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Real world research on transcranial magnetic stimulation treatment strategies for neuropsychiatric symptoms with long-COVID in Japan

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ABSTRACT

The number of patients suffering from long-COVID is currently increasing rapidly, even after the acute symptoms of COVID-19 have improved. The objective of this study was to investigate the effects of a pilot transcranial magnetic stimulation (TMS) treatment on neuropsychiatric symptoms caused by long-COVID. In this study, we examined the efficacy of the TMS treatment protocol, which has been established to be effective in refractory depression, by applying it to patients who sought TMS treatment for neuropsychiatric symptoms caused by long-COVID at TMS clinics in Tokyo, Japan in the context of the real world TMS registry study in Japan. Of the 23 patients (13 females) with long-COVID included in this case series, the main neuropsychiatric symptoms were chronic fatigue (n = 12) and cognitive dysfunction (n = 11), but most patients also showed mild depressive symptoms. The mean score on the Montgomery-Åsberg Depression Rating Scale before TMS treatment was 21.2, which improved to 9.8 after treatment. Similarly, the score on the Performance Status, which assesses the degree of fatigue, improved from 5.4 to 4.2, and the score on the Perceived Deficits Questionnaire–Depression 5-item, which reflects cognitive function, improved from 10.0 to 6.3. Although a few patients complained of pain at the stimulation site during the TMS as a side effect, there were no serious adverse events. Despite the limitations of this open-label pilot study, the TMS protocol implemented in this study may have beneficial effects on neuropsychiatric symptoms caused by long-COVID, including depressive symptoms, chronic fatigue, and cognitive impairment. These preliminary findings warrant further validation in randomized controlled trials.

1. Introduction

COVID-19 has rapidly spread from China to other parts of the world since December 2019, with a pandemic status (WHO, 2021) prevailing to date. As of 2022, although the severity of acute respiratory symptoms and associated mortality due to COVID-19 infection has decreased, "long-COVID" has become a serious medical and social problem as a post-COVID syndrome in which neuropsychiatric symptoms such as depression, chronic fatigue, cognitive impairment, anxiety, persistent hypothermia, and insomnia are observed even after the PCR test has been negative (Ceban et al., 2022; Chou et al., 2021; Collantes et al., 2021; Graham et al., 2021; Hampshire et al., 2021; Pavli et al., 2021; Phillips and Williams, 2021; Renaud-Charest et al., 2021; Taquet et al., 2021a). In fact, previous studies have already suggested that SARS-CoV-2, in particular, is infectious to the central nervous system, and that COVID-19 is an infection with a high potential for causing neurological dysfunction (Crunfli et al., 2022; de Mello et al., 2022; Murta et al., 2020; Rodriguez-Morales et al., 2022).

Long-COVID is defined as a condition in which physical symptoms such as chronic fatigue, myalgia, joint pain, and numbness, as well as neuropsychiatric symptoms such as memory impairment, poor concentration, insomnia, headache, and depressed mood persist for more than three months after the acute respiratory symptoms have resolved (Fischer et al., 2022; Greenhalgh et al., 2020). Previous studies of long-COVID reported that two thirds of non-hospitalized and infected patients who did not develop severe disease presented with lethargy, ageusia, dyspnea, and asthenia at 2 months after the onset of COVID-19 (Bliddal et al., 2021; Carvalho-Schneider et al., 2021; Petersen et al., 2021). Furthermore, the other study showed that 34 % of 279 hospitalized COVID-19 patients reported memory impairment and 28 % still

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had attention deficits three months after discharge (Garrigues et al., 2020). Moreover, the other study noted that at the six-month follow-up after discharge from the hospital for COVID-19 infection, 76 % of patients reported at least one residual symptom, specifically, fatigue (63 %), sleep disturbance (26 %), alopecia (22 %), and olfactory disturbance (11 %) were the most frequent residual symptoms (Huang et al., 2021). In addition, the other study also reported that more than 30% of hospitalized patients with COVID-19 exhibited cognitive impairment, depression, and anxiety, and that these symptoms persist for several months or more after discharge from the hospital (Nakamura et al., 2021).

Even more surprisingly, the incidence of new dementia after admission due to COVID-19 was shown to be 2–3 times higher than other diseases (Taquet et al., 2021b). Moreover, on the other hand, the prevalence of mood disorders is increasing in the current pandemic, not only because of COVID-19 infection itself and its increase secondary to the pandemic, but also because mood disorders themselves are an underlying condition that increases the risk of COVID-19 infection and makes those infected with COVID-19 more likely to have worse outcomes than those without mood disorders (Ceban et al., 2021; Collaborators, 2021; Hao et al., 2020). Specifically, in cases that develop into long-COVID after the acute phase of COVID-19, they are often forced to take leave or resign from their jobs as a result, and the psychosocial factors due to the isolation from the society and mental distress caused by this situation also have a significant impact on the neuropsychiatric symptoms associated with long-COVID. As such, long-COVID leads to a clear deterioration in mental health and quality of life (Holmes et al., 2020).

Although the specific mechanisms of COVID-19 infection-induced neurological dysfunction are not fully elucidated at present, SARS-CoV-2 targets angiotensin-converting enzyme 2, which is present in neurons, endothelial cells, glial cells, and the choroid. Such a mechanism of action is thought to trigger subsequent neuroimmune responses and neuroinflammation, contributing to the development of acute neurological symptoms such as dysgeusia, dysphonia, encephalopathy, and headache (Almutairi et al., 2021; Nazari et al., 2021). Furthermore, the emergence of neuropsychiatric symptoms due to COVID-19 infection is thought to involve an excessive release of inflammatory factors (i.e., cytokine storm) with increased permeability of the blood-brain barrier (BBB), which initiates the neuroinflammatory process (Tate et al., 2022; Zazzara et al., 2022). Thus, SARS-CoV-2 directly affects the brain through immune mechanisms (Tate et al., 2022; Zazzara et al., 2022) and may induce neuropsychiatric disorders and exacerbate cognitive function and psychiatric conditions.

COVID-19 infection itself is now becoming milder due to the effect of vaccination and the acquisition of latent herd immunity, and even if infected, there are more cases of subclinical infection or only cold symptoms, which means that COVID-19 infection remains milder and the pandemic is prolonged in a lingering manner (Noda, 2020). As noted above, since long-COVID has a significant impact on people's daily functioning, strategies for the appropriate treatment and management of these patients need to be seriously considered further. In this case series, patients suffering from neuropsychiatric symptoms due to long-COVID were treated with repetitive transcranial magnetic stimulation (rTMS) using our original TMS treatment protocol, primarily for symptoms of depressed mood, cognitive dysfunction as known as "brain fog", and chronic fatigue, as part of the real world TMS registry study (Noda et al., 2022). The purpose of this study was to examine whether the TMS neuromodulation strategy provided in this case series was effective for the typical symptoms of long-COVID. We hypothesized that the TMS treatment administered in this study would have beneficial impacts on depressive symptoms and cognitive impairment associated with long-COVID.

2. Methods

2.1. Case series setting

This study was conducted as a case series between May 1, 2022 and September 30, 2022 as part of the real world TMS registry study (jRCT1050210059) (Noda et al., 2022) for outpatients who visited the Shinjuku-Yoyogi Mental Lab Clinic and the Tokyo Yokohama TMS Clinic in the Tokyo metropolitan area with complaints of neuropsychiatric symptoms associated with long-COVID. The subjects of the case series were patients with some mental health issues, such as depression, anxiety, cognitive impairment, and chronic fatigue, caused for the first time after COVID-19 infection. The specific criteria for eligibility in this case series were described below and none of the patients were taking psychiatric prescription medications at the time of entry into this study. In this case series, TMS treatment was provided free of charge to all patients to explore the possibility of TMS treatment for neuropsychiatric symptoms associated with long-COVID.

2.2. Eligibility criteria

The selection criteria include (1) patients who have been infected with COVID-19 since January 2020, who had a positive polymerase chain reaction (PCR) test result and were negative for coronary infection at the time of psychiatric consultation; (2) patients who had developed a condition that met the diagnostic criteria for depression or anxiety disorder in the DSM-5 for the first time after COVID-19 infection; (3) patients with a severity score of 12 or higher on the Montgomery-Åsberg Depression Rating Scale (MADRS); (4) patients who had obtained written consent for the TMS Registry Study from the study subjects themselves; (5) age between 20 and 70 years old at the time of consent for this registry study; and (6) patients who were able to visit the Tokyo Yokohama TMS Clinic or Shinjuku-Yoyogi Mental Lab Clinic on a regular basis during the period of TMS treatment. On the other hand, the exclusion criteria were as follows: (1) patients with cerebral organic diseases (e.g., intracranial organic lesions of moderate severity or higher, neurodegenerative diseases, etc.); (2) patients with primary sleep disorders (sleep apnea, narcolepsy, etc.); (3) patients with a diagnosis of bipolar disorder, schizophrenia, psychotic depression, or substance abuse/dependence; (4) patients with a diagnosis of active autoimmune or endocrine-metabolic disease: (hypopituitarism, adrenal insufficiency, thyroid disease, diabetes, etc.); (5) history of convulsive seizures or epilepsy; (6) patients with serious or unstable physical illness that makes it difficult to receive outpatient TMS treatment; (7) patients who had received ECT within the past 6 months; (8) pregnant women; (9) patients with contraindications to TMS such as metal implants or pacemakers; and (10) patients who were deemed inappropriate for TMS by the treating physician.

2.3. Clinical and cognitive measures

The following measures were administered to outpatients who met the above eligibility criteria before and after 20 sessions of TMS treatment: (1) MADRS and (2) Patient Health Questionnaire-9 (PHQ-9) to assess depressive symptoms; (3) Performance Status (PS), with higher scores indicating greater difficulty with activities of daily living to assess fatigue and lethargy; and (4) Perceived Deficits Questionnaire - Depression 5 item (PDQ-D-5) to assess cognitive function. More specifically, PS is originally a scale used to define the severity of chronic fatigue syndrome in Japan, which evaluates the severity of fatigue with a score from 0 to 9 on a self-reported scale regarding the level of daily activities. Note that PS level of 3 points or higher is considered a diagnosis of chronic fatigue syndrome. Details on scoring PS are presented below (Matsuda et al., 2009; Sato et al., 2021). On the other hand, the PDQ-D is a self-administered rating scale developed to assess cognitive function in patients with depression. The PDQ-D-5 is a simplified version

of the PDQ-D, which calculates a total score and 4 subscale scores (attention/concentration, retrospective memory, prospective memory, and planning/organization) (Fehnel et al., 2016; Sumiyoshi et al., 2022). These test batteries were conducted by trained clinical psychologists in our clinics. In addition, TMS treatment providers checked each TMS session for the occurrence of adverse events, and certified psychiatrists (Y.N. and Y.N.) reviewed each patient with long-COVID at baseline, after a total of 10 sessions of TMS, and after a total of 20 sessions of TMS to confirm the efficacy, safety, and tolerability of the TMS treatment.

2.4. TMS treatment protocol for patients with long-COVID

The TMS treatment protocol for long-COVID consisted of one session of intermittent theta burst stimulation (iTBS) for the left dorsolateral prefrontal cortex (DLPFC) and one session of low frequency rTMS for the right lateral orbitofrontal cortex (LOFC) with one TMS treatment per day. TMS for the right LOFC was performed immediately after iTBS for the left DLPFC. More specifically, semi-prolonged intermittent theta burst stimulation (semi-prolonged iTBS (semi-piTBS): 1200 pulses, 6 min), doubling the original protocol of iTBS, was performed on the left DLPFC at 120% resting motor threshold (RMT) (can be reduced to 100 % RMT for patients who cannot tolerate the scalp pain) (Blumberger et al., 2018; Li et al., 2020; Richard et al., 2022). The target site on the left DLPFC was identified using the Beam_F3 method (F3 electrode site) (Beam et al., 2009). Subsequently, 1 Hz-rTMS (600 pulses, 10 min) was applied to the right LOFC at 100 % RMT (can be reduced to 70 % RMT for patients who cannot tolerate the pain). The stimulation site targeting the right LOFC was determined by identifying the EEG AF8 electrode site by means of head measurements (Feffer et al., 2018). We used the MagPro R30 TMS device with the Cool-B70 coil (MagVenture, Inc. Farum, Denmark) for this TMS treatment protocol.

The rationale for combining low-frequency rTMS for the right LOFC in addition to the usual iTBS for the left DLPFC was inspired by the TMS treatment protocol for refractory depression invented by Feffer and colleagues (Feffer et al., 2018). The development of TMS treatment protocols to date has included extending the duration of treatment, switching from high-frequency left DLPFC to low-frequency right DLPFC (McDonald et al., 2011), and the introduction of accelerated rTMS/iTBS (Baeken et al., 2013; Bakker et al., 2015; Duprat et al., 2016; Holtzheimer et al., 2010). However, other promising approaches have recently been proposed, such as switching the stimulation target site from the DLPFC to DMPFC, and even the possibility of low-frequency rTMS treatment for the right LOFC for refractory depression that also did not respond to TMS treatment for the DMPFC. Moreover, big data analysis using the UK Biobank has recently indicated that the orbitofrontal cortex and the entorhinal cortex were involved as brain regions in the pathogenesis of the CNS symptoms caused by COVID-19 infection (Crunfli et al., 2022). In this context, TMS treatment targeting the right LOFC has the potential to address these brain pathological bases in a non-invasive and direct manner. As such, the present study was conducted as a pilot case series, anticipating some additive effects of the combined technique of semi-piTBS intervention on the left DLPFC and low-frequency rTMS on the right LOFC.

2.5. Statistical analysis

Since this case series was a preliminary open-label trial, effect sizes (Cohen's d) were calculated along with paired t-tests to examine the change in scores before and after treatment on each outcome measure under the hypothesis that our TMS treatment protocol for patients with long-COVID would improve scores on each of the clinical and cognitive assessment measures. Here, we also performed Shapiro-wilk tests to examine the data distribution of the outcome measures. In addition, correlation analyses between clinico-demographic data and the percent change in each test score were conducted exploratively. In this case series, the significance level was set at 0.05.

3. Results

A total of 23 patients with long-COVID were included in this case series, comprising patients at the Shinjuku-Yoyogi Mental Lab Clinic and the Tokyo-Yokohama TMS Clinic. Clinico-demographic information, including the patient's history of vaccination for novel coronaviruses and hospitalization due to COVID-19 infection, is summarized in Table 1. With regard to the stimulation intensity to the left DLPFC, 19 patients were able to increase the stimulation intensity to 120 % RMT, but for the remaining 4 patients, 2 were performed at 110 % RMT, 1 at 105 % RMT, and 1 at 100 % RMT in terms of tolerability regarding the stimulation site pain. On the other hand, with respect to stimulation intensity to the right LOFC, all patients were able to increase it to 100 % RMT. The results at baseline and final assessment for clinical measures of depression, fatigue and lethargy, and cognitive function are summarized in Table 2. Note that 4 out of 23 patients complained of the scalp pain at the stimulation site during the TMS session but no other significant adverse events were observed in this case series.

The patients included in this case series had a mean MADRS score of 21.2 (± 7.0) at baseline, indicating a moderate level of depressive symptoms. Following a total of 20 sessions of TMS treatment, the mean MADRS score improved significantly to 9.8 (± 7.8), with approximately 65 % (15/23) of patients showing response (≥ 50 % improvement in depressive symptoms) and approximately 70 % (16/23) reaching remission (MADRS score ≤ 10). See Fig. 1, which shows the longitudinal change in MADRS score for each patient. Furthermore, the mean score on the self-administered PHQ-9 also showed a significant improvement from 12.9 (± 4.7) to 8.2 (± 4.6), and most patients were subjectively aware of the improvement in their depressive symptoms Table 2). With regard to chronic fatigue specific to long-COVID, the self-administered PS score significantly changed from 5.4 (± 1.6) to 4.2 (± 1.8), but, on psychiatric consultation, subjective improvement in fatigue appeared to be only at a minor level. Of note, none of the patients experienced worsening fatigue after the TMS treatment. On the other hand, the cognitive function assessed by PDQ-D-5 improved from 10.0 (± 5.2) to 6.3 (± 4.7), showing a significant improvement in cognitive function, with none of the patients showing deterioration in their cognitive function, following the TMS treatment.

In addition, sub-analyses on the relationship between clinico-demographic data and the improvement rate by the TMS treatment yielded the following results: (1) no significant correlation was found between age and treatment efficacy with the TMS treatment in each

Table 1
Clinico-demographic information.

Characteristics	
Age, years (mean ± S.D.)	38.2 (± 11.7)
Males	37.6 (± 12.3)
Females	38.7 (± 11.8)
Duration from COVID-19 infection to initiation of TMS treatment, weeks	48.6 (± 30.2)
Vaccination history against COVID-19 (number)	Three times (6) Two times (6) One time (3) None (8)
History of hospitalization due to COVID-19 infection (number)	Two times (2) One time (5) None (16)
Main symptom of long-COVID	Chronic fatigue (12) Cognitive dysfunction (11)
Stimulus intensity for the left DLPFC (%MSO)	53.9 (± 8.5); 117.6% RMT (± 5.6 %)
Stimulus intensity for the right LOFC (%MSO)	47.1 (± 8.2); 100% RMT

S.D.: standard deviation; DLPFC: dorsolateral prefrontal cortex; RMT: resting motor threshold; LOFC: lateral orbitofrontal cortex; MSO: maximum stimulator output

Table 2
Clinical outcomes and cognitive measures following TMS therapy.

Clinical outcomes		Scores	statistics
MADRS score	pre-TMS (baseline)	21.2 (± 7.0)	$t_{22} = 9.073$, $p < 0.0001$
	post-TMS	9.8 (± 7.8)	Cohen's d = 1.538
PHQ-9	pre-TMS (baseline)	12.9 (± 4.7)	$t_{22} = 6.049$, $p < 0.0001$
	post-TMS	8.2 (± 4.6)	Cohen's d = 1.011
PS score	pre-TMS (baseline)	5.4 (± 1.6)	$t_{22} = 4.230$, $p < 0.0001$
	post-TMS	4.2 (± 1.8)	Cohen's d = 0.705
PDQ-D-5 score	pre-TMS (baseline)	10.0 (± 5.2)	$t_{22} = 7.756$, $p < 0.0001$
	post-TMS	6.3 (± 4.7)	Cohen's d = 0.747

MADRS: Montgomery–Åsberg Depression Rating Scale; PHQ-9: Patient Health Questionnaire-9; PS: performance status; PDQ-D-5: Perceived Deficits Questionnaire – Depression 5 item

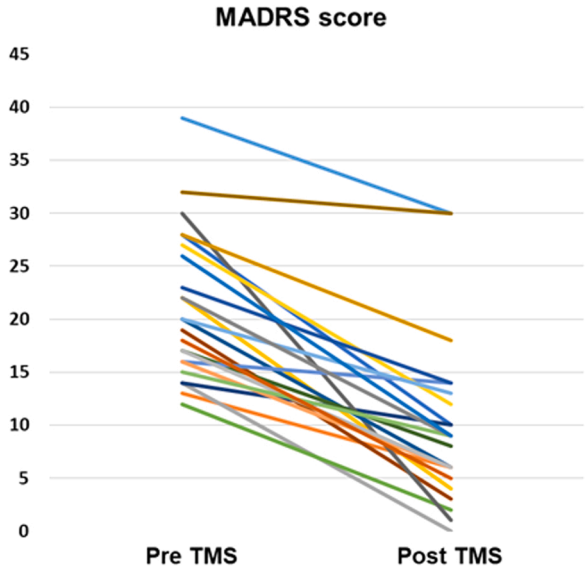

Fig. 1. Longitudinal changes in MADRS score before and after a total of 20 sessions of TMS treatment in patients with long-COVID. Note that none of the cases in this case series showed worsening of depressive symptoms as a result of TMS treatment.
MADRS: Montgomery–Åsberg Depression Rating Scale.

outcome; (2) regarding the difference in improvement rates by the TMS treatment for each outcome by sex, a significant sex difference was observed for the improvement rates of MADRS score, with male patients showing a more significant improvement in depressive symptoms than female patients; (3) regarding the difference between the severity of COVID-19 infection as indexed by history of hospitalization and treatment response to the TMS treatment, there was no significant association between the two in particular. Furthermore, there was also no significant correlation between the number of hospitalizations and treatment response to the TMS treatment; and 4) there was no specific association between the number of COVID-19 vaccinations and treatment response to the TMS treatment.

4. Discussion

This case series was a part of the real world TMS registry study as one of the charitable activities, providing the novel TMS treatment free of charge at the two TMS clinics in the Tokyo metropolitan area for 23 patients suffering from neuropsychiatric symptoms caused by long-COVID. As a result, the following important findings were observed. First, significant improvement in subjective and objective depressive symptoms. Second, significant but mild improvement in subjective chronic fatigue. Third, significant improvement in subjective cognitive impairments as represented by brain fog. Fourth, we were able to confirm a certain level of safety and tolerability of our TMS treatment protocol designed for long-COVID in this study. Since effective treatments for long-COVID are currently quite limited and have not yet been adequately studied, a preliminary study applying such non-invasive TMS neuromodulation therapy to a limited number of patients with their consent, as in the present case series, would be of great clinical significance.

Given the lack of sufficient evidence on TMS treatment for long-COVID, we first devised and implemented our own TMS treatment protocol specifically for long-COVID in this case series. Specifically, we based the iTBS treatment protocol for the left DLPFC in depression (Blumberger et al., 2018), which has already been approved by the U.S. FDA, and added a TMS treatment protocol that takes into account the pathophysiology of long-COVID, focusing on the right LOFC (Feffer et al., 2018). In more detail, to enhance the therapeutic effect as much as possible, we combined semi-piTBS for the left DLPFC (Li et al., 2020) with low-frequency 1 Hz-rTMS for the right LOFC (Feffer et al., 2018), which has been performed successfully for refractory depression, in this case series. The reason for adopting this special TMS protocol was based on our earlier experience in the clinical practice of TMS treatment in both TMS clinics, where standard TMS therapy has previously been administered to a small number of depressive patients with long-COVID, with the result that such a standard approach unfortunately did not achieve sufficient therapeutic effect.

In this case series, depressive symptoms associated with long-COVID were significantly improved. The TMS protocol used in this pilot study was exactly the treatment protocol used for refractory depression and thus could have induced a beneficial effect on depressive symptoms associated with long-COVID via neuromodulation to the shared neural network substrate (Siddiqi et al., 2021). This TMS treatment protocol also showed ameliorative effects on cognitive impairment represented by brain fog. The reason behind the improvement in cognitive function with this TMS treatment protocol may be that the TMS treatment targeted the left DLPFC, the most common target site of TMS treatment for depression, resulting in significant improvement in cognitive impairment, including executive dysfunction. Furthermore, administration of iTBS, which has a facilitatory effect on the DLPFC, may strengthen neural rhythms, including theta-phase and gamma-amplitude coupling, which is also related to cognitive function, and may even lead to enhanced neuroplasticity (Jannati et al., 2022) in the same region, thereby improving cognitive function (Buzsaki and Draguhn, 2004; Luber and Lisanby, 2014; Noda et al., 2018, 2017; Thut et al., 2011). Regarding chronic fatigue of long-COVID, we observed a significant improvement on PS score; however, subjective improvement on chronic fatigue was limited, suggesting that TMS neuromodulation by itself might not be effective enough to address the systemic pathophysiology of long-COVID (Busatto et al., 2022; Montes-Ibarra et al., 2022; Nunes et al., 2022; Tate et al., 2022) other than the brain that may cause chronic fatigue. Thus, it would be necessary to consider the combination therapy with bottom-up neuromodulation approach, such as acupuncture, in addition to the TMS treatment in the future (Lee and Chae, 2022; Noda et al., 2015).

While the results of this case series are still preliminary due to the small sample size, they are of high medical and social significance as they may provide a reasonably promising and novel treatment option for patients suffering from neuropsychiatric symptoms associated with long-COVID. Based on these preliminary results, further clinical studies with a randomized controlled trial (RCT) design should be conducted to provide solid evidence that this unique TMS treatment protocol is useful for neuropsychiatric symptoms associated with long-COVID.

5. Limitations

There are several limitations to this study. First, this case series was an open-label preliminary trial, and thus the placebo effect could not be

excluded. Second, due to the small sample size, no explicit conclusions can be drawn at this time. Third, this case series demonstrated some usefulness as an acute TMS treatment but did not examine its long-term lasting effects. Thus, it is necessary to follow up and examine the long-term effects of this TMS neuromodulation therapy in the future. Fourth, since this case series was a pilot study conducted on Japanese patients, it is not clear at this point whether these results can be generalized to other racial groups. On the other hand, however, since the neurobiological basis of the brain pathology induced by long-COVID is assumed to be common regardless of race, this limitation would not be of much significance.

6. Conclusion

This case series study is the first to demonstrate that the TMS treatment protocol for refractory depression applied to patients with long-COVID has the potential to improve depressive symptoms as well as cognitive dysfunction in these patients. The results of this case series warrant further investigation in a large-scale clinical study with an RCT design to confirm its usefulness and to evaluate its long-term efficacy.

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CRediT authorship contribution statement

YN conceived the idea and methodology for this study. YN, RK, and RO were involved in the conceptualization level of the study. AS, KF, MS, AS, YN, and MI collected the data. AS, KF, and YN analyzed the data. YN wrote the first draft of the manuscript. All the authors contributed to the preparation of the final manuscript and approved its submission.

Declaration of Competing Interest

The authors declare that there is no conflict of interest.

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