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Research paper

# Repetitive transcranial magnetic stimulation ameliorates symptoms in patients with myalgic encephalomyelitis (chronic fatigue syndrome)

Kunihisa Miwa [a,*], Yukichi Inoue [b,1]

[a] Miwa Naika Clinic, Toyama, Japan
[b] Department of Neurology, Toyama Prefectural Rehabilitation Hospital & Support Center for Children with Disabilities, Toyama, Japan

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ABSTRACT

*Background:* Central nervous system dysfunction has been postulated to cause debilitating symptoms in patients with myalgic encephalomyelitis (ME) (originally called "chronic fatigue syndrome"). Repetitive transcranial magnetic stimulation (rTMS) is a newly developed neuromodulatory procedure and has been suggested to facilitate the cortical neural activity.

*Methods:* This study enrolled 30 patients with ME (7 men and 23 women) with a mean age of 39 ± 12 years, who received rTMS treatment of both the left dorsolateral prefrontal cortex and the left primary motor area in the brain. The performance status score (0−9) for restricting activities of daily living, orthostatic intolerance (OI) during a 10-min standing test, neurologic disequilibrium diagnosed as unstable standing with their feet together and eyes closed, neuropathic pain or fibromyalgia, and muscle weakness were compared before and after treatment.

*Results:* After therapy, favorable effects were observed with a decrease in performance status score or index for restriction of activities of daily living of ≥ 2 points in 20 patients (67%). OI with the inability to complete the 10-min standing test was resolved in 10 (83%) out of 12 patients, and disequilibrium was resolved in 15 (88%) out of 17 patients. Neuropathic pain or fibromyalgia was attenuated in seven (70%) out of 10 patients. Muscle weakness with grip power of < 10 kg was resolved in two (50%) out of four patients. No untoward effects were encountered in all the study patients.

*Conclusion:* The treatment with rTMS is effective in alleviating various symptoms, especially OI and disequilibrium, and in improving the activities of daily living in patients with ME.

## 1. Introduction

Myalgic encephalomyelitis (ME) which was originally called "chronic fatigue syndrome (CFS)" is characterized by severe disabling fatigue, prolonging post-exertional malaise, and unrefreshing sleep (Fukuda et al., 1994; Afari and Buchwald, 2003; Carruthers et al., 2011). The dysfunction of central nervous system associated with ME markedly reduces activities of daily living and impairs quality of life through debilitating symptoms in the patients (Carruthers et al., 2011).

Recently the dorsolateral prefrontal cortex (DLPFC) has been identified as the affected region in the brain of ME/CFS patients resulting in functional and structural abnormalities, and the region seems to be an important part of the neural network involved in the generation of their symptoms (Ichise et al., 1992; Tirelli et al., 1998; Kuratsune et al., 2002; Okada et al., 2004). Repetitive transcranial magnetic stimulation (rTMS) is a newly developed neuromodulatory procedure and is being studied as a treatment for a wide variety of neurological as well as psychiatric disorders, such as stroke and depression (Ludemann-Podubecka et al., 2015; Silverstein et al., 2015). A recent pilot study by Kakuda et al. (Kakuda et al., 2016) has revealed that symptoms with general fatigue were subjectively alleviated in patients with CFS after rTMS treatment applied over the DLPFC, although only a few patients were included. According to recent reports, rTMS of the primary motor cortex (M1) can have pain-relieving effects in patients with neuropathic pain or fibromyalgia (Lefaucheur et al., 2008; Villamar et al., 2013; Seavedra et al., 2014; Khedr et al., 2017) which is often co-morbid with ME/CFS (Shafran, 1991; Fukuda et al., 1994; Afari and Buchwald, 2003; Carruthers et al., 2011). In addition, a growing amount of evidence indicated that

* Correspondence to: Miwa Naika Clinic, 1-4-3 Shintomicho, Toyama 930-0002, Japan.
*E-mail address:* info@miwa-naika.com (K. Miwa).
[1] Dr. Y Inoue died on April 16, 2021

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the left prefrontal cortex is involved in pain modulation (Graff-Guerrero et al., 2005; Fierro et al., 2011).

In the present study, we tried to clarify the possible therapeutic effects of high-frequency rTMS applied over both the DLPFC and M1 in patients with ME. Specifically, the therapeutic effects of rTMS on the restricted activities of daily living, orthostatic intolerance (OI) during a conventional active 10-min standing test, neurologic disequilibrium, co-morbid neuropathic pain or fibromyalgia, and muscle weakness were evaluated.

## 2. Materials and Methods

### 2.1. Study patients

Consecutive patients who visited our clinic, diagnosed with ME, and gave informed consent to participate, were included in the present study from May in 2015 up to March in 2021. ME was diagnosed according to the International Consensus Criteria (Carruthers et al., 2011). Briefly, symptoms related to neuroimmune exhaustion, such as marked, rapid physical and/or cognitive fatigability in response to exertion, prolonged recovery period and low threshold of physical and mental fatigability, were compulsory for the diagnosis of ME. In addition, at least one symptom from 3 of the 4 symptom categories related to neurological impairments, including neurocognitive impairments, pain, sleep disturbance and neurosensory, perceptual and motor disturbances, and at least one symptom from 3 of the 5 symptom categories related to immune, gastro-intestinal and genitourinary impairments, including recurrent or chronic flu-like symptoms, susceptibility to viral infections, gastro-intestinal tract symptoms, genitourinary symptoms and sensitivities to food, medications, odors or chemicals, were required. Also at least one symptom of the symptoms related to Impaired energy metabolism/ion transportation, including cardiovascular symptoms such as OI, respiratory symptoms, loss of thermostatic stability and intolerance of extremes of temperature, was required.

Patients with significant, co-morbid disease unrelated to ME were excluded from this study. Also, pregnant or lactating women were not included in this study. Of the 30 study patients, seven were men and 23 women with a mean age of 39 ± 12 years (range, 13 – 61 years). Ongoing medications including nutritional supplements and multi-enzyme tablets were not discontinued throughout the study, although both β adrenergic receptor blocking agents and vasopressors were discontinued before the study. All the study patients gave informed consent, and the study was approved by the Ethics Committee of our institute (approval#: 47) and was conducted according to the Declaration of Helsinki (World Medical Association, 2013).

To establish an initial performance baseline and the possible therapeutic effects of our treatment, we used a performance status (PS) scoring for restricted activities of daily living and also the following tests for individual symptom evaluation: a conventional active 10-min standing test, neurologic testing for disequilibrium, and the digital palpation for 18 specified tender points proposed by the ACR 2010 (Wolfe et al., 1990), and grip power estimation. All patients underwent testing before and in the first week after the last rTMS session.

### 2.2. Performance status (PS) grading

The information concerning the activities of daily living was obtained from each patient and verified by the attendant physician. PS was graded as Table 1, according to symptom severity as reported previously (Miwa, 2016).

### 2.3. Conventional active 10-min standing test

The conventional active 10-min standing test was performed as reported previously (Miwa, 2016; Miwa and Fujita, 2011). Postural orthostatic tachycardia was diagnosed as an increase in the heart rate of ≥ 30/min and/or ≥ 120 beats/min during the test. Instantaneous or delayed orthostatic hypotension was diagnosed as a decrease in the systolic blood pressure of ≥ 20 mm Hg and/or a systolic blood pressure of ≤ 90 mm Hg or a decrease in the diastolic blood pressure of ≥ 10 mm Hg.

**Table 1**
Performance Status (PS) Grading.

| | |
|---|---|
| PS 0: | The patient can perform the usual activities of daily living and social activities without malaise. |
| PS 1: | The patient often feels fatigue. |
| PS 2: | The patient often needs to rest because of general malaise or fatigue. |
| PS 3: | The patient cannot work or perform usual activities for a few days in a month. |
| PS 4: | The patient cannot work or perform usual activities for a few days in a week. |
| PS 5: | The patient cannot work or perform usual activities but can perform light work. |
| PS 6: | The patient needs daily rest but can perform light work on a “good day”. |
| PS 7: | The patient can take care of himself/herself but cannot perform usual duties. |
| PS 8: | The patient needs help to take care of himself/herself. |
| PS 9: | The patient needs to rest the whole day and cannot take care of himself/herself without help. |

### 2.4. Neurologic examination for disequilibrium

In order to diagnose disequilibrium, the study patients were asked to stand with their feet together and eyes closed (Miwa and Inoue, 2017; Miwa and Inoue, 2018; Miwa and Inoue, 2020). When the patient exhibited unstable standing with wide oscillations and the possibility of falling, disequilibrium was diagnosed as positive.

### 2.5. Tender points examination

The number of the tender points on digital palpation for 18 specified tender points proposed by the ACR in 1990 (Wolfe et al., 1990) was determined in all the study patients including those who had chronic neuropathic pain or fibromyalgia.

### 2.6. Delivering rTMS based on patterns of theta burst stimulation

The high-frequency rTMS was delivered using a MagstimRapid 2 (Miyuki Giken, Tokyo, Japan) equipped with a figure-of-8 stimulating coil. The patterns of rTMS all consisted of bursts containing three pulses at 50 Hz and an intensity of 80% of the active motor threshold repeated at 200-ms intervals (5 Hz). In the intermittent theta burst stimulation pattern (iTBS), a 2-s train of TBS is repeated every 10 s for a total of 190 s (600 pulses) (Huang et al., 2005). The Burst Stimulator (Medical Try System, Tokyo, Japan), a magnetic stimulation control software, was employed for the delivery of TBS. Both the DLPFC and M1 of the left hemisphere were selected as the target areas for iTBS, irrespective of the patient’s right or left handedness. To determine the location of left DLPFC, MRI-guided neuronavigation was employed (Ahdab et al., 2010; Mir-Moghtadaei et al., 2015). The optimal stimulus site of M1, motor hot spot, was determined according to visual detection of muscle twitches of the first dorsal interosseous muscle of the contralateral or right upper limb, and a resting motor threshold was defined as the minimal intensity necessary to induce at least one visible muscle twitch. The stimulating coil was placed on the left DLPFC first and then the left M1. The intensity of stimulation was initially planned to set at 80% of the measured resting motor threshold. The intensity was lessened depending on the patient’s tolerance. During iTBS application, the patient was asked to be seated while leaning against a 45-degree reclining chair, with the back of the

head in close contact with the head–holding cushion. All patients were monitored carefully throughout the rTMS session by the physician applying rTMS. All patients underwent rTMS treatment, including 10 sessions for DLPFC and M1 each over 2 weeks of hospitalization at the Department of Neurology, Toyama Prefectural Rehabilitation Hospital & Support Center for Children with Disabilities, Toyama, Japan.

### 2.7. Statistical analysis

Continuous variables are presented as mean ± standard deviation. The Student t-test was used to compare continuous variables. Proportional data were analyzed using the Fisher's exact test with Yates' correction. Mann−Whitney's U test was used to compare median PS scores between the study patients with and without favorable effects from rTMS treatment. Wilcoxon signed-rank test was used to compare both median values of PS scores and numbers of tender points between the study patients before and after treatment. Statistical significance was set at $p < 0.05$.

## 3. Results

The clinical features and therapeutic effects of the treatment with rTBS in the study patients are summarized in Table 2. The intensity of stimulation was lowered due to patients' complaints of uncomfortableness, headache, and dizziness. Eventually the intensity needed to be set at below 60% of the measured resting motor threshold in 7 patients. No patient suffered subsequent adverse effects from the rTMS procedure.

### 3.1. Performance status (PS) scoring

Among the study 30 patients, 20 (67%) had a PS score or index for restricted activities of daily living that decreased by at least 2 points, which was counted as the favorable therapeutic effect of rTMS, whereas the PS score of the remaining 10 (33%) patients was essentially unchanged (Table 2). Comparative data between patients with and without favorable therapeutic effects by rTMS are presented in Table 3. Neither the gender and age distribution nor disease duration was not significantly different between the patients with and without favorable therapeutic effects. Also, the PS scores at baseline were not significantly different between those with and without favorable effects. The rates of favorable effects for OI evaluated using the active 10-min standing test, disequilibrium, neuropathic pain or fibromyalgia and muscle weakness are shown in Fig. 1.

**Table 3**
Comparison of the clinical data between the study patients with ME with and without therapeutic favorable effects after rTMS treatment.

| | Patients with favorable effects | Patients without favorable effects | *P* value |
|---|---|---|---|
| **Number of patients** | **20 (67%)** | **10 (33%)** | |
| **Female** | **15 (75%)** | **8 (80%)** | **1.00** |
| **Age (years)** | **40 ± 12** | **38 ± 15** | **0.66** |
| **< 30** | **3(15%)** | **4 (40%)** | **0.18** |
| **≥ 40** | **11 (55%)** | **6 (60%)** | **1.00** |
| **Disease duration (years)** | **5.5 ± 5.1** | **8.2 ± 8.9** | **0.29** |
| **Performance status score** | **3 − 8** | **4 − 8** | |
| **Median score** | **6.5** | **7** | **NS** |
| **≥ 7** | **10 (50%)** | **7 (70%)** | **0.44** |
| **≤ 5** | **5 (25%)** | **1 (10%)** | **0.63** |
| **Failed to stand for 10 min** | **11 (55%)** | **1 (10%)** | **0.02** |
| **Disequilibrium** | **15 (75%)** | **2 (20%)** | **0.01** |
| **Tender points ≥ 6** | **8 (40%)** | **2 (20%)** | **0.42** |
| **Stimulation intensity < 0.6MT** | **2 (10%)** | **5 (50%)** | **0.03** |

ME: myalgic encephalomyelitis; Disequilibrium: instability upon standing with feet together and eyes closed; MT: measured resting motor threshold; Values are presented as mean ± standard deviation

**Table 2**
Clinical characteristics and effects of rTMS on the 30 study patients with ME.

| Patient | Age/Sex | History | Handedness | Intensity | Disequilibrium | | Standing test | | PS score | | Tender points | | Grip power (kg) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| # | | (years) | (Left or Right) | (%) | before | after | before | after | before | after | before | after | before | after |
| 1 | 53/F | 1 | R | 60 | + | − | 8′30″ | C | 8 | 4 | 0 | 0 | R5L22 | R22L22 |
| 2 | 24/F | 3.5 | L | 70 | + | − | 5′ | C | 6 | 2 | 6 | 0 | | |
| 3 | 45/F | 14 | R | 60 | − | − | C | C | 7 | 3 | 0 | 0 | | |
| 4 | 46/M | 11 | L | 68 | − | − | C | C | 8 | 5 | 12 | 10 | | |
| 5 | 49/M | 0.8 | R | 61 | + | − | C | C | 6 | 3 | 0 | 0 | | |
| 6 | 34/F | 3 | R | 80 | + | − | 8′40″ | C,POT | 6 | 3 | 18 | 10 | | |
| 7 | 32/F | 1.0 | R | 60 | + | − | C | C,POT | 4 | 1 | 4 | 0 | | |
| 8 | 30/M | 0.7 | R | 72 | + | − | C | C | 4 | 1 | 0 | 0 | | |
| 9 | 50/M | 0.8 | R | 62 | − | − | C | C | 3 | 0 | 0 | 0 | | |
| 10 | 46/F | 12 | R | 60 | + | − | 7′30″ | 7′ | 8 | 6 | 4 | 2 | R7L7 | R18L16 |
| 11 | 44/F | 1.7 | L | 65 | + | − | C,OH | C,OH | 8 | 6 | 18 | 14 | | |
| 12 | 45/F | 12 | R | 40 | + | − | 5′30″ | C | 7 | 5 | 0 | 0 | | |
| 13 | 32/F | 0.7 | R | 65 | − | − | C | C | 7 | 5 | 0 | 0 | | |
| 14 | 61/F | 12 | R | 70 | + | − | 9′ | C | 7 | 5 | 0 | 0 | | |
| 15 | 51/F | 6.0 | R | 65 | + | − | C | C | 7 | 5 | 16 | 12 | | |
| 16 | 30/F | 15 | R | 60 | + | − | 8′ | C | 7 | 5 | 2 | 0 | | |
| 17 | 25/F | 2.5 | R | 60 | + | − | 9′30″,POT | C,POT | 6 | 4 | 10 | 2 | | |
| 18 | 32/F | 7 | R | 50 | + | − | 5′ | C | 6 | 4 | 18 | 12 | | |
| 19 | 18/F | 1.7 | R | 60 | − | − | 7′,POT | C | 4 | 2 | 0 | 0 | | |
| 20 | 50/M | 3.3 | R | 75 | + | − | 15″ | C | 3 | 1 | 18 | 0 | | |
| 21 | 49/M | 9.0 | R | 55 | − | − | C,POT | C, POT | 8 | 7 | 0 | 0 | | |
| 22 | 28/F | 5.0 | R | 32 | − | − | C | C | 7 | 6 | 4 | 6 | | |
| 23 | 49/F | 21 | R | 45 | − | − | C | C | 6 | 5 | 2 | 0 | | |
| 24 | 13/F | 0.7 | R | 65 | − | − | C,POT | C,POT | 4 | 3 | 0 | 0 | | |
| 25 | 46/F | 2.0 | R | 70 | + | + | C | C | 8 | 8 | 16 | 18 | | |
| 26 | 19/F | 1.4 | R | 55 | + | + | 15 ” | 20″ | 8 | 8 | 18 | 18 | R5L5 | R5L5 |
| 27 | 25/F | 16 | R | 37 | − | − | C | C | 7 | 7 | 2 | 2 | R6L11 | R7L12 |
| 28 | 51/F | 0.7 | R | 65 | − | − | C | C | 7 | 7 | 0 | 0 | | |
| 29 | 48/M | 24 | R | 60 | − | − | C | C | 7 | 7 | 4 | 4 | | |
| 30 | 49/F | 2.5 | R | 70 | − | − | C | C | 6 | 6 | 0 | 0 | | |

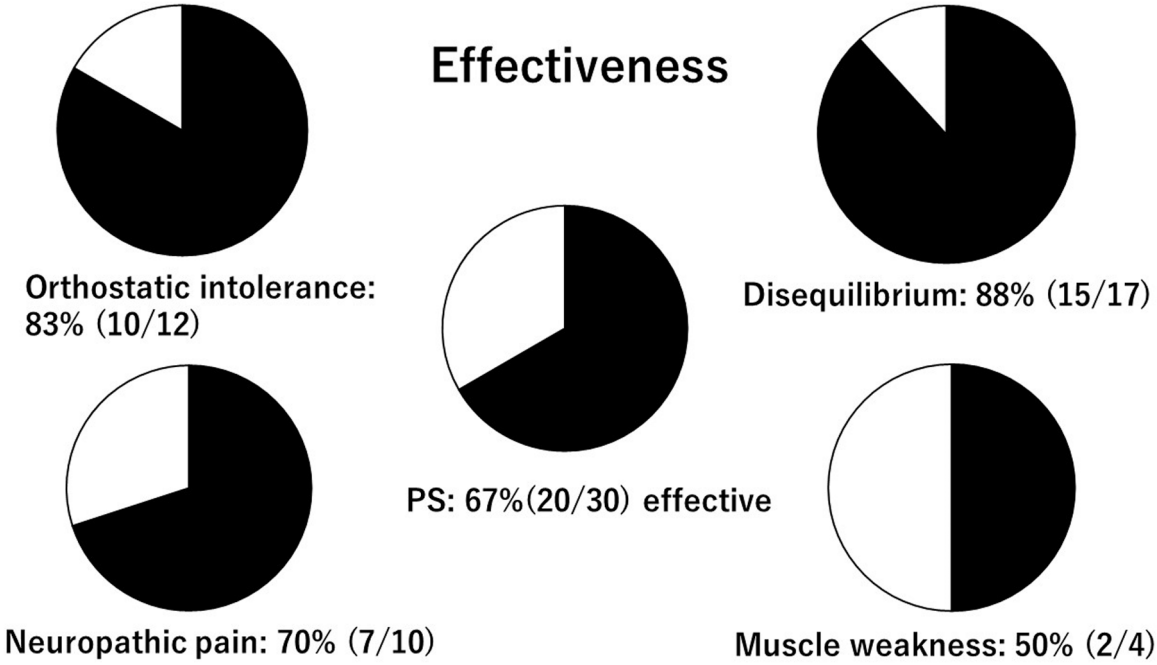


**Fig. 1.** Comparative rates of the favorable effects for various specific symptoms in the study patients with ME. Black portions show patients with favorable effects for each specific symptom after rTMS. PS: performance status; See text for details.

### 3.2. Active 10-min standing test

Among the study 30 patients, 12 (40%) had OI demonstrated as the failure of completion of the 10-min standing test before therapy. Of the 12 patients, disequilibrium was positive in 11 (92%). After therapy, 10 (83%) of the 12 could complete the test (Fig. 1). All 10 patients had been classified as being with favorable therapeutic effects by rTMS evaluated by PS score changes, while 2 patients who failed to complete the 10-min standing still after treatment had been classified as being without favorable effects by PS score changes. Prevalence of postural orthostatic tachycardia or orthostatic hypotension appeared not to be different between the standing tests before and after treatment. Both heart rate and blood pressure at rest and at maximal heart rate, and also increase in heart rate, during the 10-min standing test, were not significantly different between the tests before and after treatment (Table 4).

### 3.3. Disequilibrium

Among the 30 patients, 17 (57%) had disequilibrium before treatment. In 11 (65%) of these 17 patients, OI was demonstrated as the failure to complete the 10-min standing, whereas among the other 13 patients without disequilibrium, only one (8%) had OI. Among the 17 patients with disequilibrium, disequilibrium was resolved in 15 (88%) patients after treatment (Fig. 1). All the 15 patients had been classified as receiving beneficial effects from rTMS based upon PS score changes, while 2 patients who had disequilibrium did not benefit from rTMS treatment (Table 2). Notably, in all of the 10 patients who failed to complete the 10-min standing test before therapy but completed it after treatment, disequilibrium was resolved after treatment (Table 2). Typical Romberg tests before and after the treatment with rTMS in patient #6 are shown in the supplementary files.

**Table 4**
Comparison in hemodynamic changes during the 10-min standing tests before and after the treatment with rTMS.

| | At rest | | at maximal HR during the standing test | | Difference between at rest and at maximal HR | |
|---|---|---|---|---|---|---|
| | **HR** | **BP** | **HR** | **BP** | **ΔHR** | **ΔBP** |
| **Before rTMS** | **66 ± 8** | **110 ± 10/ 66 ± 8** | **89 ± 16** | **111 ± 10/ 78 ± 9** | **23 ± 11** | **0.3 ± 7/ 11 ± 7** |
| **After rTMS** | **67 ± 11** | **110 ± 12/ 68 ± 8** | **88 ± 15** | **111 ± 11/ 77 ± 8** | **21 ± 10** | **0.8 ± 10/9 ± 6** |
| ***P* value** | **0.59** | **0.84/0.43** | **0.84** | **0.86/0.42** | **0.24** | **0.75/ 0.09** |

rTMS: repetitive transcranial magnetic stimulation; HR: heart rate (beats/min); BP: systolic/diastolic blood pressure (mmHg)

### 3.4. Neuropathic pain or fibromyalgia

According to the ACR 1990 diagnostic criteria (Wolfe et al., 1990), eight patients were diagnosed with fibromyalgia (tender points ≥11), and the other two patients had neuropathic pain (tender points: 6–10). Among combined these 10 patients, the number of tender points remarkably (≥4) decreased in seven (70%), including five with fibromyalgia and two with neuropathic pain (Table 2 and Fig. 1).

### 3.5. Muscle weakness or lessened muscle power

Low grip power of < 10 kg was observed in either hand in four of the patients. Among them, the low grip power increased to > 10 kg after the treatment with rTMS in two (50%) (Table 2 and Fig. 1).

### 3.6. Summary of amelioration of symptoms after treatment with rTMS

Both median values of PS scores and numbers of tender points were significantly lower in the study patients after treatment as compared with before (Table 5). Both orthostatic intolerance and disequilibrium were significantly less prevalent in the study patients after treatment as compared with before.

## 4. Discussion

The present study clearly demonstrated that treatment with rTMS is useful in alleviating various symptoms of ME. This treatment was found to improve symptoms in patients with ME regardless of baseline severity

**Table 5**
Comparison of the performance status scores and the prevalence of various symptoms between the study 30 patients with ME before and after rTMS treatment.

| | Before rTMS treatment | After rTMS treatment | *P* value |
|---|---|---|---|
| **Performance status score** | **3-8** | **0-8** | |
| **Median score** | **7** | **5** | **< 0.01** |
| **Orthostatic intolerance** | | | |
| **Failed to stand for 10 min** | **12 (40%)** | **2 (7%)** | **< 0.01** |
| **Disequilibrium** | **17 (57%)** | **2 (7%)** | **< 0.01** |
| **Number of tender points** | **0–18** | **0–18** | |
| **Median number** | **2** | **0** | **< 0.01** |
| **Muscle weakness** | | | |
| **Grip power < 10 kg** | **4 (13%)** | **2 (7%)** | **0.43** |

ME: myalgic encephalomyelitis; Disequilibrium: instability upon standing with feet together and eyes closed

of fatigue symptoms, similarly to the previous report (Yang et al., 2020). The favorable effects induced by rTMS on various specific symptoms of ME, including impaired activities of daily living, as measured by PS scores, OI during the 10-min standing test, disequilibrium, neuropathic pain, and muscle weakness in patients with ME, have not been reported previously.

### 4.1. *The primary favorable effects by rTMS*

The conventional active 10-min standing test and neurologic examination revealed that most patients with ME who could not stand for 10 min had disequilibrium demonstrated as evidenced by their inability to stand stably with their feet together and eyes closed. In addition, most of the patients with ME with accompanying disequilibrium failed to complete the 10-min standing test, whereas failure to complete the test was extremely rare in ME patients who did not exhibit disequilibrium, suggesting the etiologic role of disequilibrium or truncal ataxia for OI, which confirmed our previous results (Miwa and Inoue, 2017; Miwa and Inoue, 2018; Miwa and Inoue, 2020). Moreover, patients whose disequilibrium was alleviated after rTMS could complete the 10-min standing test after treatment, demonstrating the improvement of OI, which suggests that postural stability is essential in maintaining an erect position. The dysfunction of postural reflex or disequilibrium appears to play an important role in the etiology of OI. OI appeared to be caused mainly by neurologic abnormalities in the central nervous system in most patients with ME rather than be of cardiovascular origin. OI is a primary factor in restricting daily functional capacity (Costigan et al., 2010). It has been reported that patients with disequilibrium had higher PS scores than those without it, suggesting more severely restricted activities of daily living (Miwa and Inoue, 2018; Miwa and Inoue, 2020). Patients with disequilibrium possibly require an increased effort to maintain an orthostatic position, resulting in an exaggerated sympathetic activation, which leads to severe fatigue or exhaustion.

### 4.2. *Putative pathogenesis of disequilibrium in ME*

The exact cause of the observed disequilibrium in patients with ME remains unknown. It appears to be of central vestibular origin, which is consistent with the previously revealed results of vestibular function tests in patients with CFS (Furman, 1991; Ash-Bernal et al., 1995), although other mechanisms except central vestibular origin cannot be excluded. The pathogenesis of the observed neurologic defect of disequilibrium is probably caused by neural inflammation in the brain (Nakatomi et al., 2014).

Not much is known about the cortical organization of human vestibular information processing. rTMS to the DLPFC and M1 may have facilitated the recovery of central vestibular function by enhancing the activity of neural network including the known vestibular function center located in the brain stem. The vestibular system supplies us with information about head translation, rotation, and orientation in a gravitational environment (Raiser et al., 2020). The corticovestibular network has been reported to be distributed throughout the brain and has a high-degree functional connectivity that may buffer the network and reestablish network integrity quickly in case of injury (Raiser et al., 2020; Brandt et al., 1997; Brandt and Dieterich, 2017). Disorders or lesions of central or cortical vestibular regions rarely cause vestibular deficits in the acute phase, and symptoms never persist in patients probably because of a highly robust redundant vestibular cortical network. In ME, evidence of widespread metabolic abnormalities in the brain has been reported (Mueller et al., 2019) and nerve inflammation encompasses almost the entire central nervous system (Nakatomi et al., 2014), both of which are probably why disequilibrium in association with central vestibular dysfunction develops and persists in many patients with ME. The DLPFC and/or M1 appears to be important modulators for this neural network.

### 4.3. *Putative favorable effects through neural activation of DLPFC by rTMS*

The mechanism by which treatment with rTMS to DLPFC effectively ameliorates various symptoms of ME should be elucidated. Dysfunction and inactivation of DLPFC has been suggested as an important part of the network for fatigue sensation as well as broad brain function in patients with ME/CFS (Kuratsune et al., 2002).

The voxel-based morphometry of Okada et al. (Okada et al., 2004) using magnetic resonance imaging revealed that patients with CFS had reduced gray matter volume in the bilateral prefrontal cortex, especially DLPFC, suggesting that the DLPFC might be an important element of the neural system that regulates the sensation of fatigue. A single site in the DLPFC revealed the parallel between volume reduction and fatigue sensitivity (Okada et al., 2004). The DLPFC has been known to have dense widespread subcortical and cortical connections, such as frontal-subcortical circuits including corticostriatal and thalamocortical connections (Goldman-Rakic, 1987; Alexander and Crutcher, 1990). The DLPFC also has widespread reciprocal corticocortical connections with posterior temporal, parietal, and occipital association areas (Okada et al., 2004). Malfunction of the DLPFC was suggested to cause a functional interruption of the striatal-thalamic-frontal cortical loop, resulting in an enhanced fatigability (Chaudhuri and Behan, 2000). Furthermore, at the level of the frontal lobes, the orbitofrontal, anterior cingulate and DLPFC are linked to each other without cross connections at subcortical levels (Cummings, 1995). According to the model (Chaudhuri and Behan, 2000), hypofunction of DLPFC might interrupt the associated strio-thalamo-cortical loop, resulting in enhanced fatigability. Kakuda et al. (Kakuda et al., 2016) speculated from their pilot study that the effect by rTMS was mediated through the neural activation of the DLPFC when they applied high-frequency rTMS over the DLPFC in several patients with CFS to obtain decreased fatigue symptoms in most of the CFS patients they studied.

Pain symptoms were also markedly ameliorated after rTMS application on the DLPFC and M1 in the patients whose presentation included myalgia. Probably rTMS on both DLPFC and M1 might be responsible for the observed pain-relief effects as reported previously in the patients with fibromyalgia (Lefaucheur et al., 2008; Villamar et al., 2013; Seavedra et al., 2014; Khedr et al., 2017; Graff-Guerrero et al., 2005; Fierro et al., 2011).

Also, the exact cause of muscle weakness in a small number of ME patients remains unknown. Whether the favorable therapeutic effects on muscle weakness by rTMS depends on the stimulation to DLPFC or M1, or both should be elucidated in the future study.

### 4.4. *Limitations*

This study has several limitations. First, the present study had no

control patients with sham treatment with which to compare. Second, in the present study the treatment with rTMS was applied to DLPFC together with M1 in all of the study patients. Consequently, the effects by rTMS via DLPFC and M1 could not be evaluated individually. Third, some patients could not tolerate to rTMS stimulation with 80% of motor threshold. A lower stimulation intensity below 60% of MT was significantly less prevalent among the patients with favorable effects exerted by rTMS treatment (Table 3). Stimulation intensity appeared to be an important factor determining therapeutic effects of rTMS. Nevertheless, the optimal intensity of rTMS for ME patients should be individually determined for safe and useful introduction for each patient. Fourth, the duration of the efficacy by rTMS has not been determined in the present study. Obviously further investigation will be required to determine the duration of the efficacy in patients with ME and specific conditions. Fifth, no patient had undergone specific tests for detection of neuroinflammation. Sixth, whether these results are influenced by geographic or genetic differences has not been determined at this time. The finding of benefit of rTMS in this study needs to be repeated in other parts of the world.

Recently it became clear that some patients remained unwell for months to years after “recovering” from the acute COVID-19 infection. The illness (Long COVID) is similar to ME/CFS (Komaroff, Lipkin, 2023). The treatment with rTMS may have potential therapeutic value for Long COVID and needs to be further examined.

## 5. Conclusions

rTMS treatment when applied to both the DLPFC and M1 effectively alleviated various symptoms, and improved the abilities of many ME patients participating in this study to perform the activities of daily living. The most favorable outcome of treatment was the alleviation of disequilibrium associated with OI resolution. We find disequilibrium or postural reflex dysfunction is an important cause of OI. Treatment with rTMS should be considered as a therapeutic option.

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## CRediT authorship contribution statement

**Kunihisa Miwa:** Conceptualization, Formal analysis, Investigation, Methodology, Resources, Writing. **Yukichi Inoue:** Conceptualization, Methodology, Data curation.

## Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

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## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.ibneur.2023.10.008.

## References

Afari, N., Buchwald, D., 2003. Chronic fatigue syndrome: A review. Am. J. Psychiatry 160, 221–236.

Ahdab, R., Ayache, S.S., Brugières, P., Goujon, C., Lefaucheur, J.-P.P., 2010. Comparison of “standard” and “navigated” procedures of TMS coil positioning over motor, premotor and prefrontal targets in patients with chronic pain and depression. Neurophysiol. Clin. 40, 27–36.

Alexander, G., Crutcher, M., 1990. Neural representations of the target goal of visually guided arm movements in three motor areas of the monkey. J. Neurophysiol. 64, 164–178.

Ash-Bernal, R., Wall, C., Komaroff, A.L., Bell, D., Oas, J.E., Payman, R.N., Fagioli, L.R., 1995. Vestibular function test abnormalities in patients with chronic fatigue syndrome. Acta Otolaryngol. (Stock. 115, 9–17.

Brandt, T., Strupp, M., Arbusow, V., Dieringer, N.N., 1997. Plasticity of the vestibular system: central compensation and sensory substitution for vestibular deficits. Adv. Neurol. 73, 297–309.

Brandt, T., Dieterich, M., 2017. The dizzy patient: don’t forget disorders of the central vestibular system. Nat. Rev. Neurol. 13, 352–362.

Carruthers, B.M., van de Sande, M.I., DeMeirleir, K.L., Klimas, N.G., Broderick, G., Mitchell, T., Staines, D., Powles, A.C.P., Speight, N., Vallings, R., Bateman, L., Baumgarten-Austrheim, B., Bell, D.S., Carlo-Stella, N., Chia, J., Darragh, A., Jo, D., Lewis, D., Light, A.R., Marshall-Gradisbik, S., Mena, I., Mikovits, J.A., Miwa, K., Murovska, M., Pall, M.L., Stevens, S., 2011. Myalgic encephalomyelitis: International Consensus Criteria. J. Intern. Med. 270, 327–338.

Chaudhuri, A., Behan, P.O., 2000. Fatigue and basal ganglia. J. Neurol. Sci. 179, 34–42.

Costigan, A., Elliott, C., McDonaldo, C., Newton, J.L., 2010. Orthostatic symptoms predict functional capacity in chronic fatigue syndrome: implications for management. Q. J. Med. 103, 589–595.

Cummings, J.L., 1995. Anatomic and behavioral aspects of frontal-subcortical circuits. Ann. N.Y. Acad. Sci, 769 (1), 13.

Fierro, B., Tommaso, M., Giglia, G., Palermo, A., Brighina, F., 2011. Repetitive transcranial magnetic stimulation (rTMS) of the dorsolateral prefrontal cortex (DLPFC) during capsaicin-induced pain: modulatory effects on motor cortex excitability. Exp. Brain. Res. 203, 31–38.

Fukuda, K., Straus, S.E., Hickle, I., Sharpe, M.C., Dobbins, J.G., Komaroff, A., 1994. International Chronic Fatigue Syndrome Study Group. The chronic fatigue syndrome: A comprehensive approach to its definition and study. Ann. Int. Med. 121, 953–959.

Furman, J.M.R., 1991. Testing of vestibular function: an adjunct in the assessment of chronic fatigue syndrome. Rev. Infect. Dis. 13 (11 Suppl), S109–S111.

Goldman-Rakic, P.S., 1987. Circuitry of primate prefrontal cortex and regulation of behavior by representational memory. In handbook of Physiology Section I: the Nervous System. High. Funct. Brain. Vol. V. Bethesda.: Am. Physiol. Soc. 373–417.

Graff-Guerrero, A., González-Olvera, J., Fresán, A., Gómez-Martín, D., Méndez-Núñez, J. C., Pellicer, F., 2005. Repetitive transcranial magnetic stimulation of dorsolateral prefrontal cortex increases tolerance to human experimental pain. Cogn. Brain. Res. 25, 153–160.

Huang, Y.-Z., Edwards, M.J., Rounis, E., Bhatia, K.P., Rothwell, J.C., 2005. Theta burst stimulation of the human motor cortex. Neuron 45, 201–206.

Ichise, M., Salit, I.E., Abbey, S.E., Chung, D.G., Gray, B., Kirsh, J.C., Freedman, M., 1992. Assessment of regional cerebral perfusion by $^{99}$Tcm-HMPAO SPECT in chronic fatigue syndrome. Nucl. Med. Commun. 13, 767–772.

Kakuda, W., Momosaki, R., Yamada, N., Abo, M., 2016. High-frequency rTMS for the treatment of chronic fatigue syndrome; a case series. Intern. Med. 55, 3515–3519.

Khedr, E., Omran, E.A.H., Iamail, N.M., El-Hammady, D.H., Goma, S.H., Kotb, H., Galal, H., Osman, A.M., Farghaly, H.S.M., Karim, A.A., Ahmed, G.A., 2017. Effects of transcranial direct current stimulation on pain, mood and serum endorphin level in the treatment of fibromyalgia: a double blinded, randomized clinical trial. Brain Stimul. 10, 893–901.

Komaroff, A.L., Lipkin, W.I., 2023. ME/CFS and long COVID share similar symptoms and biological abnormalities: road map to the literature. Front. Med. 10, 1187163 https://doi.org/10.3389/fmed.2023.1187163.

Kuratsune, H., Yamaguti, K., Lindth, G., Evengård, B., Hagberg, G., Matsumura, K., Iwase, M., Onoe, H., Takahashi, M., Machii, T., Kanakura, Y., Kitani, T., Langstrom, B., Watanabe, Y., 2002. Brain regions involved in fatigue sensation: reduced acetylcarnitine uptake into the brain. Neuroimage 17, 1256–1265.

Lefaucheur, J.-P., Antal, A., Andab, R., de Andrade, D.C., Fregni, F., Khedr, E.M., Nitsche, M., Paulus, W., 2008. The use of repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) to relieve pain. Brain Stimul. 1, 337–344.

Ludemann-Podubecka, J., Bosl, K., Nowak, D.A., 2015. Repetitive transcranial magnetic stimulation for motor recovery of the upper limb after stroke. Prog. Brain Res. 218, 281–311.

Mir-Moghtadaei, A., Caballero, R., Fried, P., Fox, M.D., Lee, K., Giacobbe, P., Daskalakis, Z.J., Blumberger, D.M., Downar, J., 2015. Concordance between beamF3 and MRI-neuronavigated target sites for repetitive transcranial magnetic stimulation of the left dorsolateral prefrontal cortex. Brain Stimuk. 8, 965–973.

Miwa, K., Fujita, M., 2011. Small heart with low cardiac output for orthostatic intolerance in patients with chronic fatigue syndrome. Clin. Cardiol. 34, 782–786.

Miwa, K., 2016. Variability of postural orthostatic tachycardia in patients with myalgic encephalomyelitis and orthostatic intolerance. Heart Vessels 31, 1522–1528.

Miwa, K., Inoue, Y., 2017. Truncal ataxia or disequilibrium is unrecognised cause of orthostatic intolerance in patients with myalgic encephalomyelitis. Int. J. Clin. Prac. https://doi.org/10.1111/ijcp.12967.

Miwa, K., Inoue, Y., 2018. The etiologic relation between disequilibrium and orthostatic intolerance in patients with myalgic encephalomyelitis (chronic fatigue syndrome). J. Cardiol. 72, 261–264.

Miwa, K., Inoue, Y., 2020. Paradigm shift to disequilibrium in the genesis of orthostatic intolerance in patients with myalgic encephalomyelitis and chronic fatigue syndrome. Int. J. Cardiol. Hyp. 5, 100032 https://doi.org/10.1016/j.ijchy.2020.100032.

Mueller, C., Lin, J., Sheriff, S., Maudsley, A., Younger, J., 2019. Evidence of widespread metabolic abnormalities in myalgic encephalomyelitis/chronic fatigue syndrome:

assessment with whole-brain magnetic resonance spectroscopy. Brain Imaging Behav. 14, 562–572.
Nakatomi, Y., Mizuno, K., Ishii, A., Wada, Y., Tanaka, M., Tazawa, S., Onoe, K., Fukuda, S., Kawabe, J., Takahashi, K., Kataoka, Y., Shiomi, S., Yamaguti, K., Inaba, M., Kuratsune, H., Watanabe, Y., 2014. Neuroinflammation in patients with chronic fatigue syndrome/myalgic encephalomyelitis: an $^{11}$C-(*R*)-PK11195 PET study. J. Nucl. Med. 55, 945–950.
Okada, T., Tanaka, M., Kuratsune, H., Watanabe, Y., Sadato, N., 2004. Mechanisms underlying fatigue: a voxel-based morphometric study of chronic fatigue syndrome. B. M. C. Neurol. 14, 4.
Raiser, T.M., Flanagin, V.L., Duering, M., van Ombergen, A., Ruehl, R.M., zu Eurenberg, P.R., 2020. The human corticocortical vestibular network. NeuroImage 223, 117362. https://doi.org/10.1016/j.neuroimage.2020.117362.
Seavedra, L.C., Mendonca, M., Fregni, F., 2014. Role of the primary motor cortex in the maintenance and treatment of pain in fibromyalgia. Med. Hypotheses 83, 332–336.
Silverstein, W.K., Noda, Y., Barr, M.S., Vila-Rodriguez, F., Rajji, T.K., Futzgerald, T.B., Downar, J., Mulsant, B.H., Vigod, S., Daskalakis, Z.J., Blumberger, D.M., 2015. Neurological predictors of response to dorsolateral prefrontal cortex repetitive transcranial magnetic stimulation in depression: a systematic review. Depress Anxiety 32, 871–891.
Tirelli, U., Chierichetti, F., Tavio, M., Simonelli, C., Bianchin, G., Zanco, P., Ferlin, G., 1998. Brain positron emission tomography (PET) in chronic fatigue syndrome: preliminary data. Am. J. Med. 105, 54S–58S.
Villamar, M.F., Wivatvongvana, P., Patumanond, J., Bikson, M., Truong, D.Q., Datta, A., Fregni, F., 2013. Focal modulation of primary motor cortex in fibromyalgia using 4×1-ring high-definition transcranial direct current stimulation (HD-tDCS): immediate and delayed analgesic effects of cathodal and anodal stimulation. J. Pain, 14, 371–383.
Wolfe, F., Smythe, M.B., Yunus, M.B., Bennett, R.M., Bombardier, C., Goldenberg, D.L., Tugwell, P., Campbell, S.M., Abeles, M., Clark, P., Fam, A.G., Farber, S.J., Fiechtner, J.J., Franklin, C.M., Gatter, R.A., Hamaty, D., Lessard, J., Lichtbroun, A.S., Masi, A.T., Mccain, G.A., Reynolds, W.J., Romano, T.J., Russell, I.J., Sheon, R.P., 1990. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Report of the multicenter criteria committee. Arthritis Rheum. 33, 160–172.
World Medical Association, 2013. Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 310, 2191–2194.
Yang, D.G., Gu, R., Kubo, J., Kakuda, W., 2020. Is the efficacy of repetitive transcranial magnetic stimulation influenced by baseline severity of fatigue symptom in patients with myalgic encephalomyelitis. Int. J. Neurosci. 130, 64–70.