in 2000, drawing inspiration from vagus nerve stimulation and auricular acupuncture for epilepsy,[38] as well as the distribution of the ABVN in the external ear. This innovation marked a significant advancement in neuromodulation therapy. tVNS is a noninvasive neuromodulation technique that is noninvasive, safe, and portable Stimulation of these afferent fibers should have therapeutic effects similar to those of conventional VNS,[39,40] that is, both tVNS and iVNS stimulate the same neural pathway.[41] taVNS is one of the main types of tVNS therapy, taVNS exerts a therapeutic effect through the stimulation of the afferent branches of the vagus nerve in the auricular skin and is thus a promising form of VNS. In addition, a recent meta-analysis confirmed the long-term efficacy and safety of taVNS.[42] taVNS has been confirmed to be effective in treating epilepsy,[43,44] depression,[45,46] migraine,[47] cognitive impairment,[48,49] and disorders of consciousness.[50,51] Recently, taVNS has been shown to have a good treatment effect on insomnia.

Stimulation Sites and Stimulation Modes of taVNS

The optimal stimulation target of taVNS is currently not clearly defined.[12] An fMRI study compared the activation effects of stimulation of the internal tragus, the inferoposterior wall of the ear canal, the cymba conchae, and the earlobe, and it was concluded that stimulation of the cymba conchae is more likely to activate the NTS and LC of the VN center;[52] therefore, the cymba conchae is a potential site for effective delivery of auricular VNS. When taVNS is used, the stimulation parameters also need to be considered. However, the safe and optimal stimulation mode of taVNS has not been clearly defined. The common stimulation frequency is 20 hz or 25 hz, but the optimal stimulation frequency may vary between diseases.[30] The results of a previous study demonstrated that healthy volunteers tolerated all stimulation parameter settings well; however, the reduction in heart rate was the greatest under stimulation conditions of 10 hz and 25 Hz.[53] The findings of another imaging study suggested that, compared with earlobe stimulation in the control group, taVNS (500 μs, 25 hz) delivered to the left tragus for 1 minute, could produce significant cortical effects on the vagal afferent pathway.[54] Currently, a frequency of 20 hz is often used in studies of taVNS for the treatment of insomnia. Different diseases have different stimulation timing recommendations.[30] For example, Beatrice et al showed that after receiving 15 min of taVNS treatment every day for 2 weeks, the participants experienced some improvements in autonomic nervous function, quality of life, mood, and sleep.[55] In addition, the intensity of taVNS is often adjusted by the subjects according to their own tolerance. However, there is currently no evidence on the safe range of taVNS intensity. In the future, more high-quality large-sample trials are needed to optimize the selection of stimulation parameters. In addition, the side effects of stimulation, the type of sham or control stimulation, the location of stimulation, and the placement of sham electrode may affect the results of taVNS. Notably, because the right VN has efferent fibers leading to the heart, right VNS may cause more severe bradycardia. To avoid cardiac side effects, performing percutaneous VN stimulation in the left ear is safe.[56,57] However, a study showed that right-sided stimulation did not elevate the risk of adverse events.[58] Therefore, studies in this area are still insufficient, necessitating additional evidence, particularly regarding the contentious issues of unilateral versus bilateral and left versus right-side stimulation.

Application of taVNS in the Treatment of Insomnia

Currently, taVNS has been proposed as a potential treatment for insomnia. fMRI studies have shown that taVNS can stimulate branches of the VN in the cymba conchae to transmit information to the brainstem NTS and thus affect brainstem nuclei such as the LC, RN, and PBN, as well as the brain regions associated with sleep and emotion, such as the cortical and limbic systems.[59] Studies have also shown that brain wake and sleep state switching is achieved through direct mutual inhibition between the VLPO of the hypothalamus and monoaminergic cell population (nuclei) neurons (LC, RN, TMN).[60] It is known that the VLPO is the slow wave sleep center of the body and contains many γ-aminobutyric acid (GABA) ergic neurons.[61] The fibers sent to neurons in the TMN, LC, RN and other wake-promoting structures directly inhibit wakefulness and promote the occurrence of non-rapid eye movement sleep (NREM). On the other hand, the PBN and pedunculus tegmentum receive and send out cholinergic fibers to promote the occurrence of rapid-eye movement (REM) sleep, increase the number of cortical waves in the pons-genu-occipital region, and prolong the duration of REM sleep.[62,63] The above pathways overlap with most

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Table 1 Recently Completed Trials of taVNS for Insomnia

Year	Author	Subjects	n	Site	Protocol	Main Results
2024	Zhang S et al	Patient with chronic insomnia	taVNS: 36 Sham taVNS: 36	Bilateral auricular cymba conchae (CO_{10}) and cavum conchae (CO_{15})	4/20Hz, 30 min, bid, 8 weeks	taVNS demonstrated significantly greater reductions in PSQI (4.2 points), HAMD, HAMA, and FFS scores compared to sham. No significant differences were observed in ESS scores.
2023	Zhang L et al	Patients with insomnia at high altitude	Treatment group: 35 Sham group: 35 CBTI group: 35	Tragus of the left ear	25Hz, qd, 5d/w, 4 weeks Treatment: 45mins Sham: 30s	taVNS demonstrated significantly greater reductions in PSQI, ISI, and GAD-7 scores versus control. Shortened sleep latency and longer deep sleep in the patients after taVNS. No significant difference in the change in clinical scale scores between the taVNS and CBTI groups.
2022	Wu Y et al	Primary insomnia patients	Experimental group: 16 Control group: 16	Experimental group: bilateral auricular concha area Control group: bilateral periauricular area	20Hz, 20 mins, bid, 4 weeks	The PSQI score of the treatment group decreased significantly. No statistical differences in changes of HAMA and HAMD scores between the two groups.
2022	Zhao YN et al	Primary insomnia patients	21	Xin (CO15) and Shen (CO10)	4/20Hz, 30 mins, bid, 4 weeks	The total scores of PSQI and SL were reduced, and SE was increased compared with pre-treatment values.
2022	He JK et al	Patient with chronic insomnia	Chronic insomnia group (CI): 24 Health controls (HC): 18	CI: taVNS, bilateral cymba conchae HC: no treatment	4/20 hz, 30 mins, bid, 4 weeks	The scores of PSQI and FFS decreased in the chronic insomnia group.
2022	Zhang S et al	Primary insomnia patients	Primary insomnia patients: 19 Healthy subjects: 16	Bilateral auricular points of Xin (CO15) and Shen (CO10)	4/20Hz, 30 mins, bid, 5d/w, 4 weeks	The total score of PSQI in primary insomnia patients was lower than that before treatment.
2021	Zhang S et al	Primary insomnia patients	20	Concha region	20Hz, 30 mins, bid, 5d/w, 4 weeks	The total score of PSQI and the scores of subjective sleep quality, SL, sleep duration, and sleep disturbances were significantly lower than those before treatment. No significant difference in the scores of habitual SE, use of sleeping medication, and daytime dysfunction.
2020	Jiao Y et al	Insomnia patients	taVNS: 31 tnVNS: 32	taVNS: bilateral auricular concha tnVNS: bilateral scapha of the auricle	20Hz, 30 mins, bid, 5d/w, 4 weeks	taVNS treatment significantly decreased the PSQI, ESS, FFS, HAMD, HAMA scores and increased the SF-36 score compared to baseline. Clinical scale scores showed no statistically significant differences compared to tnVNS.
2017	Luo M et al	Primary insomnia patients	35	Bilateral auricular concha	20Hz, 30 mins, bid, 5d/w, 4 weeks	The PSQI was significantly decreased at the end of 2nd week. The 17HAMD and HAMA were significantly decreased at the end of 4th week and 6th week.

Abbreviations: CBTI, Cognitive Behavioral Therapy for Insomnia; PSQI, Pittsburgh Sleep Quality Index; ISI, Insomnia Severity Index; GAD-7, General Anxiety Disorder-7; HAMA, Hamilton anxiety scale; HAMD, Hamilton depression scale; SL, sleep latency; SE, sleep efficiency; FFS, Flinders Fatigue Scale; ESS, Epworth Sleepiness Scale; SF-36, 36-item Short-Form Health Survey Questionnaire; taVNS, transcutaneous auricular vagus nerve stimulation; tnVNS, transcutaneous nonvagus nerve stimulation.

structures of the VN projection pathway. Therefore, VNS can cause activity changes in related brain regions and thus participate in the regulation of sleep.

Multiple studies have shown improvements in quality of life, mood, and sleep in people with normal sleep patterns after taVNS treatment, and taVNS can regulate autonomic nerve function.[55,64,65] In the clinical application of VNS in the treatment of epilepsy, depression and other diseases, some patients also showed improvements in nighttime sleep quality and reductions in daytime sleepiness.[66,67] However, there are few studies on taVNS treatment for primary insomnia (Table 1). Luo et al studied 35 patients with insomnia and affective disorders after 4-week taVNS treatment and found that PSQI, Hamilton Rating Scale for Depression (HAMD) and Hamilton Rating Scale for Anxiety (HAMA) scores were decreased in different degrees,[34] suggesting that taVNS effectively improved sleep quality and anxiety and depression symptoms, but the lack of a control group in this study limits interpretation. Subsequent studies have similarly validated the above results,[68–74] but most were small sample studies (n<50) with short follow-up periods (mostly 4 weeks), which may weaken the quality and reliability of the evidence. Combined with polysomnography analysis, Zhang et al found that SE and sleep percentage of NREM stage 3 in insomnia patients significantly increased and SL significantly decreased after taVNS treatment,[75] indicating that taVNS may help partially adjusted objective sleep continuity and sleep structure. A recent randomized clinical trial extended the taVNS treatment course to 8 weeks for the first time. The study results showed that taVNS significantly reduced PSQI scores, leading to clinically significant improvements in patients with chronic insomnia, with effects lasting for 20 weeks.[76] However, the study was still limited by a small sample size and lacked dynamic monitoring of objective indicators such as imaging and EEG. Some studies have also pointed out that, compared to the control group, taVNS improved questionnaire scores related to sleep or mood, but did not show statistically significant differences in alleviating insomnia, depression, and anxiety.[69,71,77] This may be due to individual efficacy differences and insufficient follow-up time. It should also be noted that some research methods have limitations, and the treatment regimens (stimulation site, stimulation parameters, and stimulation duration) of taVNS are not exactly the same in different studies, which may affect the comparability of results.

Possible Mechanism of Action of taVNS in the Treatment of Insomnia

Figure 3 shows the taVNS device and the four possible mechanisms by which taVNS treats insomnia.

Analysis of the Mechanisms Underlying Insomnia Through Neuroimaging

Neuroimaging methodologies have substantially advanced the investigation of insomnia. Patients with insomnia exhibit various metabolic, functional, and structural abnormalities associated with cortical and subcortical regions. fMRI has been extensively used to clarify the functional and structural responses to insomnia. Currently, there are few published studies on the mechanisms of taVNS in treating insomnia, with resting-state functional MRI (rs-fMRI) and functional connectivity (FC) analysis being the predominant methodologies employed. FC was used to determine the synchrony in functional activities between brain regions. The development of insomnia may involve interactions among multiple brain regions. The difficulty in initiating or maintaining sleep is associated with increased FC between primary sensory areas and supplementary motor areas.[79]

taVNS Regulates the DMN or Regulates the Relationship Between the DMN and Other Networks

DMN-related brain regions (precentral region, PFC, posterior cingulate gyrus, etc). in patients with insomnia may have increased levels of activity during the sleep stage.[80,81] A case report demonstrated that the posterior cingulate cortex (PCC) and other brain regions belonging to the DMN presented increased FC before treatment, whereas DMN connectivity decreased after 4 weeks of taVNS treatment.[82] Zhang et al reported that taVNS may improve sleep disorders by reducing FC left ventral superior striatum and DMN, and also reduce FC between the ventral superior striatum and other DMN regions, the visual cortex and the primary motor cortex in insomnia patients, thereby reducing excessive arousal in the cortex and improving sleep quality.[83] The pathogenesis of insomnia is also related to thalamic dysfunction, several mechanisms in sleep-wake control involve the thalamus, ie, cortical activation and synchronization and sleep consolidation.[84] Compared with those of healthy people, several brain regions of insomnia patients show reduced resting-state functional connectivity (RSFC) due to thalamus dysfunction, such as the ACC, orbitofrontal cortex, hippocampus, caudate core and putamen, and are negatively correlated with the PSQI score in patients with insomnia.[85] Zhao et al

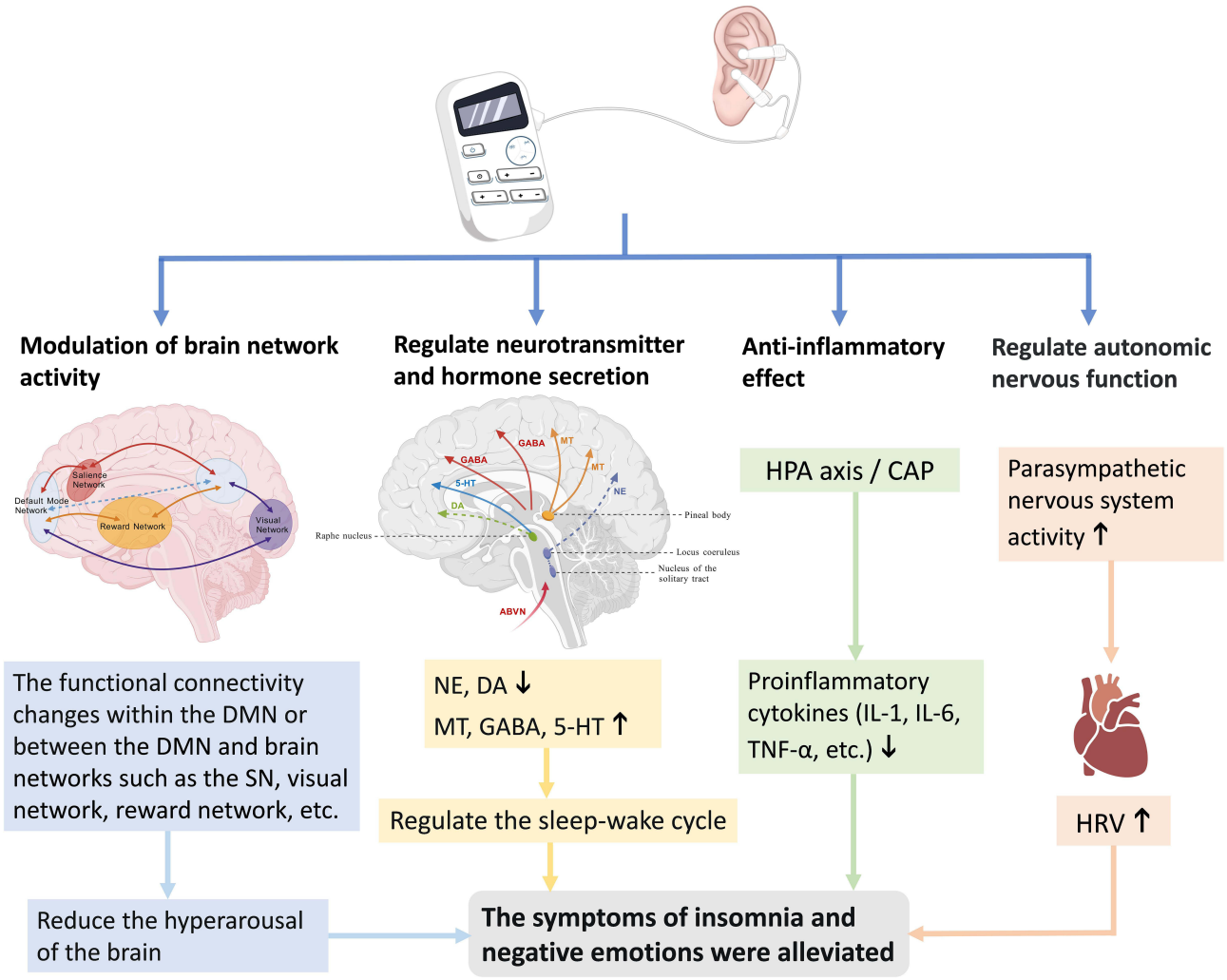

Figure 3 Possible mechanisms of taVNS in the treatment of insomnia. The taVNS device is portable, and the stimulation sites are mostly the cymba conchae and cavum concha of the left ear. Its mechanisms for treating insomnia may involve four pathways: 1) taVNS regulates the functional connectivity within the DMN or between the DMN and other brain networks such as the salience network, visual network, and reward network, reducing the brain's state of hyperarousal, thereby improving sleep and its accompanying negative emotions. 2) taVNS introduces external stimuli through the ABVN, increasing the levels of melatonin, GABA, and serotonin in the central nervous system, maintaining prolonged sleep; and possibly reducing the levels of norepinephrine and dopamine (the mechanism is not yet clear) to reduce wakefulness time and improve sleep. 3) The vagus nerve exerts immune effects through the HPA axis or CAP, reducing pro-inflammatory cytokines, thereby inhibiting systemic or local inflammation to regulate sleep rhythms. 4) taVNS stimulates the parasympathetic nervous system, regulates the autonomic nervous function of insomnia patients, thereby reducing heart rate and increasing HRV, and improving both subjective and objective sleep.

Abbreviations: DMN, default mode network; SN, salience network; ABVN, the auricular branch of the vagus nerve; NE, norepinephrine; DA, dopamine; MT, melatonin; GABA, γ-aminobutyric acid; 5-HT, 5-hydroxy-tryptamine; HPA axis, hypothalamic pituitary adrenal axis; CAP, cholinergic anti-inflammatory pathway; HRV, heart rate variability. Several elements in the image were obtained from https://biogdp.com.[78]

reported that the RSFC between the thalamus and the right insula and inferior frontal gyrus was increased in patients with insomnia, and after taVNS treatment, the RSFC between the thalamus and the right angular gyrus, anterior cingulate gyrus and precuneus was significantly decreased in insomnia patients. These results suggest that taVNS mitigate the heightened arousal state of DMN brain regions resulting from thalamus dysfunction in insomnia patients; this may be one of the important mechanisms of action of taVNS in the treatment of primary insomnia.[86]

The medial prefrontal cortex (mPFC) is the core area of the DMN, which is very important in maintaining sleep and is particularly sensitive to sleep disorders.[87] Previous studies have shown that in patients with long-term insomnia, the mPFC and DMN show abnormal FC with multiple brain regions.[68] Zhang et al reported that taVNS treatment reduced the FC between the left mPFC and the dorsal bilateral anterior cingulate gyrus and between the right mPFC and the occipital cortex in patients with insomnia, ie, reducing the FC between the DMN and the SN, thereby reducing the PSQI score and SL and extending sleep duration.[71] He et al hypothesized that taVNS can improve symptoms of insomnia

patients, such as daytime fatigue, sleepiness, and inability to concentrate, by increasing the FC between the ascending reticular activating system and reward circuits and between the sensorimotor network and the CEN.[88] Their follow-up study also revealed that taVNS had a regulatory effect on the PFC in insomnia patients. Patients with low function of the dorsolateral prefrontal cortex (dlPFC) had higher PSQI and Flinders Fatigue Scale (FFS) scores after 4 weeks of treatment.[72] The dlPFC is the core region of the cognitive control network (CCN),[89] and there is evidence that taVNS reduced the FC between the right PCC and the right mPFC and the FC between the bilateral PCC and the left middle frontal gyrus (belonging to the dlPFC) in insomnia patients; ie, taVNS reduced the FC between the DMN and other networks by modulating the abnormal FC between the DMN regions and reducing the FC between the DMN and CCN, thereby reducing the level of conscious arousal, improving the cognitive control ability of patients, and thus improving sleep quality.[74] It can be seen that taVNS can improve sleep by regulating FC within the DMN or between the DMN and other networks.

Effects of taVNS on the Visual Cortex/Visual Network

Insomnia symptoms are also correlate with reduced negative connectivity between sensory regions, especially those engaged in visual information processing.[23] Visual thinking is an important form of cognition that occurs before sleep. The suprachiasmatic nucleus located in the preoptic area of the hypothalamus can receive light and dark rhythm stimulation signals from the optic nerve and transmit this information to the intermediate and lateral nuclei of the thalamus and the pineal gland to affect sleep rhythm.[90] Killgore et al reported that in patients with sleep onset problems, the greater the FC between the DMN and the visual network is, the longer the SL, and the poorer the sleep quality.[91] Previous studies have demonstrated that there are general abnormalities in spontaneous neuronal activities among the temporal lobe, prefrontal cortex, occipital lobe and visual cortex-related brain regions in patients with insomnia or insufficient sleep; subjects with insufficient sleep show reduced activation in the visual cortex[92] and reduced information processing ability.[93] However, neurons in vision-related cortical areas were abnormally active at rest.[94] taVNS can regulate the activity of neurons in the vision-related cortex and reduce the FC between the mPFC and the precuneus, which have a direct effect on patients with insomnia.[95] Previous case reports using taVNS for post-stroke depression and insomnia also suggest that taVNS can modulate the function of visual-related cortices.[82,96] Patients with insomnia have a widespread excessive arousal state in the cerebral cortex. He et al reported that immediately after taVNS, the FC between the anterior rostral cingulate gyrus and the auditory and visual networks decreased,[88] which may indicate that taVNS reduces the excessive arousal state in the visual and auditory cortex, and reduces the hypersensitivity of insomnia patients to sound and light stimuli during sleep onset and sleep maintenance.

Regulation of Emotion and Introspection by taVNS

Insomnia, the result of a hyperarousal state, may lead to cognitive fatigue and anxiety, which can lead to depression symptoms.[16,20] Sleep interruption can exacerbate anxiety, and impaired DMN connectivity is the basis of the association between poor sleep quality and anxiety symptoms.[97] Many studies have demonstrated the regulatory role of taVNS in the negative emotions of depressed patients. According to the brain areas of VN projection, the VN and depression-related cortical-limbic-thalamo-striatal neural circuit abnormalities have direct and indirect relationships and can affect the activities in these regions.[98] For example, Fang et al reported that taVNS can achieve its antidepressant effect by mediating the activity of the DMN of the nucleus tractus solitaries - limbic lobe.[99] It is known that the basal ganglia are involved in some emotional functions,[100] whereas the PCC and emotion-related basal ganglia regions of poststroke insomnia patients exhibit increased FC after taVNS treatment.[81]

The ventral striatum, anterior thalamus, and anterior cingulate gyrus are important structures related to reward and emotion. The anterior cingulate gyrus and bilateral insula are critical nodes of the SN,[21] with the insula and dorsal anterior cingulate gyrus serving as primary components of the negative emotion network, strongly associated with the amygdala. Compared with healthy individuals, the increased amygdala reactivity in patients with insomnia seems to be related to the negative emotional stimuli associated with the experience of insomnia.[101] After immediate stimulation with taVNS, the FC between the bilateral medial hypothalamus and the precuneus and posterior cingulate gyrus was shown to be increased, as was the FC between the left preoptic area and the left precuneus, bilateral posterior cingulate gyrus, and

bilateral cuneus. The precuneus and posterior cingulate gyrus are important parts of the posterior DMN (pDMN). taVNS can reduce the severity of insomnia and mood disorders by increasing the FC between arousal, reward-related brain regions and the cingulate gyrus, pDMN.[87] Later studies by Zhao suggested that after insomnia patients received taVNS treatment, the FC between the bilateral thalamus and anterior cingulate gyrus decreased. Therefore, the authors hypothesized that taVNS could use the SN and negative emotion network to process negative stimuli and improve the negative emotional symptoms that often accompany insomnia, which in turn improves sleep itself.[86]

The precuneus primarily participates in episodic memory, emotion regulation, and introspection. After taVNS therapy, the RSFC between the precuneus and the right horn, right superior frontal gyrus, and right middle frontal gyrus was significantly found to be reduced.[95] The DMN is related to the monitoring of introspection status,[102] whereas insomnia patients' introspection can excite the DMN, thus affecting the sleep of these patients.[103] Consequently, modulating the spontaneous activity of precuneus neurons can suppress patient introspection and subsequently influence the DMN to enhance sleep quality. The anterior cingulate gyrus and temporal lobe are the main brain regions of the DMN. taVNS may reduce excessive arousal during brain introspection in patients and improve insomnia symptoms by regulating the function of the anterior cingulate gyrus and temporal lobe in patients with insomnia.[104]

taVNS Regulates Neurotransmitter and Hormone Secretion

Sleep disorders are closely related to the abnormal secretion of neurotransmitters and hormones. The melatonin level also affects sleep–wake regulation. Melatonin is a neurohormone secreted by the pineal gland that is related to the circadian rhythm and is important for sleep initiation and maintenance.[105,106] Therefore, insomnia is closely related to a decline in central melatoninergic function. Previous studies have shown that taVNS can treat depression by triggering melatonin secretion,[107] and another animal experiment by the same group also revealed that taVNS can increase the plasma melatonin concentration.[108] The mechanism of action may be that taVNS stimulates the ABVN, thereby stimulating the parasympathetic nervous system and then promoting the synthesis and release of melatonin from the adrenal glands, which, in turn, stimulates the parasympathetic nervous system, thus forming a beneficial cycle. Therefore, parasympathetic predominant vagus nerve excitation and melatonin secretion promote each other, thereby increasing melatonin production for the treatment of insomnia.

Several studies have shown that taVNS may improve sleep by synergistically modulating various neurotransmitters, such as norepinephrine (NE), γ-aminobutyric acid (GABA) and serotonin (5-hydroxy-tryptamine, 5-HT).

NE is a key mediator of attention and arousal.[109] Insomnia patients often exhibit elevated NE levels, which are associated with sympathetic nervous system hyperactivity and emotional disorders such as anxiety and depression.[110,111] taVNS may enhance parasympathetic nervous activity to inhibit sympathetic overactivity, thereby reducing NE levels and improving nighttime sleep. The LC is one of the main sources of NE in the brain.[112] The activity of the LC-NE system is closely related to maintaining alertness and mediating arousal,[113] and its excessive activation may be associated with the occurrence of insomnia.[114] Research shows that taVNS can regulate the LC-NE system through the vagus nerve-NTS-LC pathway.[115] It is worth noting that the impact of taVNS on NE varies across different studies, which may be related to taVNS stimulation parameters and individual differences.[115,116] Research has found that pupil dilation (reflecting LC discharge) and reduced occipital alpha activity caused by taVNS suggest that it may promote NE release and enhance attention,[117,118] which may help to enhance daytime alertness and indirectly strengthen nighttime sleep stability. We speculate that taVNS can improve the circadian rhythm by dynamically regulating the NE system in patients with insomnia, but its specific molecular mechanism and time effect still need to be further studied.

GABA is a key neurotransmitter for initiating and maintaining sleep, and its ability to reduce neuronal excitability by inhibiting neurotransmission makes it an important target for hypnotic drugs. Cai et al reported that the activation of the GABAergic neuron pathway from the dorsal raphe nucleus to the ventral tegmental area can increase wakefulness duration and maintain long-lasting wakefulness.[119] Studies have shown that insomnia is associated with a decrease in cortical GABA levels during the day. Proton magnetic resonance spectroscopy revealed that in patients with insomnia, GABA levels are reduced throughout the brain, especially in the occipital cortex and the anterior cingulate cortex.[120,121] taVNS has been shown to modulate GABA and NE levels to affect related cognitive performance.[122,123] In addition, taVNS may modulate GABAergic inhibitory effects by increasing the level of GABA in the central nervous

system.[124,125] Some research shows that taVNS can enhance short-interval intracortical inhibition (SICI), modulate cortical excitability and motor system function,[126–128] but changes in GABA activity are region-specific rather than globally increased.[127] In summary, taVNS may improve sleep quality by enhancing GABA levels in specific brain regions, inhibiting cortical hyperexcitability, and restoring the sleep-wake balance.

The RN is the main source of serotonergic (5-HT) neuronal nuclei.[129] Serotonin primarily promotes wakefulness and inhibits slow-wave sleep or rapid eye movement sleep,[130] and its systemic dysfunction is considered another factor in the development and progression of insomnia.[131] The influence of VNS on the 5-HT system is facilitated by an increase in the firing rate and changing the firing pattern of NE neurons.[132] The RN also contains other types of neurons. Dopaminergic (DA) neurons are key regulators of the sleep–wake pattern and can predict the duration of wakefulness.[133] Long-term vagus nerve stimulation can change the concentrations of monoaminergic neurotransmitters, thereby improving symptoms of depression and insomnia.[134]

Anti-Inflammatory Effects of taVNS

Inflammation is a protective response to external stimuli. The anti-inflammatory pathways of the VN have been described, such as the HPA axis and the cholinergic anti-inflammatory pathway (CAP), which are extensively used to treat inflammatory bowel disease, rheumatoid arthritis and other diseases.[24] The degree of impairment of sleep quality is positively correlated with increases in several inflammatory cytokines, such as interleukin-1 (IL-1), IL-6, and tumor necrosis factor-α (TNF-α).[135,136] These inflammatory cytokines are involved in the regulation of sleep, the regulation of sleep structure and the regulation of the sleep circadian rhythm.[137] Sleep behavior is regulated by cholinergic neurons of the vagus nerve.[138] The efferent fibers of the VN are mainly cholinergic fibers, with ACh as the main neurotransmitter. The VN exerts its immunomodulatory effect through the CAP, reducing proinflammatory cytokines, activating microglia and macrophages, and altering the consequences of neuroinflammation.[139] In addition, taVNS activates the CAP in the area of brain injury, promotes the secretion of ACh, and inhibits the secretion of inflammatory cytokines such as ILs and TNF, thereby mediating neuroprotection.[140,141] The specific mechanisms underlying these effects remain to be investigated. Since taVNS can produce similar therapeutic effects as VNS, these findings indicate that taVNS may relieve the clinical symptoms of insomnia through the inhibition of systemic or local inflammation.

taVNS Regulates Autonomic Nerve Function

Autonomic nerve dysfunction is present in patients with insomnia and is especially related to VN activity.[142] Past evidence has shown that this dysfunction is related to a slow response in heart rate variability (HRV). Insomnia patients have increased heart rates before going to bed and during nocturnal sleep.[143] However, a review of existing studies still cannot support the hypothesis that HRV is attenuated in insomnia patients.[144,145] Studies have shown that taVNS can increase HRV. For example, Burger et al reported that increased efferent vagus nerve activity stimulates neurons projecting to the cardiac sinus node to produce ACh, thereby reducing heart rate and increasing VN-mediated HRV (vmHRV).[146] However, some meta-analyses have shown that the effect of taVNS on HRV is still unclear.[147] taVNS can rapidly enhance HRV parameters, indicating that HRV may serves as a physiological marker for autonomic nerve tension in taVNS.[148] Wu et al reported that the HRV value under continuous taVNS treatment could reflect the efficacy of taVNS in the treatment of insomnia.[149] Zhao et al reported that after taVNS treatment, the nocturnal HRV and subjective and objective sleep parameters of insomnia patients improved. Therefore, the authors hypothesized that taVNS can stimulate the VN in the concha of the ear, activate parasympathetic nerves, and regulate autonomic nerve function in insomnia patients, thereby improving subjective and objective sleep.[73] More interestingly, some scholars have reported that increased sympathetic nerve activity may also have a stronger effect on taVNS.[150] The latest study revealed that sleep duration was inversely correlated with the severity of depression. In animal models, a lack of sleep continuously impairs HRV, whereas taVNS attenuates this effect.[151] Therefore, the potential benefits of VNS may be quantified through HRV, but further studies with larger sample sizes, a longer duration of HRV recording, an established control group, an insomnia classification and a longer follow-up time are needed to further explore the therapeutic mechanism of taVNS.

Limitations

Several limitations of this review should be noted. First, there are few studies on the treatment of insomnia with taVNS, and most studies are observational reports, and there is a lack of multi-center, large sample randomized controlled trials to verify its long-term efficacy. Our narrative review focused only on English and Chinese studies, which may have affected the comprehensiveness of the study results. Second, most of the subjects in the studies that we reviewed had primary insomnia, and we did not perform a separate evaluation according to the various insomnia subtypes (such as primary and secondary insomnia). The differentiation of insomnia subtypes may be critical for assessing treatment efficacy, subgroup analysis would be more rigorous if the data permitted. Third, we did not perform a systematic review or meta-analysis, nor did we perform standardized quality assessments of the included studies, which may have led to bias.

Future Research Directions

taVNS has shown great potential in the treatment of insomnia, but many issues remain to be further explored. In future studies, the following should be considered: increasing the sample size; standardizing the control group and stimulation programs; classifying the types of insomnia to evaluate the efficacy; exploring the optimal stimulation method of taVNS; so as to develop a more optimized programs for insomnia patients and provide safer, more effective, personalized and precise rehabilitation programs for insomnia patients. Second, most of the current studies have focused on the changes in the activity of cortical brain area and autonomic nervous system after taVNS treatment, but did not explore the pathways through which the stimulation before, after or during taVNS treatment affects the changes in sleep-related brain regions or the autonomic nervous system status of the human body. The correlation between the indicators of the autonomic nervous system status and clinical efficacy was also not analyzed. Therefore, it is not yet possible to accurately explain the brain functional mechanism of taVNS treatment for insomnia. In addition, there may be individual differences in the therapeutic effect of taVNS, the mechanism of which has not yet been clarified, or we should know the appropriate population for taVNS to treat insomnia. Moreover, we also encourage the use of a variety of technical means of research, such as MRI, PET/CT, electroencephalography (EEG) and animal experiments, etc. to observe the structural and functional changes in the brain before and after taVNS stimulation and to observe the effects of different stimulation modes on the neuro-endocrine-immune function of insomnia patients. A recent study found that, compared with taVNS alone, the comprehensive effect of taVNS combined with slow breathing is more helpful in increasing the efficacy of treatment for insomnia, and the beneficial effects lasted for two weeks after treatment; patients with more severe insomnia and poorer sleep quality were more likely to show improvements.[152] Therefore, further exploration of the therapeutic efficacy of taVNS in combination with other treatments is also one of the directions for future research.

Conclusion

Our review suggests that taVNS may be a promising neuromodulation method that is convenient and safe, may help reduce the symptoms and severity of insomnia, and improve the negative emotions associated with insomnia. The impact of taVNS on the human body is systemic and extensive. We speculate that taVNS can relieves symptoms of insomnia by regulating brain network, neurotransmitter and hormone secretion, and autonomic nerve function, but the exact mechanism remains unclear. Currently, some research protocols for using taVNS to treat insomnia have flaws, and most studies have small sample sizes, which are insufficient to provide high-quality evidence for insomnia treatment. In addition, a consensus has not been reached on the duration of efficacy, the optimal stimulation sites or the parameters. Therefore, it is necessary to conduct rigorously designed, large-scale, and long-term follow-up studies.

Data Sharing Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Author Contributions

Chenshi Liu: Writing - original draft, Conceptualization, Investigation, Visualization. **Shiyin Chen**: Writing - review & editing, Investigation. **Yuwen Zhang**: Writing - review & editing, Data curation, Visualization. **Xiao Wu**: Writing - original draft, Conceptualization, Funding acquisition. **Jie Liu**: Writing - review & editing, Investigation, Supervision.

All authors have reviewed and approved the final version of the manuscript, agreed on the journal to which the article has been submitted, and take full responsibility for all aspects of the work.

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