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NEUROTHERAPY IN PARKINSON'S DISEASE: THE PATH FORWARD AFTER SARS-CoV-2 INFECTION AND CONTRACTING COVID-19, AND LONG COVID?

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SUMMARY

There is growing evidence to support the view that a variety of neurological, neurocognitive and neuropsychiatric sequelae occur following SARS-CoV-2 infection and NeuroCovid 19. Furthermore, scholars report that various syndromes, including Parkinson's disease (PD), can develop within a short period of time following on from COVID-19. Although the mechanism of this phenomenon is not fully understood and it is not known whether this is in fact an acceleration of the development of PD already 'smouldering' in the body or related to a viral infection, these patients need rehabilitation assistance. Recently, as adjuvant therapy, transcranial direct current stimulation (tDCS) has been shown to improve the motor and non-motor function of patients with Parkinson's disease (PD), including neurocognitive impairment and therefore potentially change their quality of life. The aim of this article is to show the effectiveness of tDCS in the treatment of the patient with newly diagnosed Parkinson's disease after infection with the SARS-CoV-2 virus and the contracting of NeuroCovid 19, and equally developing long COVID. The motivation would be to help other patients with a similar situation during the COVID-19 pandemic.

A 62-year-old man, an academic Art Teacher, was infected with SARS-CoV-2 and contracted NeuroCOVID-19 on November 11, 2021. Initially, he lost his sense of smell (anosmia), of taste (ageusia), developed headaches, and dizziness. After 10 days of illness, the patient developed severe, level two inflexion (according to Wise 2020), and he was hospitalized, sedated and mechanically ventilated for 30 days. After discharge from hospital, the patient was still weak with different symptoms. Four months later he was diagnosed with long COVID and also the neurodegenerative disease PD (according to the DSM-5 criteria). He received levodopa therapy, and was referred to the Reintegration and Training Center of the Polish Neuropsychological Society for further treatment. The functional neuromarker, that is hypoactivation of the left dorsolateral prefrontal cortex (DLPFC), obtained with the use of QEEG/ERPs was helpful in choosing the appropriate tDCS protocol. Neurostimulation with the use of anodal tDCS over these area of the brain was administered systematically for 20 days. He also received individual sessions of art therapy for 20 day. After the treatment the patient improved and returned to his previous work as a university art teacher. The proposed anodal tDCS over the left dorsolateral prefrontal cortex (DLPFC), in combination with goal-oriented individual art therapy, offered to the patient, was effective in the reduction of all his syndromes.

ERPs can be useful in the diagnosis and treatment of patients following infection by SARS-CoV-2 who contracted COVID-19, developed long COVID and additionally PD. It allows for the detection of the functional neuromarker of PD (e.g., hypoactivation of the dorsolateral prefrontal cortex, DLPFC) and enabled the choosing of a proper tDCS protocol with the anode over these region of the brain, and also the selection of effective neurostimulation. The proposed protocol of tDCS tailored by the neuromarker offered to our patient, was effective in the reduction of longCOVID symptoms as well as early PD symptoms.

Key words: neurotherapy, tDCS, Art Therapy, LongCOVID, Parkinson's disease (PD)

INTRODUCTION

Coronavirus (SARS-CoV-2), since the first confirmed case in Wuhan, China on December 31, 2019, has spread quickly throughout the world infecting 608.9 million people, with more than 6.49 million (about 1 %) dying from Covid-19, as of the beginning of September 2022. The most affected regions of the world are Europe (more than 221.9 million cases), Asia (more than 184.0 million), and North America (with more than 114.4 million infections). Since this first detection, research has indicated that people infected by the virus may suffer neurological and mental disorders and deficits, in addition to the respiratory and other organ challenges caused by COVID-19 (Chen 2020; Pačalska et al. 2021; Smeyne et al. 2021). One of such possible consequences is the acceleration of the development of neurodegenerative diseases, including Parkinson's disease (PD).

Neurological sequelae after a viral infection is not new. Historically, starting in 1917, an epidemic of Encephalitis lethargica, also called von Economo's Encephalitis or "sleepy-disease", was possibly related to the 1918 Spanish flu pandemic. However, even with the use of modern molecular diagnostic tests on appropriate corpses, no link between Encephalitis lethargica with flu has been established (Evidente & Gwinn 1998). Although Parkinsonism was occasionally seen during the acute phase of Encephalitis lethargica, it was also often encountered in the post-encephalitic phase, delayed in some cases by several years (Jang, Boltz, Sturm-Ramirez et al. 2009). It took more that 100 years to present any possible relation between the neurological syndrome called "post-encephalic Parkinsonism", a disease that triggers degeneration of the nerve cells in the substantia nigra, and possibly the infection of SARS-CoV-2 and the contracting of Neuro COVID-19 (Smeyne et al. 2021).

More than 6 million individuals worldwide have Parkinson disease(PD) (Armstrong & Okun 2020).Neuroscientists point out that PD is the most common form of Parkinsonism, a group of neurological disorders (Marxreiter & Winkler 2016). The best known forms being:

1. *Idiopathic Parkinson's disease (IPD)*, a neurodegenerative disorder, with the severity of the disability usually increasing with disease duration like motor problems (eg. rigidity, slowness, and tremor) and non-motor problems (e.g., cognitive and executive functions).
2. *Vascular Parkinsonism (VP)* results from cerebral vascular disorders that feature white matter lesions and small vessel pathology, typically presents as lower body Parkinsonism with predominant gait impairment. Urinary incontinence and cognitive decline are additional features of the disease. There is a considerable overlap between vascular Parkinsonism and vascular dementia (VD).

PD is widely believed to be caused by a combination of genetic and environmental factors (Chen and Ritz 2018). However, in recent articles, authors have attempted to demonstrate that a bacterial or viral infection may be a potential risk factor for PD development (Marras, Canning, Goldman 2019). Supportive, but not entirely consistent, epidemiological and basic science data are cited as

evidence to support this hypothesis. It has been found only recently that the epidemiological evidence is the most convincing in supporting an association between PD and hepatitis C virus (Forton, Allsop, Main et al. 2001; Wilkinson, Radkowski, Laszuk 2009; Wu, Kang, Chen et al., 2015; Tsai, Liou, Muo et al. 2016; Pakpoor, Noyce, Goldacre et al. 2017; Wijarnpreecha, Chesdachai, Jaruvongvanich et al. 2018; Goldstein, Fogel-Grinvald, Steiner 2019; Lin, Lin, Weng et al. 2019; Su, Yang, Tseng et al. 2019). It has also been found that helicobacter pylori infection may be associated with a response to levodopa, and also with the risk of PD development (McGee, Lu, Disbrow 2018; McGee, Lu, Disbrow 2018; Shen, Yang, Wu, Zhang et al. 2017). Rapidly developing knowledge of the role of the microbiome also suggests a role for resident bacteria in the risk of PD development (Scheperjans, Aho, Pereira et al. 2015; Zhernakova, Kurilshikov, Bonder et al. 2016; Sampson, Debelius, Thron et al. 2016).

The biological plausibility of a role for infectious agents is supported by the known neurotropic reactions of specific viruses, the particular susceptibility of the substantia nigra and even the promotion of the alpha-synuclein aggregation in risk of PD development (Bhattacharyya, Mohite, Krishnamoorthy et al. 2019). A common feature of viruses is the production of high levels of cytokines and chemokines that can cross the blood-brain barrier, leading to activation of microglia and inflammation, and ultimately to neuronal cell death (Hayes, Woodroffe, Cuzner et al. 1988; Rostami, Fotaki, Sirois et al. 2020). Based on a wealth of evidence, it seems likely that certain bacterial and especially viral infections, including SARS-CoV-2 infection may increase susceptibility to PD development (Smeyne et al. 2021).

However, those neuropathologists who looked at a large number of brains of people who had died of COVID reported that in the substantia nigra, the brain area that is affected in PD, there was in fact very little to see; and there is no evidence of nerve cell degeneration. There is, of course, a lot of changes in other areas of the brain including hypoxia that likely results from pulmonary (lung) problems with COVID or small infarcts after a brain stroke. There is no clear evidence in the activation of microglial cells, the brain's immune cells, which is a sign of inflammation, which can cause damage to brain cell function (Marxreiter, Winkler, Vaskuläres et al. 2016; Polidoro, Hagan, de Santis et al. 2020). There is a great deal of pathology that occurs in the brains of those who die from COVID, but nothing we can directly relate to the known pathology PD (Smeyne et al. 2021). These findings are based on facts seen in patients who die from COVID-19 infection, and therefore they have the most severe course of the disease. It should be added, however, that some of these lesions are also present in the brains of people who survived the acute phase of SARS-CoV-2 infection and the contracting of severe COVID-19, but died months later from another disease (for example, cancer or heart disease). Therefore, we are not sure whether they appeared after the virus infection or whether they resulted from the disease that caused the person's death, and infection by the virus only hastened their deaths (Rostami, Fotaki, Sirois et al. 2020).

The authors, based on a large cohort study involving tens of thousands of survivors who have continued to struggle with a variety of symptoms for at least 12 weeks after infection, categorise them (see: Wise 2020). However, it is not an easy task, because the symptomatology of long COVID is incompletely understood and characterized by an extremely wide range of manifestations that are difficult to analyze computationally. Therefore accurate stratification of patients with post-acute sequelae of SARS-CoV-2 infection (PASC, or long COVID) would allow precision clinical management strategies and more focussed investigation of the molecular pathogenetic mechanisms of this disease (Reese, Blau, Bergquist et al. 2022). Despite these difficulties, Wise (2020), on the basis of the analysis of the data obtained from a symptom tracker app, has developed an extremely useful classification of the six distinct “types” of COVID-19, each distinguished by a cluster of symptoms. These include:

1. “Flu-like” with no fever – headache, loss of smell, muscle pains, cough, sore throat, chest pain;
2. “Flu-like” with fever – headache, loss of smell, cough, sore throat, hoarseness, fever, loss of appetite;
3. *Gastrointestinal* – headache, loss of smell, loss of appetite, diarrhoea, sore throat, chest pain, no cough;
4. *level one (with fatigue)* – headache, loss of smell, cough, fever, hoarseness, chest pain, fatigue;
5. *Severe level two (with fatigue and confusion)* – headache, loss of smell, loss of appetite, cough, fever, hoarseness, sore throat, chest pain, fatigue, confusion, muscle pain;
6. *Severe level three, (abdominal and respiratory)* – headache, loss of smell, loss of appetite, cough, fever, hoarseness, sore throat, chest pain, fatigue, confusion, muscle pain, shortness of breath, diarrhoea, abdominal pain.

These classification could be used not only to predict the need for respiratory support in severe COVID-19, but also for reaserch, and we shall use this in the classification of our patient’s symptoms.

Another problem that arises in the evaluation of the association between SARS-Cov-2 virus infection and the development of PD are the difficulties associated with the problem of the overlapping of long COVID symptoms (also known as post COVID) and PD. Long COVID refers collectively to the constellation of long-term symptoms that some people experience after they have had COVID-19. From a review of the global subject literature, we know that long COVID-19 symptoms occur in individuals with a history of probable or confirmed COVID-19 infection, usually 3 months after the onset of COVID-19 with symptoms that persist for at least 2 months and cannot be explained by another diagnosis (cf. Aknin et al. 2021). Neuroscientists added to this definition the fact that the “distinction between very sick people who have recovered to an extent and [and have been] left with some impact of their severe sickness, versus those who had a relatively mild sickness from the start, in whom it is ongoing.” (NICD, 2022).

Although the mechanism of the association of SARS-CoV-2 virus infection with the development of PD, as well as the coexistence of long COVID and PD

symptoms is not fully understood and it is not known whether it is an acceleration of the development of a disease already 'smouldering' in the body or related to a viral infection, these patients need rehabilitation assistance. Recently, as adjuvant therapy, transcranial direct current stimulation (tDCS) has been shown to improve the motor and non-motor function of patients with Parkinson's disease (PD), including reduction of neurocognitive impairment and potentially a change in their quality of life (Elsner, Kugler, Pohl et al. 2016; Liu, Liu, Liu et al. 2021).

The aim of this article is to show the effectiveness of tDCS in the treatment of a person with newly diagnosed Parkinson's disease following infection with SARS-CoV-2 and contracting NeuroCovid 19. The motivation would be to help other patients with a similar situation during the COVID-19 pandemic.

Ethics statement

According to the guidelines of the Helsinki Declaration (2008), the patient participating in the experiment was informed in detail about the test procedure and he provided written consent for his participation in the project. The study protocols received ethical approval from the Ethical Committee of the Regional Medical Chamber (KB6/16).

CASE STUDY

A 62-year-old man, an academic art teacher, was infected with SARS-CoV-2 and contracted NeuroCOVID-19 on November 11, 2021. Initially, he lost his sense of smell (anosmia), of taste (ageusia), and had latent blinks (heterophila), headaches, and dizziness. After 10 days of illness, the patient developed headaches, loss of smell, loss of appetite, a cough, fever, hoarseness, sore throat, chest pain, fatigue, confusion, muscle pain, and a shortness of breath, and he was hospitalized, sedated and mechanically ventilated for 30 days. He was classified as **severe, level two infection** (according to Wise 2020). Additionally he had mild, untreated hypercholesterolaemia but no vascular risk factors and had been a lifelong non-smoker.

After discharge from hospital, the patient was still weak and his general practitioner diagnosed him with brain fog, headache and severe fatigue (he could only walk a few dozen steps and was unable to climb stairs), and prescribed appropriate symptomatic treatment. Four months later the patient's symptoms worsened: he had difficulty using his right hand to perform fine movements and periodic tremors of this hand, stiffness of the right shoulder when lecturing and showing details from a slide presented on the wall or of a painting. It was very stressful for him and he stopped paint. He always goes through traffic lights at intersections with big problem, which made him dependent on random passers-by. He complained of having real problems in daily functioning, and his general practitioner referred him this time to the neurology clinic, where a neurodegenerative disease specialist diagnosed him with PD (according to the DSM-5 criteria), prescribed levodopa therapy, and referred to the Reintegration and Training Center of the Polish Neuropsychological Society for further treatment.

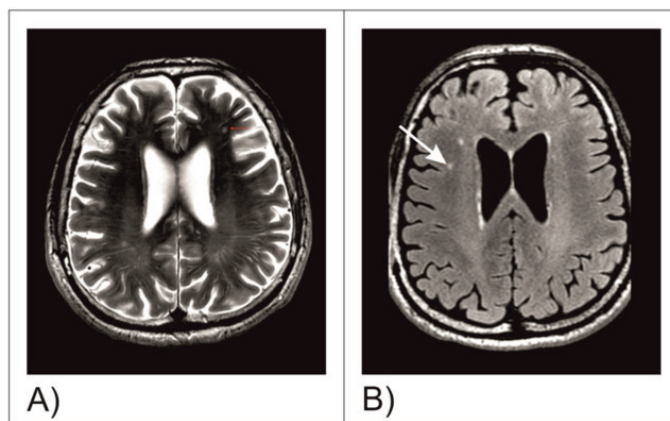


Fig. 1. Brain MR, 3Tesla, axial plane: A) frFSET2 sequence, B) FLAIR sequence small foci of high signal intensity in the hemispheric white matter (white arrow)

At this time, as part of a research study, he underwent a magnetic resonance imaging (MRI) brain scan. It showed diffuse ischaemic white matter change, but no focal infarct (see: Fig. 1 A, B) except for small foci of high signal intensity in the hemispheric white matter (white arrow) seen in the FLAIR sequence (see: Fig. 1 B). His *Hachinski Ischaemic Score*, HIS was ≤ 4 which does not suggest Vascular Dementia (VD).

Neurophysiological testing

EEG recording

The electroencephalogram (EEG) was recorded with the Mitsar 21-channel EEG system, with a 19-channel electrode cap with tin electrodes that included Fz, Cz, Pz, Fp1/2, F3/4, F7/8, T3/4, T5/6, C3/4, P3/4, O1/2. The electro-cap was placed on the scalp according to the standard 10–20 system. Electrodes were referenced to linked earlobes (off-line), and the input signals were sampled at a rate of 250 Hz (bandpass 0.5–30 Hz). The ground electrode was on the forehead. Impedance was kept below 5 k Ω . The patient was sitting in a comfortable chair looking at a computer screen (17 inches) 1.5 meters in front of him. All recordings were conducted by the first author of this article. The ERP wave forms were averaged and computed off line, and trials with omission and commission errors were automatically excluded.

Behavioral task

The task consisting of 400 trials were sequentially presented to the subject every three seconds. Three categories of visual stimuli were used:

1. 20 different images of animals – referred to later as A;
2. 20 different images of plants – P;
3. 20 different images of people of different professions (presented together with an artificial "novel" sound), referred to as H.

Artifact correction procedures

Eyeblink artifacts were corrected by zeroing the activation curves of individual independent components corresponding to eye blinks. These components were obtained by the application of Independent Component Analysis (ICA) to the raw EEG fragments as described in Kropotov (2016). Epochs with an excessive amplitude of filtered EEG and/or excessive faster and/or slower frequency activity were automatically marked and excluded from further analysis. The exclusion thresholds were set as follows:

1. 100 μ V for non-filtered EEG;
2. 50 μ V for slow waves in the 0–1 Hz band; and
3. 35 μ V for fast waves filtered in the band 20–35 Hz.

In addition, we visually inspected the recordings and excluded the remaining artifacts.

EEG spectra

EEG spectra were computed for Eyes Open, Eyes Closed and the GO/NOGO task conditions separately. The artifact free fragments of EEG were divided into 4 sec epochs with a 50% overlap. The Hanning time window was applied. The EEG spectra were computed for each epoch and averaged. The mean value and standard deviations for each 0.25 Hz bin were computed. For comparison of the EEG spectra pre and before intervention, the t-test was used.

RESULTS

Behavior

The behavioral parameters of the patient in the cued GO/NOGO task are presented in Table 1.

It can be observed that the patient is 100 ms faster than the average, but he produces more commission errors than the norm (100 persons from the normative data base of the Human Brain Index, HBI, in Chur, Switzerland).

Spectra

Spectra differences and maps for the largest deviation from normality: the difference with p-values in vertical bars are shown at the top (left), and they correspond to the deviation from the norms (Fig. 2).

Tab. 1. Comparison of the patient's behavioral parameters in the cued GO/NOGO task with the normative data

Tested persons	Omission errors	Commission errors	RT1	var(RT1)
Patient	0%	1%	313 ms	6.3 ms
Norms	2.2	0.6	404ms	7.3 ms
P value	0.59	0.5	0.05	0.67

It should be stressed that clinically no signs of neurological abnormality are observed. EEG is characterized by posterior alpha. This is the most common EEG phenotype. The dominant frequency is 11 Hz which indicates high functional abilities.

The spectra of the independent component and sLORETA image and are shown at the top (right) and the bottom, and they correspond to the deviation from the norms (Fig. 3). It was found that EEG spectra deviations from the norm (100 persons from the normative data base of the Human Brain Index, HBI, in Chur, Switzerland) indicate hypoactivation of the left temporal cortex.

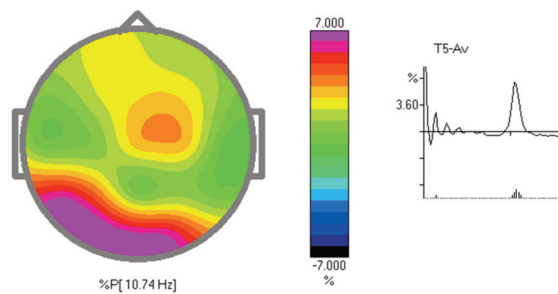


Fig. 2. Spectra differences and maps for the largest deviation from normality (100 persons from the normative data base of the Human Brain Index, HBI, in Chur, Switzerland)

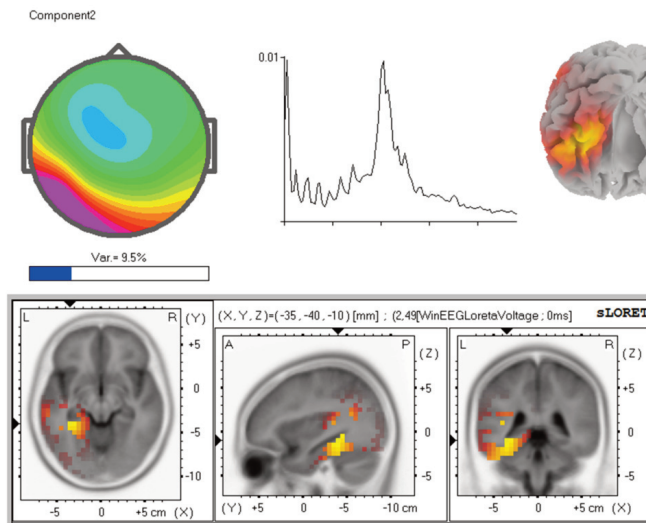


Fig. 3. Spectra of independent component and sLORETA image corresponding to the deviation from the norms (100 persons from the normative data base of the Human Brain Index, HBI, in Chur, Switzerland)

Event related potentials (ERPs)

The ERPs deviations from the reference are shown in Fig 4. The ERPs deviations from the norm (100 persons from the normative data base of the Human Brain Index, HBI, in Chur, Switzerland), indicate hypoactivation of the left dorso-lateral prefrontal cortex (DLPFC).

Neurotherapy

The patient took part in 20 sessions of individually tailored anodal transcranial direct current stimulation (atDCS). The protocol was tailored by the findings of the neuromarker in ERPs, with the anode on the left dorsolateral prefrontal cortex (DLPFC). This protocol was also suggested for PD treatment by other authors in successful large cohort studies (Doruka, Gray, Bravoa et al. 2014; Liu, Liu, Liu et al. 2021). It should be added that the patient did not have implanted electrodes and a generator for deep brain stimulation or foreign bodies such as a pacemaker, an implanted medical pump, an implanted hearing aid, a metal plate in the skull or a metal implant in the skull or eyes. Neurostimulation was administered systematically, every day, 15-20 and 30-40 minutes for each session, for 20 days. He also received individual sessions of art therapy every day, 30-40 minutes for each session, for 20 days (see: Pączalska 2008).

Neuropsychological examination

The patient was examined three times using the standard Polish version of the Mindstreams™ Interactive Computer Tests. The first examination was conducted before the neurostimulation by tDCS, the second after the completion of 20 sessions of tDCS, which lasted 20 days, and the third examination after a 3-month follow up. The effect of tDCS on the neuropsychological functioning is presented in Fig. 5. It was found that in the first examination (before tDCS) disturbances for all the tested cognitive functions occurred. The greatest changes were to occur however in the areas of memory, attention, and executive functions. In the second test, a return to the norm was achieved for the disturbed cognitive and

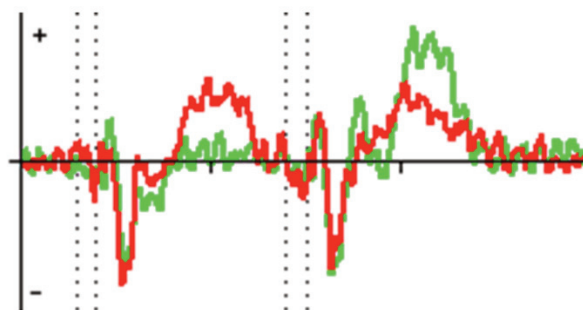


Fig. 4. The ERPs deviations from the norm (100 persons from the normative data base of the Human Brain Index, HBI, in Chur, Switzerland). Green – patient, red – normative data

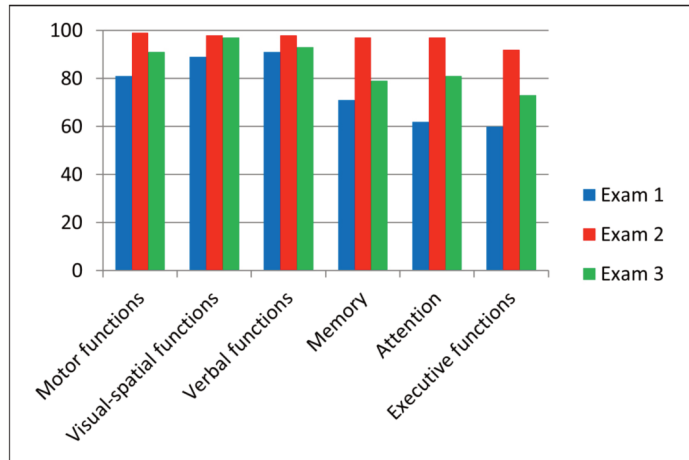


Fig. 5. The effect of tDCS on the neuropsychological functioning as measured by the standard Polish version of the Mindstreams™ Interactive Computer Tests



Fig. 6. Patient-made copy of Małgorzata Kaczmarska's work, *Rhythm*, 140 × 178 cm, 2013, diptych, oil on canvas
Source: clinical material by M. Pączalska

executive functions. In the third examination the cognitive and executive functions were still not bad, but had slightly decreased.

In our last testing, the patient says that he feels well. The unpleasant symptoms he suffered for a long time after being infected with the SARS-CoV-2 virus have disappeared, and he is independent. He walks about 2 km every day, does his shopping on his own, goes through traffic lights at intersections without any problem. Interestingly, the limb tremor and shoulder stiffness he used to experience during lectures have disappeared. He has returned to work as an art teacher. He has started to paint again, mainly by copying the works of other artists (see: Fig. 6), but occasionally begins to create new works himself.

The patient claims that when copying this image, his hand dexterity returned.

DISCUSSION

The last two years have been dominated by articles on SARS-CoV-2 infection, the survival of NeuroCOVID-19 and, in particular, treatment, vaccination and complications resulting from the infection. Not all the effects of this virus have yet been described, making it difficult to effectively help these patients, especially in times of pandemic, when the need is great. The case study presented here shows us how challenging it is to manage the effective rehabilitation of a patient infected with SARS-CoV-2 and NeuroCOVID-19 who developed symptoms of long COVID and Parkinson's disease (PD) four months after infection with the virus. A common feature is the recurrent, remission nature of the disease, where the patient feels as if he has recovered and then the illness hits back at him, which was also pointed out by our patient (Reese, Blau, Bergquist 2022).

There is uncertainty about the diagnosis, incidence, phenotype, duration and treatment of Long COVID (Stephenson, Shafran, De Stavola 2021). It is also uncertain whether there is, and if so what, a link between SARS-CoV-2 infection and PD. However, the quality of life of these patients is diminished by both the symptoms of the disease and the expectations of those closest to them, for fast recovery. Therefore, the clinicians need to consider the multiple symptoms that affect the function of the particular patient, recognise the different symptom clusters, find the neuromarkers of the illness (Kropotov 2016; Góral-Półtola, Mirski, Knapik, Pączalska 2021), and to select effective treatment (Smeyne et al. 2021).

A major difficulty in the treatment and rehabilitation of a SARS-CoV-2 patient who has developed long COVID and PD is that the symptoms overlap and it is difficult, even for an experienced clinician, to separate them and establish a final treatment profile. Indeed, we know from the subject literature that the diagnosis of Parkinson's disease is usually based mainly on case history, baseline and additional investigations, including neuroimaging to detect prodromal features (e.g., rapid eye movement sleep behavior disorder, hyposmia, constipation), characteristic motor difficulties (e.g. tremor, rigidity, slowness), and psychical problems (e.g., cognitive decline, executive function, depression, anxiety). Examination usually reveals bradykinesia with tremor, rigidity or both.

Dopamine-based therapies typically help initial motor symptoms. Nonmotor symptoms require nondopaminergic approaches (e.g., selective serotonin reuptake inhibitors for psychiatric symptoms, cholinesterase inhibitors for cognition problem). Usually, rehabilitative therapy and exercise complement pharmacologic treatments. Individuals experiencing complications, such as worsening symptoms and functional impairment when a medication dose wears off ("off periods"), medication-resistant tremor, and dyskinesias, benefit from advanced treatments such as therapy with levodopa-carbidopa enteral suspension or deep brain stimulation (Kropotov 2016). However, not all patients can benefit from it.

At the beginning of the 21st century the situation is fortunately improving. Thanks to the revolution in neuroscience and the introduction of new neurotechnologies, it is possible to search for the PD neuromarkers (Kropotov 2016). Rarely

conducted, mainly because of the high costs, is dopamine transporter single-photon emission computed tomography and brain SPECT to differentiate vascular Parkinsonism (VP) from Parkinson's disease (PD) which can improve the accuracy of diagnosis when the presence of Parkinsonism is uncertain. However, as was stressed by Tzen, & Lu, Chin-Song et al. (2001) further studies are needed, including those to differentiate Parkinson's disease from arteriosclerotic Parkinsonism and patients with both VP and Parkinson's disease, are needed to help rule out the possibility of Parkinson's disease as early as possible. A great help in diagnosis and the selection of appropriate therapies can be provided by relatively inexpensive techniques, such as QEEG, ERPs and sLoreta tomography to observe the work of the brain in milliseconds, and comparison, thanks to the Human Brain Index (HBI) methodology of the results obtained by a given patient with the results of the normative database held in Chur, Switzerland (cf. Kropotov 2016). This procedure allows for the proper assessment of neurocognitive and emotional dysfunctions (Pączalska, Kaczmarek, Kropotov 2021).

Current neuropsychological rehabilitation methods have limited efficiency in improving non-motor outcomes in patients with PD. A possible adjunct to rehabilitation may be non-invasive brain stimulation using transcranial direct current stimulation (tDCS) to modulate cortical excitability, thereby improving outcomes. The effectiveness of this method can be increased if tailored based on a neuro-marker, as we guided our patient. The results showed that active anodal neurostimulation **over the dorsolateral prefrontal cortex (DLPFC)** resulted in prolonged improvements neuropsychological functioning as measured by the standard Polish version of the Mindstreams™ Interactive Computer Tests. The effects of the therapy lasted a relatively long time and only after a six-month follow up was a slight deterioration in neuropsychological functioning observed.

It is worth pointing out that we obtained similar results to other authors who also suggested a beneficial long-term effect on executive functions in PD patients following active tDCS over the dorsolateral prefrontal cortex (DLPFC). As we know these part of the cortex are highly dependent on the neurotransmitters dopamine and noradrenaline (Arnsten 2009; Ott and Nieder 2019; Xing, Li, Gao 2016; Arnsten, Girgis, Gray et al. 2017; Fang, Lv, Mao et al. 2020; Stuart, Morris, Giritharan 2020; Vitorio, Stuart, Giritharan et al. 2021; Boberg, Iacobaeus, Greenfield et al. 2022). Both neurotransmitters are involved in the cognitive dysfunction seen in Parkinson's disease (Berridge & Waterhouse 2003).

It is worth mentioning that art therapy played a role in the treatment of this patient, which promoted improvement in motor function and gave the patient the hope of returning to work. An individualised goal-directed treatment profile (in the case of our patient, who wanted to return to work as an art teacher), which has also been shown in other work, can produce better results than pharmacological treatment or neurostimulation alone (Pączalska 2022; Pączalska, Góral-Pótróla, Chojnowska-Ćwiąkała 2021; Pączalska & Nowaczyk 2021).

Our results suggest the existence of a beneficial long-term effect on executive functions in PD patients following active tDCS over the dorsolateral prefrontal

cortex (DLPFC). Our findings encourage further investigation exploring tDCS as an adjuvant therapy for cognitive and behavioral treatment in PD. However, further multicenter research with larger sample sizes is needed. Future research should focus on determining the tDCS parameters that are most beneficial to the functional recovery of patients with PD who were additionally infected by SARS-CoV-2, and who have contracted long COVID.

CONCLUSIONS

ERPs can be useful in the diagnosis and treatment of patients following infection by SARS-CoV-2 who contracted COVID-19, developed long COVID and additionally PD. It allows for the detection of the functional neuromarker of PD (e.g., hypoactivation of the dorsolateral prefrontal cortex, DLPFC) and enabled the choosing of a proper tDCS protocol with the anode over these region of the brain, and also the selection of effective neurostimulation. The proposed protocol of tDCS tailored by the neuromarker offered to our patient, was effective in the reduction of longCOVID symptoms as well as early PD symptoms.

Acknowledgements

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