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REVIEW

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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[a], Kate Slade[b], Marie McLaughlin[c], Paige Metcalfe[d], Ethan Berry[e], Eleanor J. Thornton[a] and Lawrence D. Hayes [b]

[a]School of Health and Society, University of Salford, Salford, UK; [b]Lancaster Medical School, Lancaster University, Lancaster, UK; [c]School of Education and Sport, University of Edinburgh, Edinburgh, UK; [d]Faculty of Science and Engineering, University of Manchester, Manchester, UK; [e]Sport and Physical Activity Research Institute, School of Health and Life Sciences, University of the West of Scotland, Glasgow, UK

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 1st January 1985 to 16th February 2024. Only literature in English was included.

Results: Following initial database searches, 1040 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.

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Myalgic encephalomyelitis; chronic fatigue; ME/CFS; transcranial magnetic stimulation; rTMS; therapeutic use

CONTACT Nilihan E. M. Sanal-Hayes n.e.m.sanal-hayes@salford.ac.uk

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1. Introduction

1.1. 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.

1.2. 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.

2. Methods

2.1. 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].

2.2. 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.

2.3. Literature search

We conducted a systematic literature search of CINAHL Ultimate, MEDLINE, ScienceDirect, and Scopus from 1st January 1985 to 16th February 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.

2.4. 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.).

2.5. 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 (Table 1).

2.6. Outcome measures

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

3. Results

3.1. Study selection

Following initial database searches, 1040 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 1038 titles and abstracts were screened. These were screened for inclusion, with 1020 removed, resulting in 18 full text articles being screened. Of these 15 were excluded, and therefore a total of 3 articles were included (Figure 1).

3.2. 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

Table 1. Study characteristics.

Reference	Participant demographics Diagnostic criteria	Comorbidities	Medication	Treatment length	Study recruitment and setting	Location	TMS intensity and frequency	Coil placement	TMS System (brand, coil type)	Study design Funding information
Kakuda et al. (2016)	7 CFS patients (age range 15–70 years, mean 37.0 ± 13.2 years). Time since diagnosis more than 6 months (ranged from 3 to 11 years). Ethnicity and gender not reported. US Centers for Disease Control and prevention (CDC) criteria	No history of seizures or of any major depression	No medication pumps prior to study participation	Six 25-min high-frequency rTMS sessions over three days (two sessions per day)	University hospital at the Department of Rehabilitation Medicine, Jikei Daisan Hospital	Tokyo, Japan	**Type:** Facilitatory rTMS. **Frequency:** 10-Hz high-frequency rTMS. **Stimulation pattern:** Delivered in 10-s trains of 100 pulses with 50-s intervals between each train (2500 pulses per session). There were two sessions per day, resulting in 50 min (5,000 pulses) of rTMS per day, and a total of 150 min or 15,000 pulses, over three days. **TMS Intensity:** 90% of rMT. **Definition of MT:** rMT was measured for the first dorsal interosseous (FDI) muscle (dominant hand) at rest. Whether the MT was determined using EMG to obtain MEPs or via visual observation of muscle movement was not specified	**Cortex location:** Coil placed over either: (1) the left dorsolateral prefrontal cortex (DLPFC), identified as electroencephalography (EEG) electrode position F3, in right-hand dominant participants; or (2) the right DLPFC, identified as EEG electrode position F4, in left-hand dominant participants. **Coil orientation:** No further details on localisation or coil placement provided	MagPro R30 (MagVenture Company) with a figure-of-eight coil	Before-After Studies with No Control Group. No funding information was mentioned
Miwa and Inoue (2023)	30 ME patients (23 females, age range 13–61 years, mean age 40 ± 12 years). Ethnicity and	Patients with significant, co-morbid disease unrelated to ME were	Medication including nutritional supplements were not discontinued	All patients underwent ten sessions for DLPFC and M1 each over	Patients who visited the clinic diagnosed with ME were included in the study following consent.	Toyama, Japan	**Type:** Facilitatory rTMS. **Frequency:** High-frequency intermittent Theta Burst Stimulation (iTBS), with pulses	**Cortex location:** Left DLPFC, the specific location was determined using MRI (magnetic resonance imaging)-guided neuronavigation. As well as,	MagstimRapid 2 (Miyuki Giken, Tokyo, Japan) equipped with a figure-of-8 stimulating coil	Before-After Studies with No Control Group. No funding was received for this research

(*Continued*)

Table 1. Continued.

Reference	Participant demographics Diagnostic criteria	Comorbidities	Medication	Treatment length	Study recruitment and setting	Location	TMS intensity and frequency	Coil placement	TMS System (brand, coil type)	Study design Funding information
	time since diagnosis not reported. International Consensus Criteria	excluded from this study	prior to study participation	two weeks hospitalisation	Participants were hospitalised for two weeks for study purpose at the Department of Neurology		delivered at 50 Hz. **Stimulation pattern:** Bursts of three pulses (at 50 Hz) at 200-ms intervals. A 2-s train of the burst stimulation was repeated every 10-s for a total of 190-s (totalling 600 pulses). **TMS intensity:** The study reports different intensities within the paper: 80% of the active MT (aMT), and 80% of the rMT. It is not entirely clear which intensity was employed, though 80% rMT is more frequently mentioned. The intensity was lowered depending on the patient's tolerance. The authors report each participant's individual TMS intensity (as % of the rMT). **Definition of motor threshold:** rMT was defined as the minimal intensity necessary to induce at least one visible muscle twitch in the FDI muscle (right hand)	left primary motor cortex (M1), the specific location was determined by observing muscle twitches in the right-hand FDI muscle. **Coil orientation:** No further details on localisation or coil placement provided		

Yang et al. (2020)	22 ME patients (age range 16–65 years). Time since diagnosis more than 6 months. Gender and ethnicity not reported. US Centers for Disease Control and prevention (CDC) criteria	No comorbidities reported	Not reported	three–four days hospital stay for six–eight sessions of rTMS	Patients were recruited and treated at the International University of Health and Welfare, Ichikawa Hospital, Japan	Ichikawa, Japan	**Type:** Facilitatory rTMS **Frequency:** 10-Hz high-frequency rTMS. **Stimulation pattern:** Delivered in 10-s trains of 100 pulses with 50-s intervals between each train (1800 pulses per session). There were two sessions of rTMS per day (total 3,600 pulses per day), and six–eight sessions were provided for three–fourdays. Resulting in between 10,800–14,400 pulses over the treatment period. **TMS intensity:** 90% of rMT. **Definition of motor threshold:** The method to determine the MT was reported to be the same as in the author's previous study, Kakuda et al (2016), which reported that the rMT was measured for the first dorsal interosseous (FDI) muscle (dominant hand) at rest. Whether the MT was determined using EMG to obtain MEPs or via visual observation of muscle movement was not specified	**Cortex location:** Dorsolateral Prefrontal Cortex (DLPFC) of the dominant hemisphere. **Coil orientation** No further details on localisation or coil placement provided	MagPro R30 stimulator (MagVenture Company, Farum, Denmark) equipped with a 70-mm figure-of-8 coil	Before-After Studies with No Control Group. Japan Agency for Medical Research and Development (AMED1010322)

Table 2. Study outcome characteristics.

Reference	Outcome variables	Results	Author's conclusion
Kakuda et al (2016)	Visual Analogue Scale (VAS), and Brief Fatigue Inventory (BFI) for fatigue symptoms. VAS was assessed before first rTMS session, 1 h after first session, 24 h after first session, at discharge, and one/two weeks after discharge. BFI was assessed before first rTMS session, at discharge, and one/two weeks after discharge	Results from 7 CFS patients: After first rTMS session, 2 patients showed > 30% decrease in VAS. At discharge, 5 patients showed > 30% decrease in rate and 3 patients exhibited >50% decrease in VAS. Moreover, 4 patients showed >30% decrease in one week, and 3 patients two weeks after discharge. Mean VAS decreased by 17% at one hour after first rTMS session, significant decrease both at discharge and one week after discharge. BFI score of more than one point decrease shown at discharge in 6 patients	Results showed that high-frequency rTMS was safe (only 2 patients developed mild adverse events). Fatigue symptoms improved significantly at discharge and this effect was maintained until at least one week after discharge. This study is the first to report safety, feasibility and clinical usefulness of high-frequency rTMS over DLPFC in CFS patients
Miwa & Inoue (2023)	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. All patients underwent testing before the first rTMS session and in the first week after the last rTMS session.	Results from 30 ME patients: 20 patients showed decrease by at least 2 points on PS for restricted activities of daily living, while it was unchanged for 10 patients. Before intervention, 12 of 30 patients (40%) showed orthostatic intolerance, with 11 of them (92%) reporting disequilibrium. After intervention, 10 of the 12 (83%) were able to complete the standing test. Before treatment, 17 of 30 patients (57%) had disequilibrium; 11 of them (65%) also showed orthostatic intolerance (OI), compared to just 1 of 13 (8%) without disequilibrium. After treatment, disequilibrium resolved in 15 of the 17 patients (88%), all of whom showed improvement in PS scores. The 2 who did not improve continued to experience disequilibrium. Among the 10 patients diagnosed with fibromyalgia ($n = 8$) or neuropathic pain ($n = 2$), tender points significantly decreased (by ≥ 4) in 7 (70%) – five with fibromyalgia and two with neuropathic pain. Four patients had grip strength <10 kg; in two (50%), it improved to >10 kg after rTMS treatment.	Results showed favourable effects of rTMS, post-treatment, median PS scores and tender point counts were significantly lower and both orthostatic intolerance and disequilibrium were notably less prevalent.

(*Continued*)

Table 2. Continued.

Reference	Outcome variables	Results	Author's conclusion
Yang et al. (2020)	Fatigue assessed by Brief Fatigue Inventory (BFI) and Visual Analogue Scale (VAS) before first rTMS session and after last rTMS session	Results from 22 ME patients: Patients grouped into mild group ($n = 13$) and severe group ($n = 9$). A significant reduction in both BFI and VAS scores was observed at discharge compared to before the first rTMS session for both groups. Two weeks after discharge, BFI and VAS scores in 19 cases were significantly lower than before the first rTMS session. Mild and severe group did not differ in the improved rate of BFI and VAS scores at discharge and two weeks after discharge. Moreover, no significant correlation was found between baseline BFI severity and the improvement rates of BFI and VAS at discharge or 2 weeks after discharge	rTMS improved fatigue symptoms in some ME patients with effects lasting at least two weeks after discharge irrespective of baseline fatigue severity

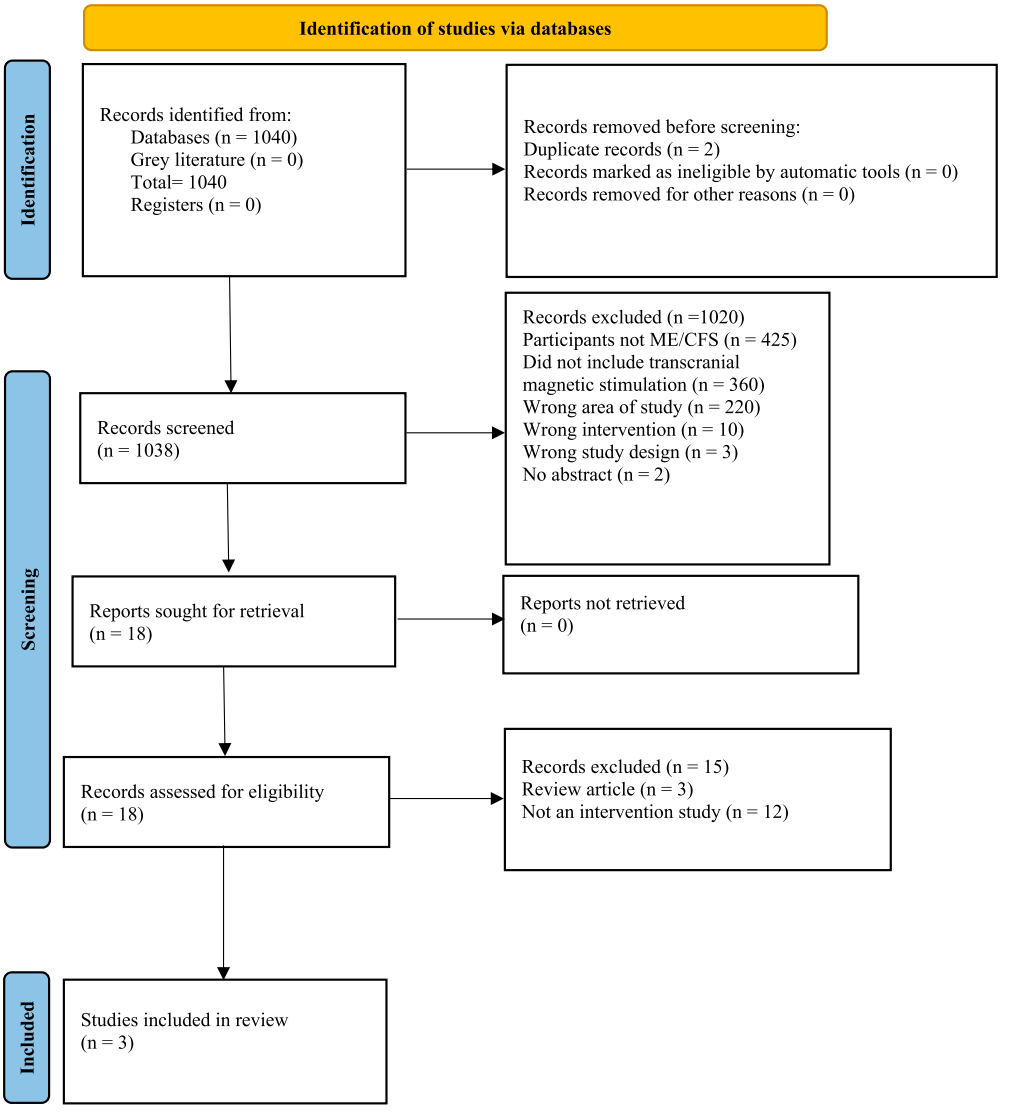

Figure 1. Records identified through reference list searching.

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.

3.3. 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.

3.4. rTMS intensity and frequency

All studies reported rTMS parameters, which varied across studies. Two studies employed 10 Hz high-frequency rTMS, delivering 10-s trains of 100 pulses with 50-s intervals between each train in two sessions per day. In one of the two studies, 2500 pulses were delivered per 25-min session over three days (15,000 pulses in total), in the other 1800 pulses were delivered per 18-min 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 were administered in bursts of three pulses (at 50 Hz) at 200-ms intervals in 2-s trains which were repeated every 10-s for 190-s. The stimulation intensity was planned to be 80% rMT but was adjusted for each participant based on tolerance.

3.5. 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.

3.6. 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 ($\geq$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 one week 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 (Figure 2).

4. 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

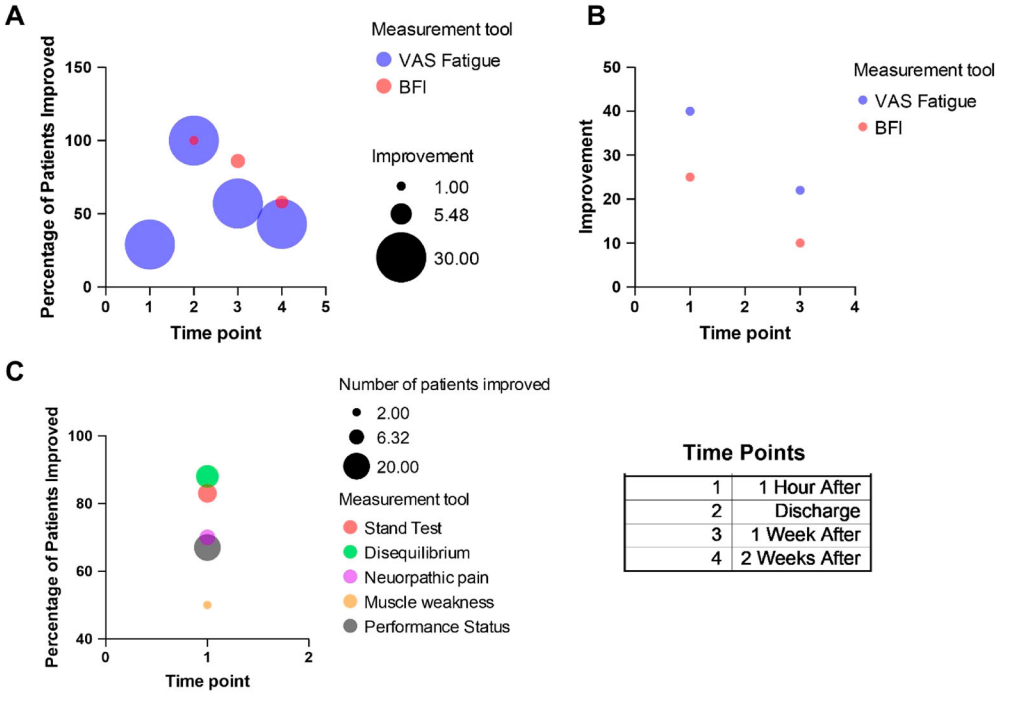

Figure 2. Bubble plots of changes in fatigue (A, B), stand test, disequilibrium, neuropathic pain, muscle weakness, and physical performance (C) over time. *X*-axis time points 1–4 represent 1 h after TMS, discharge, 1-week after TMS treatment, 2-weeks after TMS treatment, respectively. *Y*-axis display 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.

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 two weeks, and Yang et al. [37] hospitalised participants for three-four days. Kakuda et al. [35] followed up after two weeks, Miwa and Inoue [36] after less than a week, and Yang et al. [37] after two 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 five days for treatment (burden), for three weeks of symptom alleviation (benefit). A discrete choice experiment could provide information on what duration of benefit justifies the significant patient burden.

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

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

In the third study [36], the researchers employed an alternative faciliatory type of rTMS, intermittent 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, individuals 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 randomised controlled trials (RCTs) focusing on the therapeutic use of TMS in PwME should be conducted to validate its effectiveness.

5. 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.

Authors contribution

Conceptualisation: 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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Notes on contributors

Dr Nilihan E. M. Sanal-Hayes is a Lecturer in Psychology specialising in cognitive development and functioning, particularly in clinical populations. Her research focusses on cognitive challenges in long-term health conditions such as long COVID, MS, dementia, and ME/CFS, aiming to improve diagnosis, treatment, and quality of life.

Dr Kate Slade is a lecturer in Psychology in the Sport and Exercise Science team within Lancaster Medical School. Alongside teaching, Kate is really passionate about research into ageing and hearing loss, and Kate is particularly interested in how these factors affect the body and brain.

Dr Marie McLaughlin is currently a teaching fellow in Physical Activity for Health at the University of Edinburgh. Previously, they completed a postdoctoral position in exercise oncology at the University of Hull. Prior to this, they were both a lecturer and postdoctoral fellow at the University of the West of Scotland.

Paige Metcalfe is a Senior Technical Specialist in Robotics at the University of Manchester, with an interdisciplinary background in neuropsychology. They have technical expertise in neurostimulation, psychophysiology, and brain–computer interfaces, with a focus on the development of semi-automated robotic control systems for transcranial magnetic stimulation systems.

Ethan Berry is a PhD candidate at the University of the West of Scotland, where his research focuses on developing a mobile health intervention to promote muscle strengthening in older adults. He holds a BSc in Sport and Exercise Science (2022) and an MRes with a focus on profiling young-

onset dementia for targeted exercise interventions. Ethan has additional experience in applied sport science, football coaching, and clinical research assistance.

Eleanor J. Thornton is an undergraduate student studying Psychology at Durham University. She previously worked as a research assistant in Dr Nilihan Sanal-Hayes's lab.

Dr Lawrence D. Hayes' recent research has focussed on people living with chronic conditions and how those conditions can be monitored and improved, often using an mHealth approach. Another area of Dr Hayes' research is to develop targeted exercise approaches to enhance health and prevent disease. Primarily, he is interested in how exercise influences health and has interests in endocrinology, exercise biochemistry, high intensity interval training (HIIT), meta-science, and nutrition. Over his career, he has authored >100 scientific articles and received >£1.3 m in research grant income.

ORCID

Lawrence D. Hayes http://orcid.org/0000-0002-6654-0072

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