

High-frequency rTMS for the Treatment of Chronic Fatigue Syndrome: A Case Series

Wataru Kakuda^{1,2}, Ryo Momosaki¹, Naoki Yamada¹ and Masahiro Abo¹

Abstract

Structural and functional abnormalities of the prefrontal cortex seem to correlate with fatigue in patients with chronic fatigue syndrome (CFS). We consecutively applied facilitatory high-frequency repetitive transcranial magnetic stimulation (rTMS) to the dorsolateral prefrontal cortex (DLPFC) of seven CFS patients over three days. Five patients completed the 3-day protocol without any adverse events. For the other two patients, we had to reduce the stimulation intensity in response to mild adverse reactions. In most of the patients, treatment resulted in an improvement of fatigue symptoms. High-frequency rTMS applied over the DLPFC can therefore be a potentially useful therapy for CFS patients.

Key words: repetitive transcranial magnetic stimulation, chronic fatigue syndrome, fatigue, prefrontal cortex, brain stimulation

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Introduction

Chronic fatigue syndrome (CFS) is a chronic, complex pathological condition characterized by extreme fatigue and other non-specific symptoms including pain, sleep disturbance and difficulty in concentration, which do not improve by rest alone (1, 2). CFS patients often experience significant disability in their activities of daily living (ADL) and thus may become homebound and bedbound. The etiology and pathogenesis of CFS remain unclear and there are no known effective treatments for this condition at present. However, recent studies identified certain functional and structural abnormalities in the brain of CFS patients (3-6), including lesions in the dorsolateral prefrontal cortex (DLPFC), which seems to be an important part of the neural network involved in the sensation of such fatigue symptoms.

Repetitive transcranial magnetic stimulation (rTMS) is a new neuromodulatory therapy used in patients with neurological and psychiatric disorders, such as stroke and depression (7, 8). The effect of rTMS on the local neural activity of the cerebral cortex differs depending on the frequency of stimulation. High-frequency rTMS (≥ 10 Hz) facilitates the

cortical neural activity, whereas low-frequency rTMS (≤ 1 Hz) suppresses the activity (9). To our knowledge, rTMS has not yet been used either therapeutically or for research purposes in CFS patients. Theoretically, the application of rTMS to the DLPFC should improve neural malfunction and thus improve such fatigue symptoms. The purpose of this pilot case-series study was to evaluate the safety and feasibility of high-frequency rTMS applied over the DLPFC in the treatment of CFS.

Case Report

This study was carried out in compliance with the Declaration of Helsinki. The study protocol and intervention were approved by the ethics committee of Jikei University School of Medicine (permitted number: 22-134 6311), and informed consent was obtained from all subjects before the study.

Seven CFS patients were enrolled as the subjects of this study. They comprised consecutive patients referred to our hospital as potential candidates for therapeutic high-frequency rTMS between October, 2015 and December, 2015. Each patient was admitted to the Department of Rehabilitation Medicine, Jikei Daisan Hospital, Tokyo, Japan, for

¹Department of Rehabilitation Medicine, The Jikei University School of Medicine, Japan and ²Department of Rehabilitation Medicine, Mita Hospital, International University of Health and Welfare, Japan

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Correspondence to Dr. Wataru Kakuda, wkakuda@iuhw.ac.jp

five days to receive high-frequency rTMS. Based on the known risks associated with rTMS application (10), the inclusion criteria were applied: 1) Meeting the diagnostic criteria for CFS formulated by the Centers for Disease Control and prevention (CDC) (1); 2) An age of between 15 and 70 years at study entry; 3) A period between disease onset and study entry of more than 6 months; 4) No past history of seizures; 5) No contraindications for rTMS as suggested in the guidelines established by Rossi et al (e.g., cochlear implants, medication pumps, implanted brain electrodes, pregnancy).

Each patient was hospitalized for 5 days in order to receive six treatment sessions of 25-minute high-frequency rTMS over three days (two sessions per day, excluding the days of admission and discharge). Throughout the 5-day hospitalization period, all patients were monitored continuously through clinical and neurological examinations by the attending physicians, with special attention paid to the development of adverse events associated with rTMS application, such as headache, nausea, and seizure attacks.

Application of high-frequency rTMS: For the delivery of high-frequency rTMS, a MagPro R30 stimulator (MagVenture Company, Farum, Denmark) equipped with a figure-of-eight stimulating coil was used. In the 25-minute high-frequency rTMS session, 10-Hz rTMS was applied in 10-second trains (100 pulses per train) with 50-second intervals between the trains (2,500 pulses per session). In total, high-frequency rTMS was delivered for 50 minutes (5,000 pulses) per day (i.e., 150 minutes or 15,000 pulses, over three days). For this study, the DLPFC of the dominant hemisphere was selected as the target area for high-frequency rTMS. To determine the location of DLPFC, the international 10-20 system for electroencephalograms was used, since the methods for establishing specific cortical areas with this system are relatively widely accepted (11). It has been reported that the F3 and F4 positions identified by the 10-20 system correspond to left and right DLPFC, respectively (12). Therefore, the stimulating coil was placed on the F3 in right-handed and F4 in left-handed patients. To determine the intensity of stimulation, the resting motor threshold was measured for the first dorsal interosseous muscle of the contralateral upper limb of the dominant hemisphere. The intensity of stimulation was set at 90% of the measured resting motor threshold. During rTMS 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.

Clinical evaluation of fatigue: For the evaluation of the fatigue symptoms, two self-assessment scales, including the Visual Analogue Scale (VAS) rate for fatigue and the Brief Fatigue Inventory (BFI) were applied. The VAS rate was evaluated before the first session of rTMS, 1 hour after the first session, 24 hours after the first session, at discharge, and one/two weeks after discharge. At the time of evaluation,

the patient was asked to rate the severity of the fatigue symptoms using a 10-cm horizontal line with a “score of 0” meaning “no pain” written on the left end and a “score of 10” meaning the “worst imaginable fatigue” on the other end (13). For this study, we calculated the VAS rate, which was defined as the relative value of fatigue severity at the time after rTMS application in comparison to that before the first rTMS application for each patient. The VAS rate was calculated by the following equation: $\text{VAS rate (\%)} = \text{VAS score at after rTMS application} / \text{VAS score before the first rTMS session} \times 100$. The VAS rate before rTMS was considered to be 100, and any decrease in the VAS rate indicated an improvement in fatigue.

In addition, the BFI consisting of nine questionnaire items was evaluated before the first session of rTMS, at discharge, and one/two weeks after discharge (14).

The first three items of the BFI assess the current, usual and worst fatigue in the past 24 hours. The next six items evaluate the extent to which fatigue interfered with different aspects of life, such as work or social relations, during the preceding 24 hours. Each of the items rates fatigue severity on a 0-to-10 scale, with a score of “0” representing “no fatigue” or “no impact on functioning”, and “10” being the “worst fatigue” or “fatigue that dramatically interferes with normal daily functioning”. The mean score of the nine items was calculated and recorded. For this study, the Japanese version of BFI (BFI-J) was used, since Japanese was the native language of all studied patients. The validity and reliability of this version of BFI has already been confirmed (15).

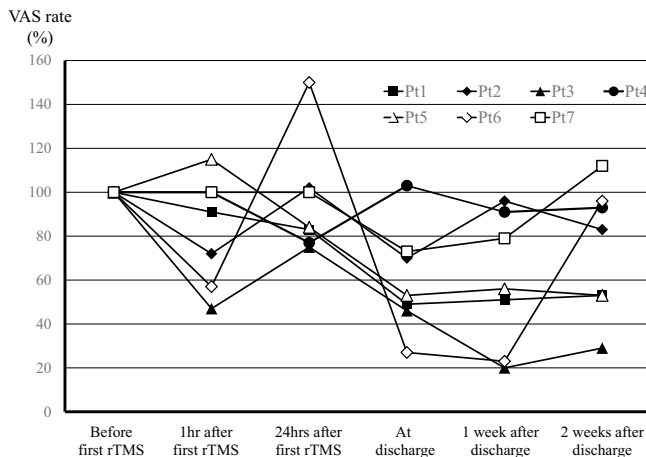
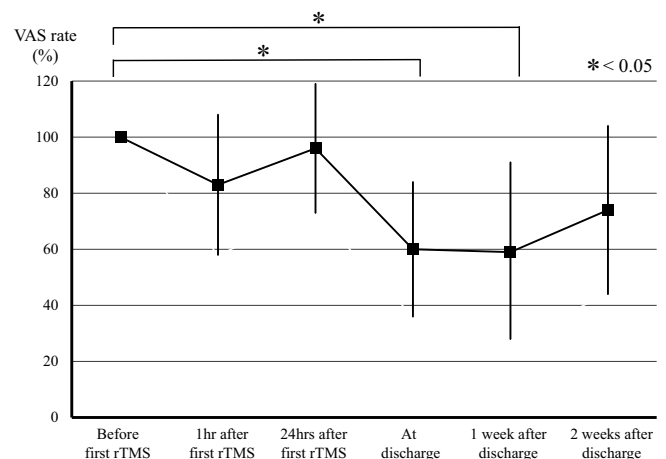
Statistical analysis: Data are expressed as the mean \pm SD. Differences in BFI and VAS between before rTMS and at the time points after rTMS application were examined for statistical significance using Dunnett’s multiple comparison test. A p value of less than 0.05 was considered to be statistically significant. All statistical analyses were performed using The Statistical Package for Social Sciences, v17.0 (SPSS Inc., Chicago, IL, USA).

Results: Table summarizes the clinical features of the participating patients. The mean age at admission was 37.0 \pm 13.2 years, and the time between the onset of the fatigue symptoms and the commencement of therapeutic rTMS ranged from 3 to 11 years. Six patients were right-handed, thus suggesting a dominant left cerebral hemisphere. No patient had a history of any major depression.

Among the seven patients, 5 completed the scheduled six rTMS sessions over three days. These 5 patients showed no adverse events during hospitalization. The other two studied patients (Patients 6 and 7) showed certain pathological reactions that could be considered adverse events of rTMS application. One patient experienced nausea, vomiting and headache after two sessions of rTMS. The other patient developed acute hypotension due to vasovagal reflex during the first session of rTMS. However, the symptoms were transient in both patients and disappeared within several hours without any medical intervention. Therefore, after

Table. Clinical Characteristics of the Patients.

Patient number	1	2	3	4	5	6	7
Gender	Female	Female	Male	Female	Female	Female	Male
Age at admission (years)	57	42	17	41	33	25	44
Duration of illness (years)	3	5	3	7	11	3	9
Handedness	Right	Right	Right	Right	Right	Right	Left
Karnofsky Performance Status at admission (%)	60	80	70	90	80	60	70
Comorbidity	None	Fibromyalgia	Irritable bowel syndrome	None	None	Fibromyalgia	None
Number of rTMS session provided during hospitalization	6	6	6	6	6	3	2

**Figure 1a. Changes in VAS in individual patients.****Figure 1b. Mean change in VAS in the entire group.**

more than 24 hours, one 25-minute session of 10-Hz high frequency rTMS with a stimulation intensity of 80% was administered to both patients. After the session with less intensity, none of the two patients showed any adverse symptoms. None of the seven patients experienced any pathological symptoms during the two-week period after discharge.

Fig. 1a shows the effect of rTMS on the VAS rate. One hour after the first rTMS session, two patients showed a more than 30% decrease in the VAS rate. At discharge, five patients showed a more than 30% decrease in the rate. Of these, three patients exhibited a more than 50% decrease in the VAS rate. Furthermore, four patients showed a more than 30% decrease in one week and in three patients two weeks after discharge. The mean VAS rate decreased by 17% at one hour after the first rTMS session ($p=0.59$, Fig. 1b). The decrease in the rate from the baseline value before the first rTMS was significant not only at discharge, but also at one week after discharge (all $ps < 0.05$). However, the decrease in the VAS rate relative to the baseline at two weeks after discharge was not significant ($p=0.21$).

Figs. 2a and 2b show the change in the BFI score for each patient and the mean change in BFI for all patients, respectively. At discharge, a decrease in the BFI score of more than one point was found in six patients. The decrease in the mean score from the baseline score before the first rTMS was significant only at discharge ($p < 0.05$).

Discussion

Several neuroimaging studies have demonstrated the presence of local functional or structural abnormalities in certain brain areas in CFS patients, and suggested that these local abnormalities in the brain can contribute to the development of fatigue. The initial studies demonstrated the presence of regional SPECT abnormalities in certain cortical areas of CFS patients, including the frontal, parietal and temporal cortex (3). A subsequent study using ^{18}F FDG PET showed a hypometabolism in the mediofrontal cortex and brainstem of CFS patients (4). Furthermore, $[2-^{11}\text{C}]$ acetylcarnitine PET studies showed significantly low acetylcarnitine uptake levels in DLPFC, temporal cortex and cingulate cortex in CFS patients, suggesting a possible neural circuitry malfunction in these areas (5). Other MRI-based studies identified a smaller gray-matter volume in the prefrontal cortex in CFS patients (6). Based on the above reports, one can speculate that the fatigue symptom in these patients can be clinically alleviated by modulating the neural activity in these areas.

Among these areas showing local abnormalities in CFS patients, the DLPFC has been especially considered to be an important part of the neural network involved in regulating the sense of fatigue. For example, a malfunction of the DLPFC is considered to cause a functional interruption of the striatal-thalamic-frontal cortical loop, resulting in an en-

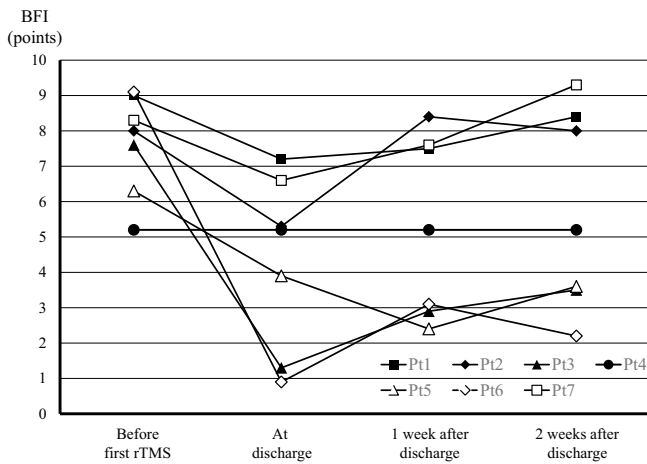


Figure 2a. Changes in BFI in individual patients.

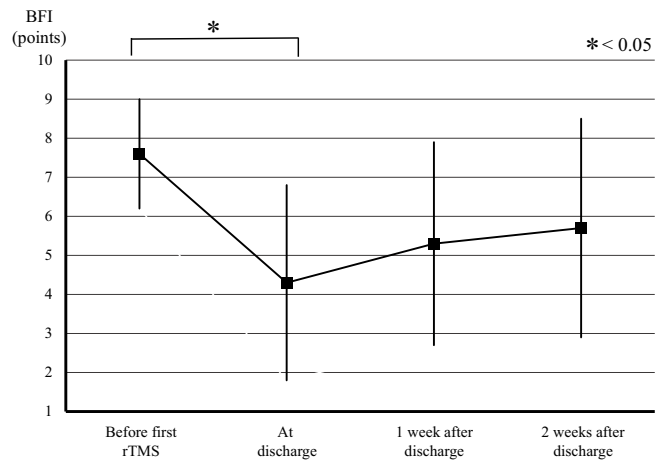


Figure 2b. Mean change in BFI in the entire group.

hanced fatigability (16). Another study showed that cognitive behavioral therapy improved the fatigue symptoms and that such an improvement correlated with increased grey matter volume of the prefrontal cortex, including the DLPFC (17). Furthermore, unlike other pathological areas in CFS patients, the DLPFC is superficially located on the surface of the brain, which thus makes it easier to target by rTMS. We considered that high-frequency rTMS can stimulate the DLPFC and increase the neural activity in that area, leading to the alleviation of fatigue symptoms. The results of this pilot study showed the safety of high-frequency rTMS (only two patients developed mild adverse events). The fatigue symptoms had improved significantly at discharge, and this beneficial effect was maintained until at least one week after discharge. To our knowledge, this is the first report that describes the safety, feasibility and clinical usefulness of high-frequency rTMS over DLPFC for CFS patients.

For stroke patients, it has been reported that interhemispheric inhibition is disrupted. Due to the occurrence of a stroke lesion, the inhibition towards the lesional hemisphere is pathologically increased. To modulate such a disruption of the inhibition, suppressive low-frequency rTMS is applied over the non-lesional hemisphere as a therapeutic tool for stroke patients. However, for CFS patients, no researcher reported the development of such a disruption in the interhemispheric inhibition. Therefore, we determined to apply high-frequency rTMS in order to activate the target area directly for our CFS patients, instead of low-frequency rTMS. While our pilot study did not investigate the underlying mechanisms for the obtained improvement, we speculate that the effect was mediated through the neural activation of the DLPFC in the dominant hemisphere. To determine the mechanism of this improvement, future studies using functional neuroimaging, such as functional MRI or PET, are needed.

In this study, the stimulation intensity was set at 90% of the motor threshold of the finger muscle in the contralateral upper limb. This selection was based on previous studies

that demonstrated good tolerance of rTMS applied at this intensity in patients with chronic stroke and depression (18, 19). Interestingly, the two patients who developed adverse reactions were able to tolerate high-frequency rTMS at a reduced stimulation intensity and thereafter showed an improvement in fatigue symptoms. The optimal intensity of rTMS for CFS patients should be determined for a safe and useful introduction of rTMS for such patients. The treatment protocol included six 25-minute rTMS sessions applied over three days. This was based on previous studies that demonstrated the superiority of several applications of rTMS over several days compared to a single application in stroke patients (20). However, the duration of each rTMS session and the total number of rTMS sessions were determined arbitrarily. It is desired to investigate the optimal treatment duration for CFS patients. Such an investigation could help to elucidate the correlation between the length of treatment and the long-term clinical benefits.

The present study has certain limitations. First, this is a case-series pilot study with only a small number of patients that lacked a control group. Comparative studies, such as randomized controlled design studies that include a large number of patients, are needed to confirm the efficacy of rTMS in CFS patients. Second, although all patients met the inclusion criteria for rTMS application, they were a heterogeneous group based on the wide variability of age, duration of illness and severity of the fatigue symptoms. The identification of the clinical factors that correlate with the efficacy of rTMS can help in the selection of patients who will best benefit from the treatment. Third, although it is difficult to stimulate deep brain lesions using the currently available technology, the stimulation of other brain areas with functional or structural abnormalities in CFS, such as the cingulate cortex and brainstem, may produce a better clinical improvement. Furthermore, for one left-handed patient, we applied high-frequency rTMS to the right hemisphere unlike the other six patients. The appropriateness of this therapeutic strategy of rTMS depending on whether patients were right-handed or left-handed should be also confirmed.

The present pilot study demonstrated the feasibility and safety of high-frequency rTMS applied over the DLPFC for the treatment of CFS patients. Further large-scale studies are needed to confirm the therapeutic benefits of high-frequency rTMS, determine the optimal cortical target area and find the optimal duration and intensity of treatment for CFS.

All procedures performed in this study were in accordance with the ethical standards of the institutional and national research committees and with the 1964 Helsinki declaration and its later amendments.

Informed consent was obtained from all individual participants included in the study.

The authors state that they have no Conflict of Interest (COI).

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