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Case Report

The utilization of electroencephalogram and repetitive transcranial magnetic stimulation for case of COVID-19 brain fog

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ABSTRACT

Although it is not a medical diagnosis, brain fog composes of sluggish or fuzzy thinking, impaired memory, confusion, and difficulty in focus. In general, this can be caused by stress, sleep disorder, or other illnesses. After the outbreak of COVID-19, an increasing number of patients suffer from COVID-19 brain fog. Since the symptoms of brain fog represent the dysfunction of the brain, electroencephalogram (EEG) plays a role in the evaluation of brain condition due to its convenience. Repetitive transcranial magnetic stimulation (rTMS) has long been a tool to modulate brain function. Here, we demonstrate the EEG changes of a patient with COVID-19 brain fog before and after rTMS. Before rTMS, we measured the EEG of a 29-year-old male who reported impaired memory, difficulty in concentration, and poor working performance after recovery from COVID-19. After the acquisition of EEG, we analyzed it with quantitative EEG (qEEG) methods and calculated the TMS treatment frequency. Then we used rTMS to stimulate the patient over the frontal region with the calculated frequency. After rTMS, EEG was acquired again. Initially, the EEG revealed dominant delta waves and lower alpha band power in the frontal region. After treatments, there was an increase in the power of the alpha band in the frontal region in EEGs. There is a similar finding in coherence. These results indicated that rTMS with calculated frequency could raise the power of the alpha band and the connectivity of brain regions. Clinically, improvement of symptoms was reported by the patient himself. rTMS seems to be one of the modalities to help ameliorate the symptoms of brain fog while EEGs can be a useful tool to evaluate neurological conditions before and after neuromodulation.

Keywords: COVID-19, brain fog, qEEG, rTMS, frequency.

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INTRODUCTION

Since the outbreak of COVID-19, there are increasing research reporting the neurological impacts of COVID-19 (Horesh and Brown, 2020). The most reported symptoms are impaired memory, problems with spatial orientation, difficulty in concentration, and a feeling of chronic fatigue (Hellmuth et al., 2021, Kopanska et al., 2022). These neurological sequelae are referred to as brain fog (Sharifian-Dorche et al., 2020).

Although it is not a clinical diagnosis, brain fog represents a psychobiological state (Van Cutsem et al., 2017). The possible mechanism of COVID-19 brain fog may be the chronic inflammatory processes (Matias-Guiu et al., 2021) and disturbed neurotransmitters (Ortelli et al., 2021) in the central nervous system (CNS). Furthermore, changes in brain metabolism have also been described in a positron emission tomography study (Hugon et al., 2022).

Among many measures to identify the abnormality of CNS, electroencephalography (EEG) is a convenient and cost-effect tool to record the changes in brain oscillations caused by COVID-19. Changes in EEG of post-COVID-19 patients with cognitive impairment have been reported (Pasini et al., 2020). Predominant delta or theta activity in the frontal region is one of the signatures observed in the EEGs.

Although many measures for the management of COVID-19 brain fog have been suggested, there is still no consensus on the treatment (Yong, 2021). Since brain fog composes of cognitive problems and altered brain activity, neuromodulation might be effective. Currently, one of the most widely used neuromodulations is transcranial magnetic stimulation (TMS). TMS uses electromagnetic induction to generate a transient and localized electric current in the cortex, causing the firing of neurons. It has been approved by Food and Drug Administration for medical-resistant depression in 2008. Since then, researchers have used repetitive TMS (rTMS) to treat a variety of neuropsychiatric diseases (Diefenbach et al., 2016, Chou et al., 2020). But there are some drawbacks to the use of rTMS. First, most of the studies used fixed frequency but the frequencies of these studies differentiate from each other. To date, there is no consensus on which frequency is suitable for most patients. Second, there is no objective evidence to evaluate the difference before and after treatments despite the clinical evaluation scale being widely used. EEG is a convenient tool to evaluate the condition of brain function, meanwhile, EEG also could be a way to calculate the fine frequency to induce better oscillations that could increase better connection. So, it’s reasonable to combine EEGs and rTMS for the treatments of neuropsychiatric disease.

Here, we report a case of COVID-19 brain fog who had EEGs as evaluations of brain function. rTMS was applied for treatment but the frequency was not traditional 10 Hz or fixed. We calculate the individualized frequency based on every EEG according to the resonance principle aiming to induce greater oscillations. We call this individualized rTMS (iTMS). The results of EEGs before and after treatments were analyzed by quantitative EEG (qEEG) to identify the details of the changes in the alpha band relative power and connectivity which is represented by coherence between two leads. We also evaluated a patient with clinical rating scales while recording EEG.

CASE REPORT

This 29-year-old male suffered from COVID-19 infection in May 2022. After quarantine, he sustained some non-specific neurological symptoms, including problems with remembering and recalling, difficulty in concentration, and a feeling of chronic fatigue which affected his working performance. In the initial assessment, the Chalder Fatigue Scale score was 24. He also scored 31 on the Impact of Events Scale-Revised. First, we recorded resting-state eyes-closed EEG by applying two ear electrodes and another 19 scalp electrodes according to the 10-20 International System of Electrode Placement. Data was recorded with Cadwell Easy III EEG (Cadwell Industries Inc., WA, USA). After the acquisition of EEG, we analyzed the waves with independent components analysis and discrete Fourier transform and calculated the treatment frequency based on the resonance principle for iTMS. iTMS treatment was administered using a Magstim Rapid2 device (Magstim Corp., Wales, UK) at the Fz location of the EEG cap.

The patient received one course of 20 daily iTMS stimulations on weekdays for consecutive 4 weeks with the calculated frequency and the power at 80% of the motor threshold. Three months after the first course of treatments, he received another course. We recorded EEGs after every course of treatments and evaluated the patient’s response with the Chalder Fatigue Scale and Impact of Events Scale-Revised. We used Persyst v 14 (Persyst Development Co., CA, USA) to generate qEEG data including relative alpha power of the frontal lobe and alpha-band coherence between frontal, parietal, and occipital regions. Relative alpha power was calculated by dividing the spectrum power of the alpha band (8 to 13 Hz) by the summation power of all four frequency bands (delta, theta, alpha, and beta bands). Coherence represents the synchronization in a frequency band between two leads with the quantification of the extent to which they share a constant oscillating frequency and phase difference (Mohammad-Rezazadeh et al., 2016). The coherence is denoted as a number between 0 to 1 and a higher number implies more commonality between two channels in a frequency band. We chose a 2-minute EEG from each record to calculate the relative power of the alpha band at each frontal lead, except Fp1 due to damage of signals at this electrode in one of the records, and coherence between C3-C4, F3-P3, F3-O1, P3-O1, F4-P4, F4-O2, and P4-O2 in the alpha band. Clinically, his Chalder Fatigue Scale score was 7 and the Impact of Events Scale-Revised score lowered to 9 at the end of treatments. Improvement in memory, concentration, and working performance was reported by himself. In the aspect of EEGs, dominant delta waves and slowing of background activity are presented in the initial EEG. After treatments, there was an increase in the relative power of the alpha band and a decrease in the power of the delta band at each frontal lead (Figure 1). There was also an increase in the coherence between two hemispheres and bilateral fronto-parieto-occipital regions, implying better connectivity (Figure 2). The Fast Fourier transform of each EEG is shown in Figure 3.

DISCUSSION

In this report, we demonstrate for the first time in the literature that combination of rTMS and EEG could be a

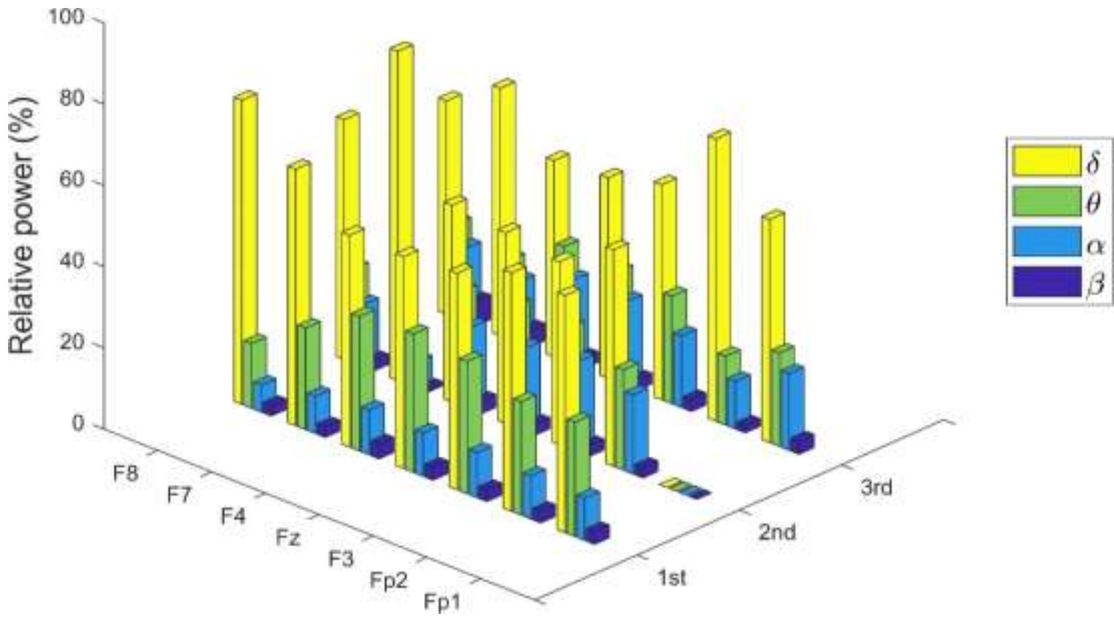

Figure 1. The relative power of different bands of oscillations at each frontal lead. There was an increase in alpha power while the power of the dominant delta decreased after treatments. The lack of the Fp1 power spectrum in the second record was due to damage to signals.

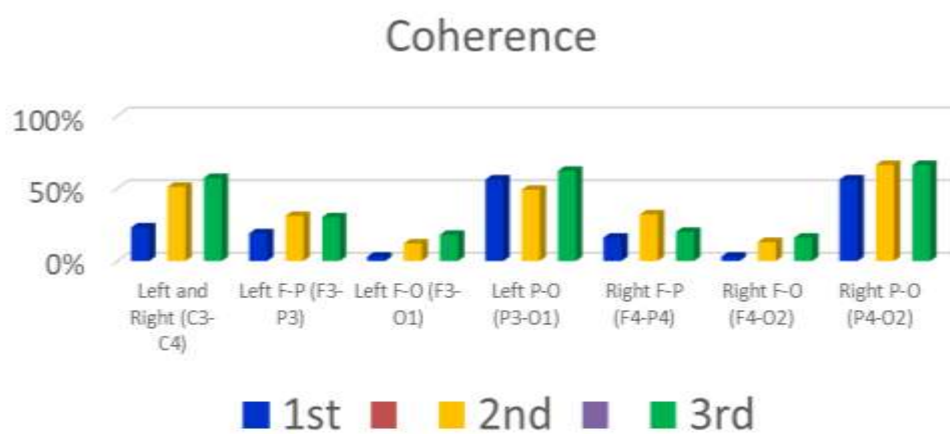

Figure 2. Coherence between bilateral hemispheres and different regions of the brain. Coherence was enhanced after treatments, indicating better connectivity among different regions. F-P: frontal and parietal regions; F-O: frontal and occipital regions; P-O: parietal and occipital regions.

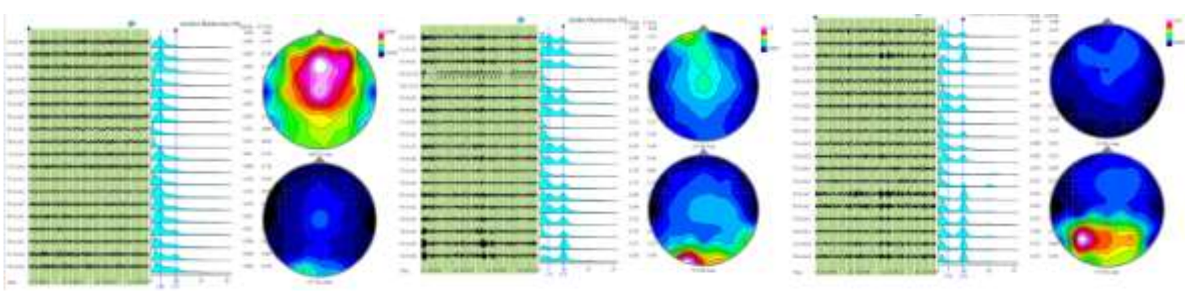

Figure 3. The Fast Fourier Transform of each EEG. The Fourier Transform of 1st to 3rd EEGs is shown from left to right. There was a trend toward increased alpha power after treatments while there was a decrease in the power of the delta band.

useful tool for the treatment of COVID-19 brain fog. Since rTMS has been approved by Food and Drug Administration to treat depressive disorder, it was utilized in treatments for kinds of neuropsychiatric diseases. However, the evaluation of the treatment effects depended mainly on rating scales and clinical responses without objective neurophysiological parameters. On the other hand, EEG serves as a tool to detect oscillation power and connectivity, which represent the state of the brain (Kopanska et al., 2022). Therefore, EEG seems to be an objective measure to evaluate the changes in the brain after rTMS treatment.

In the present case, the improvement of the brain fog symptoms seemed to be accompanied by the increase of alpha power and reduction of delta power in the frontal region. Research had found that alpha-band oscillations are the dominant rhythm of the brain in an awake state and are related to many basic cognitive processes. Many studies using magnetoencephalography and EEG to detect brain function strongly suggested desynchronization of alpha power facilitated processing in the task-relevant regions and increment of alpha power suppress the task-irrelevant areas, representing the inhibitory property of alpha oscillations. The greater the desynchronization accompanied better regional function (Klimesch, 2012). Furthermore, alpha-band oscillations can regulate the change of neuron firing rate which is related to the processing of information by power and phase while higher power is related to a lower firing rate and trough in phase results in a higher firing rate. Alpha oscillations serve as a regulating system by the inhibitory ability to control the firing rate of neurons. So, it is reasonable that an increment in alpha power facilitates the control of neuronal firing (Haegens et al., 2011). Research had found that applying rTMS at individual alpha frequency could influence alpha dynamics to improve cognitive performance (Klimesch et al., 2003). Based on the concept of an individual’s alpha frequency, we further calculated the frequency for delivery based on the resonance principle to induce greater oscillations. iTMS seems effective in influencing alpha dynamics.

Recently, Vellieux et al. (2020) reported two cases of COVID-19 showing a unique EEG pattern of dominant delta waves and suggested that this pattern could be typical of COVID-19 brain dysfunction. Furthermore, the research found slowing of background activity and intermittent rhythmic delta waves in the frontal region in COVID-19 patients (Pasini et al., 2020). These findings are consistent with our current EEG results that dominant delta waves are presented in the EEGs. The improvement of clinical symptoms may be related to the reduction of the power of the delta band.

Many studies had identified reduced brain connectivity in kinds of neurodegenerative diseases (Pievani et al., 2014). We also found a reduction in brain connectivity in our case. Generally, groups of neurons in the brain are active at the same time. It is intriguing how they interact with each other and how their communication goes flexibly and can be modulated to present our cognition. Research had found neuronal coherence played a key role in neuronal communication. Temporal windows were necessary for neuronal communication and these windows were produced by neuronal oscillations and rhythmic excitability fluctuations. Only neuronal groups in coherent oscillations could interact effectively because their communication windows for input and output were open simultaneously (Fries, 2005). So, the increase of coherence between brain regions may help neuronal groups communicate more effectively and the brain functions better subsequently. This may be why the symptoms improved after iTMS.

Although we demonstrate the relationships between the increase of alpha-band power and coherence to the improvement of COVID-19 brain fog symptoms, there are some drawbacks. The alpha-band power in each lead did not increase persistently, this raises the concern of fade away from treatments. There was a similar finding in coherence. Further evaluation is necessary to assess the effects of treatments.

CONCLUSIONS

In this report, we demonstrate the efficacy of the combination of rTMS and EEG for the treatment of COVID-19 brain fog. Improvement in clinical symptoms seemed to be accompanied by the increment of frontal alpha power and connectivity between brain regions. rTMS neuromodulation and EEG evaluation are both non-invasive techniques. In addition to COVID-19 brain fog, the combination may provide another tool for treatments in many neuropsychiatric diseases. Further randomized double-control studies are necessary to verify the efficacy of this combination.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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