Original Research

Transcranial Direct Current Stimulation (tDCS) as a Therapeutic Tool for Chronic Insomnia

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Abstract

Background and Objective: Insomnia is the most common sleep problem which is associated with cortical over-excitation. Transcranial direct-current stimulation (tDCS) potentially modifies insomnia-related cortical state. Therefore, we tested the hypothesis that insomnia severity can be modulated by tDCS.

Materials and Methods: The current study was conducted with a pretest-posttest design and a control group. A total of 32 women with insomnia were randomly categorized into an intervention group (active stimulation) and a control group (sham stimulation). In the intervention group, tDCS was used with an intensity of 2mA for 20 to 30 minutes during 12 sessions (3 times a week). Anodal stimulation was performed on the left primary motor cortex (M1) and cathodal stimulation was performed on the right dorsal lateral prefrontal cortex (DLPFC). The control group received sham stimulation for 20 to 30 minutes during 12 sessions (3 times a week). All participants were evaluated before and after the intervention using the Insomnia Severity Index (ISI) and Positive Affect and Negative Affect Schedule (PANAS).

Results: The results of univariate analysis of covariance (ANCOVA) and multivariate analysis of covariance (MANCOVA) showed a significant difference between the tDCS group and the sham group in terms of reduction in the severity of insomnia. We also observed that positive affect increased and negative affect decreased following insomnia treatment ($P \leq 0.005$).

Conclusion: The results of our study indicated that performing our designed tDCS protocol for treating insomnia can be effective in treating insomnia and improving positive and negative affect.

Keywords: Transcranial direct current stimulation; Insomnia; Motor cortex; Dorsolateral prefrontal cortex

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Introduction

Insomnia is defined as difficulty initiating or maintaining sleep, or experiencing nonrestorative sleep (NRS) concurrent with distress or impairment in critical areas of everyday functioning, such as increased daytime fatigue, negative mood, and poor concentration (1). Insomnia is the most prevalent sleep disturbance (2, 3). A review study has reported the pooled prevalence of insomnia in the general population as 22.0% and showed a significantly higher prevalence of insomnia among women compared with men (4). A considerable quantity of studies reported that women complained more often of insomnia than men (5).

Research results have shown that compared to healthy people, patients with insomnia show increased cortical excitability, decreased intracortical facilitation, and cortical hyperexcitability in sleep and wakefulness states (6-10). Increased activity in the prefrontal cortex of the brain during sleep was seen in insomniac patients (11, 12). In

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addition, differences in the activity of alpha and beta waves have been reported among people with insomnia compared to the control group (13, 14).

Approximately 80-90% of patients with insomnia also have a concurrent medical or psychological diagnosis (15). Alvaro et al. explained that there is a bidirectional relationship between insomnia and affective disorders and they suggested that insomnia can predict the prevalence of anxiety and depression and vice versa (16). It has also been suggested that sleep quality can predict positive and negative affect, but not vice versa (17). Additionally, it has been shown that poor sleep quality can influence emotional reactivity to everyday events in healthy individuals and those with minor or major unipolar depression. The recording of emotional reactivity to daily events throughout participants' daily lives showed that sleep difficulties were associated with increased negative affect to unpleasant events and decreased response to neutral events. However, in individuals with unipolar depression, sleep difficulties were associated with increased negative affect for all everyday events (18). In general, the results of studies indicate that insomnia is associated with various psychiatric conditions like depression and anxiety (19-21).

It seems that in all diseases, the association between sleep disturbances and neurological and neuropsychiatric diseases is bidirectional and worsening or improvement of one condition will influence the other conditions (22-24). Increased positive affect has been associated with improved sleep quality, and increased negative affect has been associated with reduced sleep quality (25). The results of studies have shown that following therapeutic interventions aimed at improving insomnia, symptoms, mood, and quality of life (QOL) also improve (26). Therefore, it can be argued that with the improvement of insomnia, the accompanying condition also improves including positive and negative affect.

Short-term pharmacotherapy (e.g., benzodiazepines, hypnotics, etc.) and cognitive behavioral therapy (CBT-I) are the most common interventions for the treatment of chronic insomnia and improvement of sleep quality. Drug treatments may be associated with numerous side effects, including tolerance, dependence, and addiction. Cognitive behavioral therapy may also be limited by adherence issues and elevated costs (27, 28). Therefore, the investigation of other treatment options that can alleviate symptoms or potentiate other treatment modalities for the management of sleep disturbances and improvement of sleep quality is necessary (29).

Alterations of cortical excitability and activity play an essential role in the initiation of sleep and the transition between sleep stages through the release of several neurotransmitters that regulate the arousal system (30, 31). Therefore, it can be assumed that an external modulation of cortical activity might be suited to affect sleep-wake transition, and transition between sleep stages and improves insomnia.

A non-invasive method of brain stimulation is transcranial direct current stimulation (tDCS), which has the potential to modulate the cortical state associated with insomnia, due to its ability to induce changes in sleep-wake electroencephalography (EEG) parameters and its effects on cortical activity and excitability (32). During tDCS, a constant and weak current flows from one electrode to another, and the excitability of the target cortical area is shifted in a specific direction. In general, anodal stimulation causes excitation in cortical activity and cathodal stimulation causes inhibition of cortical activity (33). Furthermore, the effects of tDCS depend on the polarity, position, and duration of the application (34).

However, most of the previous studies that used noninvasive brain stimulation (NIBS) for insomnia selected the frontal cortex as the target area, especially the dorsolateral prefrontal cortex (DLPFC) (35-39). Among other sleep disorders, the pathophysiology of restless legs syndrome-related difficulty in sleep onset and quality has led researchers to stimulate the primary somatosensory cortex instead of motor areas, producing both beneficial clinical outcomes and short-term neuroplasticity (40, 41).

A study demonstrated that repetitive bilateral anodal tDCS to the prefrontal cortex before sleep significantly increases cortical arousal during wakefulness (high-frequency EEG power) and decreases total sleep time (TST) compared to cathodal and sham stimulation in healthy humans (42). Moreover, the results of studies have demonstrated that slow-oscillating tDCS over the frontal cortex during slow-wave sleep (SWS) increases SWS immediately after stimulation (43, 44). Researchers found that anodal stimulation over the primary motor cortex (M1) increased sleep efficiency and decreased cortical excitation,

while anodal stimulation of the DLPFC decreased sleep efficiency and increased cortical excitation (45). In addition, other researchers suggest that anodal tDCS over the DLPFC increases activity in the locus coeruleus (LC) region of the brain (46), and that this region is the location of the primary norepinephrine nucleus and it is believed to regulate attention, arousal, wakefulness, memory formation, and memory retention (47).

Despite the treatments available for insomnia to date, many people still suffer from insomnia. To the best of our knowledge, the effects of tDCS on treating chronic insomnia have not been tested yet. Thus, we have tried to investigate whether insomnia could be treated using an assembled protocol of excitatory and inhibitory stimulation of two different cortical regions. We also investigated whether the positive and negative affect of patients with insomnia improve after the treatment of insomnia.

Materials and Methods

Study design and participants: The current study was a randomized clinical trial (code: IRCT20190620043954N2). The statistical population included all women who were referred to the sleep disorders clinic of Imam Khomeini Hospital and the Occupational Sleep Disorders Research Center of Baharloo Hospital of Tehran, Iran, in 2022. Participants were selected based on their score on the Insomnia Severity Index. Then, all of them were evaluated based on the DSM5 diagnostic criteria by a clinical psychologist to complete the diagnosis process.

A total of 32 women with chronic insomnia were selected from the statistical population with informed consent to participate in this research. All participants were healthy in terms of visual, auditory, and sensorimotor abilities, and had no history of neurological disease or psychiatric disorders and drug abuse. An equal number of participants were assigned to the active and sham tDCS groups. Sixteen participants received active tDCS and the other 16 received a sham stimulation. There were no considerable differences in terms of age and duration of disease between groups.

In the present study, to reduce the bias or distortions related to the intervention and evaluation of the results, a single-blind method was used. In this way, none of the participants knew whether they were assigned to the intervention or control group, but the researcher and the evaluator were aware of this. The participants declared their agreement with this type of blinding in the consent form before the research. In both groups, the same transcranial electrical stimulation device was used for the same duration and number of sessions. The present study proposal was approved by the research ethics committee of the School of Nursing and Midwifery and the School of Rehabilitation of Tehran University of Medical Sciences, Iran, (Ethics code: IR.TUMS.FNM.REC.1400.165).

Inclusion and exclusion criteria: The inclusion criteria for the research include: 1) being a woman, 2) being between the ages of 18 and 55 years, 3) not having a history of neuropsychiatric diseases (Alzheimer's, epilepsy, Parkinson's, mental retardation, etc.) and brain damage, 4) not having drug, alcohol, and caffeine abuse according to the DSM5 diagnostic criteria, 5) having a minimum education level of diploma, 6) not taking sleeping medicines or resistance to medical treatment despite taking them, 7) not being pregnant, and 8) absence of bioelectrical devices implanted in the body like a pacemaker. The exclusion criteria were not completing the number of treatment sessions and being infected with diseases whose treatment interfered with the results of our intervention.

Determination of the sample size: The statistical sample included 32 women with chronic insomnia, who were selected voluntarily from the statistical population. The sample size was calculated using the sample size formula to compare the averages of the two groups with equal variance.

$$\text{Formula 1: } n_A = \frac{\left(1+{}^{1}/_{\varphi}\right)\left(z_{\vdash\alpha/2}+z_{\vdash\beta}\right)^2}{\Delta^2} + \frac{z^2_{1-\alpha/2}}{2(1+\varphi)}$$

Where n_A is the sample size of the first group and φ is the ratio of the sample size of the first group to the second group, which we considered as one. Thus, by inserting it in the above formula, we will have:

$$\text{Formula 1: } \quad n_A = \frac{2\left(z_{\vdash {}^{\alpha}/_{2}}+z_{\vdash\beta}\right)^2}{\Delta^2} + \frac{z^2_{\vdash\alpha/2}}{4}$$

In our study, $\alpha = 0.05$, $\beta = 0.2$, and Δ (standardized effect size) was considered equal to one. By placing the values of each index in the mentioned formula, the sample size in each group is approximately 16 people. Finally, our total sample size was calculated to be 32 people, who were randomly assigned to the intervention and control groups. Random blocks of 4 were used to random-

ly assign participants to groups and avoid wasting time until the sample population was completed. The four randomized complete blocks method was performed to assign the subjects randomly to the test and control groups and prevent the wasting of time until the sample population is fully completed.

In the current study, tDCS was applied using a brain stimulation device (SN: T-NS2-2020F131, NeuroStim 2, Medina Teb Gostar Company, Tehran, Iran). The tDCS was delivered through two sponge electrodes (5 cm.5cm) humidified with a saline solution. The anode electrode was placed on the left M1 and the cathode electrode was placed on the right dorsolateral prefrontal cortex (rDLPFC). In the intervention group, tDCS was used with an intensity of 2mA for 20 to 30 minutes during 12 sessions (3 times a week). The control group received sham stimulation for 20 to 30 minutes during 12 sessions (3 times a week) with electrodes placed on the same areas as in the intervention group protocol. All participants were evaluated before (pretest) and after (posttest) the intervention using the Insomnia Severity Index (ISI) and Positive Affect and Negative Affect Schedule (PANAS).

In the present study, two different outcomes of the intervention were defined and evaluated independently. The primary outcome included the effects of applying the tDCS treatment protocol on the severity of insomnia and the secondary outcome was the changes in the positive and negative affect of the participants following insomnia treatment.

Insomnia Severity Index: The ISI designed by Morin in 1993 is a brief self-assessment tool that measures the symptoms of insomnia along with their negative effects on people's lives in the previous two weeks. This tool consists of 7 questions that evaluate the severity of insomnia by measuring items including sleep onset, staying asleep and waking up early, satisfaction with sleep status, interference of sleep problems with daily functions, the significance of sleep problems for others, and worrying about sleep problems. Each question is scored on a 5-point Likert scale ranging from 0 to 4, and the total score of the questionnaire, which is obtained from the sum of the scores of the questions, ranges from 0 to 28. A higher score in this questionnaire indicates a more severe insomnia, and a score of 0-7 indicates no insomnia, a score of 8-14 indicates insomnia below the clinical threshold, a score of 15-21 indicates moderate insomnia, and a score of 22-28 indicates severe insomnia (48). In the present study, the reliability rate of the ISI was 0.88.

Positive Affect and Negative Affect Schedule: This scale was created in 1988 by Watson, Clark, and Tellegen to measure two the dimensions of negative affect and positive affect, and it has 20 items that are scored on a 5-point Likert scale ranging from very low (score 1) to very high (score 5), which is rated by the subject. The range of scores for each subscale is 10-50 (49). In Iran, the internal validity and consistency (Cronbach's alpha coefficient) of the positive affect scales have been reported to range from 0.86 to 0.90, and the negative affect scales from 0.84 to 0.87 (50).

Statistical analysis: The data of this study were summarized and analyzed in SPSS software (Version 23; IBM Corp., Armonk, NY, USA). Mean and standard deviation were used to describe the data, and univariate analysis of covariance (ANCOVA) and multivariate analysis of covariance (MANCOVA) were used to analyze the relationships between variables.

Results

In this research, the intervention and control groups each had 16 participants, who had a mean age of 44.5 ± 11.63 and 42.69 ± 10.76 years, respectively. There was no significant difference between the two groups in terms of age ($t = 0.43$; $P = 0.67$) and duration of the disorder ($t = 1.32$, $P = 0.19$), that is, at the very beginning of the study, the two groups were the same in terms of age and duration of the disease, and these two variables were not considered as intervening variables. The results of the chi-square test showed that there was no statistically significant difference between the two groups in terms of marital status ($P = 0.41$).

The distribution of the mean and standard deviation of positive and negative affect and insomnia severity in the intervention and control groups in the pretest and posttest phases are presented in table 1. As can be seen in table 1, the studied groups did not differ significantly in terms of the research variables in the pretest stage, but in the posttest stage, the mean and standard deviation of the groups changed.

MANCOVA was used to evaluate the effectiveness of tDCS. The assumptions of MANCOVA were used. Levene's test, Shapiro-Wilk test, homogeneity of the slope of the regression line, and Box's M test were checked and these tests confirmed that MANCOVA could be used.

Table 1. The positive and negative affect and insomnia severity in the experimental and sham groups

Dependent variables	tDCS group (n = 16)		Sham group (n = 16)	
	Pretest	Posttest	Pretest	Posttest
Positive affect	29.56 ± 9.98	35.31 ± 7.88	26.43 ± 7.87	26.25 ± 8.02
Negative affect	28.93 ± 7.21	19.87 ± 5.40	33.93 ± 8.19	32.56 ± 9.54
Insomnia severity	21.68 ± 3.43	10.50 ± 3.75	22.37 ± 3.07	21.12 ± 4.88

tDCS: Transcranial direct current stimulation

Table 2 shows that after pretest control, there is a significant difference between the intervention and sham groups in the dependent variables in the posttest ($P < 0.001$). There is a significant difference in at least one of the dependent variables between the two groups in the posttest stage. The effect size coefficient shows that 63% of the difference in the two groups is related to the experimental intervention. To find the single-variable differences, ANCOVA was performed, the results of which are presented in table 3.

Table 3 shows the results of ANCOVA regarding the significance of the difference between the means of the variables of negative mood, positive mood, and intensity of insomnia. According to the results of table 3 and the F-value, there is a significant difference between the adjusted averages of the scores of the research variables according to the group membership in the posttest stage ($P < 0.001$). Considering the averages presented in table 1, it can be concluded that tDCS affected the severity of insomnia, negative mood, and positive mood. The amount of this effect in the intensity variable of insomnia, negative mood, and positive mood is 0.62, 0.42, and 0.41, respectively.

Discussion

The present study was carried out to investigate the effects of tDCS on the treatment of insomnia and its effects on positive and negative affect in women with chronic insomnia. Our research has used, for the first time, anodal and cathodal stimulation assembled in different cortical areas for the treatment of chronic insomnia. Our results showed a significant reduction in insomnia severity in the active tDCS group compared to the sham stimulation group. In addition, we observed a significant increase in positive affect and decrease in negative affect in these participants.

It seems that the therapeutic effects of tDCS are multifactorial, and its underlying effects cannot be attributed to a single simple mechanism. Therefore, the reduction of insomnia severity in response to tDCS treatment may have happened for various reasons.

The first possible explanation of the results of this research is related to the excitatory and inhibitory target areas of our protocol for insomnia. Anodal stimulation is considered to promote depolarization of neuronal membranes (excitatory stimulation), while cathodal stimulation inhibits depolarization and induces hyperpolarization (inhibitory stimulation) (51).

In addition, electrical current stimulation affects several neurons and increases their membrane potential for inducing depolarization. These events have been proposed to explain the ability of tDCS to improve brain function in the vicinity of neural membranes (52).

As mentioned above, anodal stimulation of the M1 increases sleep efficacy and reduces cortical excitation, while anodal stimulation of the DLPFC decreases sleep efficacy and increases cortical excitation in patients with fibromyalgia (45). The results of a study demonstrated that after the sleep deprivation vigil (sleep-deprived participants), those receiving anodal stimulation over the left DLPFC slept significantly less than the M1 and sham groups in the nights following sleep deprivation (47).

Table 2. Multivariate analysis of covariance of the positive and negative affect and insomnia in the experimental and control groups

Variable	Test	Value	F	df	P-value	Eta^2	Observed power
Group	Pillai's Trace	0.636	14.53	3	0.001	0.63	1
	Wilks' Lambda	0.364	14.53	3	0.001	0.63	1
	Hotelling's Trace	1.744	14.53	3	0.001	0.63	1
	Roy's Largest Root	1.744	14.53	3	0.001	0.63	1

df: Degree of freedom

Table 3. Analysis of covariance results of the comparison of the mean of insomnia, and negative and positive affect

Variable	Subscale	Sum of squares	Mean of squares	F	P-value	Eta^2	Observed power
Negative affect	Group	537.186	537.186	19.558	0.001	0.42	0.989
	Error	741.825	27.475				
Positive affect	Group	227.110	227.110	18.868	0.001	0.41	0.987
	Error	324.992	12.037				
Insomnia	Group	630.350	630.350	44.790	0.001	0.62	1
	Error	379.920	14.070				

Moreover, the M1 stimulation group reported significantly higher alertness ratings than the DLPFC stimulation group in the days following sleep deprivation, which probably indicates increased alertness/arousal for the M1 group. In addition, it is possible that anodal stimulation of M1 promotes faster recovery from fatigue (47).

EEG studies have shown that the activity of DLPFC is related to sleep performance (53). Neuroimaging studies have shown that patients with insomnia have hyperarousal in the DLPFC compared to good sleepers (54). The right DLPFC has been identified as a potential target for NIBS stimulation in the treatment of chronic insomnia. The right DLPFC has a widespread positive correlation with other cortical and subcortical regions related to sleep in patients with chronic insomnia (55). The prefrontal cortex is one of the cortical areas whose modulation via tDCS might influence the physiology and quality of sleep. Via modulation of prefrontal cerebellar connectivity, combined tDCS could also be a promising approach to modulating the quality of sleep or improving symptoms in some sleep disturbances, such as insomnia (35). A repetitive anodal tDCS protocol applied bilaterally to the frontal cortex before sleep increased indices of arousal during wakefulness (high-frequency resting-state EEG power) and reduced the total sleep time in healthy humans (42) as well as in a patient with hypersomnia (56), but not in patients with insomnia (57), which is indicative of the brain state-dependent effects of the protocol.

The results of the studies reviewed in this section indicate that inhibitory stimulation of the right DLPFC would be an effective condition for treating chronic insomnia. Our study results show that cathodal stimulation of the right DLPFC, most likely reduces the severity of insomnia by reducing the metabolism, cerebral blood flow, and cortical excitation of this area. As a result, it has led to increases in the duration and efficiency of sleep.

Other studies have demonstrated that anodal tDCS stimulation of the motor cortex can increase excitatory post-synaptic potential (58). Furthermore, Merzagora et al. reported that increasing the excitability of local neurons through anodal stimulation leads to increased blood flow in the surrounding area and subsequent metabolic changes (59). It was demonstrated that stimulation over the M1 for 15 days, significantly improved subjective sleep quality and lessened fatigue symptoms in patients with the post-polio syndrome (60). Generally, studies that have targeted M1 alone or in combination with other brain regions and used more than 10 sessions of tDCS have reported improvements in sleep (61).

In our study, patients reported having more energy and less fatigue throughout the day for their daily activities during treatment and even after completing the treatment, and this change is likely due to stimulation of the M1 region excitation and increased alertness and excitation in the days after the stimulation, leading to faster recovery from fatigue following improved sleep.

The next explanation for our study results is that they may most likely be related to the changes in brain neurotransmitters followed by tDCS. Anodal stimulation and cathodal stimulation of the tDCS regulated the concentration and activity of glutamate and gamma-aminobutyric acid (GABA) (62). On the other hand, anodal tDCS modulates the dopamine system, increases serotonin transport, and suppresses acetylcholine transportation (63). GABA is the neurotransmitter that most widely promotes sleep, whereas norepinephrine and dopamine promote wakefulness; serotonin is necessary for both optimal sleep and wakefulness (64, 65). On the other hand, the application of anodal tDCS over M1 improves motor response inhibition and might be a promising adjuvant therapeutic intervention for the modulation of motor response inhibition (66). Therefore, considering the effect of tDCS on neurotransmitter damping and enhanced motor response inhibition, it can be expected that an appropriate and compat-

ible therapeutic protocol can reduce insomnia severity. The results of our therapeutic protocol implementation confirmed this expectation.

In addition, as discussed earlier, it has been shown that anodal DLPFC stimulation causes increased activity in the locus coeruleus (LC) region (46), and the LC region is the primary norepinephrine nucleus and can regulate attention, arousal, wakefulness, memory formation, and memory retention (47). Therefore, it is also possible that the cathodal DLPFC stimulation in our treatment protocol has led to a decrease in activity in the LC region, resulting in a reduction in norepinephrine and a decrease in cortical alertness and excitation, followed by facilitated drowsiness and sleep flow.

Another explanation for our data results may be the changes in EEG following tDCS treatment. There is evidence to demonstrate the opinion that transcranial electrical stimulation (TES) can enhance sleep onset and/or the EEG oscillations of transition to sleep in healthy people (67). Functional magnetic resonance imaging (fMRI) and EEG imaging studies have shown that SWS is associated with central cortical activity located in the right and left DLPFC (68). Slow oscillations are crucial prerequisites for the reduction of excitation and the beginning of sleep (69). The results of some studies support the idea that tDCS can potentially modulate aspects of arousal and sleep. For instance, Marshall et al. performed tDCS in the EEG δ frequency range during SWS. The results demonstrated that tDCS enhanced δ wave activity and improved sleep-related declarative memory consolidation (70). Slow-wave activity (SWA) in EEG (0.5-4.0 Hz) is considered to be a marker of restorative function and related to beneficial functions of sleep, such as learning, cognitive performance enhancement, and mood stabilization (71, 72). In addition, studies have demonstrated that increased SWS during non-rapid eye movement (NREM) sleep improves sleep quality and memory (73).

Furthermore, Mariani et al. reported that there is an inverse correlation between the quality of nocturnal sleep and EEG complexity (74). The study results of Li et al. showed that daily tDCS reduces EEG complexity significantly during REM sleep in patients with depression. They used left DLPFC anodal stimulation and right DLPFC cathodal stimulation (75). The results of our study indicate that employment of our treatment protocol has likely increased SWS and decreased EEG complexity.

Our second hypothesis was also confirmed based on the improvement in the positive and negative affections of patients with insomnia after the insomnia treatment using tDCS. Our study results showed a significant increase in positive affect and decrease in negative affect following the treatment. It has been reported that glial cells, including astrocytes, are activated by tDCS (76). As these cells regulate the chemical substances and neurotransmitters concentration in the space between neurons, the mechanisms by which tDCS improves psychiatric symptoms may include its indirect modulating effects on neurons (77). Moreover, many studies have demonstrated that the right DLPFC is more active than the left prefrontal cortex in patients with depression. Cerebral blood flow of the left DLPFC is reduced in these individuals, and it has a slower metabolism, while the right DLPFC has increased blood flow and metabolism (78). Moreover, tDCS improves emotional processing in the DLPFC of patients with major depressive disorders (79). The results of a study demonstrated that tDCS stimulation not only improved symptoms of depression and anxiety, but also had a positive effect on sleep quality in patients with major depression (80). A review article examining the relevant literature provides evidence that the right DLPFC is associated with depression, anxiety, and fear (81). In addition, the DLPFC plays an important role in attention, active memory, and executive brain functions, all of which have a key role in regulating emotions (82). As expected, based on the studies mentioned in this section and the discussion of the first hypothesis, particularly with the inhibitory stimulation of the right DLPFC by tDCS, tDCS not only improved insomnia, but also improved positive and negative affect.

Limitations: Our study had several limitations. The stimulation location is one of the most essential topics in the clinical application of transcranial electrical stimulation, and the best way to determine these areas is brain mapping. We used the results of previous studies to determine target areas for insomnia treatment due to the impossibility of using brain mapping techniques**.** Another limitation of this study was the lack of long-term follow-up due to the geographical dispersion of the participants and their high numbers. Recalling all participants several months after conducting the study was not possible. Although follow-ups were conducted over the phone at different intervals, their statistical analysis was not included in the

research results due to incomplete questionnaires. Another limitation was the exclusion of men from the study. We only included women since insomnia has a higher prevalence rate among them.

Therefore, it is recommended that tDCS be implement specifically in areas that have been identified for each individual using brain mapping in future studies. In addition, it is recommended that the changes in neurotransmitter levels be examined and EEG be used to investigate changes in the brain waves of each individual for further analysis. Furthermore, examining the effects of treatment during follow-ups can also be effective in selecting this type of treatment for insomnia. Including men in the implementation of these treatment protocols can also provide the possibility of comparing the therapeutic effects of tDCS between women and men.

Conclusion

Overall, our therapeutic protocol had significant effects on the reduction of the severity of insomnia and improvement of positive and negative affect. Therefore, psychiatrists, psychologists, and neurology and sleep medicine specialists can use the results of this study to treat insomnia disorder independently or in combination with drug therapy, psychotherapy, or other treatments.

Conflict of Interests

Authors have no conflict of interests.

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References

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders: DSM-5-5th ed. Arlington, VA: American Psychiatric Publishing, Inc.; 2013.
2. Buysse DJ. Insomnia. JAMA 2013; 309: 706-16.
3. American Academy of Sleep Medicine. International Classification of Sleep Disorders – Third Edition (ICSD-3). Darien, IL: American Academy of Sleep Medicine; 2014.
4. Zeng LN, Zong QQ, Yang Y, et al. Gender difference in the prevalence of insomnia: A meta-analysis of observational studies. Front Psychiatry 2020; 11: 577429.
5. Zhang B, Wing YK. Sex differences in insomnia: A meta-analysis. Sleep 2006; 29: 85-93.
6. van der Werf YD, Altena E, van Dijk KD, et al. Is disturbed intracortical excitability a stable trait of chronic insomnia? A study using transcranial magnetic stimulation before and after multimodal sleep therapy. Biol Psychiatry 2010; 68: 950-5.
7. Bonnet MH, Arand DL. Hyperarousal and insomnia: state of the science. Sleep Med Rev 2010; 14: 9-15.
8. Riemann D, Spiegelhalder K, Feige B, et al. The hyperarousal model of insomnia: a review of the concept and its evidence. Sleep Med Rev 2010; 14: 19-31.
9. Fernandez-Mendoza J, Li Y, Vgontzas AN, et al. Insomnia is associated with cortical hyperarousal as early as adolescence. Sleep 2016; 39: 1029-36.
10. Huang Z, Zhan S, Li N, et al. Abnormal recovery function of somatosensory evoked potentials in patients with primary insomnia. Psychiatry Res 2012; 198: 463-7.
11. Corsi-Cabrera M, Figueredo-Rodriguez P, del Rio-Portilla Y, et al. Enhanced frontoparietal synchronized activation during the wake-sleep transition in patients with primary insomnia. Sleep 2012; 35: 501-11.
12. Perrier J, Clochon P, Bertran F, et al. Specific EEG sleep pattern in the prefrontal cortex in primary insomnia. PLoS One 2015; 10: e0116864.
13. Schwabedal JT, Riedl M, Penzel T, et al. Alpha-wave frequency characteristics in health and insomnia during sleep. J Sleep Res 2016; 25: 278-86.
14. Riedner BA, Goldstein MR, Plante DT, et al. Regional patterns of elevated alpha and high-frequency electroencephalographic activity during nonrapid eye movement sleep in chronic insomnia: A pilot study. Sleep 2016; 39: 801-12.
15. Taylor DJ, Mallory LJ, Lichstein KL, et al. Comorbidity of chronic insomnia with medical problems. Sleep 2007; 30: 213-8.
16. Alvaro PK, Roberts RM, Harris JK. A systematic review assessing bidirectionality between sleep disturbances, anxiety, and depression. Sleep 2013; 36: 1059-68.
17. Bouwmans MEJ, Bos EH, Hoenders HJR, et al. Sleep quality predicts positive and negative affect but not vice versa. An electronic diary study in depressed and healthy individuals. J Affect Disord 2017; 207: 260-7.
18. O'Leary K, Small BJ, Panaite V, et al. Sleep quality in healthy and mood-disordered persons predicts daily life emotional reactivity. Cogn Emot 2017; 31: 435-43.
19. Mason EC, Harvey AG. Insomnia before and after treatment for anxiety and depression. J Affect Disord 2014; 168: 415-21.
20. Oyane NM, Pallesen S, Moen BE, et al. Associations between night work and anxiety, depression, insomnia, sleepiness and fatigue in a sample of Norwegian nurses. PLoS One 2013; 8: e70228.

21. Terauchi M, Hiramitsu S, Akiyoshi M, et al. Associations between anxiety, depression and insomnia in peri- and post-menopausal women. Maturitas 2012; 72: 61-5.
22. Herrero Babiloni A, De Koninck BP, Beetz G, et al. Sleep and pain: Recent insights, mechanisms, and future directions in the investigation of this relationship. J Neural Transm (Vienna) 2020; 127: 647-60.
23. Chahine LM, Amara AW, Videnovic A. A systematic review of the literature on disorders of sleep and wakefulness in Parkinson's disease from 2005 to 2015. Sleep Med Rev 2017; 35: 33-50.
24. Fang H, Tu S, Sheng J, et al. Depression in sleep disturbance: A review on a bidirectional relationship, mechanisms and treatment. J Cell Mol Med 2019; 23: 2324-32.
25. Latif I, Hughes ATL, Bendall RCA. Positive and negative affect mediate the influences of a maladaptive emotion regulation strategy on sleep quality. Front Psychiatry 2019; 10: 628.
26. Dirksen SR, Epstein DR. Efficacy of an insomnia intervention on fatigue, mood and quality of life in breast cancer survivors. J Adv Nurs 2008; 61: 664-75.
27. Matthews EE, Arnedt JT, McCarthy MS, et al. Adherence to cognitive behavioral therapy for insomnia: A systematic review. Sleep Med Rev 2013; 17: 453-64.
28. Morin CM, Drake CL, Harvey AG, et al. Insomnia disorder. Nat Rev Dis Primers 2015; 1: 15026.
29. Herrero Babiloni A, Bellemare A, Beetz G, et al. The effects of non-invasive brain stimulation on sleep disturbances among different neurological and neuropsychiatric conditions: A systematic review. Sleep Med Rev 2021; 55: 101381.
30. Ding F, O'Donnell J, Xu Q, et al. Changes in the composition of brain interstitial ions control the sleep-wake cycle. Science 2016; 352: 550-5.
31. Riemann D, Nissen C, Palagini L, et al. The neurobiology, investigation, and treatment of chronic insomnia. Lancet Neurol 2015; 14: 547-58.
32. Polania R, Nitsche MA, Paulus W. Modulating functional connectivity patterns and topological functional organization of the human brain with transcranial direct current stimulation. Hum Brain Mapp 2011; 32: 1236-49.
33. Nitsche MA, Cohen LG, Wassermann EM, et al. Transcranial direct current stimulation: State of the art 2008. Brain Stimul 2008; 1: 206-23.
34. Nitsche MA, Paulus W. Transcranial direct current stimulation--update 2011. Restor Neurol Neurosci 2011; 29: 463-92.
35. Rivera-Urbina N, Nitsche M, Molero-Chamizo As. Transcranial direct current stimulation (tDCS) in the context of sleep and insomnia. J Sleep Med Disord 2016; 3: 1060.
36. Jiang CG, Zhang T, Yue FG, et al. Efficacy of repetitive transcranial magnetic stimulation in the treatment of patients with chronic primary insomnia. Cell Biochem Biophys 2013; 67: 169-73.
37. Feng J, Zhang Q, Zhang C, et al. The Effect of sequential bilateral low-frequency rTMS over dorsolateral prefrontal cortex on serum level of BDNF and GABA in patients with primary insomnia. Brain Behav 2019; 9: e01206.
38. Zhang YP, Liao WJ, Xia WG. Effect of acupuncture cooperated with low-frequency repetitive transcranial magnetic stimulation on chronic insomnia: A randomized clinical trial. Curr Med Sci 2018; 38: 491-8.
39. Etoom M, Alwardat M, Alghwiri A, et al. Effects of transcranial direct current stimulation on sleep in athletes: A protocol of a randomized controlled trial. J Clin Med 2022; 11.
40. Lanza G, Cantone M, Arico D, et al. Clinical and electrophysiological impact of repetitive low-frequency transcranial magnetic stimulation on the sensory-motor network in patients with restless legs syndrome. Ther Adv Neurol Disord 2018; 11: 1756286418759973.
41. Lanza G, Lanuzza B, Arico D, et al. Impaired short-term plasticity in restless legs syndrome: A pilot rTMS study. Sleep Med 2018; 46: 1-4.
42. Frase L, Piosczyk H, Zittel S, et al. Modulation of total sleep time by transcranial direct current stimulation (tDCS). Neuropsychopharmacology 2016; 41: 2577-86.
43. Eggert T, Dorn H, Sauter C, et al. No effects of slow oscillatory transcranial direct current stimulation (tDCS) on sleep-dependent memory consolidation in healthy elderly subjects. Brain Stimul 2013; 6: 938-45.
44. Passmann S, Kulzow N, Ladenbauer J, et al. Boosting slow oscillatory activity using tdcs during early nocturnal slow wave sleep does not improve memory consolidation in healthy older adults. Brain Stimul 2016; 9: 730-9.
45. Roizenblatt S, Fregni F, Gimenez R, et al. Site-specific effects of transcranial direct current stimulation on sleep and pain in fibromyalgia: A randomized, sham-controlled study. Pain Pract 2007; 7: 297-306.
46. Sherwood MS, Madaris AT, Mullenger CR, et al. Repetitive transcranial electrical stimulation induces quantified changes in resting cerebral perfusion measured from arterial spin labeling. Neural Plast 2018; 2018: 5769861.
47. McIntire LK, McKinley RA, Goodyear C, et al. The effects of anodal transcranial direct current stimulation on sleep time and efficiency. Front Hum Neurosci 2020; 14: 357.
48. Morin CM, Belleville G, Belanger L, et al. The Insomnia Severity Index: Psychometric indicators to detect insomnia cases and evaluate treatment response. Sleep 2011; 34: 601-8.
49. Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. J Pers Soc Psychol 1988; 54: 1063-70.
50. Bakhshipour R, Dezhkam M. A confirmatory factor analysis of the Positive Affect and Negative Affect

Scales (PANAS). Journal of Psychology 2006; 9: 351-65. [In Persian].
51. Fertonani A, Pirulli C, Miniussi C. Random noise stimulation improves neuroplasticity in perceptual learning. J Neurosci 2011; 31: 15416-23.
52. Silvanto J, Muggleton N, Walsh V. State-dependency in brain stimulation studies of perception and cognition. Trends Cogn Sci 2008; 12: 447-54.
53. Murphy M, Huber R, Esser S, et al. The cortical topography of local sleep. Curr Top Med Chem 2011; 11: 2438-46.
54. Spiegelhalder K, Regen W, Baglioni C, et al. Neuroimaging studies in insomnia. Curr Psychiatry Rep 2013; 15: 405.
55. Gong L, Xu R, Qin M, et al. New potential stimulation targets for noninvasive brain stimulation treatment of chronic insomnia. Sleep Med 2020; 75: 380-7.
56. Frase L, Maier JG, Zittel S, et al. Bifrontal anodal transcranial direct current stimulation (tDCS) improves daytime vigilance and sleepiness in a patient with organic hypersomnia following reanimation. Brain Stimul 2015; 8: 844-6.
57. Frase L, Selhausen P, Krone L, et al. Differential effects of bifrontal tDCS on arousal and sleep duration in insomnia patients and healthy controls. Brain Stimul 2019; 12: 674-83.
58. Fritsch B, Reis J, Martinowich K, et al. Direct current stimulation promotes BDNF-dependent synaptic plasticity: Potential implications for motor learning. Neuron 2010; 66: 198-204.
59. Merzagora AC, Foffani G, Panyavin I, et al. Prefrontal hemodynamic changes produced by anodal direct current stimulation. Neuroimage 2010; 49: 2304-10.
60. Acler M, Bocci T, Valenti D, et al. Transcranial direct current stimulation (tDCS) for sleep disturbances and fatigue in patients with post-polio syndrome. Restor Neurol Neurosci 2013; 31: 661-8.
61. Lee YJ, Kim BJ, Lee CS, et al. Application of transcranial direct current stimulation in sleep disturbances. Chronobiol Med 2022; 4: 141-51.
62. San-Juan D, Morales-Quezada L, Orozco Garduno AJ, et al. Transcranial direct current stimulation in epilepsy. Brain Stimul 2015; 8: 455-64.
63. Okun M, Lampl I. Instantaneous correlation of excitation and inhibition during ongoing and sensory-evoked activities. Nat Neurosci 2008; 11: 535-7.
64. Fuller PM, Gooley JJ, Saper CB. Neurobiology of the sleep-wake cycle: sleep architecture, circadian regulation, and regulatory feedback. J Biol Rhythms 2006; 21: 482-93.
65. Saper CB, Fuller PM, Pedersen NP, et al. Sleep state switching. Neuron 2010; 68: 1023-42.
66. Bashir S, Bamugaddam A, Alasheikh M, et al. Anodal Transcranial direct current stimulation (tDCS) over the primary motor cortex (M1) enhances motor response inhibition and visual recognition memory. Med Sci Monit Basic Res 2022; 28: e934180.
67. D'Atri A, De Simoni E, Gorgoni M, et al. Electrical stimulation of the frontal cortex enhances slow-frequency EEG activity and sleepiness. Neuroscience 2016; 324: 119-30.
68. Murphy M, Riedner BA, Huber R, et al. Source modeling sleep slow waves. Proc Natl Acad Sci USA 2009; 106: 1608-13.
69. Steriade M. Corticothalamic resonance, states of vigilance and mentation. Neuroscience 2000; 101: 243-76.
70. Marshall L, Molle M, Hallschmid M, et al. Transcranial direct current stimulation during sleep improves declarative memory. J Neurosci 2004; 24: 9985-92.
71. Tononi G, Cirelli C. Sleep function and synaptic homeostasis. Sleep Med Rev 2006; 10: 49-62.
72. Cirelli C, Tononi G. Is sleep essential? PLoS Biol 2008; 6: e216.
73. Zhang Y, Gruber R. Can slow-wave sleep enhancement improve memory? A review of current approaches and cognitive outcomes. Yale J Biol Med 2019; 92: 63-80.
74. Mariani S, Borges AF, Henriques T, et al. Analysis of the sleep EEG in the complexity domain. Annu Int Conf IEEE Eng Med Biol Soc 2016; 2016: 6429-32.
75. Li Z, Zhao X, Feng L, et al. Can daytime transcranial direct current stimulation treatment change the sleep electroencephalogram complexity of REM sleep in depressed patients? A double-blinded, randomized, placebo-controlled trial. Front Psychiatry 2022; 13: 851908.
76. Ruohonen J, Karhu J. tDCS possibly stimulates glial cells. Clin Neurophysiol 2012; 123: 2006-9.
77. Yamada Y, Sumiyoshi T. Neurobiological mechanisms of transcranial direct current stimulation for psychiatric disorders; neurophysiological, chemical, and anatomical considerations. Front Hum Neurosci 2021; 15: 631838.
78. Shiozawa P, da Silva ME, Cordeiro Q. Transcranial direct current stimulation for treating depression in a patient with right hemispheric dominance: A case study. J ECT 2015; 31: 201-2.
79. Brunoni AR, Zanao TA, Vanderhasselt MA, et al. Enhancement of affective processing induced by bifrontal transcranial direct current stimulation in patients with major depression. Neuromodulation 2014; 17: 138-42.
80. Zhou Q, Yu C, Yu H, et al. The effects of repeated transcranial direct current stimulation on sleep quality and depression symptoms in patients with major depression and insomnia. Sleep Med 2020; 70: 17-26.
81. Huang D, Chen S, Wang S, et al. Activation of the DLPFC reveals an asymmetric effect in risky decision making: Evidence from a tDCS Study. Front Psychol 2017; 8: 38.
82. Rock PL, Roiser JP, Riedel WJ, et al. Cognitive impairment in depression: A systematic review and meta-analysis. Psychol Med 2014; 44: 2029-40.