Therapeutic use of transcranial magnetic stimulation (TMS) for people with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS): A scoping review

Nilihan E.M. Sanal-Hayes[1], Kate Slade[2], Marie Mclaighlin[3], Paige Metcalfe[4], Ethan Berry[5], Eleanor J. Thornton[1], Lawrence D. Hayes[2*]

[1]School of Health and Society, University of Salford, Salford, UK

[2]Lancaster Medical School, Lancaster University, Lancaster, UK

[3] School of Education and Sport, University of Edinburgh, Edinburgh, UK

[4] Faculty of Science and Engineering, University of Manchester, Manchester, UK

[5] Sport and Physical Activity Research Institute, School of Health and Life Sciences, University of the West of Scotland, Glasgow, UK

*** Correspondence:**
Lawrence D. Hayes
l.hayes4@lancaster.ac.uk

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1 Abstract

Background: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is characterised by persistent fatigue, cognitive issues, headaches, disrupted sleep, myalgias, arthralgias, post-exertional malaise (PEM), and orthostatic intolerance. Transcranial magnetic stimulation (TMS) is a non-invasive method using magnetic fields to stimulate nerve cells in the brain which shows therapeutic potential for conditions like depression, chronic pain, and cognitive impairments. However, the National Institute for Health and Care Excellence (NICE) does not recommend TMS for ME/CFS symptom management, making exploration of its therapeutic potential for people with ME/CFS (PwME) a logical step.

Objective: Our review aimed to systematically search the published literature on therapeutic use of TMS for PwME, map study characteristics and methodologies, and offer recommendations to advance research in this area.

Methods: We conducted a systematic literature search of CINAHL Ultimate, MEDLINE, ScienceDirect, and Scopus from January 1st 1985, to February 16th 2024. Only literature in English was included.

Results: Following initial database searches, 1,040 articles were identified and a total of three articles met inclusion criteria and were included. This review indicated that, whilst studies indicate positive findings for fatigue-related symptoms and functional abilities, the evidence for rTMS being a promising non-invasive treatment for ME/CFS is limited by small-sample pilot data and the critical absence of control groups within the current literature.

Conclusions: Larger cohorts, control groups, and standardised protocols are needed to improve generalisability and optimise reporting. Future research on rTMS in PwME should focus on feasibility, acceptability, and longer follow-up durations to track symptom improvement.

2 Introduction

2.1 Rationale

Transcranial magnetic stimulation (TMS) is a type of non-invasive brain stimulation method, which uses a coil placed on the scalp to deliver magnetic pulses. Through the process of electromagnetic induction, the discharge of the pulse creates a magnetic field which induces an electrical current in the cortex beneath the coil [1]. TMS can be used to exert acute or prolonged effects depending on various parameters, including the intensity of the stimulation, the shape and orientation of the coil, and the frequency and pattern of pulses. Single pulse TMS is typically used to investigate brain function. For example, a single pulse of TMS applied over a specific region of the primary motor cortex (M1) can elicit motor evoked potentials (MEPs) in the associated muscle, recorded using electromyography (EMG) [2]. The amplitude and latency of the MEP can be used to infer the excitability of the motor cortex [3]. Conversely, repetitive TMS (rTMS) can induce changes in neuronal activity which last beyond the stimulation period [4]. Depending on the frequency and specific pattern of the repetitive pulses, rTMS can exert inhibitory or excitatory effects on neural activity. Multiple sessions of repetitive protocols have been investigated for the treatment of psychiatric and neurological disorders, due to potential long-lasting effects on neural plasticity [5,6].

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a complex, multisystem disorder with poorly understood aetiology, affecting nearly 0.9% of the global population [7,8]. Symptomology is broad, heterogenous, and often overlapping with many other conditions making diagnosis difficult [9]. Despite its significant impact on quality of life and functional capacity, the pathophysiology of ME/CFS remains undetermined, hindering development of efficacious treatments. However, mounting evidence suggests neurological abnormalities play a role in the manifestation of ME/CFS symptomatology, particularly cognitive impairments, fatigue, and post-exertional malaise (PEM) [9–13]. PEM, a key symptom of ME/CFS, is associated with nervous system dysfunction [9,10,13], including autonomic nervous system dysregulation [14], neuroendocrine disturbances (particularly within the hypothalamic-pituitary-adrenal axis) [15], and immune system abnormalities, such as elevated pro-inflammatory cytokines that lead to neuroinflammation [16]. PEM describes the worsening of symptoms following physical, cognitive, or emotional exertion, often requiring an extended recovery period [13,17–19].

Repetitive TMS has shown promise as a therapeutic intervention for various neurological and psychiatric conditions such as depression, chronic pain, and cognitive impairments. Repetitive TMS has been used to treat symptoms analogous to ME/CFS [20–25]. The mechanism by which rTMS is suggested to induce long-term cortical changes, i.e. increased or reduced cortical excitability, may be

akin to long-term potentiation (LTP) or long-term depression (LTD), respectively[26]. These are forms of activity-dependant plasticity which result in enhanced, or reduced, synaptic transmission. Repetitive TMS is suggested to induce LTP- and LTD-like changes in the brain, through enhancing or disrupting neural activity. In ME/CFS, there is evidence for structural, functional, and metabolic neural changes, including reduced grey matter and metabolic dysregulation in frontal cortices[27,28]. Through possible LTP-like changes in plasticity, rTMS may be an effective method for targeting neural systems which may be dysregulated in certain clinical disorders, such as ME/CFS. However, at present, rTMS is not a recommended symptom management strategy by the National Institute for Health and Care Excellence (NICE), naming only 'energy management' in the 2021 update, and removing graded exercise therapy [19]. Therefore, as rTMS has been used to treat symptoms experienced by people with ME/CFS (PwME) in other conditions, it would be pragmatic to investigate rTMS as a therapy for PwME. By modulating cortical excitability and neural plasticity, rTMS could alleviate symptoms associated with ME/CFS.

2.2 Objectives

As a result of the therapeutic potential of rTMS, and the rapidly improving technology, we aimed to conduct a scoping review assessing rTMS in PwME. Our three specific objectives of this scoping review were to 1) conduct a systematic search of the published literature concerning rTMS in PwME, 2) map study characteristics and methodologies, and 3) provide recommendations for the advancement of the investigative area.

3 Methods

3.1 Protocol and Registration

The review was not preregistered, as the Arksey and O'Malley framework[29] does not require it. This review was conducted and reported in accordance with the preferred reporting items for systematic reviews and meta-analyses extension for scoping reviews (PRISMA-ScR) guidelines [30].

3.2 Eligibility Criteria

Studies were included if TMS was employed as a potential intervention or treatment. Studies were excluded if the index measurement was conducted using EEG or laser stimulation; the paper did not include PwME; the paper was not an original article (i.e., utilised a database, or data from a secondary source); the paper was a review; there was no abstract or full text available.

3.3 Literature Search

We conducted a systematic literature search of CINAHL Ultimate, MEDLINE, ScienceDirect, and Scopus from January 1st, 1985, to February 16th 2024, with the following search key: TI ((ME OR CFS OR MECFS OR ME/CFS OR CFS OR “myalgic encephalomyelitis" OR "chronic fatigue syndrome” OR encephalomyelitis)) OR AB ((ME OR CFS OR MECFS OR ME/CFS OR CFS OR “Myalgic encephalomyelitis" OR "chronic fatigue syndrome” OR encephalomyelitis)), which were developed through examination of previously published original and review articles. Only literature written in English were included.

3.4 Study Selection

Studies were identified by the fifth author (E.B.) and evaluated by N.E.M.S-H. and E.T. independently and compared in an unblinded and standardised manner. Once database searches were complete, all studies were downloaded to a single reference list (Zotero software [version 6.0.26]) and duplicates were removed. The remaining articles were exported to the Rayyan application for further duplication removal and then screening [31]. First, titles and abstracts were screened for eligibility (N.E.M.S-H. and E.T.). Full text articles were then read and coded in relation to exclusion criteria, utilising “tags” in Rayyan, which was reviewed by the first author (N.E.M.S-H.) and third author (M.M.). This process involved a thorough assessment of all eligibility criteria with authors N.E.M.S-H and M.M. confirming inclusion and exclusion. Disagreements were addressed by a third reviewer (L.D.H.).

3.5 Data Extraction

Data extracted from each study included author(s) and publication year, sample size, participant age, time since diagnosis, ethnicity and gender, diagnostic criteria, comorbidities, medication control, treatment length, study recruitment and setting, location, TMS parameters utilised in terms of frequency, number of pulses, number and duration of TMS sessions, coil placement, orientation and brain region targeted, participant supervision during and after TMS, and primary outcome measures.

3.6 Outcome Measures

Our primary focus was on studies that assessed the therapeutic impact of TMS in PwME. (**see; Table 2**).

4 Results

4.1 Study selection

Following initial database searches, 1,040 articles were identified. Duplicates were then removed before the remaining articles titles and abstracts were exported to the Rayyan application for further duplicate removal and screening [31]. Two duplicates were removed so 1,038 titles and abstracts were screened. These were screened for inclusion, with 1,020 removed, resulting in 18 full text articles being screened. Of these fifteen were excluded, and therefore a total of three articles were included (**Figure 1**).

*****INSERT FIGURE 1 NEAR HERE*****

Figure 1. Records identified through reference list searching.

4.2 Study characteristics

The included studies shared several commonalities in design, all studies employed a before-after studies with no control group design as defined by NIH [32], and were conducted in specifically in Japan which is considered a high-income setting, which may have implications for interpreting the findings. Sample sizes ranged from 7 to 30 participants, with two studies focusing on ME patients and one on CFS patients. All studies reporting participant age or age range, though only one study provided gender distribution, indicating a predominance of female participants. Ethnicity was not reported in any of the studies, two studies documented time since diagnosis, while the third omitted this detail. Reporting on comorbidities and medication use was inconsistent, with only one study specifying the absence of comorbidities and another noting medication use prior to the intervention.

All studies reported diagnostic criteria, two reported US Centers for Disase Control and prevention (CDC) criteria, and one reported International Consensus Criteria.

4.3 Treatment length, Recruitment and Study Setting

Treatment lengths were diverse for all reported studies, ranging from six sessions over three days to ten sessions over two weeks, reflecting differing intervention protocols. Recruitment strategies and study settings were consistently reported, though some variation was noted. Two studies recruited participants through university hospitals, one through a clinic setting, and while two identified the study setting as a university hospital, one specified the Department of Neurology.

4.4 rTMS Intensity and Frequency

All studies reported rTMS parameters, which varied across studies. Two studies employed 10Hz high-frequency rTMS, delivering 10-second trains of 100 pulses with 50-second intervals between each train in two sessions per day. In one of the two studies, 2,500 pulses were delivered per 25-minute session over three days (15,000 pulses in total), in the other 1,800 pulses were delivered per 18-minute session over 3-4 days (10,800-14,400 pulses in total). In both studies, the stimulation intensity was reported as 90% of the resting motor threshold (rMT), but this was reduced in one study to 80% rMT for two participants. The third study employed intermittent Theta Burst Stimulation (iTBS), in which 600 pulses are administered in bursts of three pulses (at 50 Hz) at 200-ms intervals in 2-second trains which are repeated every 10-secords for 190-seconds. The stimulation intensity was planned to be 80% rMT but was adjusted for each participant based on tolerance.

4.5 Coil Placement and Hardware

All studies targeted the dorsolateral prefrontal cortex (DLPFC) as the stimulation site, with some variability in localisation methods. In two studies, either the left or right DLPFC was targeted depending on the participant's dominant hemisphere. In one of these studies, electroencephalography (EEG) electrode positions were reportedly utilised as specific target locations, electrode position F3 was the target location in right-hand dominant participants and F4 was the target location in left-hand dominant participants. In a third study, MRI-guided neuronavigation was reportedly utilised to target the left DLPFC, though no coordinates were reported. In the same study, the left primary motor cortex (M1) was also targeted, the location of which was reportedly determined by observing TMS-

induced muscle twitches in the right-hand FDI muscle. All studies used figure-of-8 coils, with two employing the MagPro R30 system and one the MagStim Rapid 2.

4.6 Outcome Measures and Findings

The studies reported diverse outcome measures. Two studies utilised Visual Analogue Scale (VAS), and Brief Fatigue Inventory (BFI) for fatigue symptoms, whilst another one employed Performance status (PS) scoring for restricted activities of daily living, a conventional active 10-min standing test, neurologic testing for disequilibrium, the digital palpation for 18 specified tender points, and grip power estimation.

Findings varied across studies. One study found that after the first rTMS session, two patients experienced a >30% reduction in VAS scores. At discharge, five patients showed a >30% decrease, and three had a >50% decrease. Four patients maintained a >30% reduction one week post-discharge, with three continuing this improvement two weeks later. The mean VAS score decreased by 17% one hour after the first session, with significant reductions at discharge and one week post-discharge. Additionally, six patients showed a reduction of more than one point in their BFI scores at discharge. Findings from this study indicate that high-frequency rTMS is safe, with only two patients experiencing mild adverse events. Fatigue symptoms improved significantly by discharge, with these improvements lasting at least one week post-discharge. This study is the first to demonstrate the safety, feasibility, and clinical effectiveness of high-frequency rTMS over the DLPFC in CFS patients.

Another study found that 20 patients showed at least a two-point decrease on the PS for restricted activities of daily living, while ten patients had no change. Prior to intervention, 40% (12/30) of patients had orthostatic intolerance (OI), with 92% of those reporting disequilibrium. After intervention, 83% (10/12) were able to complete the standing test. Before treatment, 57% (17/30) had disequilibrium, and 65% of these also had OI. After treatment, 88% (15/17) of disequilibrium cases improved, with all showing better PS scores. The remaining two patients still experienced disequilibrium. In the fibromyalgia (n=8) and neuropathic pain (n=2) group, 70% (7/10) showed a significant decrease in tender points (≥4). Additionally, four patients with grip strength <10 kg saw improvement, with two (50%) increasing to >10 kg after rTMS. Results from this study showed that rTMS had favourable effects, with significant reductions in median PS scores and tender point counts

post-treatment. Additionally, both orthostatic intolerance and disequilibrium were notably less common after treatment.

In the final study, patients that were divided into mild (n=13) and severe (n=9) groups showed no differences in the improvement rates at discharge or two weeks post-discharge. Both groups showed significant reductions in BFI and VAS scores at discharge compared to baseline. Two weeks post-discharge, BFI and VAS scores were significantly lower than before the first rTMS session in 19 patients, and no significant correlation was found between baseline BFI severity and improvements in BFI or VAS scores. Overall, the results from these studies suggest that high-frequency rTMS is both safe and effective for treating fatigue symptoms in CFS and ME patients. The treatment led to significant improvements in fatigue, with effects lasting at least one-week post-treatment. It also reduced tender points, orthostatic intolerance, and disequilibrium. Findings from this study highlight that rTMS improved fatigue symptoms in some ME patients, with benefits lasting at least two weeks post-discharge, regardless of baseline fatigue severity.

Overall, the findings from two studies demonstrated that high-frequency rTMS is both safe and effective for treating fatigue symptoms in CFS and ME patients. The treatment resulted in significant improvements in fatigue, with effects lasting up to at least one week post-discharge. Finding from the remaining study demonstrated that rTMS led to significant reductions in PS scores and tender point counts, while also reducing the prevalence of orthostatic intolerance and disequilibrium in ME patients.

*****INSERT FIGURE 2 NEAR HERE*****

Figure 2. Bubble plots of changes in fatigue (A, B), stand test, disequilibrium, neuropathic pain, muscle weakness, and physical performance (C) over time. X-axis time points 1-4 represent 1 hour after TMS, discharge, 1-week after TMS treatment, 2-weeks after TMS treatment, respectively. Y-axis display percentage of patients improved (A, C) and improvement in outcome score (B). Size of bubbles represent % improvement in outcome score (A) and number of patients improved (C), with plot B having no available data to differentiate size of bubbles. Individual plot legends explain the representation of the colour of bubbles.

a

5 Discussion

This scoping review provides the first systematic overview of existing literature regarding therapeutic use of TMS for PwME, with the aim of mapping methodologies and thus facilitating improvements in future potential treatment. It is encouraging to note that the majority of studies examined outcome variables aligned with the Core Outcome Measures in Effectiveness Trials (COMET) initiative and the minimum data set outlined by the British Association of Clinicians in ME/CFS (BACME) [33,34]. However, PEM was not evaluated in any study, possibly due to difficulty in recording and analysing. PEM analysis can only be achieved with prospective symptom tracking and longitudinal data analysis which was absent in the included studies herein. Also, to date, there is no robust measure of PEM as the commonly used questionnaire, the DePaul Symptom Questionnaire – Post-Exertional Malaise (DSQ-PEM [18] was developed to be diagnostic rather than track changes over time.

Studies examined outcome variables such as pain, fatigue, performance status for restricted activities of daily living, active 10-min standing test, neurologic testing for disequilibrium, digital palpation for 18 specified tender points and grip power estimation. Results indicated rTMS was generally well tolerated; in one study only two out of seven patients experienced mild adverse events, nausea, vomiting, headache, and acute hypotension due to a vasovagal reflex during the first session [35]. Regarding primary outcomes, fatigue showed significant improvement by discharge, with effects sustained for at least one-week post-discharge. This was the first study to demonstrate safety, feasibility, and explore clinical potential of high-frequency rTMS over the DLPFC in seven CFS patients [35]. Another study reported positive effects on performance scores, orthostatic intolerance, disequilibrium, neuropathic pain, and muscle weakness in a high proportion of ME patients [36]. In the final study, rTMS improved fatigue in 22 ME patients regardless of baseline severity, suggesting its promise as a novel therapeutic approach for ME symptom management [37]. In terms of tolerability, these findings provide insight into the application of high-frequency rTMS in a small cohort, establishing a low incidence of adverse events [35]. Studies did not report any serious adverse effects, reinforcing the notion of rTMS as a safe intervention. In terms of efficacy across symptoms, these findings [35] focused primarily on fatigue and pain, while Miwa and Inoue [36] expanded the scope to include orthostatic intolerance and neuropathic pain, indicating that rTMS may have potential for addressing symptoms associated with ME. Yang et al. [37] specifically noted improvements in fatigue regardless of severity, suggesting that rTMS may be universally beneficial across varying levels of symptom intensity. In terms of sample size and generalisability, these studies had small sample sizes (7-30 patients), which raises questions about the generalisability of their findings. Additionally, all of these studies were conducted in Japan, which raises a key concern about the generalisability of the

findings, as the differences in how ME/CFS is diagnosed and treated in Japan compared to other countries are not addressed or mentioned in the studies. Therefore, there may be specific factors, beyond chance, that explain why TMS has been considered in Japan but not in other countries.

Together, these studies suggest that rTMS may be a promising non-invasive treatment option for ME/CFS patients, particularly for managing fatigue and related symptoms, though future controlled studies are required to confirm this. While Kakuda et al. [35] laid the groundwork for understanding its safety and initial efficacy, the subsequent two studies expanded the understanding of rTMS's potential impact on various symptoms and functional capacities. The collective evidence supports further investigation into the use of rTMS as a viable therapeutic approach in this patient population, particularly in larger, more diverse cohorts to enhance the generalisability and applicability of findings. Moreover, current evidence highlights the need for a feasibility study to determine its applicability to a wider range of individuals with varying ME/CFS severity. We were struck by the fact that, despite extensive therapeutic use of rTMS in other populations, only three studies considered PwME. Concerningly, there were no randomised controlled trials (RCTs) to support rTMS's use for PwME. We are uncertain as to why this research area has not progressed along the translational pathway [38].

There were no RCTS included in this review, possibly due to significant participant burden. For example, Kakuda et al. [35] hospitalised participants for five days to receive the treatment. Miwa and Inoue [36] hospitalised participants for 2 weeks, and Yang et al. [37] hospitalised participants for 3-4 days. Kakuda et al. [35] followed up after 2 weeks, Miwa and Inoue [36] after less than a week, and Yang et al. [37] after 2 weeks. This implies that participants in the Kakuda et al. [35] study and Yang et al. [37] study, were in hospital for roughly half of the follow up period. To ask a patient to commit this amount of time for treatment is a significant commitment. Participants in the Miwa and Inoue [36] study were hospitalised for two weeks and the follow-up was done within a week of discharge. We suggest the follow-up period in these studies has not been long enough to determine lasting effects, or there are no lasting effects which would render rTMS potentially unfeasible in a natural setting. Indeed, studies which investigated the treatment potential of rTMS for depression utilised outpatient procedures [5,6] , this is also the recommendation within the NICE-approved rTMS guidelines for depression treatment [39] . To address this concern, we propose longitudinal serial monitoring (ideally remotely to reduce burden) could elucidate time course of symptom improvement and eventual return to baseline. Secondly, with this information, patient and public involvement and engagement (PPIE) is necessary to explore acceptable burden versus benefits. By this we mean, would patients give up 5

311 days for treatment (burden), for 3 weeks of symptom alleviation (benefit). A discrete choice experiment
312 could provide information on what duration of benefit justifies the significant patient burden.

313 To progress rTMS for PwME along the translational pathway, an adequately statistically powered RCT
314 would be required to provide convincing efficacy data. Therefore, an estimated effect size is required
315 from pilot data. Using the data from Yang et al. [37] , their change in fatigue VAS resulted in a pairwise
316 difference of d=1.1. Using the WebPower R studio package, a desired statistical power of 0.8 and an
317 alpha level of 0.05, to detect an effect of this magnitude from a two-way analysis of variance (ANOVA)
318 (interaction effect), assuming two time points and two groups (treatment and control), a sample size of
319 n=40 would be required to allow for 30% attrition. However, in reference to the above paragraph, this
320 effect size is after 2 weeks follow-up and it is possible that we would observe a return to baseline as
321 time progressed. Indeed, the improvement in fatigue VAS in the Yang et al. [37] study appeared to
322 reduce from discharge to 2 weeks in the mild ME/CFS group (from ~60% original fatigue to ~80%
323 original fatigue). Interestingly, in the severe group the opposite was true, as fatigue VAS was ~80%
324 original fatigue at discharge but ~70% original fatigue at 2 weeks.

325 All three studies included in this review employed a facilitatory type of repetitive TMS, with the aim
326 of increasing cortical excitability in brain regions hypothesised to be dysregulated in ME/CFS. Across
327 two of these studies [35,37], the rTMS protocol was relevantly homogenous. In these studies, high-
328 frequency rTMS (at 10Hz) was applied to the dorsolateral prefrontal cortex (DLPFC), the specific
329 neural target was identified using the 10-20 system electrode placement system as F3 (left) or F4
330 (right), depending on the individual participant's dominant hemisphere. The stimulation intensity in
331 both studies was reported as 90% of the resting motor threshold (rMT). In one study, stimulation
332 intensity was reduced to 80% of rMT for two participants who reported side effects which may have
333 been associated with TMS. It appears that the determination of the rMT was also homogenous across
334 these studies; reported by the researchers as the resting motor threshold as measured for the first dorsal
335 interosseous (FDI) muscle of the contralateral upper limb of the dominant hemisphere. Typically, if
336 the researchers are not employing concurrent electromyography (EMG) to record muscle activation,
337 the rMT is defined as the lowest stimulation intensity required to elicit a visible muscle contraction.
338 Both studies reported the use of the MagPro stimulator with a figure-of-eight stimulating coil, and
339 reported following published TMS safety guidelines [40].

340 In the third study [36] , the researchers employed an alternative faciliatory type of rTMS, intermittent
341 theta burst stimulation (iTBS). This paradigm also facilitates cortical excitability, but shorter (faster)

paradigms are utilised, which may be more efficient. In this study, the left DLPFC was targeted, but the specific neural target was identified using MRI-guided neuronavigation. The researchers also targeted a second location, the left primary motor cortex (M1), which was identified using the 'hotspot' technique. This involves adjusting the stimulating coil position to achieve reliable visual detection of muscle twitches of the FDI muscle, on the right hand. The left cortex was targeted for both these locations regardless of participant handedness. This study did not report following the published Rossi [40] guidelines for TMS safety. Despite all three studies reporting significant improvements in various ME/CFS symptoms, including in fatigue [35,37] and in activities of daily living, orthostatic intolerance, disequilibrium and neuropathic [36], the specific effects of rTMS are difficult to disentangle. Crucially, none of the three studies included a control group, so we cannot reliably conclude that any effects are due to rTMS without a useful comparison. For example, it is well known that uncontrolled trials produce greater mean effect estimates than a controlled trial, thereby inflating the expectations from the intervention. There is a threat of inherent bias and results are considered less valid than RCT[41]. Moreover, having a placebo control group would ameliorate the placebo effect of rTMS. This is especially pertinent when sham rTMS, which mimics the appearance, sound, and sensations of active rTMS, is known to improve symptoms of headache[42]. Therefore, high-quality, adequately powered randomised placebo-controlled trials are needed to determine effectiveness of rTMS for ME/CFS symptom frequency and severity.

As stated in the introduction of this paper, iindividuals with ME/CFS experience persistent fatigue, cognitive deficits, headaches, disrupted sleep, myalgias, arthralgias, PEM, and orthostatic intolerance [9,43]. Given that TMS holds promise as a therapeutic intervention for various neurological and psychiatric conditions—including depression, chronic pain, and cognitive impairments—it was reasonable to explore its potential in alleviating symptoms like those experienced by PwME [20–25]. In line with previous research that found favourable outcomes in various conditions, collectively, these studies outlined in the scoping review indicate that rTMS is a promising non-invasive treatment for PwME, especially in addressing fatigue and associated symptoms. However, rTMS is not currently recommended by the National Institute for Health and Care Excellence (NICE) as a management strategy for ME/CFS, which emphasises 'energy management' in its 2021 update while omitting graded exercise therapy [43]. Studies reported in this scoping review display variability in frequency of sessions, delivery, outcome measures and sample sizes. Thus, general guidelines concerning use of rTMS in PwME needs to be established before its integration within NICE recommendations. Future studies should explore validating rTMS as a potential intervention through rigorous controlled trials,

to determine efficacious stimulation parameters. This will help determine the optimal number of sessions needed for symptom relief and the duration of their effectiveness. Ultimately, feasibility studies and larger randomized controlled trials (RCTs) focusing on the therapeutic use of TMS in PwME should be conducted to validate its effectiveness.

6 Conclusions and practical recommendations

The studies reviewed reveal some variability in rTMS application and suggest that rTMS may be effective in reducing fatigue-related symptoms, with some patients experiencing lasting benefits. High-frequency 10-Hz rTMS and iTBS were utilised, employing various protocols and settings. A common approach involved using a figure-of-eight coil, targeting the DLPFC. To improve consistency and comparability, future studies should standardise the number of rTMS sessions and clearly define treatment durations. This will help determine the optimal session count for symptom relief and the duration of effectiveness. Researchers should also follow best practices for coil placement to ensure precise targeting, utilising standardised methods for coordinate selection or MRI-guided neuronavigation during DLPFC stimulation. Uniformity in rTMS parameters, including intensity adjustments relative to standardised pulse counts, is essential for enhancing result reproducibility and enabling cross-study comparisons. Finally, incorporating longer follow-up periods could provide valuable insights into the sustained efficacy of rTMS treatments and uncover any delayed effects of the intervention. It is recommended to conduct pilot studies with larger and more representative sample sizes, including well-matched control groups, to enhance the reliability and generalisability of findings before moving on to larger trials.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Author contributions according to the credit taxonomy

Conceptualization: NS-H; Methodology: NS-H, PM, ET, EB, MM, LH, KS; Formal analysis and investigation: NS-H, MM, ET, EB, PM, KS; Investigation: NSH, LH; Resources: NS-H; Writing - original draft preparation: NS-H, LH; Writing - review and editing: NS-H, LH, KS; Visualisation: NS-H, LH, M.M; Supervision: NS-H, LH; Project administration: NS-H; Funding acquisition: NS-H; All authors have approved the final manuscript.

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