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ORIGINAL ARTICLE

Effect of Repetitive Transcranial Magnetic Stimulation on Long Coronavirus Disease 2019 with Fatigue and Cognitive Dysfunction

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Objectives: There is no established treatment for chronic fatigue and various cognitive dysfunctions (brain fog) caused by long coronavirus disease 2019 (COVID-19). We aimed to clarify the effectiveness of repetitive transcranial magnetic stimulation (rTMS) for treating these symptoms. **Methods:** High-frequency rTMS was applied to occipital and frontal lobes in 12 patients with chronic fatigue and cognitive dysfunction 3 months after severe acute respiratory syndrome coronavirus 2 infection. Before and after ten sessions of rTMS, Brief Fatigue Inventory (BFI), Apathy Scale (AS), and Wechsler Adult Intelligence Scale-fourth edition (WAIS4) were determined and *N*-isopropyl-*p*-[^{123}I]iodoamphetamine single photon emission computed tomography (SPECT) was performed. **Results:** Twelve subjects completed ten sessions of rTMS without adverse events. The mean age of the subjects was 44.3 ± 10.7 years, and the mean duration of illness was 202.4 ± 114.5 days. BFI, which was 5.7 ± 2.3 before the intervention, decreased significantly to 1.9 ± 1.8 after the intervention. The AS was significantly decreased after the intervention from 19.2 ± 8.7 to 10.3 ± 7.2. All WAIS4 sub-items were significantly improved after rTMS intervention, and the full-scale intelligence quotient increased from 94.6 ± 10.9 to 104.4 ± 13.0. Hypoperfusion in the bilateral occipital and frontal lobes observed on SPECT improved in extent and severity after ten sessions of rTMS. **Conclusions:** Although we are still in the early stages of exploring the effects of rTMS, the procedure has the potential for use as a new non-invasive treatment for the symptoms of long COVID.

Key Words: long COVID; non-invasive brain stimulation; severe acute respiratory syndrome coronavirus 2

INTRODUCTION

The coronavirus 2019 (COVID-19) pandemic continues to have a huge negative impact on the world. To date, more than 8.3 million people have been infected in Japan, and the cumulative number of deaths has exceeded 30,000 (as of May 18, 2022). Although COVID-19 is considered to be a causative virus of severe pneumonia, the virus also harms other areas of the body in addition to the lungs because it enters through the ACE2 membrane protein. This means that the virus can be widely distributed in other parts of the body, allowing it to cause inflammation and necrosis of the heart, kidneys, intestines, and vascular endothelium.[1)] Furthermore, inflammation of the vascular endothelium induces vascular events in the brain and heart.[2)] Moreover, sequelae that continue for a long time occur at a high rate after the patient has been cured of the initial viral infection. Long COVID[3)] is a post-COVID-19 condition that is characterized by persistent sequelae, which can include chronic fatigue, cognitive dysfunction (e.g., decreased memory/spontaneity) collectively

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referred to as brain fog, chest symptoms (e.g., shortness of breath and chest pain), gastrointestinal symptoms, muscle and joint pain, psychiatric symptoms (e.g., depression), otolaryngological symptoms (e.g., impaired sense of taste and smell), and dermatological symptoms.[4] Similarly, in the 1918 Spanish flu, 40% of survivors were found to have chronic fatigue, lethargy, and poor concentration. Similar symptoms were observed in approximately 30% of Severe Acute Respiratory Syndrome (SARS) survivors in 2002 and 20% of Middle East Respiratory Syndrome (MERS) survivors in 2012.[5] Because these sequelae last for a long period, the number of patients will continue to increase even if the pandemic wave ends, affecting social and economic activities.

Although no effective treatment exists for these sequelae, we have started therapeutic intervention using repetitive transcranial magnetic stimulation (rTMS) for chronic fatigue associated with long COVID and cognitive dysfunction (brain fog) since September 2021. rTMS is a non-invasive brain stimulation that changes local neural activity in the brain using a magnetic field from a coil placed on the surface of the head. In addition to being covered by insurance for depression, this treatment is effective against various brain-derived symptoms such as post-stroke paralysis and higher brain dysfunction.[6] To the best of our knowledge, this is the first report to describe the effect of rTMS on chronic fatigue and cognitive dysfunction in long COVID.

MATERIALS AND METHODS

At our hospital, we conduct therapeutic interventions with rTMS for various cognitive dysfunctions derived from the brain, with the approval of the Committee on Unapproved Medical Devices and Therapies (approval number 5389). We retrospectively analyzed changes in chronic fatigue, cognitive function, and single-photon emission computed tomography (SPECT) in long COVID patients who underwent rTMS.

Subjects

The subjects were patients who visited our outpatient department from September 8, 2021, to April 11, 2022, and met the following criteria: 1) age of 16 to 60 years; 2) diagnosed with COVID-19 for at least 3 months; 3) had chronic fatigue (beyond the need to rest at home and unable to socialize or work for several days a month), decreased spontaneity, and cognitive dysfunction (e.g., memory disorder, brain fog); 4) consented to undergo regular outpatient rTMS; and 5) completed a total of ten sessions of rTMS every 1–2 weeks without adverse events. Given that rTMS stimulates the brain using electromagnetic waves, those with metal implants or tattoos on the head and neck, those with a cardiac pacemaker, and those with a history of epileptic seizures were excluded from the study. Additionally, those with a history of cognitive dysfunction or psychiatric disorders before COVID-19 and those with significant lesions on brain magnetic resonance imaging (MRI) or head computed tomography (CT) were excluded from the analysis.

Application of RTMS

An 80-mm double-cone coil and a MagPro R30 stimulator (MagVenture, Denmark) were used for rTMS. The two stimulation sites were located on the midline of the forehead 45° above the external auditory meatus and the midline of the occipital region 135° above the orbitomeatal line (**Fig. 1**). A double-cone coil was installed at each site to be orthogonal to the midsagittal plane. First, 1200 10-Hz rTMS (10-s stimulation at 10 Hz and 10-s inter-train intervals were repeated alternately) were applied to the occipital region, followed by another 1200 10-Hz rTMS to the forehead in one session. This was done consecutively 10 times once every 1–2 weeks (24,000 stimuli in total). The stimulus intensity was set to 80% of the minimum resting motor threshold (RMT) at which contralateral index finger movement was induced by stimulation of the hand motor cortex.

Assessments

The Brief Fatigue Inventory (BFI) and Apathy Scale (AS) were evaluated for all cases immediately before the start of the first rTMS, immediately after the end of the first rTMS, and immediately after the end of the tenth rTMS. BFI is used for assessing patient fatigue, such as in cancer; a higher score on a 10-point scale indicates higher fatigue.[7] AS is an evaluation of spontaneity; a higher score indicates lower spontaneity.[8] Both are simple questionnaire tests that can be performed in a few minutes.

Detailed cognitive function was evaluated using the Wechsler Adult Intelligence Scale-fourth edition (WAIS4) immediately before the start of the first rTMS session and immediately after the end of the tenth rTMS session. WAIS4 calculates the overall full-scale intelligence quotient (FSIQ) for cognitive function between the ages of 16 and 90 years based on the evaluation of the verbal comprehension index (VCI), perceptual reasoning index (PRI), working memory index (WMI), and processing speed index (PSI).[9] Because testing took approximately 1–2 h to conduct and the cogni-

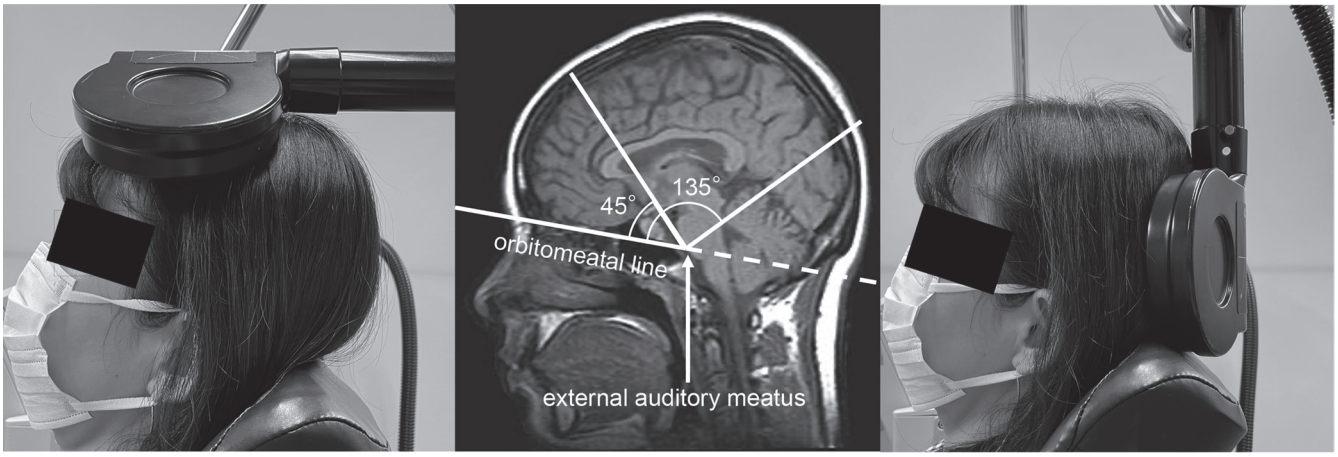

Fig. 1. Stimulation site of rTMS. Double-cone coils were installed at two locations on the midline of the forehead 45° above the external auditory meatus and on the midline of the occipital region 135° above the orbitomeatal line to straddle the left and right cerebrums. This allowed the simultaneous stimulation of the dlPFC and the occipital cortex on both sides.

tive load was high, subjects who wished to discontinue the testing were not forced to continue.

For consenting patients, cerebral blood flow was measured using *N*-isopropyl-*p*-[^{123}I]iodoamphetamine (^{123}I-IMP) SPECT within 1 month before the start of a series of rTMS interventions and within 1 month after the end of the intervention. For cerebral blood flow data of patients able to receive SPECT twice (before and after intervention), the blood flow deviation value (Z-score) with respect to the normal database of the same age group was calculated pixel by pixel based on the cerebellum using three-dimensional stereotactic surface projection (3D-SSP).[10] A decreased image was constructed as a group by averaging between groups before and after rTMS.

Data Analysis

To confirm the bias between all long COVID patients who visited our outpatient department for the purpose of treatment and the subjects of this analysis, the data for each were compared. The categorical data, such as the male/female ratio, the presence or absence of hospitalization in the acute phase of SARS-CoV-2 infection, and the presence or absence of intensive care unit management, were analyzed using the chi-square test. The continuous data such as age and duration of illness were analyzed using the unpaired *t*-test.

Bonferroni multiple comparisons were conducted after performing the Friedman test to see if there was a difference in the transition of the evaluation points of BFI and AS between the three phases [immediately before the start of the first rTMS (Pre), immediately after the end of the first rTMS (immediately after: IA), and immediately after the end of the tenth rTMS (Post)]. For each IQ component of WAIS4, the Wilcoxon signed-rank test verified whether there was a difference between the two phases (Pre and Post). JMP-16 (SAS Institute, Cary, NC, USA) was used for statistical analysis, and $P < 0.05$ was considered statistically significant.

Ethical Approval

This study was approved by the ethics committee of St. Marianna University School of Medicine (approval number 5590). Patients were briefed on this intervention and informed that they could withdraw from the study at any time. The subjects provided written consent before participating in the study.

RESULTS

Fourteen patients completed ten rTMS sessions within the study period with no adverse event; 2 of them were excluded from the analysis because of a history of mental illness. All 12 subjects were right-handed, and no organic abnormalities were observed on head CT or brain MRI. **Table 1** shows the characteristics of the 12 subjects who were included in the analysis. The average age was 44.3 ± 11.4 years, and the average duration of illness was 202.4 ± 114.5 days. Only 2 patients had a history of acute hospitalization, and neither required treatment in the intensive care unit. The average time to to complete ten rTMS sessions was 78.6 ± 16.3 days, and many patients received the treatment once a week.

All 12 subjects that were analyzed were evaluated for BFI

Table 1. Characteristics of studied subjects

Characteristic	
Sex, male/female	8/4
Age, years	44.3 (10.7)
Duration of illness, days	202.4 (114.5)
History of hospitalization in acute phase, yes/no	2/10
History of ICU management, yes/no	0/12
Study period, days	78.6 (16.3)

Data given as number or mean (standard deviation).
ICU, Intensive care unit.

and AS in the three phases (Pre, IA, and Post rTMS). During WAIS4 assessment, 4 patients requested discontinuation, and 8 patients were evaluated for Pre/Post. SPECT before and after the intervention was performed in 9 patients. In the multiple comparison analysis, the Post rTMS BFI was 1.9 ± 1.8, which was significantly lower than the BFI values for Pre rTMS (5.7 ± 2.3) and IA (5.1 ± 2.2) ($P < 0.01$) (**Fig. 2A**). Similarly, the Post rTMS AS of 10.3 ± 7.2 was significantly lower than the AS values for Pre rTMS (19.2 ± 8.7) and IA rTMS (16.3 ± 7.0) ($P < 0.05$). Furthermore, IA rTMS AS was significantly lower than Pre rTMS AS ($P < 0.05$) (**Fig. 2B**).

Table 2 shows the changes in WAIS4 components between the Pre and Post rTMS assessments. All IQ components of WAIS4 (VCI, PRI, WMI, PSI, and FSIQ) were significantly improved at the Post assessment (all $P < 0.05$). In the average image of SPECT obtained from nine subjects before rTMS was performed (Pre), a wide range of decreased blood flow was shown mainly in the occipital cortices, the dorsolateral prefrontal cortices (dlPFC), and the superior longitudinal fasciculus (SLF) (slightly right dominant) that connects them. In contrast, after rTMS was performed (Post), there was a marked decrease in the range of decreased blood flow. Although the tendency of decreased blood flow remained in both the occipital lobe and the frontal lobe, the level of blood flow clearly improved (**Fig. 3**).

DISCUSSION

This is the first report to show the effect of rTMS on chronic fatigue and cognitive dysfunction (brain fog) in long COVID. Our rTMS intervention significantly improved chronic fatigue and spontaneity and significantly improved all IQ components of WAIS4. Furthermore, the range and degree of decreased cerebral blood flow may be improved.

rTMS Setup

By passing an electric current through the coil, rTMS generates a magnetic field that is orientated orthogonally

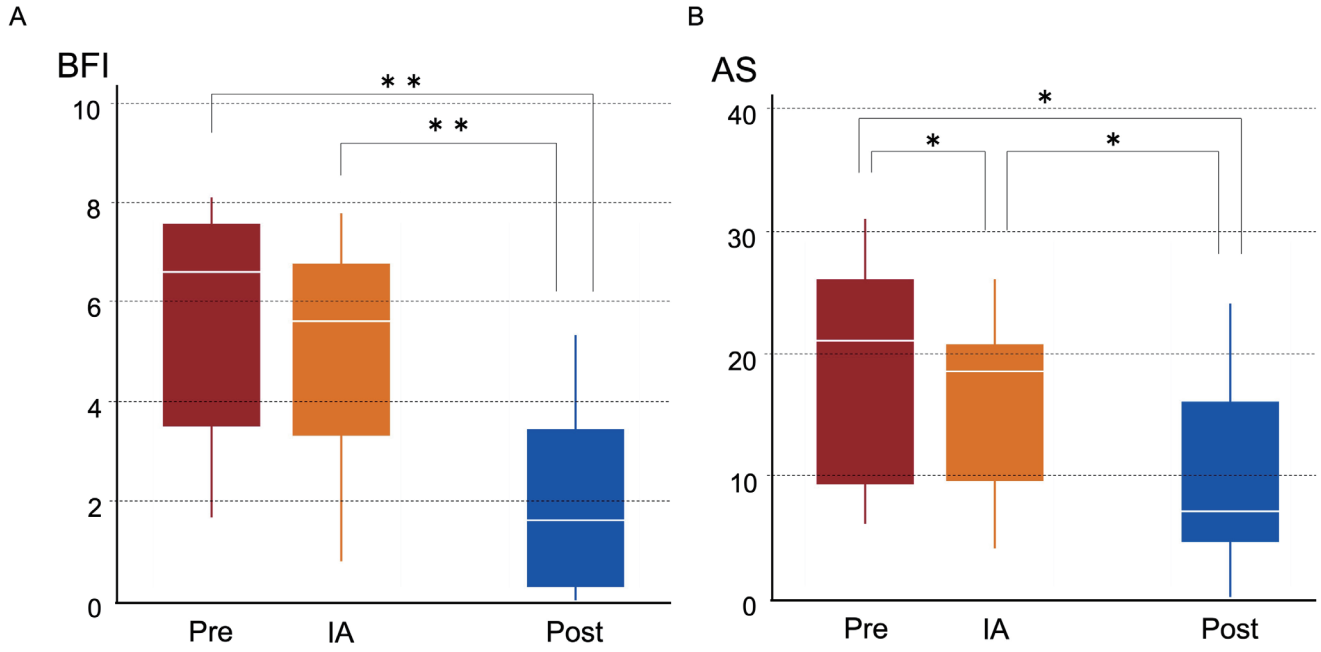

Fig. 2. Changes in BFI (A) and AS (B) during the intervention. Compared with before the start of rTMS (Pre), both BFI and AS tended to decrease immediately after the first administration (IA), and the change in AS was statistically significant. After ten rTMS sessions (Post), both BFI and AS were significantly decreased compared with Pre. **, $P < 0.01$; *, $P < 0.05$.

Table 2. Changes in IQs of WAIS4 before rTMS and after ten sessions of rTMS

	Pre	Post	P value
FSIQ	94.6 (10.9)	104.4 (13.0)	< 0.05
VCI	93.5 (9.0)	100.5 (10.0)	< 0.05
PRI	95.4 (11.5)	106.4 (10.3)	< 0.05
WMI	97.9 (17.5)	105.5 (19.5)	< 0.05
PSI	95.4 (11.5)	106.4 (10.3)	< 0.05

Data are expressed as mean (standard deviation).

to the coil. With the coil positioned on the surface of the head, the local magnetic field stimulates the local cerebral cortex by inducing an eddy current in the opposite direction to that in the coil.[11] When the stimulus is applied at a high frequency of 5 Hz or higher, the stimulated cerebral cortex is activated. Conversely, when the stimulus is applied at a low frequency of 1 Hz or lower, cerebral cortex activity is suppressed.[12] In the current study, we believed that activating stimulation was required at the selected sites, so 10-Hz rTMS was applied. The coil used for stimulation was a double-cone coil in which the lines of magnetic force were crossed by tilting the two coils while in contact with each other to increase the focal point and depth of stimulation.[13] Originally, rTMS was developed for deep stimulation of the lower limb motor cortex.[14] However, a wide magnetic field is also generated directly under each coil, and the range of the magnetic field was considered to involve the bilateral dlPFC or bilateral occipital cortices under each coil installation. In addition, we expected that a stronger stimulus would be exerted on the medial cortex where the lines of magnetic force overlap. However, the visual cortex extends to the medial occipital cortex, and the medial frontal cortex is a site involved in spontaneity. We have previously reported that 10-Hz rTMS to the medial frontal cortex using a double-cone coil effectively improves apathy.[15] Similarly, the AS, which was high before the rTMS intervention, improved after the intervention. In addition, because the outer part of the dlPFC (Brodmann area 46) is near the magnetic field boundary, we considered that dual installation of the coil to stimulate each dlPFC separately may be worthwhile. However, from the viewpoint of feasibility and to improve apathy, we selected the stimulation sites as used in this study. The intensity of rTMS applied in this study was 80% of the RMT, which is the same setting for apathy we have reported previously.[15] In depressive disorders, the standard stimulus intensity to the left dlPFC is about 100%–120% of the RMT, usually with a figure-of-eight coil.[16] However, in many cases, that intensity is too painful for the patient when a double-cone coil is installed. Preceding occipital stimulation was used to allow patients to experience the treatment discomfort, and many patients tolerated our rTMS. rTMS is generally performed on consecutive days. However, our patients had difficulty making consecutive outpatient visits and may have experienced post-exertional malaise had they been forced to do so.[17] We also believe that treatment frequency is an important matter to consider; therefore, there is a need for comparative studies to assess whether the treatment should be given once a week

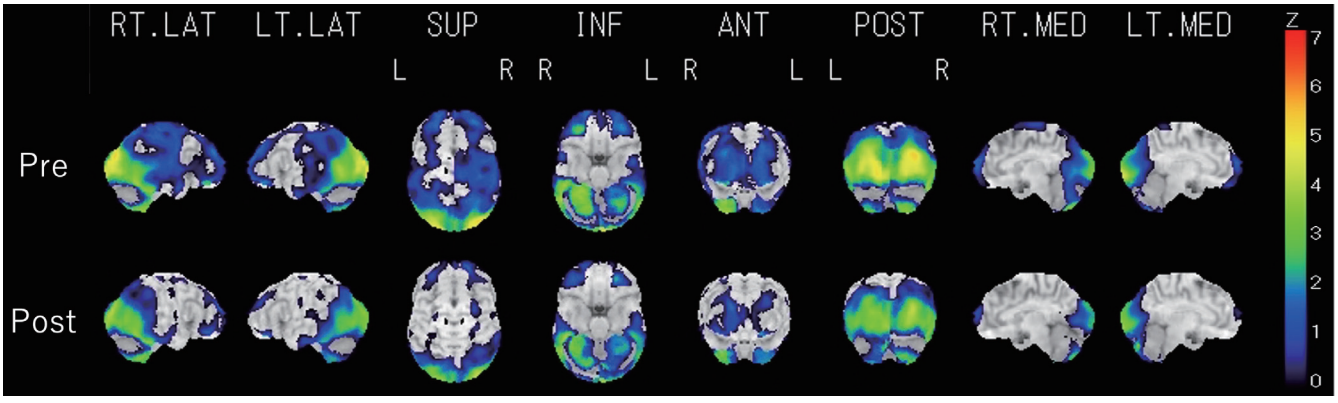

Fig. 3. Changes in decreased cerebral blood flow before and after rTMS. Before the start of rTMS (Pre), a wide range of decreased blood flow was observed in the superior longitudinal fasciculus (right dominant) that connects the bilateral occipital cortices and the lateral cortices of the bilateral frontal lobes. After ten rTMS sessions (Post), the site of decreased blood flow was considerably reduced in size, and its degree (Z-score) improved even in the occipital cortices where the decreased blood flow remained. RT.LAT, right lateral aspect; LT.LAT, left lateral aspect; SUP, superior aspect; INF, inferior aspect; ANT, anterior aspect; POST, posterior aspect; RT.MED, right medial aspect; LT.MED, left medial aspect; L, left; R, right; Z, Z-score.

(as in this study) or every day during short-term hospitalization.

Activation Sites

First, both occipital cortices and then both dlPFCs were the most prominent sites of decreased cerebral blood flow as observed by SPECT (**Fig. 3**). Before starting this rTMS intervention, we performed SPECT to assess cognitive function in several other patients with long COVID. In all of them, decreased blood flow was conspicuous in these regions. We selected ^{123}I-IMP as a tracer because of its high linearity[18] and the pathological change of the blood–brain barrier (BBB) from SARS-CoV-2 infection.[19] ^{99m}Tc-ethyl cysteinate dimer leads to inaccurate assessment when there is a breach in the BBB.[20] Strong fatigue was previously reported to be the most common sequelae observed in approximately 40% of patients,[21] and, similarly, fatigue was a common complaint among our subjects. However, as a clinical impression, symptoms related to visual input and analysis (e.g., inability to remember a person's face, being unable to instantly identify an object by looking at it) are relatively common in the background of fatigue. Even with verbal cognitive dysfunction, complaints of symptoms related to letters were particularly common. Some patients were unable to classify characters and patterns on signboards.

The occipital cortex and dlPFC are strongly linked regions of the brain. Information that is visually input to the occipital cortex is transferred via the SLF to the visual sketchbook (one of the components of working memory) in the dlPFC where it is temporarily stored and then analyzed for various cognitive activities.[22,23] That process also applies to textual information handled in the linguistic area. If a person is right-handed, the left cerebrum is mainly involved in linguistic cognition, and the right cerebrum is mainly involved in visual cognition. The fact that SLF showed a slightly right-dominant decrease in blood flow in SPECT before intervention may indicate that this visual cognition is more involved. Even for linguistic symptoms, many complaints involved reading characters regarding visual perception, such as being unable to recognize characters instantly, being unable to understand short sentences even after re-reading them, and being extremely tired.

Although there are no reports of rTMS applied to the occipital region as a therapeutic intervention, it has been reported that inhibitory low-frequency rTMS to the occipital cortex reduces working memory in the dlPFC.[24] Therefore, it may be reasonable to consider that activating the occipital cortex with facilitatory high-frequency rTMS enhances various functions in the dlPFC. The cognitive dysfunction caused by long COVID is known to include a variety of symptoms,[25] and it may be classified into several categories in the future, for example, through cluster analysis. The site of decreased cerebral blood flow and specific symptoms vary from case to case. Ideally, the causative brain site should be determined individually, and tailored rTMS should be applied. However, this study is still in the earliest stage of verifying the effectiveness of rTMS. Therefore, considering the feasibility of therapeutic intervention for the group, the most relevant occipital cortex and both dlPFCs were selected as activation sites. Given that improvement was observed in BFI, AS, and WAIS4, and an improving trend was also observed in cerebral blood flow, we considered that this judgment was valid.

Relationship with Myalgic Encephalomyelitis/chronic Fatigue Syndrome

Questions remain over whether long COVID is the same as myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Both conditions have very similar characteristics, such as chronic, strong fatigue and various other symptoms, including cognitive dysfunction,[26] and both are triggered by prior viral infection.[27] Although ME/CFS is a pathological condition for which details are unclear, long COVID can be considered a type of ME/CFS.

Cerebral blood flow decreases in ME/CFS,[28] and it is speculated that the dlPFC and SLF, especially on the right side, are deeply involved in the presentation of symptoms.[29,30] However, the occipital lobe was clearly the most prominent site of decreased cerebral blood flow in the subjects of this study. Therefore, future studies should clarify whether this is a characteristic peculiar to long COVID and whether there are differences depending on the COVID-19 variant. However, even in ME/CFS, viral infection is only a trigger, and the causes of symptoms that appear, such as autoimmune responses, changes in stress, and genetic effects, are complex.[27] Increases in pro-inflammatory cytokines have also been observed in long COVID.[27] Furthermore, the psychological burden of a global pandemic, such as changes in social conditions, changes in one's life, and confusion caused by the flood of information, may differ from that of ME/CFS. Few studies have applied rTMS to treat ME/CFS, but all of them have yielded positive results.[31,32]

There are some limitations to this study. First, this was an observational study with a small sample size and without a control group; the psychological bias of receiving special treatment may have influenced the results. Additionally, because rTMS was consecutively performed ten times (once/

week) in this study protocol, an average of 78.6 days was required for a relatively long-term intervention. Therefore, the possibility of spontaneous recovery cannot be ruled out, even though the symptoms persisted for months. Randomized controlled trials are necessary to resolve these uncertainties; however, it is ethically difficult to set up a control group given that long COVID, which occurs simultaneously and frequently, has evolved into a social problem. Therefore, we are considering a crossover trial with other treatments. Lastly, the present protocol was an experimental one considered from the feasibility perspective, and we do not consider it optimal. In modifying the protocol, there are several aspects to consider, such as the stimulation site, the number of stimulations, and the frequency.

CONCLUSION

The rTMS conducted in this study improved long COVID fatigue and cognitive symptoms as observed with SPECT findings. Because long COVID lasts for a long period, the number of patients developing long COVID will continue to increase with each wave. Furthermore, considering that the COVID-19 pandemic has occurred simultaneously worldwide, a huge wave of long COVID can be expected to develop on a global scale. Although this study is only in the early stages of exploring the effects of rTMS, the procedure has the potential to be a new treatment that can improve the symptoms of long COVID in a relatively simple and non-invasive manner.

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CONFLICTS OF INTEREST

The authors have no conflict of interest to declare.

REFERENCES

1. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, Mehra MR, Schuepbach RA, Ruschitzka F, Moch H: Endothelial cell infection and endotheliitis in COVID-19. Lancet 2020;395:1417–1418. https://doi.org/10.1016/S0140-6736(20)30937-5, PMID:32325026
2. Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, Vanstapel A, Werlein C, Stark H, Tzankov A, Li WW, Li VW, Mentzer SJ, Jonigk D: Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. N Engl J Med 2020;383:120–128. https://doi.org/10.1056/NEJMoa2015432, PMID:32437596
3. Alwan NA: The road to addressing long Covid. Science 2021;373:491–493. https://doi.org/10.1126/science.abg7113 , PMID:34326224
4. Soriano JB, Murthy S, Marshall JC, Relan P, Diaz JV, WHO Clinical Case Definition Working Group on Post-COVID-19 Condition: A clinical case definition of post-COVID-19 condition by a Delphi consensus. Lancet Infect Dis 2022;22:e102–e107. https://doi.org/10.1016/S1473-3099(21)00703-9 , PMID:34951953
5. Poenaru S, Abdallah SJ, Corrales-Medina V, Cowan J: COVID-19 and post-infectious myalgic encephalomyelitis/chronic fatigue syndrome: a narrative review. Ther Adv Infect Dis 2021;8:20499361211009385. https://doi.org/10.1177/20499361211009385, PMID:33959278
6. Lefaucheur JP, Aleman A, Baeken C, Benninger DH, Brunelin J, Di Lazzaro V, Filipović SR, Grefkes C, Hasan A, Hummel FC, Jääskeläinen SK, Langguth B, Leocani L, Londero A, Nardone R, Nguyen JP, Nyffeler T, Oliveira-Maia AJ, Oliviero A, Padberg F, Palm U, Paulus W, Poulet E, Quartarone A, Rachid F, Rektorová I, Rossi S, Sahlsten H, Schecklmann M, Szekely D, Ziemann U: Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): an update (2014–2018). Clin Neurophysiol 2020;131:474–528. https://doi.org/10.1016/j.clinph.2019.11.002, PMID:31901449
7. Suleiman K, Al Kalaldeh M, AbuSharour L, Yates B, Berger A, Mendoza T, Malak M, Salameh AB, Cleeland C, Menshawi A: Validation study of the Arabic version of the Brief Fatigue Inventory (BFI-A). East Mediterr Health J 2019;25:784–790. https://doi.org/10.26719/emhj.19.032, PMID:31782514

8. Starkstein SE, Fedoroff JP, Price TR, Leiguarda R, Robinson RG: Apathy following cerebrovascular lesions. Stroke 1993;24:1625–1630. https://doi.org/10.1161/01.STR.24.11.1625, PMID:8236333
9. Canivez GL, Watkins MW: Investigation of the factor structure of the Wechsler Adult Intelligence Scale—Fourth Edition (WAIS–IV): exploratory and higher order factor analyses. Psychol Assess 2010;22:827–836. https://doi.org/10.1037/a0020429, PMID:20822259
10. Kirino E: Three-dimensional stereotactic surface projection in the statistical analysis of single photon emission computed tomography data for distinguishing between Alzheimer's disease and depression. World J Psychiatry 2017;7:121–127. https://doi.org/10.5498/wjp.v7.i2.121, PMID:28713690
11. Barker AT, Jalinous R, Freeston IL: Non-invasive magnetic stimulation of human motor cortex. Lancet 1985;11:1106–1107. https://doi.org/10.1016/S0140-6736(85)92413-4, PMID:2860322
12. Butler AJ, Wolf SL: Putting the brain on the map: use of transcranial magnetic stimulation to assess and induce cortical plasticity of upper-extremity movement. Phys Ther 2007;87:719–736. https://doi.org/10.2522/ptj.20060274, PMID:17429003
13. Deng ZD, Lisanby SH, Peterchev AV: Coil design considerations for deep transcranial magnetic stimulation. Clin Neurophysiol 2014;125:1202–1212. https://doi.org/10.1016/j.clinph.2013.11.038, PMID:24411523
14. Sasaki N, Abo M, Hara T, Yamada N, Niimi M, Kakuda W: High-frequency rTMS on leg motor area in the early phase of stroke. Acta Neurol Belg 2017;117:189–194. https://doi.org/10.1007/s13760-016-0687-1, PMID:27502413
15. Sasaki N, Hara T, Yamada N, Niimi M, Kakuda W, Abo M: The efficacy of high-frequency repetitive transcranial magnetic stimulation for improving apathy in chronic stroke patients. Eur Neurol 2017;78:28–32. https://doi.org/10.1159/000477440, PMID:28578330
16. George MS, Taylor JJ, Short EB: The expanding evidence base for rTMS treatment of depression. Curr Opin Psychiatry 2013;26:13–18. https://doi.org/10.1097/YCO.0b013e32835ab46d, PMID:23154644
17. Stussman B, Williams A, Snow J, Gavin A, Scott R, Nath A, Walitt B: Characterization of post-exertional malaise in patients with myalgic encephalomyelitis/chronic fatigue syndrome. Front Neurol 2020;11:01025. https://doi.org/10.3389/fneur.2020.01025, PMID:33071931
18. Iida H, Akutsu T, Endo K, Fukuda H, Inoue T, Ito H, Koga S, Komatani A, Kuwabara Y, Momose T, Nishizawa S, Odano I, Ohkubo M, Sasaki Y, Suzuki H, Tanada S, Toyama H, Yonekura Y, Yoshida T, Uemura K: A multicenter validation of regional cerebral blood flow quantitation using [123I]iodoamphetamine and single photon emission computed tomography. J Cereb Blood Flow Metab 1996;16:781–793. https://doi.org/10.1097/00004647-199609000-00003, PMID:8784223
19. Lee MH, Perl DP, Steiner J, Pasternack N, Li W, Maric D, Safavi F, Horkayne-Szakaly I, Jones R, Stram MN, Moncur JT, Hefti M, Folkerth RD, Nath A: Neurovascular injury with complement activation and inflammation in COVID-19. Brain 2022;145:2555–2568. https://doi.org/10.1093/brain/awac151, PMID:35788639
20. Shimosegawa E, Hatazawa J, Aizawa Y, Shouji Y, Hachiya T, Murakami M: Technetium-99m-ECD brain SPECT in misery perfusion. J Nucl Med 1997;38:791–796. PMID:9170448
21. Nasserie T, Hittle M, Goodman SN: Assessment of the frequency and variety of persistent symptoms among patients with COVID-19: a systematic review. JAMA Netw Open 2021;4:e2111417. https://doi.org/10.1001/jamanetworkopen.2021.11417, PMID:34037731
22. Wang X, Pathak S, Stefaneanu L, Yeh FC, Li S, Fernandez-Miranda JC: Subcomponents and connectivity of the superior longitudinal fasciculus in the human brain. Brain Struct Funct 2016;221:2075–2092. https://doi.org/10.1007/s00429-015-1028-5, PMID:25782434
23. Olivers CN, Roelfsema PR: Attention for action in visual working memory. Cortex 2020;131:179–194. https://doi.org/10.1016/j.cortex.2020.07.011, PMID:32892152
24. Hilbert S, McAssey M, Bühner M, Schwaferts P, Gruber M, Goerigk S, Taylor PC: Right hemisphere occipital rTMS impairs working memory in visualizers but not in verbalizers. Sci Rep 2019;9:6307. https://doi.org/10.1038/s41598-019-42733-6, PMID:31004125
25. Groff D, Sun A, Ssentongo AE, Ba DM, Parsons N, Poudel GR, Lekoubou A, Oh JS, Ericson JE, Ssentongo P, Chinchilli VM: Short-term and long-term rates of postacute sequelae of SARS-CoV-2 infection: a systematic review. JAMA Netw Open 2021;4:e2128568. https://doi.org/10.1001/jamanetworkopen.2021.28568, PMID:34643720

26. Institute of Medicine, Board on the Health of Select Populations, Committee on the Diagnostic Criteria for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness. National Academies Press (US), Washington (DC), 2015. https://doi.org/10.17226/19012
27. Pendergrast T, Brown A, Sunnquist M, Jantke R, Newton JL, Strand EB, Jason LA: Housebound versus nonhousebound patients with myalgic encephalomyelitis and chronic fatigue syndrome. Chronic Illn 2016;12:292–307. https://doi.org/10.1177/1742395316644770, PMID:27127189
28. Schwartz RB, Garada BM, Komaroff AL, Tice HM, Gleit M, Jolesz FA, Holman BL: Detection of intracranial abnormalities in patients with chronic fatigue syndrome: comparison of MR imaging and SPECT. AJR Am J Roentgenol 1994;162:935–941. https://doi.org/10.2214/ajr.162.4.8141020, PMID:8141020
29. Okada T, Tanaka M, Kuratsune H, Watanabe Y, Sadato N: Mechanisms underlying fatigue: a voxel-based morphometric study of chronic fatigue syndrome. BMC Neurol 2004;4:14. https://doi.org/10.1186/1471-2377-4-14, PMID:15461817
30. Kimura Y, Sato N, Ota M, Shigemoto Y, Morimoto E, Enokizono M, Matsuda H, Shin I, Amano K, Ono H, Sato W, Yamamura T: Brain abnormalities in myalgic encephalomyelitis/chronic fatigue syndrome: evaluation by diffusional kurtosis imaging and neurite orientation dispersion and density imaging. J Magn Reson Imaging 2019;49:818–824. https://doi.org/10.1002/jmri.26247, PMID:30430664
31. Kakuda W, Momosaki R, Yamada N, Abo M: High-frequency rTMS for the treatment of chronic fatigue syndrome: a case series. Intern Med 2016;55:3515–3519. https://doi.org/10.2169/internalmedicine.55.7354, PMID:27904120
32. Yang DG, Gu R, Kubo J, Kakuda W: Is the efficacy of repetitive transcranial magnetic stimulation influenced by baseline severity of fatigue symptom in patients with myalgic encephalomyelitis. Int J Neurosci 2020;130:64–70. https://doi.org/10.1080/00207454.2019.1663189, PMID:31483181