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Review Article

Use of repetitive transcranial magnetic stimulation in traumatic brain injury: A systematic review and meta-analysis of randomized controlled trials

Abdulsalam Mohammed Aleid[1], Mohmmed Saud AlShammri[2], Saud Nayef Aldanyowi[1], Awn Abdulmohsen Alessa[3], Abdulmonem Ali Alhussain[3], Abbas Al Mutair[4]

[1]Department of Surgery, Medical College, King Faisal University, [2]College of Medicine, King Faisal University, [3]Department of Neurosurgery, King Fahad Hospital, Hofuf, [4]Research Center, Almoosa Specialist Hospital, Almoosa College of Health Sciences, Al Mubarraz, Saudi Arabia.

E-mail: Abdulsalam Mohammed Aleid - 225094489@student.kfu.edu.sa; *Mohmmed Saud AlShammri - 219040112@student.kfu.edu.sa; Saud Nayef Aldanyowi - saldanyowi@kfu.edu.sa; Awn Abdulmohsen Alessa - awabalessa@moh.gov.sa; Abdulmonem Ali Alhussain - abalalhussain@moh.gov.sa; Abbas Al Mutair - abbas.almutair@almoosahospital.com.sa

***Corresponding author:**
Mohmmed Saud AlShammri,
College of Medicine, King Faisal University, Hofuf,
Saudi Arabia.

219040112@student.kfu.edu.sa

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ABSTRACT

Background: Traumatic brain injury (TBI) is an injury resulting from external force exerted directly or indirectly on the skull. This is presently the major cause of mortality and disability among youth globally. Repetitive transcranial magnetic stimulation (rTMS) was proposed for the treatment of various neurological disorders such as TBI. We conducted the current systematic review and meta-analysis to investigate the efficacy of rTMS in TBI patients.

Methods: We conducted our database searching on PubMed, Scopus, and Web of Science from inception till August 2024 to look for articles that fulfil our aim. The search strategy was based on two main keywords: "Transcranial magnetic stimulation" AND "Traumatic brain injury." We conducted the pooled analysis of continuous variables using standardized mean difference (SMD) due to difference in measurement scales.

Results: Seven randomized controlled trials were included. A statistically significant improvement in cognitive function was observed after rTMS compared to control group with SMD of 0.7 (95% confidence interval [CI]: 0.25, 1.14, $P = 0.002$) with non-significant heterogeneity, and pain with SMD of −0.57 (95% CI: −1.02, −0.11, $P = 0.01$), $I^2 = 64\%$, $P = 0.04$. However, no difference was observed between the two groups regarding depression with SMD of −0.1 (95% CI: −0.54, 0.35, $P = 0.67$).

Conclusion: The use of rTMS is associated with improved cognitive functions and reduction in pain. No effect was observed regarding depression but future studies are still warranted in this important clinical field.

Keywords: Cognition, Depression, Pain, Repetitive transcranial magnetic stimulation, Traumatic brain injury

INTRODUCTION

Traumatic brain injury (TBI) is an injury resulting from external force exerted directly or indirectly on the skull. This is presently the major cause of mortality and disability among youth globally.[18] Due to economic development and an aging population, the frequency of automotive traffic accidents is rising, leading to an annual increase in the incidence of TBI.[1,39]

TBI is acknowledged as a significant global health issue that remains unresolved on an international scale. Therapeutic interventions aimed at aiding individuals with craniocerebral injuries in regaining consciousness and reintegrating into society have garnered heightened interest.[36] At present, research and treatment protocols for TBI mostly concentrate on the emergency management of severely unwell individuals. Initially, the objective was to diminish mortality.[25,51] At present, consciousness disorders represent a significant challenge in rehabilitation and recovery following TBI.[29,51] Following a severe TBI, the majority of patients often enter a persistent vegetative state (VS).[31] VS denotes a significantly compromised state of consciousness following brain injury, characterized by the absence of clinically detectable consciousness. The typical arousal cycle is generally associated with a state that is partially asleep and partially awake, like the standard consciousness cycle. The activities of the brainstem and thalamus remain relatively intact, whereas the functional connectivity of the cerebral cortex is typically impaired or absent.[40]

Chronic pain commonly occurs in patients with moderate TBI, with prevalence reported as high as 75%.[44,57] Chronic pain is characterized as enduring or recurring pain that last for over 3 months and is linked to considerable mental suffering or substantial functional impairment.[29] Chronic pain following TBI results in inadequate functional recovery, restricted activities of daily living, and diminished quality of life.[44] Central pain, a kind of pain resulting from TBI, is induced by a lesion or dysfunction within the somatosensory nerve system of the central nervous system.[59] It manifests as neuropathic pain, typically characterized by a burning sensation and hyperpathia.[13,47]

Transcranial magnetic stimulation (TMS) is an Food and Drug Administration-approved therapy for serious depression that is resistant to medicine in the United States.[7] The medication is licensed for mitigating migraine headaches and may offer an alternative method for headache prevention, treatment, and rehabilitation for the expanding number of TBI patients.[17,37] High-frequency (>1 Hz) repeated TMS (rTMS) applied to the prefrontal cortices has shown efficacy in alleviating depression and migraine headaches.[4,41] Furthermore, a prior study indicated that the treatment's placement might contribute to alleviating post-concussive symptoms.[32] Therefore, we conducted the current systematic review and meta-analysis to investigate the efficacy of TMS in TBI patients.

MATERIALS AND METHODS

We used the guidelines of Cochrane handbook for systematic reviews and meta-analysis in addition to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines to conduct this study.[42]

Database searching

We conducted our database searching on PubMed, Scopus, and Web of Science from inception till August 2024 to look for articles that fulfil our aim. The search strategy was based on two main keywords: "Transcranial magnetic stimulation" AND "Traumatic brain injury." The resulting articles were gathered together and uploaded to Rayyan.[48]

Eligibility criteria and screening

We included articles which were randomized controlled trials (RCTs) investigating the use of rTMS in TBI patients. We excluded reviews, observational studies, and case reports. We conducted the title and abstract screening to find whether the articles matched our criteria or not. This process was followed by full-text screening to ensure that the included articles from the previous step were eligible for inclusion.

Data extraction and outcome measures

We extracted the baseline data of the included studies including study ID, groups, sample size, age, gender, and comorbidities of the included patients. Regarding the outcomes, we extracted the following: pain scales at baseline and after treatment including numeric pain rating scale, McGill Pain, Debilitating headache exacerbation composite score, and Headache Impact Test-6, depression including Hamilton Depression Rating Scale, Patient Health Questionnaire-9, and Montgomery-Asberg Depression Rating Scale, and cognition using coma recovery scale revised, and Montreal Cognitive Assessment.

Risk of bias assessment

This process was conducted using the Cochrane's risk of bias assessment 2 tool (Rob-2).[55] Random sequence creation, allocation concealment, participant and staff blinding, outcome assessor blinding, incomplete outcome data, selective result reporting, and additional bias (fund and baseline balance) were the components of the evaluation. Every field was classified as having a low risk of bias, a high risk of bias, or having some bias issues.

Statistical analysis

All the statistical procedures were done using Review Manager software version 5.4.[52] We conducted the pooled analysis of continuous variables using standardized mean difference (SMD) due to difference in measurement scales. We used the random effect model for heterogeneous outcomes, and the fixed effect model for homogeneous outcomes, at confidence interval (CI) of 95%, and *P*-value of 0.05. I^2 was utilized to measure the heterogeneity at *P*-value of 0.05.

RESULTS

Screening results

After searching the databases, the search strategy yielded a total of 199 articles. We removed 77 duplicates and conducted title and abstract screening for 122 articles. We excluded a total of 112 articles and conducted full-text screening for the remaining 10 articles to include 7 of them in the meta-analysis.[10,15,24,32,34,54,56] [Figure 1].

Risk of bias assessment

According to Rob-2, five studies had low risk of bias, one had high risk, and one had some concerns [Figure 2].

Baseline characteristics

We included a total of seven RCTs comparing rTMS with sham rTMS. Some comorbidities were reported such as headache, depression, and cognitive impairment [Table 1].

Statistical analysis

A statistically significant improvement in cognitive function was observed after TMS compared to control group with SMD of 0.7 (95% CI: 0.25, 1.14, P = 0.002) with non-significant heterogeneity, and pain with SMD of −0.57 (95% CI: −1.02, −0.11, P = 0.01), I^2 = 64%, P = 0.04. However, no difference was observed between the two groups regarding depression with SMD of −0.1 (95%CI: −0.54, 0.35, P = 0.67) [Figures 3-5].

DISCUSSION

Main findings

The current systematic review and meta-analysis aimed to demonstrate the effectiveness of TMS in TBI patients. TMS was observed to be effective regarding the reduction in pain and increase in cognition. However, no significant difference was observed between patients who received TMS and those who did not receive regarding the effect on depression.

Cognition

The manifestation of consciousness disturbance following head trauma is associated with ischemic-hypoxic necrosis of cerebral tissue. Cerebral ischemia and hypoxia directly induce the cessation of function in specific brain regions; for example, the cerebral cortex fails to activate efficiently, resulting in an imbalance within the neural network associated with consciousness. Cognition and awakening are often regarded as correlated with consciousness. Hinter-Buchner

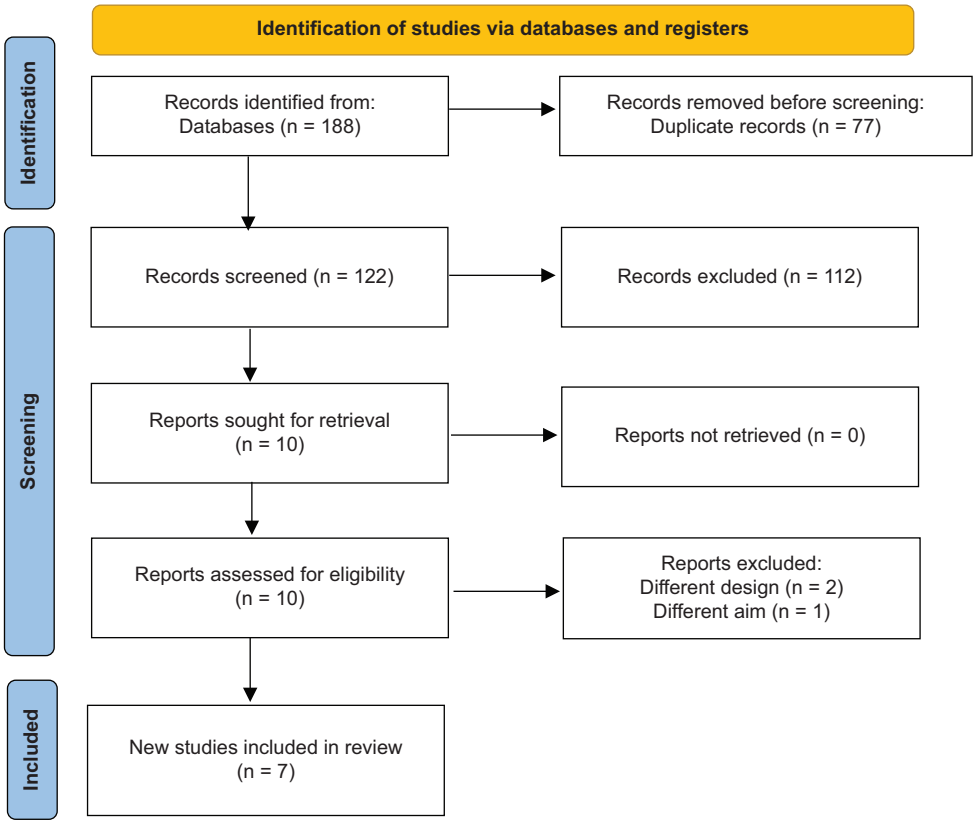

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of searching process and screening.

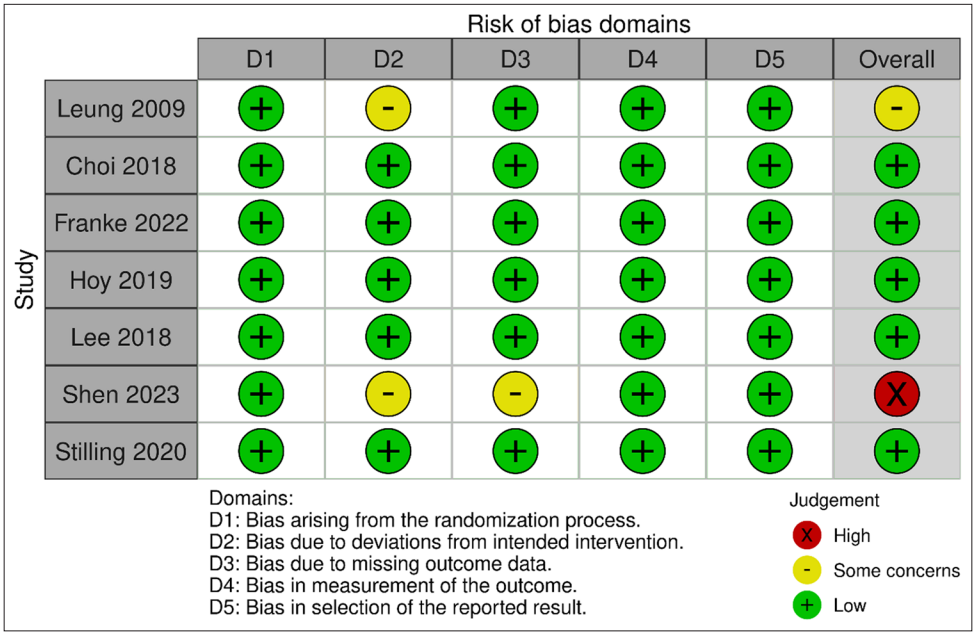

Figure 2: Risk of bias assessment of randomized controlled trials using Rob-2 tool.

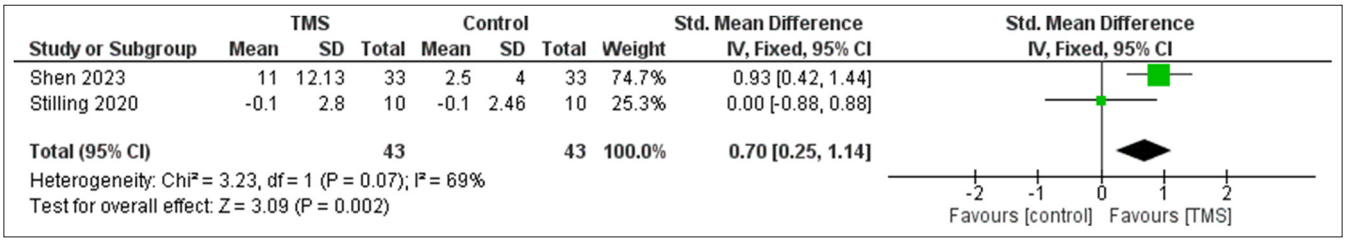

Figure 3: The effect of transcranial magnetic stimulation on cognition. TMS: Transcranial magnetic stimulation, SD: Standard deviation, CI: Confidence interval, IV: Inverse variance, Figures in bracket indicate 95% confidence intervals

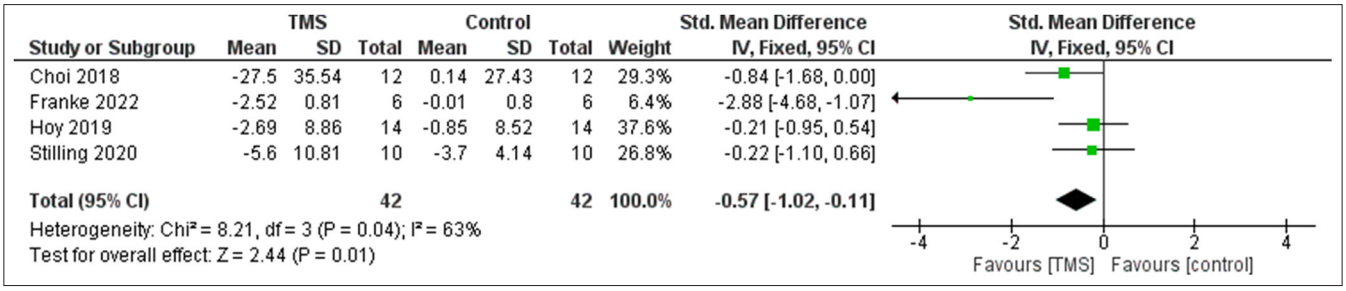

Figure 4: The effect of transcranial magnetic stimulation on pain. TMS: Transcranial magnetic stimulation, SD: Standard deviation, CI: Confidence interval, IV: Inverse variance, Figures in bracket indicate 95% confidence intervals

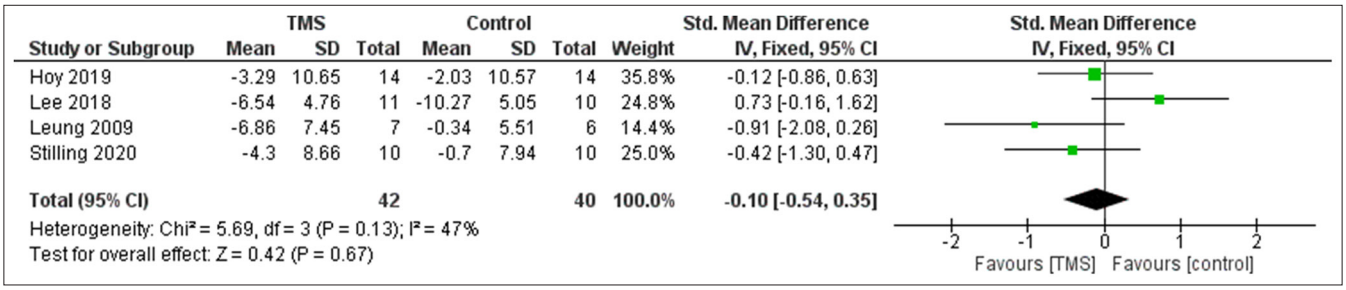

Figure 5: The effect of transcranial magnetic stimulation on depression. TMS: Transcranial magnetic stimulation, SD: Standard deviation, CI: Confidence interval, IV: Inverse variance, Figures in bracket indicate 95% confidence intervals

Table 1: Baseline characteristics of the included studies.

TMS	Control	Sample size		Age, mean (SD)		Male, *n* (%)		Associated comorbidities
		TMS	Control	TMS	Control	TMS	Control	
rTMS	sham rTMS	12	12	41 (14)	41 (12)	10 (83.33)	11 (91.66)	Headache
rTMS	sham rTMS	11	10	41.27 (10.04)	51.80 (13.38)	7 (63.63)	3 (30)	Depression
rTMS	sham rTMS	7	6	42.42 (11.32)	41.33 (11.02)	5 (71.42)	4 (66.67)	Depression, cognitive impairment
rTMS	sham rTMS	33	33	-	-	26 (78.78)	19 (57.57)	Cognitive impairment
rTMS	sham rTMS	10	10	40.3 (11.2)	31.6 (10.4)	1 (10)	1 (10)	Headache, post-concussion symptoms
rTMS	sham rTMS	6	6	43.2 (9.7)	42.0 (8.4)	3 (50)	3 (50)	Chronic central pain
rTMS	sham rTMS	14	14	45.07 (11.31)	46.07 (8.92)	13 (92.9)	11 (78.6)	Cognitive concerns, executive function, positivity, and anxiety

TMS: Transcranial magnetic stimulation, rTMS: Repetitive transcranial magnetic stimulation, SD: Standard deviation

designates these two as the constituents of awareness and the switching mechanism. The content of consciousness pertains to the advanced functions of the cerebral cortex, encompassing behavioral responses such as memory, cognition, orientation, motor skills, speech, and audiovisual processing. The mechanisms regulating consciousness can stimulate the cerebral cortex, sustain arousal, and preserve wakefulness. Consequently, the efficient activation of the cerebral cortex and the regulation of the brain–brain functional network are crucial for the emergence of disorders of consciousness. High-frequency rTMS targets the afflicted cerebral hemisphere and directly enhances its excitability.[14,46] Research has suggested that the wakefulness-promoting impact of high-frequency rTMS may facilitate axonal repair in neurons within the afflicted hemisphere, potentially reactivating dormant neurons or reconnecting isolated brain regions.[5,60] Research indicates that rTMS may activate or inhibit the functions of cortex-cortex and cortical-subcortical neural networks[33] and modulate cortical plasticity,[9] therefore altering perception. Piccione *et al.* documented that a patient in a minimally conscious condition for 5 years received high-frequency stimulation at 20 Hz.[50] Following 100 rTMS stimulations throughout ten sequences, they observed an increase in the frequency of patient-specific meaningful actions. The EEG data demonstrated enhancements, indicating that rTMS can augment the attention and responsiveness of patients with little consciousness. Pape *et al.* demonstrated that after 6 weeks of high-frequency rTMS treatment for patients with severe brain injury in a VS, there was an enhancement in the brainstem auditory-evoked V wave latency and the inter-wave difference between the I–V latency waves.[38] The conventional method for site selection involves stimulating the impaired region of the brain to subsequently activate the comparable functional area on the affected side, which positively influences recovery. Research indicates that rTMS activates the prefrontal cortex on the damaged hemisphere of the brain to facilitate patient recovery from a VS to a minimally conscious state (MCS),[38] or stimulates the M1 region to assist patients in progressing from an MCS– to an MCS+.[50]

Furthermore, some perspectives suggest that rTMS alters cortical metabolism and cerebral blood flow by modulating the excitability of the local cerebral cortex, influencing neurotransmitters and their transmission, enhancing the reversibility of damaged cells, and facilitating the recovery of brain function.[51,58] Literature indicates that rTMS stimulation of the right prefrontal lobe in depressed patients results in increased local cerebral blood flow; in healthy volunteers, significant alterations in somatosensory evoked potentials (SSEPs) and local cerebral blood flow occur following single-phase rTMS stimulation.[25,29] Research indicates that early rTMS technology primarily serves to assess the motor evoked potentials in individuals with reduced consciousness.[51] Numerous research has demonstrated that rTMS is beneficial for assessing the return of potential motor skills in individuals with reduced consciousness, although it is also utilized for evaluating the recovery of consciousness itself. Effective evidence about the extent and prognosis remains insufficient.[31,40]

Depression

In a prior study, EEG data taken a median of 4 h post-rTMS stimulation revealed a power increase in delta, theta, and alpha waves, which associated with clinical improvement in depression.[45] Franke *et al.* noted a comparable trend with strong connections between depression and enhancements in executive function symptoms and delta power rise; however, these correlations were nonsignificant, potentially due to the small sample size of complete EEG data, which may have resulted in a type 2 error.[15] This study offers supporting evidence that delta-band oscillations influence emotional and psychological states, potentially serving as significant biomarkers for the therapeutic effects of rTMS, which seem to focus on well-being. This aligns with extensive evidence connecting delta oscillations to approach/avoidance mechanisms, including motivation,[30]

reward,[8] and placebo analgesia.[12] Moreover, delta waves augment alongside cognitive processes related to interior representation, specifically inward-directed attention and working memory.[19]

Pain

rTMS may serve as an advantageous therapeutic intervention for the management of chronic central pain resulting from moderate TBI and for enhancing quality of life. In 2006, Hirayama *et al*. enrolled 20 patients suffering from intractable neuropathic pain and performed high-frequency rTMS stimulation on the primary motor cortex M1, postcentral gyrus, premotor region, and supplementary motor area. They determined that M1 is the exclusive target capable of alleviating neuropathic pain.[21] The mechanism by which rTMS stimulation alleviates pain remains inadequately defined; nevertheless, multiple potential central mechanisms for the pain-reducing actions of rTMS on the M1 exist. Prior functional magnetic resonance imaging investigations demonstrated that rTMS administered to the M1 generates modifications in the activity of cortical and subcortical areas associated with pain processing and modulation, including the medial thalamus, anterior cingulate, orbitofrontal cortices, and periaqueductal gray matter.[2,43] We assert that rTMS can alter aberrant thalamocortical excitement within the sensory system, initiating cascades of analgesic synaptic events in several pain-related regions. Furthermore, rTMS of the M1 was believed to alleviate neuropathic pain by activating descending inhibitory circuits at the dorsal horn level.[35] Another theory is that rTMS alleviated pain by enhancing blood circulation in the afflicted region. Cerebral blood flow diminishes during chronic pain, while rTMS of M1 enhances cerebral blood flow in patients with neuropathic pain as evidenced by positron emission tomography.[16,53] Furthermore, an animal investigation revealed that cortical stimulation's anti-nociceptive effects altered neuronal activity in the periaqueductal gray matter linked to pain processing.[49] Furthermore, de Andrade *et al*. indicated that rTMS administered to the M1 affects the endogenous opioid system, which may subsequently regulate different forms of pain.[11] Furthermore, diffusion tensor tractography analysis was conducted for the precise diagnosis of central pain. Patients exhibiting reduced fractional anisotropy (FA) and tract volume (TV) values of the spinothalamocortical tract (STT) on the painful side were enrolled. The reduction in FA values stemmed from the degradation of directional microstructures, including axons, myelin, and microtubules.[3] Deterioration of neuronal microstructures within a neural tract may lead to a reduction in TV.[3] A reduction in FA and TV values signified impairment to the STT.[10] An STT lesion is recognized as a requisite condition for central pain following a stroke.[6,22,61] Similarly, multiple prior investigations indicated that the onset of central pain following TBI is attributed to damage to the spinothalamic tract.[26,28,61] Numerous prior studies have evidenced the beneficial impacts of rTMS on the motor cortex (M1 or dorsolateral prefrontal cortex) in managing central pain post-stroke, with effects lasting roughly 2–4 weeks.[20,23,27]

The present systematic review and meta-analysis is limited by the variability in measurement scales and the small sample size in most of the outcomes. We recommend future large size RCTs to validate our findings.

CONCLUSION

The use of rTMS is associated with improved cognitive functions and reduction in pain. No effect was observed regarding depression but future studies are still warranted in this important clinical field.

Authors' contributions: All authors substantially contributed to the study, including drafting the manuscript, conducting literature searches, analyzing data, critically reviewing the manuscript, and approving the final version for publication.

Ethical approval: The Institutional Review Board approval is not required.

Declaration of patient consent: Patient's consent was not required as there are no patients in this study.

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