Review Article

Transcranial Direct Current Stimulation (tDCS) in the Context of Sleep and Insomnia

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Abstract

Insomnia is a sleep disorder that, in the case of primary insomnia, is due to alterations in the neural mechanisms of sleep. In addition, insomnia may be secondary to other diseases or to psychological or physical stress, or may appear as a side effect of different pharmacological agents. Considering that pathologically altered cortical activity can lead to insomnia, neuromodulation via non-invasive brain stimulation tools might be suited to restore adequate cortical activity to promote sleep. In this review we discuss data from recent studies in which transcranial direct current stimulation (tDCS), a non-invasive brain stimulation technique which alters cortical excitability and activity via application of weak direct currents, has been applied to probe effects on different parameters of sleep. Data about insomnia and tDCS are scarce, but studies on total sleep time and other sleep disturbances suggest that tDCS may be useful to modulate cortical activity associated with insomnia and to modulate sleep efficacy. However, further studies are needed to determine the potential of this neuromodulation technique for treatment of this disorder, and to elucidate the possible physiological mechanisms associated with its supposed therapeutic effects.

INTRODUCTION

Sleep and the circadian rhythm of sleep depend on complex neural mechanisms which are not entirely known [1,2]. Different neurotransmitter systems, which include acetylcholine, norepinephrine, serotonin, dopamine, histamine and orexin, regulate cortical arousal by afferents from the basal nucleus of Meynert, brainstem and hypothalamic nuclei [3] (for an overview of cortical arousal control, please refer to Figure (1). This regulation of cortical activation follows circadian rhythms that allow the transition between sleep and wakefulness. Thus, modulation of cortical activity might be a feasible target for non-invasive brain stimulation (NIBS) interventions in the treatment of sleep disturbances. Some sleep parameters whose physiological mechanisms are well described, as those of REM sleep or the specific EEG activity associated to the different stages of non-REM sleep, probably are sensitive to neuromodulation through brain stimulation approaches. For example, imagery experienced in REM sleep involves visual and motor cortical areas whose physiological activity has been modulated by NIBS [4], and NIBS is able to alter cortical oscillations [5,6].

A severe reduction of total sleep time and sleep disorders significantly affect physical health [7] and brain functions [8]. In this context, insomnia is a common disturbance of sleep. Chronic insomnia affects physical and mental performance, as well as subjective and objective health state [9,10]. Because of its extensive and complex etiology and clinical implications, insomnia is treated by a multidisciplinary approach. Pharmacological treatment is the most frequently applied therapy for secondary insomnia, i.e., insomnia caused by other diseases or side effects of psychotropic agents [11]. Non-pharmacological approaches, such as psychotherapy, including cognitive-behavioral therapy, sleep hygiene or relaxation therapy, are also used in the treatment of secondary insomnia, with however limited effectiveness [12-14]. Because alterations of cortical excitability and activity play an essential role in the onset of sleep and the transition of sleep stages through the release of multiple neuromodulators that regulate the arousal system [2,15], it can be argued that an external modulation of cortical activity might be suited to affect sleep-wake transition, and transition between sleep stages. Specific sleep-related alterations, including neuronal synchronization and functional connectivity, could also be
modulated by external cortical stimulation. A non-invasive brain stimulation tool with potential to modulate the cortical state associated to insomnia is transcranial direct current stimulation (tDCS), because of its ability to induce changes in EEG parameters of sleep and wake such as synchronization, and due to its effects on cortical activity and excitability in the waking state [16]. tDCS has been shown to have potential for application in research and clinical settings [17], when appropriately conducted, including methodological and safety aspects [18,19]. For tDCS, a subthreshold electric current, which does not induce neuronal action potentials, but modifies the excitability and spontaneous activity of cortical neurons, is applied. Current flow in the brain is induced via a positive electrode and a negative electrode (anode and cathode, respectively). The basic mechanisms of tDCS include polarization of neuronal membranes determined by the specific montage of stimulation electrodes. Anodal and cathodal tDCS have opposite effects on cortical excitability beyond the period of stimulation at the macroscopic level [20-24]. Anodal stimulation increases cortical excitability, whereas cathodal tDCS reduces cortical excitability. Thus, the placement of the anode over a specific target cortical area is able to modify the excitability of this area by increasing depolarization of cortical neuronal compartments. The placement of the cathode over the target area induces opposite effects, i.e., hyperpolarization of the respective neuronal compartments. The specific effects of tDCS on a given neuron depend on current flow direction in relation to the spatial orientation of the neuron [25]. Prolonged stimulation induces neuroplastic after-effects, which resemble mechanisms of long term potentiation (LTP) and depression (LTD) [21,23,26]. In addition to these polarization and after-effects of stimulation, tDCS mechanisms include the potential to modulate cortico-cortical [27] as well as cortico-subcortical [28] connectivity and spontaneous cortical activity as recorded by EEG and evoked potentials [29]. As a result of these mechanisms, it can be expected that tDCS impacts on sleep-related physiological and cognitive parameters. In accordance, some studies have found reduced or enhanced slow oscillatory EEG activity after oscillatory tDCS applied during non-REM sleep, dependent on stimulation frequency [30-32]. In relation to modulatory influences of tDCS on sleep-dependent cognitions, effects on memory have been described in some studies when oscillatory tDCS has been applied during sleep [30-33]. Also tonic anodal tDCS applied during REM sleep improved motor memory consolidation [34]. Some studies moreover show that prefrontal tDCS affects visual and lucid dreaming [35,36].

Although there are no specific data available to date that directly relate tDCS to insomnia, in the next section we will describe some recent studies that shed light on the potential of tDCS in the treatment of this sleep disturbance.

tDCS, Sleep and insomnia

tDCS has not been explored specifically for the treatment of insomnia. However, some recent studies have explored the relation between tDCS-generated neuromodulation and sleep efficacy in more general terms. These investigations may provide relevant information to determine the potential of tDCS in stabilizing sleep in insomnia.

Fraser et al. [37], applied bilateral prefrontal anodal, cathodal or sham tDCS in healthy humans without sleep disturbances (1mA, two sessions of 13 min and 20 min inter-stimulation interval). The stimulation was targeted to modulate the cortico-
From these results, the authors conclude that excitatory sleep efficiency, sleep disturbance and daytime dysfunction. In particular, the left dorsolateral prefrontal cortex (DLPFC) was combined with anodal tDCS approach to that mentioned above. Here, anodal tDCS over these areas was able to reduce total sleep time when compared to cathodal and sham stimulation [37]. In contrast, cathodal stimulation had no significant effect on total sleep time. Thus the results of this study demonstrate that it is possible to alter sleep efficacy by tDCS. The missing effect of cathodal tDCS might be explained by a ceiling effect. Specifically, it might have not increased total sleep time because the study was conducted in healthy participants with normal sleep duration. Potentially, under conditions of reduced total sleep time a respective effect of prefrontal cathodal stimulation might be present. Mechanistically, the authors of the aforementioned study propose that the effects of bi-frontal anodal tDCS on total sleep time might be caused by modulation of cortical afferents to the thalamus as a polarity-specific tDCS effect on cortical arousal (specifically on resting state EEG power). Consistent with this top-down model, and results of the aforementioned study in healthy humans, Frase et al. [39], reported improvements in clinical symptoms using the same tDSCS protocol in a patient with organic hypersomnia, presumably via modulation of the cortico-thalamic-cortical pathway and the resulting enhanced arousal state. Thus, this case report suggests that prefrontal anodal tDCS can be effective in patients suffering from abnormal sleepiness. The respective cortico-thalamic pathway of sleep-wake regulation could be potentially modulated also in patients with insomnia. If in healthy humans without sleep disturbances the missing effect of cathodal tDCS of the Frase et al. study [37], was indeed caused by a ceiling effect, then it could be speculated that pathologically altered brain activity and excitability state in patients with insomnia, specifically enhanced prefrontal activity, might be efficiently down-regulated by cathodal tDCS. Further studies are needed to substantiate this speculation.

Beyond the prefrontal cortex, also the cerebellum is thought to be involved in the modulation of sleep processes and some sleep disorders [40]. Increased cerebellar activity has been recorded by functional magnetic resonance imaging selectively in the slow wave sleep stage [41]. Besides, the fastigial nucleus of the cerebellum seems to be involved in the inhibition of delta waves associated to the EEG desynchronization during REM sleep and wakefulness [42]. On the other hand, in cats, REM atonia involves activity of the cerebellum [43]. In addition to their possible roles in the sleep generation, cerebellum and prefrontal cortex display abnormal activity in bipolar patients, in particular hyperactivity of the cerebellum and hypoactivity of the prefrontal cortex [44], and these patients suffer often from sleep disturbances. Given this background, it is worth mentioning another recently conducted study that followed a slightly different tDCS approach to that mentioned above. Here, anodal tDCS over the left dorsolateral prefrontal cortex (DLPFC) was combined with cathodal tDCS over the right cerebellar cortex (2mA, 20 min a day for 3 weeks) [45]. This approach improved the total score of the Pittsburgh Sleep Quality Index as well as the scores in the subdomains sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance and daytime dysfunction. From these results, the authors conclude that excitatory stimulation of the DLPFC through anodal tDCS simultaneously with inhibitory stimulation of the cerebellum through cathodal tDCS may be an effective approach to modulate the prefrontal-thalamic and cerebellar network of bipolar patients and thus to regulate their sleep disturbances [45]. As the authors suggest, if sleep and cognitive-emotional dysregulation in bipolar disorder involve overlapped neural systems, including the prefrontal cortex-thalamus-cerebellum connectivity [46], this combined stimulation approach would have the potential to modulate both processes. The participants of this study belonged however to a relatively specific patient group, i.e., patients with bipolar disorder in euthylic state. It would be interesting to examine if the procedure proposed by these authors is equally effective in the treatment of insomnia in patients with and without comorbid mental disorders.

DISCUSSION

Recent evidence suggests that tDCS could have sleep-altering effects, and might be a candidate therapeutic tool for some sleep disturbances. However, specific studies showing an impact of tDCS in insomnia are scarce. It would thus be desirable for future studies to evaluate specifically the potential of this technique in the treatment of insomnia, and to enhance understanding of the physiological mechanisms of stimulation that can induce improvements in sleep disorders. The identification of the main cortical targets with potential to modulate cortical arousal and thus the sleep-wake cycle (Figure 1) via tDCS and other NIBS techniques is an important future objective. From the results of the studies here mentioned [37,45], 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 modulate the quality of sleep or improve symptoms in some sleep disturbances, such as insomnia. On the other hand, findings about the specific physiological effects of tDCS on cortical activity and cognitive functions related to sleep may in turn help to learn about the complex mechanisms of sleep and sleep disorders.

Transcranial alternating current stimulation (tACS) is another non-invasive brain stimulation method that could be useful in the study of the physiological mechanisms of sleep and as a tool to modulate oscillatory brain activity in relation to sleep disturbances. Because oscillating transcranial electric stimulation is able to modulate sleep EEG rhythms [6,47], it can be argued that insomnia-related altered oscillatory brain activity might be sensitive to modulation by tACS. In fact, in a sham-controlled pilot study, slow oscillatory transcranial direct current stimulation at 0.75 Hz applied during stage 2 of non-REM sleep in insomnia patients increased the duration of stage 3 and decreased the duration of stage 1 of non-REM sleep [48], in accordance with a sleep-stabilizing effect of oscillatory transcranial direct current stimulation in these patients. Moreover, the potential of tACS to alter sleep-dependent EEG activity may find application not only for sleep disorders but also to modulate REM and non-REM sleep-related cognitive functions, as for example declarative memory consolidation [49,50], or sleep-dependent consciousness states [6]. Therefore, future studies on the applicability of tDCS and tACS could promote effective treatment and evaluation protocols in the clinical context of sleep, as well as new procedures to improve sleep-related cognitive functions.
CONFLICT OF INTEREST

Michael A. Nitsche is member of the advisory board of Neuroelectrics. The remaining authors declare no conflict of interest.

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