Issue Rehabil. Orthop. Neurophysiol. Sport Promot. 2022; 41: 45–50. ISSN 2300-0767
DOI: 10.19271/IRONS-000179-2022-41

SHORT COMMUNICATION

IS NEUROSTIMULATION A POTENTIAL THERAPEUTIC TOOL IN PATIENTS WITH NEUROCOGNITIVE PROBLEMS IN LONG-COVID?

CZY NEUROSTYMULACJA MOŻE SŁUŻYĆ JAKO NARZĘDZIE TERAPEUTYCZNE U PACJENTÓW Z ZABURZENIAMI NEUROKOGNITYWNYMI W PRZEBIEGU LONG-COVID?

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Abstract
Brain micropolarization has long been recognized as a therapeutic approach for the treatment of neurological disorders. In both neurological and psychiatric treatment, due to their functionality, noninvasive methods, such as Transcranial Magnetic Stimulation (TMS), transcranial Electrical Stimulation (tES), and transcutaneous Vagal Nerve Stimulation (tVNS), are preferred. The above methods are registered for clinical use worldwide as adjuvant therapy for many neurological disorders such as Parkinson's disease, Alzheimer's disease, depression, brain stroke, vascular dementia, chronic pain, and others.

Although SARS-CoV-2 is considered a respiratory pathogen, it also displays a potent neurotropism with neuropsychiatric consequences that may occur during the acute phase of infection or may be delayed even months after COVID-19 illness. People with long COVID conditions most commonly experience a 'brain fog', which is associated with cognitive deficits, concentration and memory disturbances, and headaches. Long-COVID may also include neuropsychiatric disorders such as dyssomnia, dementia, depression, or even psychosis. Neurological lesions have a multifactorial background and may be induced by the direct viral invasion of the neurons and glial cells, an inflammatory response with excessive cytokine reaction, or hypoxic injury due to respiratory impairment.

Recently, as the COVID-19 pandemic continues, it has been suggested to implement brain neurostimulation for the treatment of neurological manifestations. However, until now there are only a few studies, including clinical trials, presenting the practical use of this method. Since no authorized strategies and standards for long-COVID treatment are developed, neurostimulation may be considered as a potential therapeutic tool for alleviating neurological symptoms in patients with long-COVID19.

Materials and methods
To identify relevant papers, we searched PubMed and Wiley Online Library databases using the following keywords: neurostimulation, long-COVID, brain fog, and neuropsychiatric symptoms. A literature search was based on the current articles describing neurostimulation and Long-COVID conditions.

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Authors reported no source of funding
Authors declared no conflict of interest

Date received: 18th May 2022
Date accepted: 24th November 2022

Aim
This paper aims to present neurostimulation as a potential therapy to alleviate persistent and chronic neuro-symptoms in patients infected with SARS-CoV2.

Keywords: neurostimulation, brain fog, neurocognitive disorders, Long-COVID

STRESZCZENIE
Mikropolaryzacja mózgu od dawna uznawana jest jako jedna z metod w leczeniu zaburzeń neurologicznych. W leczeniu neurologicznym i psychiatrycznym ze względu na funkcjonalność preferowane są nieinwazyjne techniki stymulacji mózgu, takie jak przezczaszkowa stymulacja magnetyczna (TMS), przezczaszkowa stymulacja elektryczna (tES) oraz przezskórna stymulacja nerwu błędnego (tVNS). Metody te są zarejestrowane do użytku klinicznego na całym świecie jako terapia uzupełniająca wielu zaburzeń neurologicznych, takich jak choroba Parkinsona, choroba Alzheimera, depresja, udary mózgu, otępienie naczyniopochodne, przewlekły ból i inne.

Choć SARS-CoV-2 jest ogólnie postrzegany jako patogen układu oddechowego, wykazuje on również silny neurotropizm wywołując zaburzenia neurologiczne zarówno w fazie ostrej zakażenia, jak i w czasie odległym (nawet kilka miesięcy od inwazji wirusa), co określane jest jako „Long-COVID". Najczęściej opisywane dysfunkcje neurologiczne Long-COVID nazywane są „mgłą mózgową" i wiążą się z deficytami poznawczymi, zaburzeniami koncentracji i pamięci oraz bólami głowy. Long-COVID odpowiada również za wywołanie pewnych zaburzeń neuropsychiatrycznych, do których należą dyssomnia, demencja, depresja, a nawet psychoza. Zarówno powinowactwo wirusa do komórek nerwowych, reakcja zapalna z burzą cytokinową, jak i niedotlenienie wywołane hipoksemią w wyniku trudności w oddychaniu, prowadzą do uszkodzenia neuronów.

W trakcie pandemii COVID-19 zasugerowano wdrożenie neurostymulacji mózgu do leczenia powikłań neurologicznych wynikających z Long-COVID. Jednak do tej pory istnieje niewiele badań, w tym klinicznych, przedstawiających praktyczne zastosowanie tej metody u pacjentów z mgłą mózgową. Ponieważ nie sformułowano żadnych autoryzowanych strategii i standardów terapii Long-COVID, neurostymulację można uznać za potencjalne narzędzie terapeutyczne do łagodzenia objawów neurologicznych Long-COVID.

Materiały i metody
W publikacji wykorzystano najnowsze doniesienia dostępne w bazach PubMed oraz Wiley Online Library odnoszące się do tematu neurostymulacji i powikłań neurologicznych Long-COVID. W celu przeglądu literatury światowej posłużono się słowami kluczowymi: neurostimulation, long-COVID, brain fog, neuropsychiatric symptoms.

Cel
Celem pracy jest przedstawienie neurostymulacji jako potencjalnej terapii łagodzącej uporczywe i przewlekłe neuro-objawy u pacjentów zakażonych SARS-CoV2.

Słowa kluczowe: neurostymulacja, mgła mózgowa, zaburzenia poznawcze, Long-COVID

Introduction

The latest available data (May 2022) show that the COVID-19 pandemic has claimed 517M infected people of which over 6M people died. While the pandemic has been continuing, new variants of viruses and new symptoms of COVID-19 illness have emerged. Importantly, SARS-CoV-2 is characterized as a multiple-face virus having a potent tropism to different organs including the respiratory system, heart, skeletal muscles, kidneys, liver, and brain (Ondruschka *et al.* 2021). Many months after their initial infection, some Covid-19 patients started reporting long-term sequelae related to a mental health condition. Cognitive deficits, headaches. Concentration and memory disturbances were the first complications reported, even among very young people.

Neurological manifestations of SARS-CoV-2 infection

Neurological symptoms of viral infection may differ depending on the infection phase and severity. Therefore, the potential consequences of coronavirus infection could be broadly divided into three categories:

1. Acute phase manifestations: headaches, muscle pain, dizziness, disturbances of smell and taste
2. Complications that may lead to encephalitis and stroke
3. PCNS - Post-COVID neurological syndrome with symptoms: depression, fatigue, cognitive disorders, and memory deficits (Wijeratne, Crewther 2020).

The long-term consequences of SARS-CoV-2 infection are commonly described as Long-COVID syndrome and are reported by almost 60% of infected patients with at least one feature recorded (Taquet *et al.* 2021). Taquet *et al.* showed that symptoms of Long COVID may last from 6 to 12 months. SARS-CoV-2 is characterized by neuroinvasiveness (ability to enter neurons through nerve endings of cranial nerves that innervate the respiratory tract or ability to cross the blood-brain barrier), neurotropism (ability to infect and replicate in neurons), and neurovirulence (ability to cause central nervous system pathology). Headaches, concentration disturbances, cognitive blunting colloquially described by the term 'brain fog', anxiety, and depression are current features resulting from COVID-19. There is also substantial evidence that COVID-19 may cause neuropsychiatric symptoms. In 2020, British researchers described COVID-related strokes, altered mental status, and posttraumatic stress disorder (PTSD) as secondary effects of the SARS-CoV-2 pandemic (Varatharaj *et al.* 2020).

Pathophysiology of neuroinfection

Although there are no specific markers for neuroinfection of COVID-19 and changes in MRI usually show microvascular damage only (Lee *et al.* 2021), there are few assumed pathomechanisms that may clarify this phenomenon. The ongoing hyperinflammation and endotheliitis that manifest by increasing IL-1 and IL-12, activated T cells and NK (natural killers) that occur in CSF (Lee *et al.* 2021) contribute to the disruption of the blood-brain barrier followed by impaired coagulation and thrombotic microangiopathy. Reduced blood flow and hypoxia limit metabolic activity and silence the neurons and glial cells. This potential pathomechanism is considered to be the most probable cause of the long-COVID syndrome, commonly described as brain fog (Sabel *et al.* 2021). Another hypothesis suggests that hypoxia affects the cerebrum and cerebellum with the highest loss in neuronal cells of the cerebral cortex and hippocampus, resulting in memory deficiencies and cognitive difficulties (Maiese *et al.* 2021).

Neurostimulation Potentiality

Given that patients with COVID-19 can present with neurological signs and that causal management for long-COVID is currently unavailable, new research is needed to design effective treatment methods.

Neurostimulation of the brain is the worldwide tool registered as adjuvant therapy for many neurological disorders, such as Parkinson's disease (Schuepbach *et al.* 2013), Alzheimer's disease (Gangemi *et al.* 2021), chronic pain (Hofmeister *et al.* 2020), or autism spectrum disorder (Khalegi *et al.* 2020) The list of neurological manifestations that are successfully alleviated with neurostimulation could be broader, depending on severity and type of condition (Camacho Conde *et al.* 2021). Taking into account similarities of symptoms that occur in a variety of neurological disorders and long-COVID patients, neuroscientists came up with the idea to use this method as a potential treatment option for patients with long-COVID brain fog.

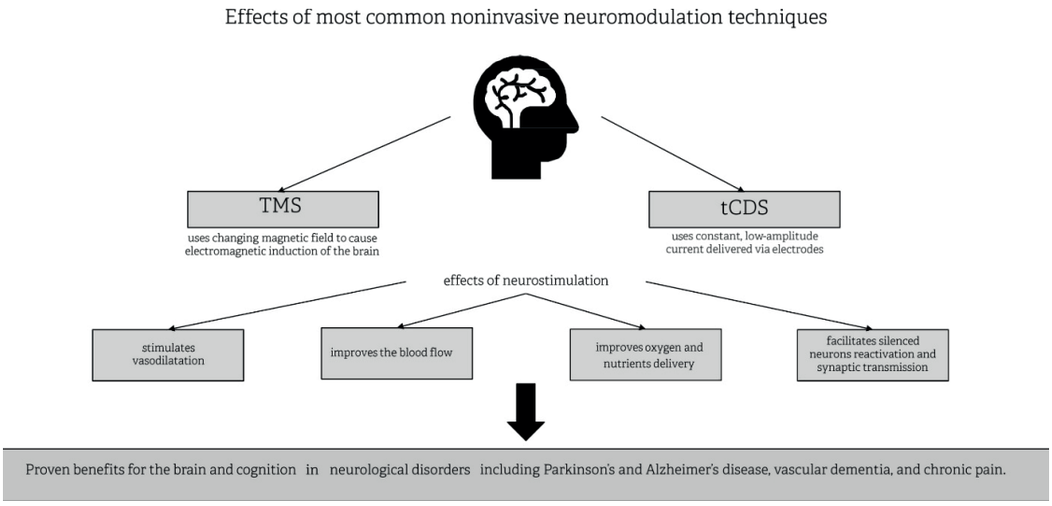
Non-invasive brain microcurrent stimulation therapy consists of two main modalities using different methods that invoke an electrical current. Transcranial Magnetic Stimulation (TMS) uses magnetic fields to induce electric current at a specific area of the brain. TMS used in a single pulse leads to depolarization of the neurons and repetitive stimulation can change cerebral blood flow, cortical activity, oxygen consumption, and file cerebral neurotransmission. (Camacho Conde *et al.* 2021). Similarly to the magnetic method, electrical stimulation can also lead to a change in cortical excitability by limiting GABA neurotransmission and promoting glutamate neurotransmission, modulating the connectivity of different regions in the brain. The axonal release of monoamine transmitters and dopamine could be present in other areas of the brain (Yamada, Sumiyoshi 2021). Transcranial direct current stimulation (tDCS) delivers low-amplitude current by electrodes directly through the scalp and beneficially affects neurotransmission. Therefore, both methods of non-invasive brain stimulation may cause functional changes and bring positive clinical effects (Figure 1).

Brain stimulation in neurocognitive disorders

Magnetic and electrical neurostimulation is used successfully in addition to default therapy strategies for neurological dysfunctions. TMS as a therapy tool can be used with different frequencies from low to high with the range most often oscillating from 0.5 to 50 Hz with 10–19 Hz frequency. Amount of pulses administered in each procedure is usually less than ten. (Camacho Conde *et al.*2021). Transcranial direct current stimulation (tDCS) with microcurrent usually does not exceed 0.08 mA/cm^2 in current density, simultaneously targeting different regions of the brain. Looking at the studies with representative groups, Spanish researchers put together a few publications to show how spectacular effects patients can acquire with neurostimulation to help alleviate neurological and neurocognitive impairments. The probability values in each study show how good therapeutic results could be reached using noninvasive brain stimulation (TMS and tDCS), which makes it a promising method to relieve neurological dysfunction. Interestingly, tDCS is used more frequently than TMS due to its charge and the lower risk of potential side effects. (Camacho Conde *et al.* 2021).

Neurostimulation as a therapeutic tool for long-COVID neurocognitive problems

So far there are no authorized strategies and standards for Long-COVID therapy, therefore neurostimulation may be considered as a promising therapeutic tool. Being aware of the diversity of neurological disorders and symptoms that could be treated with noninvasive brain stimulation, it was suggested to try this method in patients with neurocognitive problems due to past COVID-19 infection. At the end of 2021 Sabel *et al.* published a case report describing two female patients with Long-COVID syndrome subjected to neurostimulation. The patients suffered from typical features of SARS-CoV-2 post-infection, complaining of cognitive deficits and visual field loss. Patients received 10 and 13 sessions of transcranial microcurrent stimulation with each session lasting from 30 to 45 minutes, using an electric current intensity of less than 2mAmp. Both patients reported



Abbreviations: TMS – transcranial magnetic stimulations, tCDS – transcranial direct current stimulation

Figure 1. Effects of most common non-invasive neuromodulation techniques

a significant improvement in their mental state, which helped them return to normal functioning. (Sabel *et al.* 2021). Explicitly explaining the most probable mechanism, the authors suggested that neurostimulation, by its vasodilative effects in small blood vessels, brought more oxygen and nutrients to affected neurons.

Conclusions

1. As the COVID-19 pandemic continues, there is a pressing need to implement non-invasive and safe therapeutic strategies targeting neurological complications resulting from Long-COVID. Electrical nerve stimulation has been proposed as one of them.
2. Brain neurostimulation is still underappreciated in alleviating neural sequelae of SARS-CoV-2 infection.
3. More studies are needed to better understand of SARS-CoV2 contribution to pathological changes in the central nervous system.

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