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REVIEW

# The Latest Advances in Non-Invasive Neurostimulation for Insomnia: A Review

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**Abstract:** Insomnia has become a serious public health problem. Because sedative-hypnotics may cause cognitive and psychomotor impairment, serious adverse events, and long-term dependence, it is still controversial whether sleep medications are the first choice for patients with insomnia. Cognitive-behavioral therapy for sleep is limited by poor access, high cost, and poor response in some patients. With the development of sleep neuroscience, physical therapy has shown its advantages in treating insomnia. It can not only avoid the adverse reactions of drugs, but also make up for the lack of standardization of sleep cognitive behavioral therapy. In particular, non-invasive nerve stimulation technology has been increasingly used in the clinical treatment of insomnia in recent years. However, the public lacks understanding of the technology type, principle and efficacy of this treatment strategy, and the research reviews are insufficient, which may limit the choice of insomnia treatment for sleep workers. Therefore, we reviewed the latest research on non-invasive neurostimulation techniques for insomnia in recent years, mainly focusing on virtual reality, biofeedback, transcranial magnetic stimulation, transcranial electrical stimulation, transcutaneous auricular vagus nerve stimulation and other novel neuromodulation techniques, with the aim of providing more options for insomnia treatment and looking forward to the future development of sleep science.

**Keywords:** insomnia, physiotherapy, non-invasive neurostimulation, review

Sleep problems and poor sleep quality are important health challenges that have a significant impact on individual physical health, quality of life, and social and economic well-being.[1] It is estimated that 46% of the Dutch population has various types of sleep disorders.[2] A meta-analysis from China reports that one-fifth of the Chinese population has poor sleep quality.[3] It is reported that insomnia is the most common sleep disorder.[4,5] It has been proven that insomnia is associated with an increased risk of developing diabetes, and is also linked to cardiovascular diseases, age-related cognitive disorders such as dementia, obesity, depression, chronic pain sensation, and increased risk of cancer.[6–9]

Short-term pharmacological treatments (such as benzodiazepines) and sleep cognitive-behavioral therapy (CBT-I) are the most common interventions used for the treatment of insomnia.[10] However, benzodiazepines and hypnotics can be associated with multiple side effects, such as sedative-hypnotic-related cognitive and psychomotor impairment, serious adverse events, and long-term dependence.[11] Whether sleep medications are the first choice for patients with sleep difficulties remains controversial because of concerns about safety, efficacy, and side effects.[12] Clinical guidelines recommend that hypnotic prescriptions should be limited to short-term use and that patients be offered withdrawal support when possible.[13] Expert consensus in Japan suggests that orexin receptor antagonists and sleep hygiene education are recommended as first-line treatments for insomnia in most clinical situations.[14] In addition to sedatives and hypnotics, the American College of Physicians (ACP) has identified CBT-1 as the first-line treatment for insomnia because of its favorable results and reduced risk of dependence on hypnotics. However, surveys show that very few patients receive this treatment, particularly in primary care Settings where most insomnia treatments are provided, which may be the result of a combination of factors including inadequate awareness, inadequate treatment beliefs, and limited access.[15] Therefore, there is a need to investigate other treatment options to address sleep disorders and improve sleep quality.

Sleep is thought to arise due to decreased activity in the ascending reticular arousal system, which originates in the brainstem and awakens the thalamus and cortex during wakefulness.[16] With the development of sleep medicine, sleep



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neurobiology studies have found that many structures and neural circuits of the central nervous system may be related to sleep disruption. Studies have shown that the light-dark cycle affects the suprachiasmatic nucleus and melatonin levels. Changes in circadian rhythm process can lead to prolonged sleep onset latency and early sleep onset.[17] Other studies have reported that neuroendocrine mechanisms are also involved in the process of chronic insomnia. Patients with insomnia exhibit sympathetic hyperexcitability and a higher overall metabolic rate involving increased heart rate, body temperature, cortisol, and adrenocortical hormone levels.[18] These studies suggest that pathological changes in the brain and nervous system are involved in the process of insomnia, and therefore, interventions targeting the brain and nervous system may help to treat insomnia. Based on the research of sleep neuroscience, neuromodulation technology has shown its advantages in the treatment of insomnia. It can not only avoid the adverse reactions of drugs, but also make up for the lack of standardization of sleep cognitive behavioral therapy. There is no standardized definition of neurostimulation or neuromodulation, but it is a broad category that focuses on the use of a variety of therapeutic modalities (eg, electrical stimulation) to treat insomnia.[19–21] An increasing number of neuromodulation therapies have been used for the treatment of insomnia.[22] In particular, non-invasive neuromodulation or stimulation techniques are often used in the treatment of insomnia, including transcranial magnetic stimulation, transcranial electrical stimulation, transcutaneous auricular vagus nerve stimulation, etc. The use of virtual reality technology(VR) and biofeedback therapy alone or in combination can improve brain neuroplasticity through the training of multi-sensory systems.[21] These generalized neuromodulation techniques are also widely used in the treatment of insomnia. However, the lack of public understanding of the technical types, principles, and efficacy of this treatment strategy also limits the options of sleep workers for insomnia treatment. To this end, we conducted a literature search for physical therapy approaches, particularly non-invasive nerve stimulation techniques, using the search terms (insomnia or sleep disorder or Non-organic insomnia or primary insomnia) and (physical therapy or non-invasive nerve stimulation technique or non-invasive neurostimulation or virtual reality or vr or biofeedback or transcranial magnetic stimulation or TMS or transcranial electrical stimulation or tES or tDCS or tACS or vagus nerve stimulation or VNS or taVNS). Based on the search results, we reviewed the latest research in recent years and reported on the efficacy, safety and related mechanisms of relevant treatment methods, in order to provide more choices for the clinical treatment of patients with sleep disorders.The principles, device or techniques, advantages and disadvantages of various treatment methods are described in Table 1 and Figure 1, and the recent studies are reviewed in turn.

**Table 1** The Principles, Device or Techniques, Advantages and Disadvantages of Various Treatment Methods

| | |
|---|---|
| **Virtual reality (VR)**[23–30] | |
| Principle | VR is a computer-generated presentation that provides input to the user's sensory system and interacts with the user. The aim is to replace sensory input from the real world and create a presence of the user in the virtual world. To interact with the user in real time, the VR system collects information about the users' position and (head) movements via sensors and input devices such as head tracking systems or joystick. |
| Device/Technology | Types of Head-Worn Devices: Highly-immersive, semi-immersive, lowly immersive or unspecified. |
| Advantages/ Disadvantages | VR exposure has many structural advantages. It is less time consuming in its application, cost-effective, and requires less organization. Furthermore, there are fewer difficulties concerning safety and insurance arrangements. |
| **Biofeedback (BFB)**[31–38] | |
| Principle | Biofeedback is a learning technique that enables an individual to acquire psychophysiological self-regulation skills for the purpose of improving health and/or performance. The feedback is generally provided in the form of visual, auditory or sometimes tactile representations, and through this information, the subject learns to regulate the required levels of physiological activation, gain control over his or her physiological processes and, therefore, optimize his or her psychophysiological functioning. |
| Device/Technology | Respiratory biofeedback, Cardiovascular biofeedback, Neuromuscular biofeedback, Skin conductance biofeedback, Peripheral skin temperature biofeedback, Neurofeedback. |
| Advantages/ Disadvantages | The effect is similar to physical exercise, but the effect is slower, and once the subject is familiar with the adjustment method, it can be used on its own. There will be no dependence or withdrawal. |

(*Continued*)

**Table 1** (Continued).

| | |
|---|---|
| **Repetitive transcranial magnetic stimulation (rTMS)**[39–47] | |
| Principle | In TMS, a magnetic field is generated with a magnetic coil placed above the scalp, which efficiently passes through the skull and induces electrical currents in the underlying brain tissue beneath the coil, and the induced electrical stimulus activates neural elements in the cortex or subcortical white matter. It can cause prolonged neuroplastic changes that inhibit or excite the brain's activity. |
| Device/Technology | The rest motor threshold (RMT) was measured during the first treatment to determine the intensity of magnetic stimulation. The commonly used rTMS stimulation intensity in clinical practice is 80%–120% MT |
| Advantages/ Disadvantages | rTMS is effective for a variety of mental disorders, but it is contraindicated for central nervous system diseases and the cost is high |
| **Transcranial electrical stimulation (tES)**[48–55] | |
| Principle | tES is a neuromodulation technique in which weak electrical current is applied to the scalp of the brain through electrodes to stimulate specific brain areas and regulate the neural activity or excitability of the cerebral cortex. tES mainly includes two forms: Transcranial Direct Current Stimulation (tDCS) and Transcranial Alternating Current Stimulation (tACS) were performed. They have different mechanisms of action. |
| Device/Technology | The electrode sheet was placed on the scalp. tDCS and tACS both involve the application of a low-intensity electrical current (1–2 mA) to the scalp. The main difference is that tDCS involves a constant current while tACS uses an alternating current. |
| Advantages/ Disadvantages | The stimulation parameters of transcranial electrical stimulation (such as stimulation intensity, frequency, duration) can be adjusted and set individually according to the needs of the individual.The effects of transcranial electrical stimulation are usually reversible, in the sense that brain function returns to baseline after cessation of stimulation. |
| **Transcutaneous auricular vagus nerve stimulation (taVNS)**[56–62] | |
| Principle | taVNS is an emerging non-invasive neuromodulation therapy that replaces the traumatic traditional vagus nerve stimulation by stimulating the auricular branch of the vagus nerve located in the external auditory canal and widely affecting all parts of the brain. These include the thalamus, cerebellum, orbitofrontal cortex, limbic system, hypothalamus, and medulla. |
| Device/Technology | Electrodes were placed in the patient's external auditory canal and electrical stimulation was applied at different frequencies and amounts of electricity. |
| Advantages/ Disadvantages | taVNS is a non-invasive protocol to stimulate the vagus nerve through electrodes on the skin surface, which is safer and more convenient |
| **Other Treatments**[63–68] | |
| Device/Technology | Photobiomodulation therapy (PBMT),Modified electroconvulsive therapy (MECT), Transcranial focused ultrasound (tFUS),Slow-wave sleep (SWS) EEG music therapy, Forehead cooling device. |
| Advantages/ Disadvantages | There are few clinical reports, and individual research reports reflect the advantages, which are still under further study |

## Virtual Reality Technology (VR)

VR is a new digital device developed in recent years, which is a computer simulation system that creates and experiences a virtual world. It is composed of a three-dimensional digital model generated by computer technology, and the virtual world is generated by computer technology as the core. Users can experience various sensory stimuli, including sight, hearing, touch, and immerse themselves in the virtual environment through special input and output devices. With the development of technology, virtual reality technology has been further applied in clinical practice as a new treatment method. There have been reports of VR technology playing an increasingly important role in the diagnosis and treatment of mental disorders.[23]

McCrae et al recruited 12 adults with chronic insomnia and conducted a 4-week VR-guided image therapy. The preliminary trial found that the severity of insomnia, wake-up time after falling asleep, sleep latency, and sleep quality of patients were improved after treatment, and they had high compliance and satisfaction.[24] Eremita et al recruited 32 patients with insufficient sleep and conducted a 4-week treatment of three mental training sessions per week and 15 minutes of VR treatment. The results of the Pittsburgh Sleep Quality Index (PSQI) indicated good treatment effects.[25] Wan et al selected 51 chronic insomnia patients as the research subjects and divided them into two groups based on the patients' willingness: the VR combined with drug treatment group and the simple drug treatment group. The

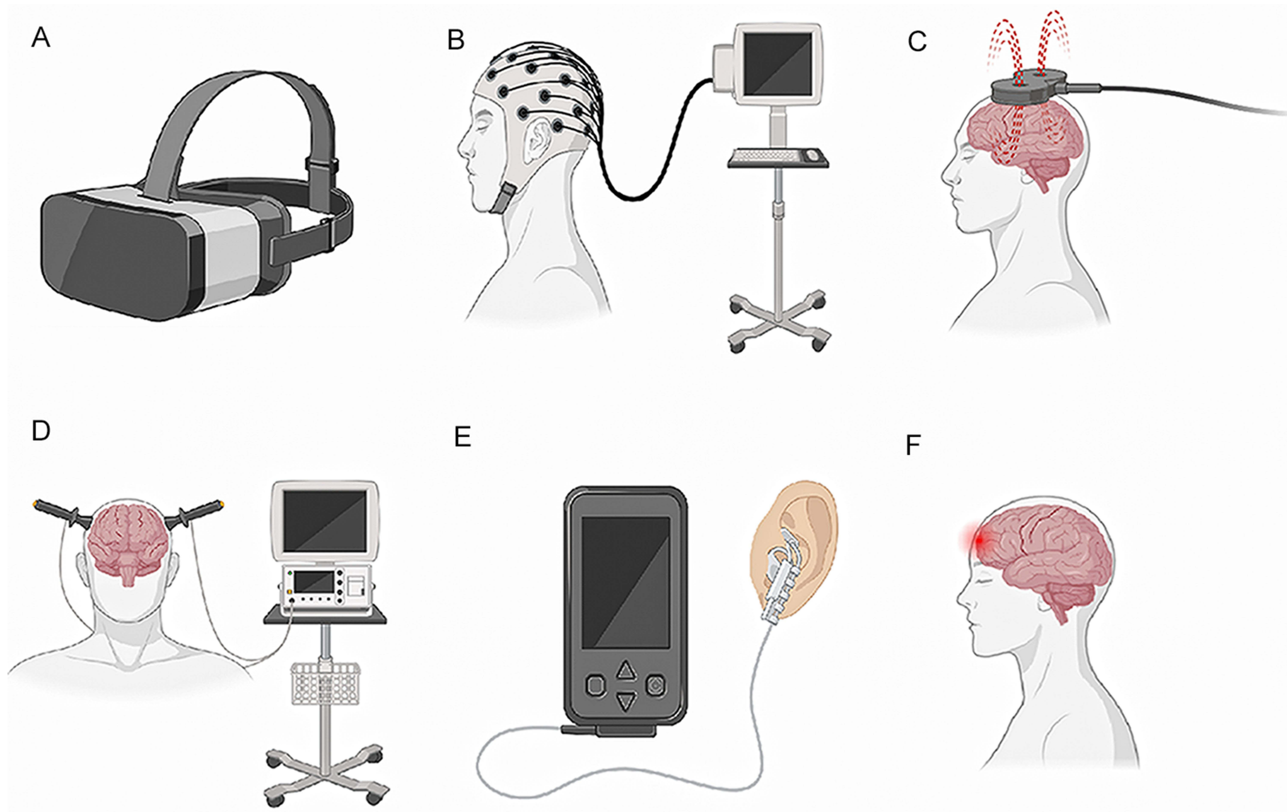


**Figure 1** Schematic representation of various therapeutic devices.
**Notes**: (**A**) VR treatment device; (**B**) EEG biofeedback therapy; (**C**) Transcranial magnetic stimulation; (**D**) Transcranial electrical stimulation; (**E**) Transcutaneous vagus nerve stimulation; (**F**) Forehead cooling therapy.

VR combined with drug treatment group received additional 30-minute VR technology treatment five days a week on the basis of the above-mentioned drug treatment. Before the treatment and 6 weeks after the treatment, the Epworth Sleepiness Scale (ESS), PSQI, and Insomnia Severity Index (ISI) were used to evaluate the subjective sleep quality of the patients, and the portable sleep monitor (PSM)-100A based on cardiorespiratory coupling technology was adopted to assess the sleep structure. The results demonstrated that compared with simple drug treatment, VR technology combined with drug treatment could more effectively improve the subjective sleep quality and sleep structure of chronic insomnia patients, alleviate depression and anxiety, and enhance memory and attention.[26] Yüksel et al applied VR treatment to adolescent insomnia patients. Polysomnography (PSG) indicated that the sleep latency of adolescent patients was shorter (reduced by approximately 6 minutes) and the sleep efficiency was higher (increased by approximately 3%) after VR treatment.[27] Zambotti et al intervened in adolescent insomnia patients through VR and found that after VR intervention, the physiological arousal of adolescents was reduced, heart rate and cortisol levels were decreased, and there was no discomfort related to VR exposure, preliminarily proving the efficacy of VR in reducing adolescent insomnia symptoms.[28] Xu et al applied virtual reality technology combined with cognitive behavioral therapy (combined therapy) to the treatment of adolescent insomnia. The results found that the combined therapy had a better treatment effect on adolescent insomnia patients, and the patient satisfaction was high. It could effectively improve the sleep quality of patients and had good clinical application value.[29] Yang et al reported the improvement effect of VR comprehensive intervention on the quality of life of elderly patients with depression after stroke. Through the evaluation of the Pittsburgh Sleep Quality Index, it was found that the sleep quality of elderly patients had been effectively improved.[30]

The above researches indicate that VR technology has a favorable effect on patients with insomnia. However, due to the relatively small scale of clinical research on VR in insomnia, larger sample sizes, longer-term follow-up studies, and randomized controlled designs are still needed in the future to explore more comprehensive treatment regimens, and the development of VR treatment protocols and system software needs to be improved.

## Biofeedback Therapy (BFB)

BFB is a physical factor treatment method that utilizes modern physiological science instruments. Through self-feedback of physiological or pathological information within the human body, patients undergo special training and then perform conscious “mental” control and psychological training, thereby eliminating pathological processes and restoring physical and mental health. It is a new type of treatment approach. Biofeedback therapy is often utilized in diseases such as nicotine addiction, sports performance, autism spectrum disorder (ASD), and attention deficit hyperactivity disorder (ADHD).[31]

Wang et al conducted 20 courses of biofeedback treatment on 14 insomnia patients. Each treatment process is 5 minutes of electromyogram and 30 minutes of electroencephalogram feedback. The study found that BFB treatment based on α power and prefrontal electromyogram can relieve insomnia as well as anxiety and depression.[32] Huang et al found that combined with biofeedback therapy, the Pittsburgh Sleep Quality Index was reduced more than taking sleep medications (zolpidem) alone.[33] Wang et al conducted a four-week randomized controlled, parallel biofeedback treatment on college students with insomnia accompanied by anxiety or depression symptoms, and found that the sleep symptoms of college students were significantly improved after biofeedback treatment.[34] Kolken et al reported the therapeutic effect of sensorimotor rhythm (SMR) neurofeedback on 37 participants with sleep problems. The results showed that the sleep quality and cognitive function of the participants were improved overall.[35] Zhang et al regulated the amygdala of patients with insomnia disorder through real-time functional magnetic resonance imaging neurofeedback (rtfMRI-NF) technology, and found that rtfMRI-NF technology can improve the sleep quality and emotional state of patients with sleep disorders. The mechanism may be related to changes in FC between the left amygdala and the default network, emotional regulation, and cognitive-related brain regions.[36] Kwan et al reported that compared with CBT-I, neurofeedback training has limited effects in reducing cognitive dysfunction, but can relieve insomnia symptoms by reducing cortical over-excitation in patients.[37] The above studies show the effectiveness of using biofeedback to treat chronic insomnia. However, a systematic review of the application of biofeedback technology found contradictory evidence on the effectiveness of biofeedback technology in treating chronic insomnia.[38] In general, biofeedback treatment technology has been applied earlier and is relatively mature. In recent years, research reports in the sleep field have gradually increased. It is generally effective for sleep disorders and no obvious adverse reactions have been reported.

## Repetitive Transcranial Magnetic Stimulation (rTMS)

rTMS is a neuromodulation technique approved by the US Food and Drug Administration for the treatment of refractory major depression. It works by generating a local magnetic field that produces a depolarizing current in neurons a few centimeters below the scalp. This local effect is thought to stimulate neural plasticity, activate compensatory processes, and affect cortical excitability. Currently, rTMS has been used in clinical trials for various neurological and psychiatric disorders such as anxiety disorders, post-traumatic stress disorder, epilepsy, insomnia and other diseases.[39]

This review presents the latest research in recent years and reports on the efficacy of different stimulation sites and parameters on patients with insomnia. Ding et al in a single-blind, randomized controlled trial randomly divided 39 patients with insomnia into a real stimulation group and a sham stimulation group. The stimulation parameters were a stimulation frequency of 1 hz, a stimulation intensity of 80% of the resting motor threshold (RMT), a total of 1500 pulses, and a duration of 25 minutes. The entire treatment course lasted for 7 days. Pre-test (baseline) and post-test (on the 7th day after intervention) evaluated the Insomnia Severity Index (ISI), Pittsburgh Sleep Quality Index (PSQI), Multidimensional Fatigue Scale (MFI), and Beck Anxiety Scale (BAI). The results suggest that rTMS stimulation of the left dorsolateral prefrontal cortex (LDLPFC) in insomnia patients can significantly improve the conflict control ability and sleep quality of insomnia patients.[40] A double-blind, pilot randomized controlled trial by scholars from the University of Arizona found that insomnia can be treated by rTMS, especially continuous theta burst stimulation (cTBS) to disrupt the default mode network (DMN). This preliminary study reported the possible mechanism of rTMS stimulation of the left inferior parietal lobule in the treatment of insomnia.[41] Holbert et al studied the therapeutic effect of bifrontal low-frequency (LF) TMS on primary insomnia. Twenty patients with primary insomnia but without major depression received 15 consecutive sessions of bifrontal LF rTMS stimulation. The results showed that the new


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bifrontal LF rTMS benefited this group of patients with primary insomnia.[42] Lin et al used low-frequency rTMS of the left dorsomedial prefrontal cortex (DMPFC) as an adjuvant therapy for insomnia. The experiment applied 1 hz rTMS to the DMPFC of the experimental group and the sham coil of the placebo group. The results suggest that low-frequency DMPFC-rTMS may improve sleep by reducing the duration of wakefulness after falling asleep.[43] In the mechanism study of rTMS regulating sleep, an animal experiment found that down-regulating the expression of kynurenine 3-monooxygenase and improving the structure and number of rat hippocampal synapses alleviated spatial learning and memory deficits. This mechanism is mainly achieved by 1 hz rTMS to improve chronic rapid eye movement sleep deprivation.[44] A clinical study analyzed resting-state functional connectivity (RSFC) in regions with different low-frequency fluctuation values by performing 4 weeks of rTMS treatment on 20 insomnia patients and sham stimulation intervention on 18 patients. It was found that the disconnection of the frontoparietal network may be a biomarker of insomnia in middle-aged people, which further provides evidence for rTMS stimulation of the frontal lobe to treat insomnia.[45] Zhang et al reported that rTMS improved the sleep quality of insomnia patients by regulating abnormal electroencephalogram coherence. Baseline electroencephalogram coherence between certain channels in the theta, alpha, and beta frequency bands can be used as a potential biomarker for predicting treatment effects.[46] In a side effect study of rTMS in the treatment of insomnia, by observing the verbal memory recall of 20 adult insomnia patients receiving continuous theta burst stimulation rTMS, no long-term effect of rTMS on verbal memory recall was found.[47]

The above researches reviews the latest research in recent years, which reports the treatment effects of different site parameters. Since the current treatment parameters have not been completely standardized, further research is still needed.

## Transcranial Electrical Stimulation (tES)

tES is a neuromodulation technique that applies a weak electric current through electrodes on the scalp to stimulate specific brain regions and regulate neural activity or excitability of the cerebral cortex. tES mainly includes two forms: Transcranial Direct Current Stimulation (tDCS) and Transcranial Alternating Current Stimulation (tACS). Although these two stimulation methods have different mechanisms of action, they are both applied in fields such as enhancing cognitive function, promoting rehabilitation, relieving pain, assisting in the treatment of mental disorders, regulating movement, and promoting neuroscience research.[48]

Zhu et al recruited 120 participants with chronic insomnia and randomly divided them into a tACS treatment group and a sham stimulation control group. They received 20 daily sessions of 40-minute brain stimulation with a frequency of 77.5 hz and an intensity of 15 mA on the forehead and bilateral mastoid regions within 4 weeks. The tACS group showed improved sleep quality and efficiency, increased total sleep time, and reduced interference with daily life. Subgroup analysis showed that in elderly participants, tACS could significantly improve sleep quality, increase sleep efficiency, and reduce the overall degree of insomnia.[49] Motamedi et al conducted tACS treatment on 9 patients with long-term insomnia in a polysomnography laboratory at intervals of 2 weeks. It was found that there were significant improvements in spontaneous awakening, total awakening, sleep quality, quality of life, recall ability, sleep time, sleep efficiency, and daytime sleepiness in patients with insomnia.[50] Shan et al reported that tACS treatment with a current of 15 mA and a frequency of 77.5 hz through the forehead and bilateral mastoid regions for more than 8 weeks is safe and effective in treating insomnia and depression, and a specific tACS procedure can transmit current to deep brain tissues.[51]

Researchers treated insomnia patients caused by traumatic brain injury with tDCS and found that after six weeks of treatment, the Pittsburgh Sleep Quality Index and Insomnia Severity Index of the patients decreased significantly.[52] Cheng et al reported that tDCS can improve cognition after sleep deprivation and will not interfere with recovery sleep and cognitive performance after recovery sleep.[53] In an insomnia mouse model experiment, Su et al found that tDCS stimulation increased the number of non-rapid eye movement (NREM) sleep during acute stress responses and improved the duration of NREM and REM sleep during subsequent acute insomnia.[54] However, there are also different results. Frase et al reported that tDCS has no effect on sleep continuity or sleep structure in insomnia patients and analyzed that the ineffectiveness of tDCS may be related to the persistent hyperarousal of insomnia patients.[55]

In conclusion, both tDCS and tACS can be applied to sleep disorders, and most studies suggest their effectiveness and safety. Like rTMS, further research on more optimized treatment parameters is still needed in the next step to provide a better choice for physical treatment plans for sleep disorders.

## Transcutaneous Auricular Vagus Nerve Stimulation (taVNS)

taVNS is an emerging non-invasive neuromodulation therapy that stimulates the auricular branch of the vagus nerve located in the external auditory canal and widely affects various parts of the brain, including the thalamus, cerebellum, orbitofrontal cortex, limbic system, hypothalamus, and medulla. taVNS has been proven to be safe and effective for epilepsy, major depression, insomnia, glucose metabolism disorders, pain, stroke, post-stroke rehabilitation, anxiety, fear, and cognitive impairment.[56]

Reports and mechanism studies of taVNS in the treatment of insomnia have gradually increased in recent years. A randomized, double-blind study reported that 30 patients diagnosed with primary insomnia received 20 hz t-VNS in the auricular concha area (treatment group) or the peri-auricular area (control group) twice a day for 20 minutes each time for one month. The effective rate of the treatment group (73% vs 27%) was significantly higher than that of the control group, and no complications occurred in all patients. It is considered a safe and effective method for treating primary insomnia.[57] Srinivasan et al applied taVNS to elderly healthcare workers after the COVID-19 pandemic and found that the sleep quality of the test population was significantly improved after 4 weeks of taVNS treatment.[58] Zhang et al conducted a randomized single-blind controlled trial on people traveling to high altitudes and showed that tVNS had a significant effect on people with high-altitude insomnia, with shortened sleep latency and prolonged deep sleep time.[59] Bottari et al conducted 1 hour of active tVNS stimulation on 13 veterans with post-traumatic stress disorder when "lights out" and found that tVNS can improve the depth and stability of sleep of veterans with post-traumatic stress disorder and increase parasympathetically mediated nocturnal autonomic activity.[60] He et al found through resting-state functional magnetic resonance imaging (Rs-fMRI) before and after taVNS treatment that taVNS has a regulatory effect on the prefrontal cortex of patients with chronic insomnia. The initial state of the left dorsolateral prefrontal cortex can predict the efficacy of taVNS on chronic insomnia.[61] Zhang et al reported the mechanism of taVNS in the treatment of primary insomnia. They believe that taVNS treatment can improve the sleep quality and prolong the sleep time of patients with primary insomnia by reducing the functional links within the brain's default network, the functional links between the default network and the salience network, and the functional links between the default network and the occipital cortex.[62] The above studies reported the effectiveness of taVNS in treating sleep disorders and elaborated on some brain function mechanisms of taVNS in treating insomnia.

## Other Types of Neuromodulation Techniques

With the in-depth development of neuromodulation technology, there are also some new regulatory technologies. For example, photobiomodulation therapy (PBMT) uses a nasal-based i-PBMT device with lasers or light-emitting diodes (LEDs), and can be used alone or in combination with transcranial devices (the latter is directly applied to the scalp) to treat various brain diseases such as mild cognitive impairment, Alzheimer's disease, Parkinson's disease, cerebrovascular disease, depression and anxiety, and insomnia.[63] Transcranial focused ultrasound (tFUS) is a new and promising non-invasive brain stimulation technology for modulating neuronal activity with high spatial specificity. The medial prefrontal cortex (mPFC) has been proposed as a potential target for neuromodulation for mood and sleep quality.[64] Modified electroconvulsive therapy (MECT) is a physical treatment method commonly used for mental and psychological diseases such as severe depression. It is rarely used for patients with simple insomnia. The first case study reported the process of a patient with intractable insomnia who was ineffective with drug combination TMS and received 9 sessions of MECT treatment. After continuous follow-up for six months, the patient's sleep quality (from 2 hours to 4–5 hours) improved, and no obvious adverse reactions were reported.[65] Some researchers also reported a new model of physical combined treatment. A 52-year-old female patient with chronic insomnia was given tDCS immediately after rTMS treatment. After 20 treatments, the sleep latency and rapid eye movement (REM) latency gradually shortened, and the total sleep time and sleep efficiency gradually increased. No obvious adverse reactions were reported.[66] Gao et al reported that a non-invasive slow-wave sleep (SWS) EEG music therapy has an improvement effect on sleep quality. The analysis of the improvement

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of sleep quality may be related to the reduction of power spectral density in the δ band and the increase of functional connectivity between the left frontal lobe and the left parietal lobe.[67] Baker et al reported the efficacy of a forehead cooling device on sleep difficulties and hot flashes in menopausal women. It is believed that the forehead cooling device can improve the sleep quality of menopausal women, but further case-control studies and mechanism explorations are still needed.[68]

## Conclusion

This manuscript mainly reviews the recent research on non-invasive neuromodulation in the treatment of insomnia, and summarizes the types, principles, methods, advantages and disadvantages of non-invasive neuromodulation, which can provide more reference for clinical practice. It should be noted that many studies are limited by small sample sizes, absence of control/sham conditions, lack of blinding, and a strong placebo effect. Moreover, these neuromodulation techniques are still in the experimental stage and have not been established or recommended for the treatment of insomnia. Their application scope in clinical practice is limited, and further research is needed in the future. The next step is to explore more optimized treatment strategies and related mechanisms. For example, the location, intensity, frequency, parameter Settings of rTMS, tDCS, tACS and other treatments, as well as the suitable population of treatment, still need to be improved and precise. In the future, neuromodulation therapy technology will be combined with real-time fMRI, EEG monitoring at different frequencies, analysis of autonomic nervous function variation, near-infrared spectroscopy brain imaging and machine algorithms. By analyzing its regulation principle and brain sleep mechanism, it is expected to provide a direction for the development of neuroscience and sleep science.

## Data Sharing Statement

All datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

## Author Contributions

WenLiang Liu: Methodology, Formal analysis and Investigation, Writing- Original draft preparation. Gongying Li: Conceptualization, Supervision, Writing-Review and Editing. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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