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Transcranial Stimulation in Sleep Disorders: A Systematic Review

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Abstract

Sleep disorders can affect people's cognition, behavior, and social life. However, the therapy used to assess and intervene in these disorders is not yet consolidated. In this context, this study aimed to verify the applicability and effectiveness of transcranial stimulation current stimulation (tACS), transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (rTMS) in sleep disorders. A systematic search was performed according to PRISMA guidelines in the Web of Science, PubMed, LILACS, and SciELO databases. Initially, 448 articles were found, according to the eligibility criteria. The physiotherapy evidence database (PEDro) was used to assess the methodological quality of the 11 final articles. In general, the results indicate favorable and unfavorable reports on the effectiveness of the therapeutic use of transcranial stimulation techniques in sleep disorders. Therefore, it is still an open question, depending on multiple methodological and conceptual factors.

Keywords: sleep disorders, transcranial stimulation, tDCS, rTMS, neuromodulation

ESTIMULAÇÃO TRANSCRANIANA PARA TRANSTORNOS DO SONO: UMA REVISÃO SISTEMÁTICA

Resumo

Os transtornos do sono podem ter várias consequências para a cognição, comportamento e vida social das pessoas. No entanto, a terapia utilizada para avaliar e intervir nesses transtornos ainda não está consolidada. Nesse contexto, o objetivo deste estudo foi verificar a aplicabilidade e eficácia da estimulação transcraniana por corrente (tACS), estimulação transcraniana por corrente contínua (tDCS) e estimulação magnética transcraniana (rTMS) nos transtornos do sono. Foi realizada uma busca sistemática de acordo com as diretrizes do PRISMA nas bases de dados Web of Science, PubMed, LILACS e SciELO. Inicialmente, foram encontrados 448 artigos, de acordo com os critérios de elegibilidade. O banco de dados de evidências de fisioterapia (PEDro) foi utilizado para avaliar a qualidade metodológica dos 11 artigos finais. Em geral, os resultados indicam que há tanto relatos favoráveis quanto desfavoráveis à eficácia do uso terapêutico das técnicas de estimulação transcraniana nos transtornos do sono e, portanto, ainda se configura como uma questão em aberto, dependendo de múltiplos fatores metodológicos e conceituais.

Palavras-chave: transtornos do sono, estimulação transcraniana, etcc, emtr, neuromodulação

ESTIMULACIÓN TRANSCRANEAL PARA LOS TRASTORNOS DEL SUEÑO: UNA REVISIÓN SISTEMÁTICA

Resumen

Trastornos del sueño pueden tener varias consecuencias para la cognición, el comportamiento y la vida social de las personas. La terapia utilizada para evaluar e intervenir en estos trastornos aún no está consolidada. En este contexto, el objetivo de este estudio fue verificar la aplicabilidad y efectividad de la corriente de estimulación transcraneal (tACS), estimulación de corriente continua transcraneal (tDCS) y estimulación magnética transcraneal (rTMS) en los trastornos del sueño. Se realizó una búsqueda sistemática según las guías PRISMA en las bases de datos Web of Science, PubMed, LILACS y SciELO. Inicialmente se encontraron 448 artículos, según los criterios de elegibilidad. Se utilizó la base de datos PEDro para evaluar la calidad metodológica de los 11 artículos finales. En general, los resultados indican que existen informes tanto favorables como desfavorables sobre la efectividad del uso terapéutico de las técnicas de estimulación transcraneal en los trastornos del sueño y, por tanto, sigue siendo una cuestión abierta, dependiendo de múltiples factores metodológicos y conceptuales.

Palabras clave: trastornos del sueño, estimulación transcraneal, etcc, emtr, neuromodulación

Sleep is a behavioral and physiological state characterized by transient changes in mobility, motricity, and, above all, consciousness compared to wakefulness. Among its functions at a neurobiological level, sleep decreases cortical arousal in the frontoparietal regions of the central nervous system (Worley, 2018). Additionally, because it is a tool for synchronizing biological rhythms, it controls homeostatic and circadian processes (Neves et al., 2013). Hence, sleep significantly strengthens the connection between neurons, favoring neural plasticity and consolidating learned mnemonic processes (Worley, 2018). Therefore, sleep is correlated with several biological, emotional, physical, and environmental factors, and a sufficient number of quality sleep hours is required (Buysse, 2014).

A normal sleep pattern among adults consists of two structures subdivided into the synchronized sleep phases, or non-rapid eye movement (NREM), and desynchronized sleep, or rapid eye movement (REM). NREM sleep is subdivided into stages in which brain activity, eye movement, and skeletal muscle tone progressively decrease, and individuals enter a deeper sleep state (i.e., N1, N2, and N3 phases) (Buysse, 2014). When an individual enters REM sleep, electrical activity increases in the brain, contributing to increased local blood flow, respiratory and heart rates change, and dreams emerge.

Different neural systems and various chemicals mediate the brain regions and regulatory circuits involved in sleep and brain arousal (Hobson & Pace-Schott, 2002). In healthy humans, REM sleep correlates with the activities of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (Lie et al., 2015). This complex and orderly interaction plays important and opposing roles in the sleep-wake cycle. For example, neurons release gamma-aminobutyric acid (GABA) and histamine in the forebrain and hypothalamus. An increase in GABA levels and a decrease in histamine release induce NREM sleep, deactivating the cortex and thalamus. The sleep-wake cycle is also affected by neurotransmitters released by neurons in the ascending reticular activating system (ARAS), such as acetylcholine, norepinephrine, and serotonin. These neurotransmitters contribute to maintaining wakefulness and decrease significantly during REM sleep. Finally, there is also the synchronizing role of melatonin, an essential hormone in biological rhythmicity, as it synchronizes the body with the environment's light-dark cycle (Worley, 2018).

The treatment of sleep disorders currently includes pharmacological interventions (Proctor & Bianchi, 2012), combined or not with behavioral therapies based on behavior modification and cognitive distortions (Babson et al., 2010). However, non-invasive brain stimulation therapies – such as transcranial alternating current stimulation (tACS), transcranial direct current stimulation (tDCS), and transcranial magnetic stimulation (TMS) – have been discussed as complementary therapies (Nardone et al., 2020a; 2020b; Sun et al., 2021). These techniques are suggested to modulate brain excitability, promoting processes underlying normal sleep, compromised in patients with sleep disorders – such as Restless Legs Syndrome (RLS). A chronic neurological disorder in this condition is caused by deregulation in motor neuron activation, resulting in a sensorimotor disorder characterized by an uncontrollable urge to move the legs (Lanza et al., 2018).

TDCS is a brain stimulation technique that delivers a constant, low-intensity electrical current (1-2 mA) through electrodes placed on the scalp (Woods et al., 2016). Current can be positive (i.e., anodic) or negative (i.e., cathodic), and the position of the anode and cathode electrodes on the head determines how the current will flow to the brain's specific regions (Coffman et al., 2020). The central hypothesis regarding its mechanism of action is that, at a neurophysiological level, tDCS modulates the membranes resting potential and strengthens synaptic transmission between the neurons, modifying local synaptic plasticity, cortical arousal, and, consequently, behavior (Giordano et al., 2017; Stagg et al., 2018).

Both tDCS and tACS share the same basic principles and goals but differ in the mechanism of action used to modify cortical arousal. In tACS, sinusoidal currents with a specific frequency deliver stimulation (Herrmann et al., 2013). In practical terms, it is assumed that it can synchronize the firing of a particular neural network to a specific phase of the electric current (Herrmann et al., 2013).

In contrast, TMS creates a magnetic field through a coil held over the head, producing electric pulses that cross the skull and reaches the cortical tissue, deriving from the electric field created perpendicular to the magnetic field (Chail et al., 2018). Different stimulation parameters (e.g., site, intensity, frequency, number of pulses, duration, type of coil, etc.) significantly influence the effects. When stimulation is produced through repetitive pulses (i.e., rTMS), it is believed to substantially modulate the excitability of the stimulated area and the areas connected to it (Chail et al., 2018). As with the other neuromodulation techniques, it is believed that the impact of rTMS involves changes in the elementary properties of synaptic plasticity, specifically in the mechanisms of long-term potentiation (LTP) and long-term depression (LTD).

Considering the therapeutic potential of non-invasive brain stimulation techniques, this systematic review focuses on transcranial stimulation to treat sleep disorders. We explored reports that described the effects of transcranial stimulation techniques on the primary clinical outcomes of interest in the treatment of sleep disorders. Therefore, we gathered reports addressing changes in symptoms based on: i) participants' self-assessment using self-report instruments, and ii) assessments based on electrophysiological indicators of sleep architecture, such as sleep onset latency and total sleep duration.

Method

Eligibility criteria

This systematic review followed PRISMA guidelines (Liberati et al., 2009; Moher et al., 2009) and was submitted to the PROSPERO platform (Protocol no. CRD42021258040). The terms or keywords adopted by certain studies summarizing the concept related to transcranial stimulation and its variables were adopted here. The papers were selected based on the following inclusion and exclusion criteria.

Eligibility criteria included papers addressing: (1) diagnosis of sleep disorders according to the International Classification of Diseases (ICD-11) and/or Diagnostic and Statistical Manual of Mental Disorders (DSM-5) and/or International Classification of Sleep Disorders (ICSD-3); (2) clinical trials, intervention studies, experimental research comparing placebo or sham control; (3) primary or independent sleep disorders; (4) the use of transcranial stimulation (tDCS, tDCS or rTMS), alone, or in combination with other therapies; (5) clinical outcomes related to the disorder's symptomatology using self-report instruments or electrophysiological measurements; (6) papers published in English, Portuguese, or Spanish; (7) full-text papers; and (8) papers published from 2010 to 2020 because understanding regarding the mechanisms underlying the effects of these techniques and parameters have evolved considerably in this period (Chail et al., 2018; Kekic et al., 2016; Stagg et al., 2018; Woods et al., 2016).

Exclusion criteria were papers: (1) providing an insufficient description of the stimulation protocol used, such as intensity, frequency, target area, site, dosage, or duration; (2) lack of relevant information, such as statistical analysis or methodological procedures; (3) studies adopting qualitative methods; and (4) reviews, letters, editorials, systematic reviews, or bibliographic reviews.

Data Collection Procedures

A comprehensive electronic search was conducted on Web of Science, PubMed, LILACS, and SciELO, from September to December 2020. The specific descriptors used were: ("transcranial direct current stimulation" OR "transcranial current stimulation" OR "tDCS," OR "transcranial magnetic stimulation" OR "rTMS," OR "non-invasive brain stimulation") AND ("sleep disorders" OR "sleep disturbances" OR "Insomnia" OR "Hypersomnia" OR "Obstructive sleep apnea" OR "Narcolepsy" OR "Circadian rhythm sleep-wake disorders" OR "Restless legs syndrome"). In addition, keywords were chosen even without specific terms to confer greater sensitivity to the search.

Analysis and selection procedures

After the initial search, identical papers in more than one database were excluded. Two volunteers independently read and assessed the papers considering the established criteria. Due to the risk of bias, the full texts of the articles selected were read and described in detail in individual tables for later comparison. The tables were reconciled, and a third researcher assessed the papers to resolve conflicts. The full texts of the studies included in the final selection were analyzed to identify the papers' objectives, the model used, participants' data, and results and organize a table to present the results and support discussions.

Assessment of the papers' quality was based on the Physiotherapy Evidence Database (PEDro). The PEDro scale is an instrument to assess the methodological quality of studies in the health field, addressing the correct use of eligibility criteria, random and concealed allocation of groups, and blinded participants and evaluators, among other aspects (Morton, 2009). The following criteria compose this scale: (1) participants' eligibility and origin; (2) participants randomly allocated; (3) concealed allocation; (4) similar groups at the baseline; (5) blinded subjects; (6) blinded therapists; (7) blinded evaluators; (8) analysis of intention to treat; (9) intergroup statistical analysis, and (10) precision and variability measures. The total score is obtained by summing the criteria from 2 to 10. Criterion 1 is related to the study's external validity. Scores between 9-10 indicate the trial has excellent methodological quality; scores 6–8=good, 4–5=regular, and scores < 4=poor methodological quality. Two researchers independently rated the papers, and discrepancies were resolved through discussions. PEDro considers two aspects related to the quality of the clinical trial, internal validity, and statistical information (Maher et al., 2003).

Results

General results

The initial search in the databases resulted in 448 papers. After the screening, 22 full texts were analyzed, and 11 met the eligibility criteria established in this review.

Figure 1

Flow diagram of the selection of studies for systematic review

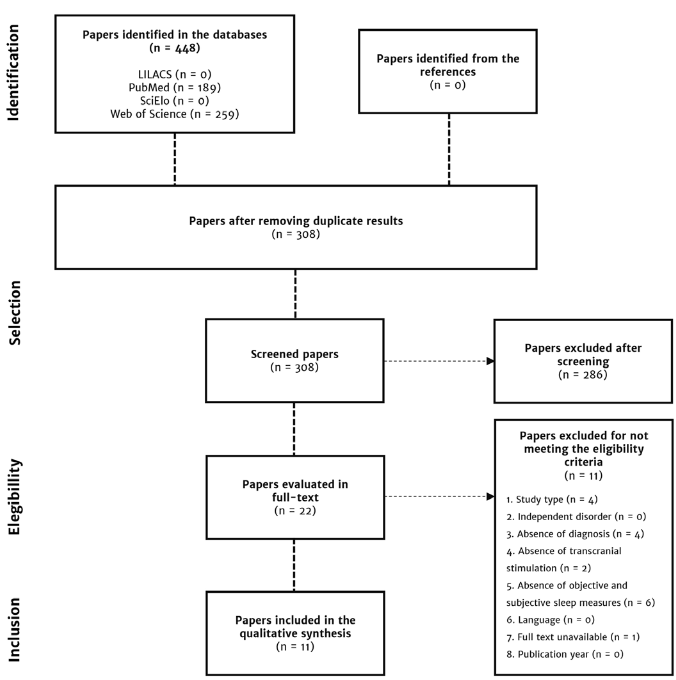

Figure 1 shows that four studies adopted tACS or tDCS to treat RLS and insomnia (Frase et al., 2019; Koo et al., 2015; Saebipour et al., 2015; Wang et al., 2020), while seven studies adopted rTMS to treat RLS and insomnia (Altunrende etal., 2014; Feng et al., 2019; Jiang et al., 2013; Lanza et al., 2018; Lin et al., 2015; Song et al., 2019; Zhang et al., 2018). Most protocols were implemented from 2018 to 2020 (54.5%; n=6). The total number of participants according to the type of stimulation in the tDCS protocols were: i) anodic, 35 participants; ii) cathodic, 29 participants; and iii) simulated, 36 participants. Regarding tACS, 31 participants composed the active stimulation group, and 31 composed the simulated stimulation group. Finally, the total number of participants in the rTMS protocol according to the type of stimulation was 181 in low frequency and 14 in high frequency (Tables 1 and 2).

Regarding the outcomes investigated to verify the effectiveness of the intervention protocols, the following were observed: i) polysomnography (PSG) records to understand slow-wave activity (SWA), K complexes, wakefulness after sleep onset (WASO), sleep onset latency (SOL), total sleep time (TST), and structural sleep phases N1, N2, N3, REM (Frase et al., 2019; Koo et al., 2015; Saebipour et al., 2015); ii) subjective behavioral measures using self-report instruments addressing sleep or specific symptoms such as the Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), Insomnia Severity Index (ISI), RLS Symptom Severity Scale, and International Restless Leg Scale (IRLS) (Altunrende et al., 2014; Feng et al., 2019; Jiang et al., 2013; Lanza et al., 2018; Wang et al., 2020); iii) neuropsychological assessments (Song et al., 2019; Zhang et al., 2018); iv) and hormonal assessments (e.g., measures of cortisol and adrenocorticotropic hormone) (Feng, et al., 2019; Jiang et al., 2013; Koo et al., 2015).

Table 1

Description of studies on transcranial electrical current stimulation applied to sleep disorders

Study	N[a] (age ± SD)	% Woman	Diagnostic	Study design		Stimulation protocol						Primary outcome	Conclusion
				Study type	Groups/ Conditions	Anode	Cathode	RE	Current	ES (cm)	Duration, sessions, frequency		
Frase et al. (2019)	19 (43.8 ± 15.1)	31,5%	ID	Repeated measures, double-blind, sham-controlled	(i) anodic tDCS; (ii) cathodic tDCS; (iii) sham	Bilateral frontal (Fp1/ Fp2)	Bilateral frontal (Fp1/Fp2)	P3/P4	One mA	5 x 7	2 x 11 min for SG and 2 x 13 min for AG (5 consecutive nights for three weeks)	PSG	tDCS did not modify the TST.
Koo et al. (2015)	31 (45.8 ± 11.2)	100%	RLS	Repeated measures, double-blind, sham-controlled	(i) anodic tDCS; (ii) cathodic tDCS; (iii) sham	M1 (Cz)	M1 (Cz)	SO area	Two mA	5 x 5	20 min, five sessions (1 time a day, five consecutive days, 5-7 PM)	IRLS, CGI-I	No significant effects were observed.
Saebipour et al. (2015)	6 (34 ± 7)	33,3%	PID	Repeated measures, double-blind randomized, sham-controlled	(i) active tDCS; (ii) sham	F3/F4	Mastoid	-	260 μA	-	5 min, four sessions	PSG	tDCS significantly altered the sleep architecture of the participants.
Wang et al. (2020)	62 (-)	75%	PID	Independent design, double-blind randomized, sham-controlled	(i) active tACS; (ii) sham	Active electrodes over Fpz/Fp1/Fp2		Mastoid	15 mA	4.45 x 9.53	40 min, 20 sessions (1 per day, Mon-Fri, for four consecutive weeks)	PSQI	The active group had a significant reduction in the total PSQI score.

Note: AG, active group; CGI-I, Clinical Global Impressions-Improvement; ES, electrode size; Fri, Friday; ID, insomnia disorder; IRLS, International RLS Group Rating Scale; M1, primary motor cortex; Mon, Monday; PID, primary insomnia disorder; PSG, polysomnography; PSQI, Pittsburgh Sleep Quality Index; RE, reference electrode; RLS, restless leg syndrome; SE, sleep efficiency; SG, sham group; SO, suboccipital; tACS, transcranial alternating current stimulation; tDCS, transcranial direct current stimulation; TST, total sleep time.
[a] *N* number of participants included in the final stage of analysis (mean age of the sample ± SD)

Table 2

Description of studies on transcranial magnetic stimulation applied to sleep disorders

Study	*N* [a]	% Woman	Diagnostic	Study design		Stimulation protocol						Primary outcome	Conclusion
				Study type	Groups/ Conditions	ED (mm)	Area	Amplitude (μ)	Frequency (Hz)	Stimuli	Duration, sessions, follow-up		
Altunrende et al. (2014)	18	68.4 %	RLS	Repeated measures	(i) active rTMS; (ii) sham	(i) EMT 75; (ii) Sham 100	ISMA	50	5	1.000	15 m, 10 SS interspersed for three days; FU after three months	IRLS-RS	rTMS significantly improved the IRLS-RS score.
Feng et al. (2019)	32	62.5 %	PID	Repeated measures	(i) active rTMS	70	Bilateral DLPFC	50	1	800	15 m, 5 SS/week, for two consecutive weeks	PSQI	Significant reduction in PSQI score after rTMS.
Jiang et al. (2013)	120	55.5 %	CID	Repeated measures	(i) rTMS; (ii) medication; (iii) psychotherapy	70	Left DLPFC	50	1	1.800	30 m, 1 SS/day daily, for two weeks; FU after three months)	PSG	rTMS induced N3 and REM stage amplification
Lanza et al. (2018)	23	76.9 %	RLS	Repeated measures	(i) active rTMS over M1; (ii) active rTMS over S1	80	Left M1 and S1	50	1	1.000	3 SS interspersed for three days, for one week	rMT, MEPs	rTMS was able to relieve the symptoms of RLS patients.
Lin et al. (2015)	14	71.4 %	RLS	Repeated measures	(i) active rTMS	-	Bifrontal	50	15	750	10 m, 14 SS for 18 days	IRLS-RS, PSQI, HAMA	rTMS was able to improve scores on both scales.
Song et al. (2019)	40	40%	PID	Repeated measures	(i) active rTMS; (ii) sham	70	Right PPC (P4)	50	1	1.500	34 m, 5 SS/week, for two consecutive weeks	ESS, ISI, PSQI	Scores on all scales were significantly reduced after active rTMS.
Zhang et al. (2018)	75	89.3 %	CID	Repeated measures	(i) active rTMS; (ii) sham	-	Right DLPFC	-	1	1.200	30 m, 3 SS/week, for four consecutive weeks	ISI, PSQI	After treatment, the scores of both groups improved, though they were higher for the active rTMS group.

Note: [a] *N* number of participants included in the final stage of analysis (mean age of the sample ± SD); CID, chronic insomnia disorder; DLPFC, dorsolateral prefrontal cortex; ED, external diameter; EMPs, evoked motor potentials; ESS, Epworth Sleepiness Scale; FU, follow-up; ISI, Insomnia Severity Index; ISMA, left supplementary motor area; M1, primary motor cortex; PID, primary insomnia disorder; PPC, posterior parietal cortex; PSQI, Pittsburgh Sleep Quality Index; RLS, restless leg syndrome; rMT, resting motor threshold; rTMS, repetitive transcranial magnetic stimulation; S1, primary somatosensory area; SS, sessions.

TDCS and tACS protocols

Koo et al. (2015) conducted a double-blind, randomized, sham-controlled clinical trial over two weeks. Thirty-three women with RLS attended five cathodic, anodic, or sham tDCS sessions. Real (i.e., anodic, or cathodic) or sham tDCS was administered in five treatment sessions (once a day, from Monday to Friday, using 2 mA current, between 5 pm and 7 pm for 20 minutes). Follow-up was implemented three (T1) and 13 days (T2) after the fifth treatment session. Because the objective stimulated the primary motor cortex (M1), the active electrode was positioned over Cz, bilaterally covering its medial portion. The reference electrode was placed on the suboccipital region. No differences were found in primary (e.g., IRLS total score) or secondary outcomes after tDCS was implemented, regardless of the condition.

Similarly, Frase et al. (2019), Saebipour et al. (2015), and Wang et al. (2020) implemented intervention protocols to assess the effects of transcranial stimulation on insomnia disorder. Saebipour et al. (2015) performed a randomized, crossover, repeated measures design over four non-consecutive nights using slow (0.75 Hz) transcranial oscillatory stimulation (0.75 Hz) applied only on the third night. Direct current was applied in six patients during stage 2 of NREM sleep for 25 minutes, approximately 11:30 pm. The active anode electrode was placed on F3 and F4. The cathodes were placed on the mastoids, with a maximum stimulation voltage of 10 V and resistance between the ipsilateral stimulation sites between 5 and 15 kOhm. The results show a stabilizing role of tDCS, which, compared to the sham stimulation, promoted positive effects on the duration of the N1 stage of NREM sleep, sleep efficiency, and the probability of transition between stages N2 and N3 of NREM sleep.

Based on the modulation of cortical activity, Frase et al. (2019) sought to clarify the neurobiology of insomnia disorder through an experimental protocol of repeated measures, in counterbalanced order (i.e., anodic, cathodic, or sham stimulation), with a one-week interval to avoid side effects. The authors used bifrontal (Fp1/Fp2), anodic and cathodic, and sham tDCS (i.e., inactive electrodes placed on P3/P4), with a constant current of 1 mA and randomized blocks of 11-13 min of stimulation to the condition. The authors found no tDCS significant effects on sleep architecture or continuity among the insomniac participants.

Finally, Wang et al. (2020) performed an eight-week, double-blind, randomized trial between an active and a sham tDCS group. The participants attended 20 daily (Monday-Friday) sessions of 40 min with 15 mA current for four consecutive weeks, followed by a four-week follow-up. Active electrodes measuring 4.45 × 9.53 cm were placed on Fpz, Fp1, and Fp2, and two sham electrodes measuring 3.18 × 3.81 cm were placed on the mastoid areas. Compared to sham tDCS, the authors report that the active stimulation positively affected all outcomes at the end of the fourth week of follow-up. They state that tDCS is a safe and potentially effective treatment of chronic insomnia.

Repetitive TMS Protocol

In a pilot study with a double-blind, repeated-measures design implemented among patients with RLS, Altunrende et al. (2014) used active and sham rTMS every three days, totaling ten sessions. All participants in the sham rTMS group were reassigned to the active rTMS group at the end of the intervention. The authors used a coil with a 75 mm diameter for the active stimulation and a 100 mm diameter coil for the sham stimulation placed on the primary motor area (M1) aligned to the midsagittal area. One thousand pulses were used, with a 5 Hz frequency and 50-second intervals between each pulse. The results indicate that, after ten sessions, only the active rTMS significantly improved the IRLS total scores.

Lanza et al. (2018) and Lin et al. (2015) also used rTMS in patients with RLS. Lanza et al. (2018) used active, low-frequency (1 Hz) rTMS in night sessions (20 pulses, 50 stimuli for each trial). The active rTMS was administered on the left M1 and left S1 areas. The rTMS interventions were repeated after each stimulation modality. Each participant attended three sessions on different days, with one one-week interval. The authors used a 70 mm diameter coil tangent at 45 degrees to the scalp surface. The participants reported significant improvement in sleep onset and maintenance, compared to the baseline measures, the night after rTMS over S1 but not after rTMS over M1.

Lin et al. (2015) implemented a high-frequency (15 Hz) rTMS in 14 sessions over 18 days on the motor cortex area. Stimulation was performed in both hemispheres, with 75 pulses administered at 10-minute intervals. The study's results suggest that high-frequency rTMS alleviate motor symptoms, sleep-related complaints, and anxiety in patients with RLS; all the measures were assessed using self-report instruments.

Other studies investigated the use of rTMS to treat insomnia disorder. Feng et al. (2019) conducted ten daily morning sessions of sequential, low-frequency (1 Hz) rTMS. The dorsolateral prefrontal cortex (DLPFC) was stimulated bilaterally, with an intensity of 50 μV over 10s with 2s intervals between pulses. Each session lasted 30min. The coil was 70 mm in diameter and was positioned tangentially to the scalp, with the loop in the occipital direction. A total of 1,500 pulses were applied. The total PSQI score significantly decreased after the intervention and was negatively correlated with changes in GABA levels.

Jiang et al. (2013) performed a low-frequency intervention (1 Hz) daily for two weeks. Thirty pulses were used per sequence, with 2s intervals between each DLPFC stimulation sequence, totaling 1,800 pulses. The authors report that rTMS significantly improved the participants' sleep architecture and hormonal indexes compared to the control situations (i.e., medication and psychotherapy. Additionally, the patients in the rTMS group presented lower levels of relapse and recurrence.

Finally, different from the previous studies, Song et al. (2019) implemented a low frequency (1 Hz) rTMS treatment for 14 consecutive days between 2 pm and 4 pm. The stimulations were applied on the right posterior parietal cortex (P4) using a 70 mm diameter coil and three pulses with 1s intervals, totaling 1,500 pulses per session. After the intervention, the scores of all the self-report instruments decreased significantly, and the authors reported that the effects lasted at least one month.

Studies' quality

In general, the studies presented well-delimited intervention protocols, establishing sample and eligibility criteria, controlled recruitment and randomization, types of intervention, and methods to assess efficacy. Table 3 summarizes the methodological quality of the studies in the final sample, reporting information that meets the PEDro scale's criteria. The studies obtained a good mean (M=7.75; SD=1.8) score on the PEDro scale. The highest score (11) was obtained by the study addressing tDCS applied to primary insomnia disorder (Wang et al., 2020) on methodological quality, and the lowest score (5), also concerning methodological quality, was obtained by the studies applying rTMS to insomnia and RLS (Feng et al., 2019; Lin et al., 2015).

Table 3

Quality assessment using the PEDro scale

Study	01	02	03	04	05	06	07	08	09	10	11	Total
Altunrende et al (2014)	Y	Y	N	Y	N	N	N	Y	Y	Y	Y	7
Feng et al. (2019)	Y	N	N	N	N	N	N	Y	Y	Y	Y	5
Frase et al. (2019)	Y	Y	Y	Y	Y	N	N	Y	N	Y	Y	8
Jiang et al. (2013)	Y	Y	N	Y	N	N	Y	Y	Y	Y	Y	8
Koo et al. (2015)	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	10
Lanza et al. (2018)	Y	Y	Y	N	Y	N	N	Y	Y	Y	Y	8
Lin et al. (2015)	Y	N	N	N	N	N	Y	Y	Y	N	Y	5
Saebipour et al. (2015)	Y	Y	Y	Y	Y	N	N	Y	N	Y	Y	8
Song et al. (2019)	Y	N	N	N	N	Y	N	Y	Y	Y	Y	6
Wang et al. (2020)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	11
Zhang et al. (2018)	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	8

Note: N, no; Y, yes.

Discussion

This study's objective was to systematically review the effectiveness and applicability of transcranial stimulation techniques (i.e., tACS, tDCS, and rTMS) to treat sleep disorders. Considering that the studies included in this review presented favorable and unfavorable results concerning the effectiveness of transcranial stimulation, the question of whether this therapy is effective remains. Additionally, it depends on many factors such as i) the parameters of each stimulation; ii) the conceptualization of the etiologic mechanisms of each disorder; iii) the types of outcomes analyzed; and iv) the participants' inter-individual factors.

Additionally, despite the growing interest in the therapeutic use of transcranial stimulation techniques, studies or protocols investigating the effects of tDCS, tACS, or rTMS interventions on sleep disorders are still incipient. These aspects indicate that this research agenda is in its exploratory phase; the period in which most studies were published shows it. Even though there are multiple sleep disorders, transcranial stimulation techniques were only analyzed for two disorders: i) RLS (Altunrende et al., 2014; Koo et al., 2015; Lanza et al., 2018; Lin et al., 2018; Lin et al. ., 2015) and ii) primary (PI) or chronic insomnia (CI) disorder (Feng et al., 2019; Frase et al., 2019; Jiang et al., 2013; Saebipour et al., 2015; Song et al., 2019; Wang et al., 2020; Zhang et al., 2018).

RLS is a chronic neurological disorder of a sensory-motor nature, mainly characterized by an urge to move the legs, generally accompanied by unpleasant sensations relieved by moving the legs (Lanza et al., 2018). Considering the mechanisms believed to underline the rTMS effects and the historical use of this technique in the study of movement disorders (Chail et al., 2018), we expected to find reports about the impact of rTMS on the characteristic symptoms of RLS. This study's final synthesis reveals three studies investigating the effects of rTMS on subjective and objective sleep parameters of participants diagnosed with RLS (Altunrende et al., 2014; Lanza et al., 2018; Lin et al., 2015). Perhaps, less predictable was the interest of researchers in using tDCS among patients with RLS, as described in one study included in this review (Koo et al., 2015).

PI is a multi-determined disorder characterized by nonrestorative sleep, accompanied by problems at sleep onset or maintenance not explained by other clinical, neurological, or psychiatric disorders (Saebipour et al., 2015). According to Buysse et al. (2017), the main characteristic of PI is a dissatisfying amount or quality of sleep related to difficulty falling asleep, staying asleep, and waking early, which affects daytime functions. Brain functioning in PI is characterized by abnormal connections between brain networks, in which cortical hyperarousal—especially in frontoparietal areas—is one of the main neurophysiological changes associated with the disorders' symptoms (Yuan et al., 2020). This hyperarousal would reflect on insomniac individuals' cognitive functioning and verbal reports. In this sense, an intervention with transcranial stimulation techniques would decrease the chronic hyperarousal state by strengthening inhibitory signals through GABAergic neuron stimulation (Song et al., 2019). Seven studies included in this review investigated transcranial stimulation techniques to treat insomnia. When we observed the areas stimulated by tDCS or tACS in these studies, we noted a preference for active stimulation in the cortex frontoparietal regions (Feng et al., 2019; Frase et al., 2019; Jiang et al., 2013; Saebipour et al., 2015; Song et al., 2019; Wang et al., 2020; Zhang et al., 2018).

Outcomes and effectiveness

Studies from the last two decades suggest that transcranial stimulation techniques can be integrated into clinical practice as an efficacious treatment for different conditions through transitory modulation of cortical hyperarousal (Kekic et al., 2016). Furthermore, as previously described, the effects of transcranial stimulation can be partially attributed to its interaction with neuroplasticity mechanisms involving LTP (in which the connection and transmission between two neurons are strengthened) and LTD (in which the lasting connection between two neurons is weakened) (Chail et al., 2018; Giordano et al., 2017). Thus, based on the pathophysiological state that characterizes the sleep architecture and behavior of patients with sleep disorders, it seems reasonable to suggest that transcranial stimulation has the potential to promote, through neuromodulation, positive effects on the different aspects of symptoms.

Eight studies in this review presented results suggesting some degree of effectiveness of non-invasive brain stimulation to treat insomnia and RLS (Alturende et al., 2014; Jiang et al., 2013; Feng et al., 2019; Lanza et al., 2018; Lin et al., 2015; Saebipour et al., 2015; Song et al., 2019; Wang et al., 2020). Considering the primary outcomes analyzed through self-report measures, the studies described the effects of stimulation on sleep subjective quality indicators, mainly the PSQI total score (Feng et al., 2019; Lin et al., 2015; Song et al., 2019; Wang et al., 2020; Zhang et al., 2018) and concerning the symptoms characteristic of a given disorder, especially the IRLS total score (Altunrende et al., 2014; Koo et al., 2015; Lin et al., 2015). Complementarily, three studies reported significant effects of transcranial stimulation techniques on the primary outcomes described through electrophysiological measures, one for insomnia disorder (Saebipour et al., 2015) and two for RLS (Jiang et al., 2013; Lanza et al., 2018). Despite these results, we should keep in mind that few studies reported effect size measures to complement data of statistical significance (Frase et al., 2019; Koo et al., 2015; Wang et al., 2020; Zhang et al., 2018). It is consensus in the medical literature that the analysis and description of data concerning the effect size of interventions are indispensable to understanding their clinical significance correctly (Kraemer & Kupfer, 2006).

In contrast, three studies did not find statistically significant effects of transcranial stimulation on the sleep parameters of patients with insomnia (Frase et al., 2019; Zhang, 2018) or RLS (Koo et al., 2015). For instance, Frase et al. (2019) report that tDCS (anodic and cathodic) had no effects on electrophysiological parameters (i.e., sleep continuity, architecture, and REM tracings) or subjective parameters (i.e., sleep efficiency, latency, and total sleep time) of patients with insomnia. Nevertheless, the baseline results showed a persistent hyperarousal state among insomniac participants compared to their healthy counterparts. According to the authors, high arousal levels predict a lack of tDCS effects on the sleep parameters of patients with insomnia. Thus, future studies should propose protocols adapted to the participants' arousal levels at the baseline.

Other reviews suggest that the tDCS therapeutic effects depend on inter-individual factors such as neuronal activity before the stimulation (Li et al., 2015). Such reports are relevant because, cumulatively, they indicate the importance of considering the specificities of each participant or condition when devising an intervention protocol. Additionally, these reports support the clarification of factors determining therapeutic stimulation success. In the context of sleep disorders, variables such as age, cortical arousal levels, and cognitive activity before sleep onset present a well-established relationship with the dysfunctional functioning of the sleep-wake cycle (Wuyts et al., 2012). Therefore, inter-individual factors should be considered in addition to the stimulation parameters when developing intervention protocols.

Adverse reactions

As previously noted, all non-invasive stimulation techniques modify brain arousal by changing electrical activity. Therefore, safe, and well-established parameters are needed to avoid compromising the activity of other brain circuits, whether in experimental or clinical applications. According to Nitsche and Bikson (2017), currents greater than 2 mA should be avoided in tDCS because they are associated with multiple side effects. Nevertheless, Koo et al. (2015) used a direct current of 2 mA and reported that 43.8% of the participants experienced at least one side effect: headache, fatigue, itching, tingling, or burning sensation. Additionally, Saebipour et al. (2015) reported transitory mild headaches two days after stimulation with a low current (260 μA). However, it is worth noting that the authors reported that none of the participants asked for the stimulation to be interrupted. Finally, Wang et al. (2020) identified epileptiform discharges as adverse effects. Other adverse effects included heat, pinching, itching, tickling, tingling, pain, or burning sensation; dizziness and nausea were less frequent side effects.

Regarding rTMS side effects, five studies did not report any adverse effects during or after the interventions (Alturende et al., 2014; Feng et al., 2019; Lanza et al., 2018; Lin et al., 2015; Zhang et al., 2020). In turn, Jiang et al. (2013) and Song et al. (2019) did not present or discuss the potential adverse effects of rTMS in their protocols, which can be considered a weakness.

In general, studies reported adverse effects only using tDCS or tACS as the stimulation technique. This fact suggests that even though this is currently considered the most promising neuromodulation technique, investigating and reporting whether significant changes are caused to brain activity and, if so, how they occur is necessary to ensure the participants' well-being. Additionally, new approaches must be adopted to constantly verify the potential side effects of this type of stimulation (Nitsche & Bikson, 2017). Considering that tDCS and tACS are accessible techniques, such investigations are part of many ethical conducts researchers and clinicians must adopt to avoid inappropriate transcranial electrical current stimulation (Wurzman et al., 2021).

Limitations and conclusion

Preliminary results suggest that non-invasive transcranial stimulation techniques are promising therapeutic tools for the clinical treatment of sleep disorders, improving objective and subjective measures of sleep quality. Nonetheless, considering existing divergences and the fact that these strategies present advantages and disadvantages, the parameters used in each technique (e.g., site of electrodes or coil, frequency, intensity, or repeated stimulation) should be based on evidence obtained in clinical trials, such as those describing the role of these techniques in synaptic facilitation and its interaction with the neural mechanisms involved in the etiology and maintenance of sleep disorders. In addition, from a practical point of view, it is essential to ensure that active tDCS, tACS, and rTMS targets are frequently under electrodes or coil because the current flow produced can also reach cortical regions between and around the electrodes, not being restricted to the area under the electrodes.

Regarding this systematic review's limitations, we note the lack of a detailed meta-analytical investigation of the data described in the studies (e.g., stimulation parameters and primary outcomes). Considering that research addressing the effects of transcranial stimulation on treating sleep disorders is still incipient, this limitation is partially due to the limited number of studies available. Although, we should also note the heterogeneity of the samples addressed (e.g., asymmetric samples in terms of gender, age groups, and a lack of precise diagnostics), primary and secondary outcomes, and methodological designs. Additionally, the fact that other databases (i.e., gray literature) or studies written in other languages were not searched also configures a source of bias already known in clinical research (e.g., publication bias). In any case, even though no conclusive results were found, the evidence summarized in this review contributes to the advancement of studies in this field as it provides a direction for future studies to implement intervention protocols or clinical designs and also reports gaps in the field of non-invasive stimulation to treat sleep disorders.

Sleep disorders are frequent complaints in clinical practice, and an accurate diagnosis is essential to establish the most appropriate therapeutic strategy. Therefore, future studies are needed to refine stimulation protocols, translate pathophysiological concepts to relate them to their symptomatology and behavior correlates, and adapt stimulation parameters to the specific needs of each clinical condition characterized by decreased or high levels of cortical arousal. Future studies are suggested to investigate the relationship between the effects of transcranial stimulation and different inter-individual factors (e.g., age groups), revealing neural mechanisms underlying the physiopathology of sleep disorders before and after interventions.

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