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Review

Effects of transcranial direct current stimulation on COVID-19 neurological symptoms: a mini-review

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ABSTRACT:

Introduction: COVID-19 patients can experience long-term effects including neurological symptoms as part of the long COVID syndrome. The most common neurological symptoms associated with this syndrome are cognitive impairments, such as brain fog, memory issues or loss of concentration, and mood changes, such as depression and anxiety. Non-invasive brain stimulation, for instance, transcranial direct current stimulation (tDCS), is a treatment currently being tested to improve cognitive deficits and mood disorders in long COVID.

Methods: We performed a systematic literature search for articles on long COVID and non-invasive brain stimulation. Electronic searches were performed in MEDLINE (via PubMed) and Cochrane databases. The Joanna Briggs Institute Critical Appraisal tool was used for quality assessment. Data regarding population, intervention, outcomes, study design, and sources of funding were collected.

Results: The search returned 21 articles, of which two case reports were included in the discussion. Three patients with long COVID and cognitive symptoms were treated with tDCS. Although these studies reported promising results, they had methodological differences, no control groups were used and the sample size is insufficient to draw definitive conclusions.

Discussion: Neuromodulation treatments like tDCS are currently being considered to treat long COVID, since they have been found to improve cognition, but so far only in observational studies with few patients. In the future, randomized clinical trials using tDCS for long COVID patients with cognitive impairment might demonstrate the effectiveness of this intervention.

Keywords: long COVID; brain stimulation; Transcranial Direct Current Stimulation; tDCS.

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Introduction

Coronavirus disease 2019 (COVID-19) became a global burden soon after a few cases of unexplained pneumonia were first reported in Wuhan, China in December 2019 (Worobey, 2021), resulting in millions of deaths worldwide (Hassine, 2022). SARS-CoV-2 infection is not limited to the lungs and may affect multiple systems, including the central nervous system (CNS; (Ahmad & Shabbiri, 2022). Moreover, it can lead to long COVID syndrome, which is defined by a history of a SARS-CoV-2 infection with a minimum of three months from the onset of COVID-19 illness, and a minimum duration of symptoms of at least two months, which cannot be explained by an alternative diagnosis (Soriano et al., 2022). The most common neurological symptoms reported due to long COVID are cognitive impairment (such as brain fog, memory issues, or loss of concentration), headache, sleep disturbance, peripheral neuropathy, dizziness, delirium, mobility impairment, and visual disturbance (Crook et al., 2021).

Transcranial direct current stimulation (tDCS) is currently being tested to improve cognitive deficits and mood disorders caused by long COVID. By delivering low-intensity current to the cortex of the brain through one anode and one cathode electrode placed on the scalp, tDCS modulates membrane polarization and cortical excitability. Upregulation of key brain areas, while decreasing stimulation in others, induces long-term potentiation (LTP) and long-term depression (LTD), respectively, resulting in long-lasting effects of the therapy (Antal et al., 2022; Nitsche et al., 2003). The use of tDCS has previously shown efficacy in the treatment of depression (Fregni et al., 2021), as well as cognitive enhancement in mild cognitive impairment and Alzheimer's disease (J. Chen et al., 2022b).

Materials and Methods

This mini-review followed The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021). On September 28th, 2022, two authors independently performed a systematic literature search for articles on long COVID syndrome and tDCS. Electronic searches were performed in MEDLINE (via PubMed) and Cochrane databases without language limitations. Titles and abstracts were first screened, and full-text studies were reviewed after screening according to the following inclusion criteria: (i) long COVID or Post-Acute COVID syndrome; (ii) cognitive impairment symptoms; (iii) tDCS intervention. We excluded studies that (i) used other stimulation techniques, or (ii), had no available results, such as ongoing trials and review articles.

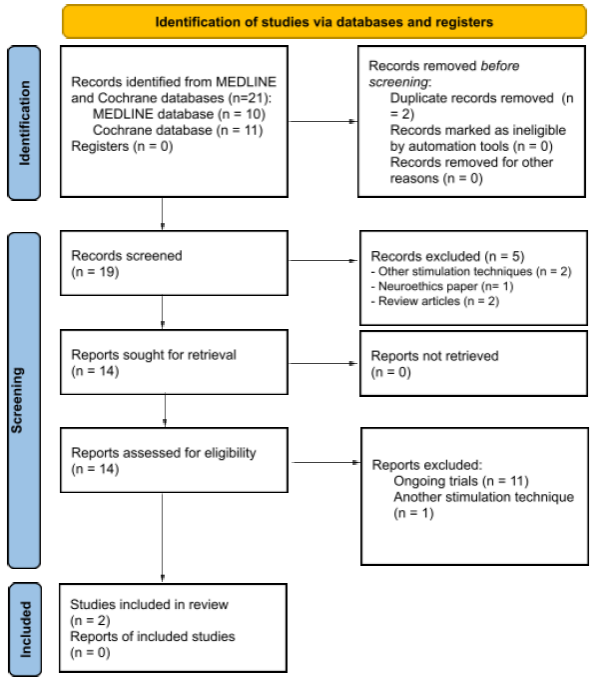
The search strategy used included the combination of the following keywords: "SARS-COV-2"[Text Word] OR "Coronavirus"[Text Word] OR "Severe acute respiratory syndrome coronavirus 2"[Text Word] OR "COVID-19"[MeSH Terms]) AND ("Transcranial Direct Current Stimulation"[Text Word] OR "Brain Stimulation"[Text Word] OR "non-invasive brain stimulation"[Text Word] OR "Neuromodulation"[Text Word] OR "tDCS"[All Fields]) AND ("Post-COVID"[Text Word] OR "Post-COVID cognitive"[Text Word] OR "PASC"[Text Word] OR "post-acute COVID-19 syndrome"[Text Word] OR "Long Covid"[Text Word] OR "Long-Term COVID-19"[Text Word]).

All full-text studies were reviewed by two authors (T. M. and A. A.) and a third author (J. G.) resolved disagreements. The studies' quality was assessed using the Joanna Briggs Institute (JBI) critical appraisal checklist for case reports (Moola et al., 2020). Two authors revised the studies according to eight questions from the JBI tool and classified them as low risk of bias if studies had 60% or higher of positive answers. Two other authors collected data from the studies. Each study's characteristics, such as population, intervention, outcomes, study design, and sources of funding were collected.

Results

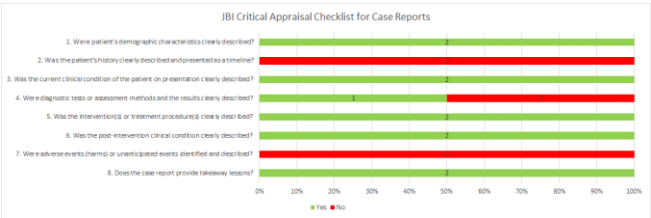
Our database search identified 21 articles. Following the removal of two duplicates, the remaining 19 titles and abstracts were screened. Five articles were excluded for not meeting the eligibility criteria and 14 full-text articles were assessed. Two case-report articles which focused on the treatment of long COVID syndrome with tDCS were included in this mini-review (Eilam-Stock et al., 2021, and Gómez et al., 2021). **Figure 1** shows the complete flow diagram for the selection of articles.

Figure 1. PRISMA 2020 flow diagram



Both articles had a low risk of bias assessed by the JBI tool (> 60% of positive answers - **Figure 2**). Data summarized from the included studies are presented in **Table 1**.

Figure 2. Quality assessment of included studies



Gómez et al. (2021) reported the case of a 58-year-old man with a history of arterial hypertension and premorbid anxiety symptoms who was hospitalized after being diagnosed with COVID-19. He was discharged after 14 days of hospitalization; after a few weeks, the patient reported moderate symptoms of long COVID, namely significant exhaustion, agoraphobia, and high levels of anxiety. Additionally, he presented with cognitive decline, sleeplessness, depression, and memory impairment. Over the course of 20 days, the patient received one 20-minute tDCS session at 2-mA every day, and his cognitive domains and health were evaluated using the Modified Fatigue Impact Scale (MFIS), Hamilton Anxiety Rating Scale (HARS), and Hamilton Depression Rating Scale (HDRS). After the final tDCS session, his HARS, HDRS, and MFIS scores showed a clinically significant decline from the initial session. He reported feeling better and worrying less, and noted improvements in anxiety symptoms and cognitive and physical functioning.

Eilam-Stock et al. (2021) developed a remotely supervised tDCS (RS-tDCS) protocol to treat long COVID syndrome. This protocol was used to treat two referred female participants (aged 42 and 57 years old) with persistent fatigue, cognitive dysfunction, and other symptoms seven to nine months after acute COVID-19 infection. Over a period of four weeks, the 42-year-old patient underwent 15 home-based sessions of RS-tDCS, each lasting 30 minutes at 2-mA. The sessions were paired with physical exercise, online adaptive computerized cognitive training, and guided mindfulness meditation. The 57-year-old patient underwent the same intervention protocol through a 7-month period. A specific long COVID inventory was developed by the authors to evaluate treatment benefit between baseline and the last session. Both participants reported improvement across physical, cognitive, emotional, and functional domains. The authors concluded that tDCS may provide a treatment option for patients with long COVID in the context of a home-based rehabilitation program.

Discussion

Transcranial direct current stimulation for long COVID syndrome

Eilam-Stock et al., 2021, and Gómez et al., 2021 addressed the following long COVID symptoms using tDCS: anxiety, depression, persistent fatigue and cognitive dysfunction.

These two case-reports had important methodological differences. The long COVID neuropsychiatric symptoms varied substantially among the studies. Gómez et al. (2021) reported a male case presenting mainly anxiety symptoms after four weeks of COVID-19 illness, while the other study reported two female cases presenting fatigue and cognitive impairment seven to nine months after acute COVID-19. Moreover, outcome assessment and the number of sessions and duration of the protocol used for tDCS were different between the studies and Eilam-Stock et al. (2021) combined the stimulation with other interventions.

Table 1. Baseline characteristics of included studies.

Study	Population	Intervention	Outcomes	Study design	Funding
Gómez et al., 2021	(1) 58-year-old man with long COVID syndrome (approximately four weeks after illness) experiencing high levels of anxiety, loss of memory and motivation, depression, decreased cognitive performance, and severe insomnia.	Daily session of tDCS (2 mA, 20 minutes) over 20 days. Used a left anodal dorsolateral prefrontal cortex montage.	HARS, HDRS, and MFIS. Subjective reports: how the patient was 'feeling' and if improved physical and cognitive performance.	Case Report	None
Eilam-Stock et al., 2021	(2)42-year-old, Black woman with long COVID syndrome (approximately nine months after illness) experiencing cognitive impairment, anxiety and depression, dyspnea, sleep disturbances, and numbness sensation in the right side of her face. (3) 57-year-old, White woman with long COVID syndrome (approximately seven months after illness) experiencing fatigue, "brain fog," emotional dysregulation, intermittent numbness in her extremities, and pain.	Daily at-home self-administrated tDCS (2 mA, 30 minutes). Used a left anodal dorsolateral prefrontal cortex montage. Paired with physical exercise, online adaptive computerized cognitive training, and guided mindfulness meditation. The combined intervention lasted four weeks for the 42-year-old patient and seven months for the 57-year-old patient.	Long COVID inventory developed by the authors (physical, cognitive, and emotional symptoms and functional abilities). Neuropsychological evaluations (not detailed).	Case Report	None

HARS: Hamilton Anxiety Rating Scale; HDRS: Hamilton Depression Rating Scale; MFIS: Modified Fatigue Impact Scale.

What is next for cognitive impairment in long COVID?

Despite the recent interest in long COVID, knowledge of its pathophysiology is still scarce. It has been challenging to establish the correlation between the clinical cognitive manifestation of COVID-19 and CNS damage, which could help identify possible therapeutic approaches.

One possible biological mechanism of damage involves neurovascular aspects of COVID-19, with insufficient perfusion affecting the neurons and their function. Neuromodulation can be used to stimulate vascular recovery in these patients (Sabel et al. 2021). However, there is still insufficient evidence that therapies aimed at increasing metabolic supply to neurons might improve cognitive symptoms of long COVID.

Neuroinflammation resulting from the SARS-CoV-2 infection seems to play an important role in the pathophysiology of neurological lesions and cognitive impairment in long COVID (D'Arcy et al., 2021; Newhouse et al., 2022). The mechanisms of neurodegeneration may be similar to those of Alzheimer's disease (F. Chen et al., 2022a), and tDCS treatment may have therapeutic effects in neurodegenerative diseases (Fregni et al., 2006; Pellicciari & Miniussi, 2018). When tDCS was used to treat cognitive impairment associated with long COVID the authors reported improvement in the three patients tested (Eilam-Stock et al., 2021; Gómez et al., 2021). Therefore, as each study used different protocols of tDCS and long COVID symptoms varied substantially among patients, it is difficult to draw conclusions.

A limitation to this review is the few number of articles included, with significant methodological differences between them. The scarcity of papers evaluating tDCS in long COVID patients demonstrates that potential treatment for the sequelae of COVID-19 infection is still an unmet need, especially regarding cognitive symptoms. The strength of this review is precisely to explore one potential beneficial therapeutic option - tDCS - for this condition.

Conclusions

Cognitive impairment from long COVID poses a significant challenge for both clinicians and patients. Though neuromodulation treatments like tDCS have been used to improve cognition in patients with long COVID, more data is needed on the efficacy and optimal implementation of tDCS treatment for these patients. Additionally, most studies in the literature were case reports including very few patients. Thus, randomized clinical trials using tDCS, compared to sham stimulation, in long COVID patients with cognitive impairment symptoms might help to reveal the neurological mechanisms involved in long COVID pathogenesis, and may also demonstrate significant results in the effectiveness of tDCS in this condition.

Supplementary Materials: Not applicable.

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