Transcranial Magnetic Stimulation in Sleep Medicine

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Abstract

Transcranial Magnetic Stimulation (TMS) is both a diagnostic and a therapeutic tool for neurological diseases. Sleep disorders can be either a primary disease or the consequence of a different primary disease that disturbs sleep. Recent evidence indicates that TMS has a promising therapeutic effect in insomnia, restless legs syndrome and in sleep disturbances associated to epilepsy, depression and post-traumatic stress disorder. The parameters of the stimulation, as well as the specific cerebral area in which the stimulation should be applied, have not been accurately defined yet. Both the frequency and the intensity of stimulation seem to be critical to induce satisfactory therapeutic results. The use of TMS in sleep disorders opens the possibility to new non-invasive therapeutic options in sleep medicine.

INTRODUCTION

During the past few decades, Transcranial Magnetic Stimulation (TMS) has shown to be a potentially important therapeutic tool for an array of diseases [1]. TMS has mostly been used because it is a non-invasive technique that stimulates the cerebral cortex inducing a modulation of neuronal excitability. Repetitive TMS (rTMS) is capable of decreasing cortex excitability when applied in trains with low frequency, and increasing cortex excitability when applied with high frequency [2,3]. Several nervous system disorders are linked to the alteration of cortical excitability; therefore, rTMS has proven to be a reliable tool for improving the clinical picture.

Some sleep and neurological disorders that induce sleep pattern alterations also present alterations in cortical excitability. Thus, it comes as no surprise that rTMS has been reported as an effective treatment for sleep disorders and sleep disorders derived from neurological diseases. Today, some of the most frequent sleep disorders among humans (insomnia, obstructive sleep apnea, and restless legs syndrome) have been treated with rTMS. Moreover, neuropsychiatric disorders such as depression and epilepsy, which frequently display sleep alterations, improve their clinical picture, and their sleep pattern after rTMS.

TMS AND INSOMNIA

Insomnia has been defined as the inability to initiate, maintain or consolidate sleep even when all the adequate conditions are present. Its clinical picture also includes large periods of nocturnal wakefulness and insufficient sleep. According to reports from the World Health Organization, this disease is present worldwide and affects more than 10% of the general population. The most recent International Classification of Sleep Disorders indicates that insomnia has multiple subtypes and multiple etiological factors [4]. Insomnia can appear as a primary disease or can also be the consequence of a different disease, becoming a particular symptom in the clinical picture of several health alterations. However, in every situation, the presence of insomnia is an element that seriously disturbs the patient’s quality of life and hinders the healing process.

Neuronal hyper excitability has been detected in insomniac patients [5]. Electroencephalographic recordings have detected the increase of beta and gamma activity during sleep onset and light sleep. Since TMS has repeatedly proven its ability to modulate neuronal excitability, researchers suggested that TMS could induce beneficial effects on insomnia. However, few studies have reported effects on different conditions associated with insomnia.

Van der Werf et al. [6], analyzed the cortical excitability linked to insomnia and made a study comparing TMS on insomniac patients to healthy controls. Despite showing sleep improvement and behavioral parameters, the authors reported that the normal cortical excitability remains unchanged after TMS. These results challenge the notion that TMS exerts beneficial effects through the modulation of cortical excitability.

Several medical societies have reached a consensus regarding cognitive behavioral therapy (CBT) as a first choice for chronic insomnia therapy [7]. However, in a 2013 study Jiang et al. [8], compared the effects of CBT, rTMS, and hypnogenic agents on several sleep pattern parameters. According to the authors, rTMS significantly improves both SWS and REM sleep when compared to CBT and medication. In addition, the rTMS group showed the lowest relapse. Therefore, the authors concluded that TMS is a better option for insomnia than CBT.
Quite frequently insomnia is a component of complex clinical pictures. In 2014, two women suffering from lower back pain, depression, and chronic insomnia were submitted to TMS five days a week for 4 and 3 weeks. Both patients reported a significant improvement to their main clinical complaints. The self-perception of pain and depression significantly ameliorated after TMS treatment. Insomnia was assessed using the Insomnia Severity Index and results indicated a significant decrease from severe to sub threshold insomnia [9].

In the most recent international classification of sleep disorders, an insomnia subtype named idiopathic insomnia is no longer considered. However, in the previous version idiopathic insomnia appears as a primary insomnia mainly characterized by the lack of any known etiological factors. In a previous study, we reported that nearly half of the patients diagnosed with idiopathic insomnia display electroencephalographic (EEG) abnormalities [10]. This abnormal EEG activity is characterized by epileptic-like activity such as sharp-wave activity with phase inversion, spikes, and sharp-wave activity in the left frontal and front-central area. These abnormal activities have been linked to neuronal hyper excitability [11]. Therefore, we analyzed the effects of TMS in patients diagnosed with insomnia associated with EEG abnormalities.

Ten patients diagnosed with insomnia associated with EEG abnormalities were studied polysomnographically (PSG) in order to determine the sleep pattern and EEG features. After the first study, patients were submitted to rTMS for 15 min during 10 consecutive days, thereafter, a second PSG was performed. Results showed a significant decrease of EEG abnormalities together with a significant improvement of sleep parameters, such as an increase in total sleep time and sleep efficiency as well as a decrease in sleep latency, total wake time and wake time after sleep onset.

Sleep quality largely depends on the adequate percentage of sleep stages. In this study, one promising result observed concerns the percentages of sleep stages. Besides improvements in sleep parameters after rTMS, the percentages of the different sleep stages remain unaltered. This means that even with this significant increase in sleep time, the relationship among sleep stages also increases harmonically.

TMS AND OBSTRUCTIVE SLEEP APNEA

Obstructive Sleep Apnea (OSA) is also a widely distributed sleep disorder, affecting almost 4% of adults [12]. OSA is characterized by frequent periods of apnea or hypopnea (> 10 sec) during sleep, which results in frequent awakenings and sleep fragmentation. Depending on its severity, OSA can produce pathological diurnal hyper somnolence, headaches, fatigue, and cognitive performance impairments [13]. Long-term effects of OSA include a severe decline in quality of life as well as cardiovascular and metabolic diseases [14].

Although the main etiological factor of OSA is located in the anatomical features of the upper airway, some recent reports have revealed neurological alterations. Neuroimaging studies using MRI techniques have exposed structural deficits related to OSA. Main findings show widespread deficits of gray matter in cortical regions as well as in limbic regions, basal ganglia, and the cerebellum [15,16].

Concerning TMS, several studies have used it as a valuable tool for determining neurophysiological features detected in OSA patients. Lanza et al. [17], reviewed studies using TMS as a non invasive tool to assess excitability of the cortex in vivo, particularly the motor cortex, and cortical spinal tract. When used as a diagnostic tool, TMS stimulation is followed by the determination of several neurophysiological indicators: cortical silent period; intracortical facilitation; intracortical inhibition; motor threshold; motor evoked potentials, among others. These indicators offer information on the functional status of some neurotransmission pathways including the cholinergic, the dopaminergic, and the gabaergic systems.

OSA patients frequently display neurocognitive impairment, which has been related to cholinergic deficits. TMS has been applied in OSA patients to analyze the short latency afferent inhibition of the motor cortex as a reliable technique to determine the cholinergic status. Results indicate that OSA patients show a correlation between cognitive impairments and alterations of the cholinergic pathway [18].

TMS AND RESTLESS LEGS SYNDROME

Restless Legs Syndrome (RLS) is a sleep disorder characterized by an unusual and annoying sensation in the lower extremities, resulting in an urge to move the legs. Symptoms are associated with sleep onset, inducing frequent awakenings, and preventing sleep consolidation. RLS has been associated with the dopaminergic system and treatment with dopaminergic agents has been the first choice of drug treatment for the past decade [19]. Also, iron deficits have been found in RLS patients [20] raising the possibility that this iron deficit could be the origin of dopaminergic impairments [21].

Cortical excitability in RLS has been defined as a hyper arousal state [22]. Previously, Entezari-Taher et al. [23], reported an impairment in the supraspinal inhibitory system in RLS patients. Since TMS has been proposed as a treatment to modulate cortical excitability, some studies have addressed this possibility. In 2014, Altunrende et al. [24], studied the effect of high frequency rTMS on RLS patients reporting an improvement based on the International RLS-rating scale after 10 sessions. In 2015, Lin et al. [25], reported that high frequency (15 Hz) for 14 sessions improved RLS symptomatology and also improved sleep impairments and anxiety levels.

We recently used low frequency TMS in a patient suffering of both RLS and periodic limb movements. A man (33 y.o.) was diagnosed with RLS with a high punctuation (25) in the International Restless Legs Scale (IRLS). A polysomnographic recording was obtained. Therefore, the patient received slow rTMS (1 Hz / 1000 pulses daily) on the left primary motor cortex during 10 days. After rTMS treatment ended, his punctuation in the IRLS decreased to 7. The second polysomnographic recording showed improvements on several sleep parameters. Also, total sleep time increased more than 2 hours (from 342 min to 474 min) and sleep efficiency increased from 70 to 80 percent. Periodic movements decreased, as did the annoying sensation that triggers leg movement and the patient reported the subjective experience of a satisfactory sleep [26].
TMS SLEEP AND POST TRAUMATIC STRESS DISORDER

Posttraumatic stress disorder (PTSD) is a clinical syndrome derived from the exposure to a traumatic event such as a natural disaster or violence of any kind. Besides anxiety, depression, and general psychiatric distress, PTSD patients exhibit sleep disturbances as a core feature. In 2000, Ohayon and Shapiro [27] performed an epidemiological study and reported a significant association between PTSD and sleep disturbances. The most frequent features were violent behavior during sleep; sleep paralysis, and hallucinations at the onset and at the end of the sleep period. The main complaint is insomnia and nightmares [28]. PTSD patients studied with a PSG revealed a decrease in sleep efficiency and a significant increase of light sleep, number of arousals, and sleep latency [29]. In addition, functional neuroimaging studies show hypo activity in the hippocampus and medial prefrontal cortex [30], while the amygdala shows hyperactivity [31].

In 2008, Spoormaker and Montgomery [32] reviewed the available information and suggested that sleep disturbances can be both the consequence of a traumatic event that triggers PTSD, and also a risk factor that facilitates the generation of PTSD's clinical picture. When the treatment targets primarily sleep disturbances, the severity of PTSD decreases significantly.

Concerning TMS treatment on PTSD patients, results are controversial and seem to depend on the frequency of stimulation. In 1998, Griseri et al. [33], reported the effects of bilateral TMS (brief and with slow frequency) on ten patients diagnosed with PTSD. They found a general improvement of the clinical picture, although only for a short time. When the effects of low (1 Hz) or high (10 Hz) TMS were compared, results indicated that high frequency on the right dorsolateral prefrontal cortex had the best effect on the improvement of general anxiety symptomatology [34].

Although sleep disturbances are a main feature in PTSD and TMS improves the clinical picture of PTSD, few studies have analyzed sleep modifications after TMS among these patients. Rosenberg et al. [35], reported that anxiety and depression inherent to PTSD were lessened after TMS. Additionally, the authors reported subjective improvement of sleep and, through the analysis of the Hamilton scale, an improvement in insomnia symptoms.

TMS, EPILEPSY AND SLEEP

Information obtained from animal models strongly suggests that TMS can be a reliable tool for alleviating epilepsy. Rotenberg et al. [36], studied an animal model of epilepsy, which induces seizures by administering kainic acid. In this model, rTMS suppresses epileptic activity. The cerebrospinal fluid from humans treated with rTMS has led to antiepileptic activity when injected into rats with a kindling seizure model [37]. Picrotoxin, a GABA receptor agonist, is frequently used in an animal model of epilepsy. Picrotoxin-induced seizures in mice can be significantly decreased if the animals are submitted to rTMS before the administration of Picrotoxin [38].

Also, the influence of low frequency repetitive TMS on epilepsy has been studied in humans for the past decades. In 2011, Hsu et al. [39], published a Meta analysis of the available literature and concluded that TMS has a positive effect on diminishing seizure activity. However, this notion is challenged by a more recent review. In 2016, Chen et al. [40], concluded that few studies reported a significant decrease in seizure activity after TMS. Thus, given the wide variability of technical approaches reported, the effects of TMS on epilepsy are still a matter of controversy and more data is still needed.

Recently, we conducted a study on the effects of low frequency rTMS on the sleep pattern and quality of life of epileptic patients treated with levetiracetam [41]. Patients were treated with 1000 pulses (frequency 1 Hz) every day for 10 days. Concerning epileptic activity, no seizures were recorded during the procedure and the epileptic form discharges in the EEG during sleep decreased almost two thirds compared to control recordings. Also, patients’ self-perceived quality of life was assessed with the QoLife31 questionnaire, going from very poor before treatment to excellent after rTMS.

Furthermore, sleep parameters improved significantly after rTMS. Total sleep time increased from a mean of approximately 5 hours to a mean of approximately 7 hrs. Sleep efficiency also showed a significant increase from 65 % to 89%. On the other hand, sleep latency, total wake time, and wake time after sleep onset decreased significantly compared to values observed before rTMS treatment. It must be noticed that the large increase in total sleep time was not due to an increase in a particular sleep stage. The percentages of all sleep stages increased harmonically, remaining within physiological values. To our knowledge, no medical treatment has shown the ability to increase sleep time without altering the percentages of sleep stages.

TMS, DEPRESSION AND SLEEP

The effectiveness of TMS on depression has not been conclusively demonstrated. An early study by Pascual-Leone et al. [42], reported the beneficial effect of high frequency rTMS on depressive symptomatology when applied to the left dorsolateral prefrontal cortex. A significant improvement was reported in the scores of the Hamilton depression rating scale and the Beck questionnaire. Due to the high prevalence of depression among the general population, the possibility of a new non-invasive antidepressant treatment has generated a cascade of studies on the effects of TMS. In 2003, Gershon et al. [43], reviewed more than a decade of studies on this issue. Despite the wide variety of technical differences among studies, most of the reviewed literature supports the notion that rTMS is a reliable antidepressant mainly used with high frequency applied to the left prefrontal cortex.

Some studies have analyzed the effect of TMS in patients with Parkinson's disease and depression [44]. The authors reported that rTMS induces an effect similar to that of fluoxetine in improving the cognitive aspects observed in Parkinson's disease patients with depression.

In a 2014 report, Lefaucheur et al. [1], made an accurate review of evidences concerning the therapeutic effects of rTMS on diverse nervous system pathologies. Concerning depression, the conclusion is that there is enough evidence to consider high
frequency rTMS as a reliable antidepressant treatment when applied to the left dorsolateral prefrontal cortex. However, other variants such as low frequency and right prefrontal cortex have proven only a probable efficacy.

Concerning sleep, one important confounding factor could be the previous level of insomnia or hypersomnia that can be present in depression. To analyze this possibility, Lowe et al. [45,46] reported the possible presence of sleep alteration before TMS treatment in depression. They reported no relationship between the effectiveness of TMS on depression with previous sleep alteration.

CONCLUSION

Nowadays, health problems derived from sleep restriction are becoming a public health issue. Lack of adequate sleep, both in duration and quality, generates pathological conditions. The American Academy of Sleep Medicine (2015) has recently generated a consensus between several medical specialties concerning the optimal duration of daily sleep. The consensus indicates that an adult must sleep, at least, seven hours on a regular basis to promote optimal health. Sleeping less than 7 hours is clearly associated with cardiovascular, metabolic, and mental diseases. Sleep restriction can be the result of both a personal decision (social, work-related or cultural) and/or a sleep disorder. Sleep restriction impairs immune response and decreases neurocognitive capabilities, increasing the risk of errors and accidents. Sleep impairment can also be the result of a pathological condition such as epilepsy, depression, and many others.

Thus, there is a need for new therapeutic tools oriented towards sleep disorders. TMS seems to be a reliable therapeutic method for several sleep alterations, as well as a non-invasive, painless, and non-addictive method that can be safely used against sleep alterations. In addition, TMS is also a powerful tool to explore the excitability of cortical and subcortical brain regions that can be associated with a wide variety of psychoneurological diseases. However, further research is needed to clarify the extent and limitations of TMS therapy.

REFERENCES


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