

REVIEW

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Transcranial magnetic stimulation therapeutic applications on sleep and insomnia: a review

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Abstract

Repetitive transcranial magnetic stimulation (rTMS) is a neuromodulatory technique approved by the US Food and Drug Administration for use in treatment-resistant major depressive disorder. It works by generating localized magnetic fields that create depolarizing electrical currents in neurons a few centimeters below the scalp. This localized effect is believed to stimulate neural plasticity, activate compensatory processes, and influence cortical excitability. Additionally, rTMS has been used in a variety of clinical trials for neurological and psychiatric conditions such as anxiety, post-traumatic stress disorder and epilepsy. Beneficial effects in sleep parameters have been documented in these trials, as well as in major depressive disorder, and have led to an interest in using rTMS in the field of sleep medicine for specific disorders such as insomnia, hypersomnia, and restless legs syndrome. It is unknown whether rTMS has intrinsically beneficial properties when applied to primary sleep disorders, or if it only acts on sleep through mood disorders. This narrative review sought to examine available literature regarding the application of rTMS for sleep disorder to identify knowledge gaps and inform future study design. The literature in this area remains scarce, with few randomized clinical trials on rTMS and insomnia. Available studies have found mixed results, with some studies reporting subjective sleep improvement while objective improvement is less consistent. Due to the heterogeneity of results and the variations in rTMS protocols, no definitive conclusions have been reached, signaling the need for further research.

Keywords: Transcranial magnetic stimulation, Insomnia, Sleep disorders

Introduction

Transcranial magnetic stimulation (TMS) is a relatively novel method for the treatment of a variety of neuropsychiatric conditions. This noninvasive procedure generates magnetic fields to create an electrical current to depolarize neurons and modulate neuronal activity in localized cortical regions a few centimeters below the scalp (Valero-cabr e et al. 2017). Repetitive TMS (rTMS) is approved by the US Food and Drug Administration for treatment-resistant major depressive disorder (MDD) (Berlim et al. 2013a; Berlin et al. 2014; Fitzgerald et al.

2012; Ray et al. 2011; George et al. 2010; O'Reardon et al. 2007) (see Fig. 1) and since 2018 for obsessive-compulsive disorder (Carmi et al. 2019; Carmi et al. 2018; Berlim et al. 2013b). In addition, it has been shown to have potential benefits in multiple other conditions, including anxiety (Rodrigues et al. 2019; Cirillo et al. 2019), posttraumatic stress disorder (Kozel et al. 2018; Watts et al. 2012; Karsen et al. 2014; Ahmadizadeh and Rezaei 2018), and fibromyalgia (Boyer et al. 2014; Passard et al. 2007; Mhalla et al. 2011).

rTMS has an excellent tolerability profile. The most common adverse effects include scalp discomfort/pain, facial muscle twitching, and headache (O'Reardon et al. 2007). Rare adverse effects include seizures, hypomania (Rossi et al. 2009). In general, caution is recommended

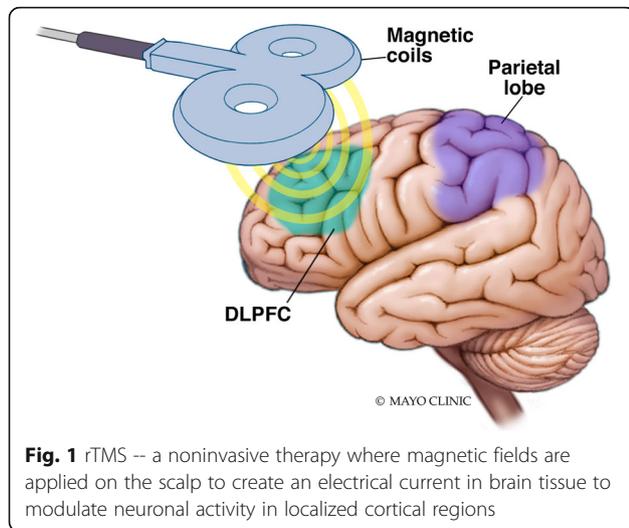
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in patients with pacemakers as well as a history of seizures (Valero-cabr e et al. 2017; Rossi et al. 2009). Absolute contraindications include metallic material in the head near the machine coil such as cochlear implants (Valero-cabr e et al. 2017; Rossi et al. 2009).

Sleep disorders are common in the general population (Ohayon 2011) and in patients suffering from MDD (Ohayon 2011; Murphy and Peterson 2015). Several studies have reported that rTMS for various conditions improved sleep quality by subjective measures (van Dijk et al. 2009; S anchez-Escand on et al. 2016), even in those who experienced no improvement with the actual mood disorder (Sonmez et al. 2020); hence, it has recently been suggested that rTMS could have an intrinsic positive effect on sleep outside of its application in MDD (Sonmez et al. 2020). Neuroimaging studies have found that patients with chronic primary insomnia often exhibit cortical hyperexcitability (Van Der Werf et al. 2010; Lanza et al. 2015). It was shown that chronic insomnia has specific pathophysiological features that differ from other sleep disordered states such as intermittent sleep deprivation, with hyperarousal being a core feature (Riemann et al. 2015; Riemann et al. 2010). Notwithstanding, sleep deprivation in healthy individuals has been shown to promote increased cortical excitability (Kreuzer et al. 2011; Civardi et al. 2001).

rTMS can be used as a mapping tool to study neuronal networks for pre-surgical planning, diagnostic purposes (Valero-cabr e et al. 2017), and to examine brain cortex functionalities (Valero-cabr e et al. 2017; Nardone et al. 2013). In addition, it has recently been explored in neurology and psychiatry communities to determine its therapeutic potential for different sleep pathologies such as insomnia (Feng et al. 2019), sleep bruxism (Zhou et al. 2016), and restless legs syndrome (Lin et al. 2015). To date, the exact mechanism by which rTMS is thought to influence sleep has yet to be fully explained.

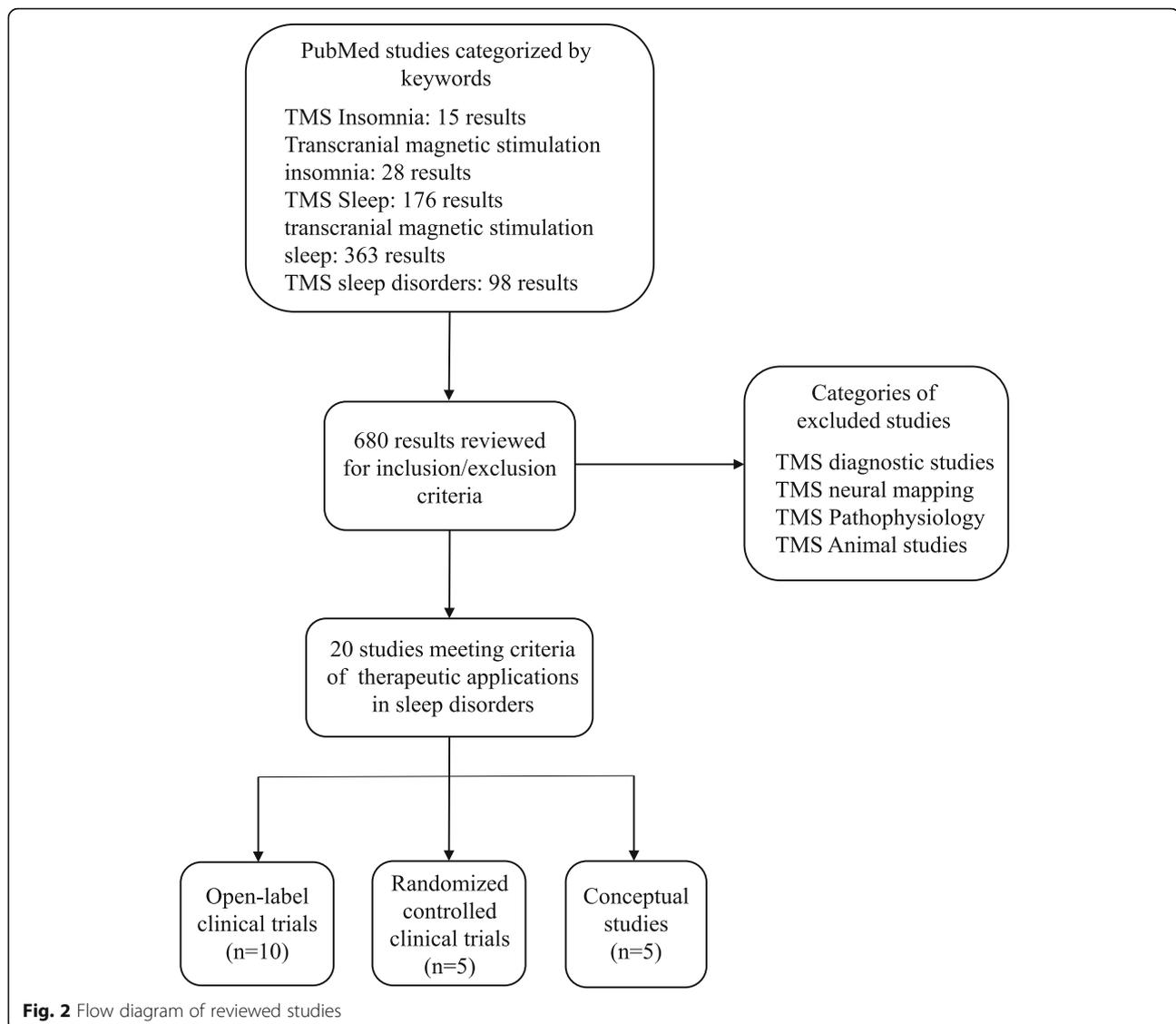
It is believed that rTMS engages neuronal plasticity to modulate compensatory brain processes (Valero-cabr e et al. 2017), and has been shown to regulate altered cortical states through the dorsolateral prefrontal cortex (DLPFC) in patients with MDD (Berlim et al. 2013a; George et al. 2010). Therefore, in theory, rTMS could benefit patients with sleep pathologies such as insomnia, obstructive sleep apnea, and restless legs syndrome which have been shown to have altered cortical features (Lanza et al. 2015). rTMS also has been found to influence sleep and its effects by, for example, increasing slow-wave activity (Huber et al. 2007) and reducing the impact of sleep deprivation on memory (Luber et al. 2013). In this review, we examine the current scientific understanding of rTMS therapy for use in sleep disorders, with a focus on insomnia, and discuss findings from various studies.

Methods

We conducted a literature search in PubMed on October 31, 2019, using keywords of "TMS", "transcranial magnetic stimulation", "sleep", "sleep disorders", and "insomnia." Scopus and Google Scholar databases were also searched but did not yield additional references. Our inclusion criteria were studies regarding therapeutic applications, both open-label and randomized controlled trials, on sleep pathologies. Studies which employed TMS for diagnosis, neural mapping, pathophysiological analysis or animal studies were excluded. Figure 2 illustrates these criteria and our search results. An example of a search performed in PubMed with MeSH is: ("Transcranial Magnetic Stimulation"[MeSH]) AND ("Transcranial Magnetic Stimulation/therapeutic use"[MeSH]) AND ("Transcranial Magnetic Stimulation/therapy"[MeSH]) OR ("Dyssomnias"[MeSH]) OR ("Sleep Initiation and Maintenance Disorders"[MeSH]) OR ("Sleep"[MeSH]) OR ("Sleep Disorders, Intrinsic"[MeSH]). We abstracted information about the sample size, stimulation location, TMS parameters (frequency, motor threshold), duration of treatment, concurrent medication use, rating scales used, and subjective and objective outcomes.

Results

A total of 680 search results were screened with 20 studies being selected for inclusion and analysis. Table 1 summarizes the principal 15 studies, while additional 5 are discussed throughout the review. Out of the principal fifteen studies in Table 1 ten were open-label, and five were randomized. A wide variety of stimulation locations, frequencies, motor thresholds, and duration of treatment were found. For the outcomes, most studies employed a combination of subjective (questionnaires) and objective (PSG, actigraphy, biological) measures.



Stimulation frequency and motor threshold

Broadly, rTMS can be dosed with high and low frequencies. High frequency (HF) is considered to be any frequency above 1 Hz, more typically set at ~ 10 Hz. HF has been shown to have an excitatory effect on the frontal cortex and is commonly used in MDD (Valero-cabr e et al. 2017; Hallett 1910; Aleman 2013; Lefaucheur et al. 2014). On the other hand, low-frequency (LF) rTMS includes frequencies 1 Hz and below. LF rTMS, when used continuously, is thought to be inhibitory (Valero-cabr e et al. 2017; Chen et al. 1997; Romero et al. 2002). Six of the studies used high frequency stimulation, 8 used low frequency, and one used a combination of high and low frequencies.

Resting motor threshold (MT), another important rTMS parameter, is the minimum amount of stimulation needed to create a motor-evoked potential to cause muscle movement. The muscle movement is usually

visually observed from a twitch of the hand muscles or the abductor pollicis brevis (thumb) muscle and indicates the required rTMS potency to stimulate neurons in each patient. The included studies used stimulation intensities ranging from 80 to 120% of MT. For MDD, a stimulation intensity of 120% of MT is commonly used.

Effect of frequency and location

A number of neurologic and psychiatric disorders have been found to display characteristic disturbances in cortical excitability. In MDD, diminished activity in the frontal cortex is commonly found (Kimbrell et al. 2002; Mayberg 2003). In contrast, chronic insomnia often shows increased cortical excitability (Van Der Werf et al. 2010; Lanza et al. 2015).

While the importance of rTMS frequency regarding clinical outcomes has been the subject of investigation

Table 1 Summary of Selected Studies

Study	Sample size	Location	TMS Parameters	Duration	Measurement Tools	Sham Control	Medication Trial Status	Subjective Improvement	Objective Improvement
Sonmez et al. 2020	17	L DLPFC	10 Hz	30 d	QIDS-A17-SR, CDRS-R	No	Allowed, hypnotics	Yes	N/A
Feng et al. 2019	32	DLPFC (bilateral)	1 Hz, 80% MT	10 d	PSQI, BDNF, GABA, MEP	No	Not allowed	Yes	Yes
Song et al. 2019	40	R posterior parietal cortex	1 Hz, 80% MT	14 d	PSQI, ISI, ESS EEG	No	Yes	Yes	Yes
Lin et al. 2019	105	Left (L) DLPFC	10 Hz, 100% MT	6 wk	PSQI, SAS, SDS	Yes	Not allowed	Yes	N/A
Huang et al. 2018	36	R posterior parietal cortex	1 Hz, 90% MT	10 d	PSQI, HRSA	Yes	Yes, SSRI and BZN	Yes	N/A
Zhang et al. 2018	75	L prefrontal cortex	1 Hz, 100% MT	12 d	PSQI, ISI, sleeping diary, actigraphy	Yes	Not allowed	Yes	No
Nishida et al. 2017	14	DLPFC (bilateral)	1 Hz (R), 10 Hz (L), 100–110% MT	10 d	PSQI, HAMID, actigraphy	No	Allowed, BZN	Yes	No
Antczak et al. 2017	13	L DLPFC	10 Hz, 110–120% MT	20 d	CGIHDRS, AIS, Sleep Diaries, actigraphy	No	Allowed, antidepressants	Yes	No
Sánchez-Escandón et al. 2016	24	Frontal, temporal, parietal	1 Hz	10 d	QOLIE-31, PSG	No	Yes, levetiracetam	Yes	Yes
Sánchez-Escandón et al. 2014	10	Frontal cortex	1 Hz	10 d	PSG, EEG	No	Not allowed	N/A	Yes
Jiang et al. 2013	120	Right (R) DLPFC	1 Hz, 80% MT	14 d	PSQI, PSG, cortisol, ACTH, TSH, T4, T3	No	Not allowed in TMS group	Yes	Partly
Rosenquist et al. 2013	301	L DLPFC	10 Hz, 120% MT	6 wk	HAMD, IDS-SR	Yes	Allowed, hypnotics, anxiolytics	No	N/A
Antczak et al. 2011	11	Motor cortex (bilateral)	15 Hz, 80–120% MT	10 d	UPDRS, HDRS, PDSS, PSG	No	Allowed, Parkinson medication	Yes	Partly (unrelated to sleep)
Arias et al. 2010	18	Vertex area	1 Hz, 90% MT	10 d	PDSS, HDS, UPDRS Actigraphy	Yes	Not allowed	Yes	No
van Dijk et al. 2009	21	Motor, parietal cortex (bilaterally)	5 Hz, 80% MT	10 d	UPDRS, BDI, actigraphy	No	Allowed, Parkinson medication	No	Partly

with variable results (Lefaucheur et al. 2014), it is possible that patients with primary insomnia, which is a condition known to present with cortical hyperexcitability (Lanza et al. 2015; Riemann et al. 2015), could benefit from a LF-continuous stimulus protocol thought to be inhibitory in nature (Valero-cabr e et al. 2017; Chen et al. 1997; Romero et al. 2002). Interestingly, a recent study using excitatory HF rTMS in depressed adolescents found that hypersomnia symptoms improved significantly, while symptoms of insomnia did not (Sonmez et al. 2020). These findings could reflect the effect of excitatory HF rTMS on potentially underactive cortex of patients with hypersomnia, an effect potentially seen in another study (Lai et al. 2017). In contrast with individuals with insomnia, whose cortex is likely to be already overactive, HF treatment may not achieve sleep improvement. In addition, the aforementioned recent study also found preliminary evidence of a seemingly positive intrinsic effect on sleep from rTMS independent of its antidepressant effects (Sonmez et al. 2020).

However, a recent study suggests how rTMS's effect on cortical areas may be more related to functional integration of each area rather than frequency settings (Castillon et al. 2019). In one study, 1 Hz rTMS was applied to patients in the frontal and occipital cortices, and the modulatory effects were different. While the occipital cortex was locally inhibited when 1 Hz rTMS was applied, the frontal cortex showed a paradoxical decrease in inhibition with the same 1 Hz stimulation. As such, this recent study highlights inconsistency in our current understanding of how rTMS frequencies work and suggests that further study is needed to investigate if there is a more complex underlying mechanism. Furthermore, occipital stimulation increased functional connectivity of local and distant areas while frontal stimulation decreased such functional connectivity.

The effects of rTMS on sleep have also been studied in Parkinson disease in two separate studies (van Dijk et al. 2009; Antczak et al. 2011), both of which applied HF over either the motor or parietal cortex. Both studies found improvement in sleep by subjective and objective measures. However, one of the studies found that the improvement seen on polysomnographic (PSG) studies was likely the result of improvement in nocturnal motor symptoms of Parkinson disease more than actual influence on sleep itself (Antczak et al. 2011). The other study found no changes in motor symptoms, but did find improvement in actigraphic recordings if rTMS was applied to the parietal cortex (van Dijk et al. 2009). These two studies used different questionnaires and measuring techniques, which could explain the conflicting results (Antczak et al. 2011). The heterogeneous results of these studies on sleep illustrate that rTMS's effect is complex, due to variations in rTMS settings, target brain regions, as well as the underlying neurological conditions.

Sleep measurement outcomes

Nearly all studies showed an improvement in the subjective or self-reported sleep measurements. The Pittsburgh Sleep Quality Index (PSQI), one of the most-used questionnaires in the studies we reviewed, reported improved results either moderately or substantially in most cases. Similar results were reported by the Epworth Sleepiness Scale (ESS) and the Insomnia Severity Index (ISI). The extent to which patient bias (e.g., a psychological component of sleep problems) may have influenced these seemingly positive results is unknown, given the potential for inaccurate reporting in patient surveys. Studies also examined objective data such as that obtained from PSG and actigraphy.

Other studies examined rTMS's effect on different conditions such as epilepsy or MDD. In one epilepsy study, patients were administered LF rTMS in areas where their epileptic activity was highest, and sleep improvements were found by questionnaires and PSG parameters (S anchez-Escand on et al. 2016). A different study focusing on rTMS in MDD and using PSQI and actigraphy had mixed findings. While PSQI questionnaires after rTMS treatment showed improvement, actigraphic results displayed no significant sleep changes (Nishida et al. 2017).

A recent systematic review examined the results of rTMS versus sham stimulation analyzing the pooled effect size of PSQI in nine selected studies (Jiang et al. 2019). rTMS was found to produce a substantial improvement in PSQI score with the highest score change in a 30-day treatment regimen. However, results observed for sham stimulation were also substantial, with 73.5% of the effect of active rTMS being produced by sham rTMS. This raises the question of whether improvement was truly due to the effect of rTMS or if placebo effect had a larger influence. It seems quite plausible that in chronic insomnia, a condition with a strong psychological component, patients may believe that their sleep will improve because of trial participation. This placebo effect could be explained by a positive feedback mechanism which has been proposed in at least one other instance (Huang et al. 2018).

One sham-controlled trial of the effect of rTMS on sleep in patients with Parkinson disease also revealed substantial placebo-related improvement on subjective questionnaires (i.e., Parkinson Disease Sleep Scale, Hamilton Depression Rating Scale, Unified Parkinson Disease Rating Scale), with sleep improvement found equally between active and sham stimulation groups (Arias et al. 2010). Interestingly, in this trial rTMS showed no changes in actigraphy parameters, which suggests that subjective measures can often yield positive results compared to objective ones.

Another sham-controlled trial with similar findings employed rTMS combined with acupuncture on chronic

insomnia while using both subjective (PSQI, ISI, sleep diaries) and objective (actigraphy) data (Zhang et al. 2018). In this trial, improvement in subjective measures were reported in both active and sham groups, though more significantly in the active group. Similar to the previous Parkinson trial (Arias et al. 2010), objective actigraphic data in this study showed no differences between groups which again suggests how rTMS trials seem to have better subjective therapeutic results than objective ones (Zhang et al. 2018).

In contrast, a third sham-controlled study measuring the effect of rTMS in sleep and mood in patients with drug abstinence found no evidence of a placebo effect, with appreciable differences between active and sham rTMS (Lin et al. 2019). However, although this study had positive PSQI changes, it was only a mild positive effect in the rTMS group. Furthermore, it used HF rTMS on patients with symptoms of depression and anxiety due to drug abstinence and therefore it was difficult to assess how much of the sleep changes resulted from an intrinsic effect of rTMS on sleep versus the experienced mood improvement.

The fourth and last sham-controlled study we examined involved the use of LF rTMS in the parietal cortex in patients who had generalized anxiety disorder with comorbid insomnia while measuring Hamilton Rating Scale for Anxiety (HRSA), and PSQI (Huang et al. 2018). In this trial, PSQI improvements were seen in active rTMS but not in sham stimulation, making this the second example of a sham-controlled trial without pronounced placebo effect. Additionally, a positive correlation was seen between improvement in the HRSA anxiety scores and PSQI scores which could suggest that sleep improvement was associated with anxiety improvement. It was questioned whether the improvement seen in both insomnia and anxiety was independent, and whether rTMS really had an intrinsic role in sleep (Rosenquist and McCall 2019). Since anxiety disorders and insomnia often manifest together, a correlation in improvement between the two conditions could be plausible.

Biological measurement outcomes

In one study of patients with primary insomnia (Feng et al. 2019), γ -aminobutyric acid (GABA) neurotransmitter levels and brain-derived neurotrophic factor (BDNF) levels in blood serum were measured as objective indicators of sleep with higher levels associated to better sleep regulation (Datta et al. 2015; Gottesman 2002). Motor-evoked potentials (MEP) were also measured to reflect cortical excitability. Analysis of results after rTMS found increased serum levels of GABA and BDNF, decreased motor evoked potentials indicative of diminished cortical excitability, and an improvement in the PSQI scale. This

study found higher BDNF and GABA levels in patients with lower (improved) PSQI scores. (Feng et al. 2019)

In another study, rTMS was compared to medication and to cognitive behavioral therapy in chronic insomnia (Jiang et al. 2013). They performed assessments with PSG and PSQI, as well as measurements on cortisol, adrenocorticotrophic hormone, thyroid-stimulating hormone, and T4/T3 levels (Jiang et al. 2013). Findings showed that individuals treated with rTMS had greater improvements in PSQI and hormonal levels, when compared to the medication and cognitive behavioral therapy groups. However, based on PSG findings, rTMS only showed superior improvement in stage 3 and rapid-eye movement sleep. Overall, this study found that the largest improvement by PSG parameters was in the medication group.

In combination with PSG and questionnaires, two studies used electroencephalogram (EEG) to examine abnormalities present in patients suffering from chronic insomnia (Sánchez-Escandón et al. 2014; Song et al. 2019). EEG recordings were done before and after rTMS sessions for comparison. In one study the frequency of EEG abnormalities decreased after rTMS treatment while PSG parameters of sleep efficiency and total sleep time improved significantly (Sánchez-Escandón et al. 2014). In the other study, EEG recordings of insomnia patients showed over-active or under-active brain regions as compared to healthy controls (Song et al. 2019). After rTMS treatment, EEG data of these areas showed moderate improvement in reversing back to normal activity level. In addition, questionnaires used in this study (PSQI, ISI, ESS) also showing improved ratings.

Discussion

This review found intriguing evidence of rTMS's potential impact in sleep disorders. While a number of studies have consistently found subjective sleep improvement after rTMS, objective sleep improvement was less consistent (see Table 1 Summary of Selected Studies). Only a minority of studies were sham-controlled (see Table 1 and supplemental Table S1) to account for placebo effect. Among sham-controlled studies, some studies indeed showed a strong placebo effect of rTMS (Jiang et al. 2019; Arias et al. 2010), while placebo effect was small in other studies (Huang et al. 2018; Lin et al. 2019). Overall, studies showed variability in study characteristics and results, with most studies applying low frequency rTMS targeting the DLPFC or parietal cortex

Limitations of recent studies

There are several limitations of this research. First, studies on rTMS and sleep are scarce. After applying exclusion criteria, only a handful of studies were found. This

is likely due to the novelty in the application of rTMS in sleep, and much more work remains to be done.

Second, the majority of studies were not sham-controlled, likely explaining the significant placebo effect in some studies (Jiang et al. 2019; Arias et al. 2010; Zhang et al. 2018). Only 5 studies employed sham stimulation in their control groups (Huang et al. 2018; Arias et al. 2010; Zhang et al. 2018; Lin et al. 2019; Rosenquist et al. 2013).

Third, a substantial number of recent studies have small sample sizes (eight of total selected studies with fewer than 30 patients). In addition, trials should strive to control for medication usage to avoid interfering with results. Finally, studies should aim to employ some form of objective measurement to evaluate if subjective improvement is mainly the result of patient expectation.

In addition, a known occurrence in previous rTMS research is the variability of results and lack of protocol standardization. Analysis of the included studies indicate how brain area, frequency, treatment duration and medication status vary. In Supplemental Table S1, sham-controlled studies were grouped for further comparison and demonstrate the heterogeneity of the studies.

Future directions

Recent findings of rTMS frequency and modulatory effects challenge the old paradigm of LF being inhibitory and HF being excitatory (Castrillon et al. 2019). Different brain locations may have different responses to the same rTMS frequency due to functional integration with the overall neural networks. More research is needed in this area.

In a recent study on MDD, a novel rTMS treatment paradigm with intermittent theta-burst stimulation (TBS) have yielded better results (Cole et al. 2019). TBS is a relatively recent protocol mode of rTMS in which magnetic pulses are applied in bursts with advantages of reduced time to complete TMS sessions from about 30–40 min to 3 min with non-inferior results (Blumberger et al. 2018; Bakker et al. 2015). This study used a novel protocol which involved multiple daily sessions, increased stimulation pulse dose, as well as guided targeting of the left DLPFC to subgenual anterior cingulate cortex circuit. This new rTMS TBS protocol resulted in 90% of patients reaching remission criteria for MDD (Cole et al. 2019).

Increasing use of TBS rTMS in MDD could provide new insights into frequency and modulatory effects on sleep (Cole et al. 2019). Indeed, previous TMS studies suggest initial nonresponders improve with further treatment sessions – with a greater and longer lasting therapeutic effects after higher total cumulative number of TMS sessions (Yip et al. 2017; Valero-Cabré et al. 2008). To our knowledge, usage of TBS rTMS in insomnia and sleep has not been reported and could be an approach worth exploring in the coming years. We theorize it

could be beneficial to use continuous TBS, a mode of theta burst delivery in which trains of pulses are delivered continuously over 40 s, and is believed to decrease cortical excitability in cortical areas for up to 50 min (Huang et al. 2005; Wischniewski and Schutter 2015). As cortical hyperexcitability can be a feature of primary insomnia, we theorize that continuous TBS could offer inhibitory effect and should be studied in primary insomnia in a sham-controlled trial.

Two of the main cortical areas of interest in previous studies for primary insomnia are the DLPFC (Feng et al. 2019; Jiang et al. 2013) and the parietal cortex (Huang et al. 2018; Li et al. 2014), which are good initial focus points for trial design as so far they appear to have been widely studied in TMS applied to insomnia and have had positive outcomes in previous trials as seen in this review. Nevertheless, as the science evolves in sleep medicine, other cortical areas or neuro circuits may appear over time as viable treatment targets, and more research is needed. For sleep pathologies other than primary insomnia, it is likely that different brain areas could be used, and exploring other rTMS settings (e.g., frequency) could also be an option depending on each pathology's specific pathophysiology.

Regarding optimal characteristics in future trials for insomnia, we propose the use of randomized sham-controlled trials with both a subjective component (i.e., questionnaires) and an objective one (i.e., polysomnography or actigraphy) to clarify if perceived rTMS sleep improvements are only due to subjective patient bias. As seen previously, sham-controlled studies showed heterogeneous results; with some studies displaying strong placebo effects (Jiang et al. 2019; Arias et al. 2010) while others were less pronounced (Huang et al. 2018; Lin et al. 2019). Due to these findings it will be important to use sham-stimulation in an attempt to account for any possible placebo effect. For comparison of sham-controlled studies and studies with improvement in objective measures, see supplemental Table S1 and S2, respectively. Based on our review, we found that studies which used both subjective and objective measures showed little or no objective measurement changes, while sleep improvement was more consistently reported by subjective measures (Nishida et al. 2017; Arias et al. 2010; Zhang et al. 2018; Jiang et al. 2013). This question of whether rTMS has an intrinsic positive effect on insomnia and sleep, demonstrated by objective measures, is what drives our interest for further study.

Conclusion

In conclusion, rTMS is a fast evolving field and holds great potential as treatment for various neurological and mental disorders. Our review on rTMS and insomnia found mixed results, with most studies showed subjective sleep improvements, while only a handful

demonstrated objective sleep improvement. The presence of placebo effect in some studies makes a strong case for the need of sham-control in future trials. However, our review suggests potential applications of rTMS in insomnia, as well as, in other sleep disorders in the future. At this time, much research remain to be done to investigate optimal modalities, brain targets and therapeutic approaches in specific sleep conditions.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s41606-020-00057-9>.

Additional file 1: Tables S1 and S2

Abbreviations

ACTH: Adrenocorticotrophic hormone; AIS: Athens insomnia scale; BDI: Beck Depression Inventory; BDNF: Brain-derived neurotrophic factor; BZN: Benzodiazepines; CDRS-R: Children's Depression Rating Scale – Revised; CGI: Clinical Global Impression; DLPFC: Dorsolateral Prefrontal Cortex; EEG: Electroencephalogram; ESS: Epworth Sleepiness Scale; GABA: Gamma aminobutyric acid; HAMD: Hamilton Depression Scale; HDRS: Hamilton Depression Rating Scale; HDS: Hamilton Depression Scale; HRSA: Hamilton Rating Scale for Anxiety; IDS-SR: Inventory of Depressive Symptoms-Self Report; ISI: Insomnia Severity Index; MEP: Motor Evoked Potential; MT: Motor Threshold; N/A: Not applicable; PDSS: Parkinson's Disease Sleep Scale; PSG: Polysomnography; PSQI: Pittsburgh Sleep Quality Index; QIDS-A17-SR: Quick Inventory of Depressive Symptomatology – Adolescent (17 Item) – Self Report; QOLIE-31: Quality of Life in Epilepsy Inventory; SAS: Self-rating Anxiety Scale; SDS: Self-rating Depression Scale; SSRI: Selective serotonin reuptake inhibitor; TSH: Thyroid stimulating hormone; TMS: Transcranial Magnetic Stimulation; UPDRS: Unified Parkinson's Disease Rating Scale

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Authors' contributions

RO conducted the literature search. RO and JC were involved in conception, analysis, and interpretation of this review. All authors were involved in the writing, revision and final approval of this article.

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Consent for publication

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Competing interests

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