CASE STUDY

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EEG NEUROFEEDBACK IN THE TREATMENT OF COGNITIVE DYSFUNCTIONS AFTER THE INFECTION OF SARS-CoV-2 AND LONG COVID-19

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SUMMARY

Background: Coronavirus disease 2019 (COVID-19) is likely to have long-term mental health effects on individuals who have recovered from COVID-19. According to Centers for Disease Control and Prevention (CDC), individuals diagnosed with COVID-19 can see a range of long-term side effects. The aim of the study was to evaluate the effectiveness of neurotherapy (EEG neurofeedback and goal-oriented cognitive training) in the treatment of neurocognitive dysfunctions in a patient after the infection of SARS-CoV-2 and the long long-term side effects after the contraction of COVID-19.

Case study: The 48-year-old woman ZR, an accountant by profession, an employee of the administration of the Municipal Board of Municipal Resources, fell ill on October 13, 2020. The disease began with very severe burning headache, eyeballs pain, muscle aches. Ten days later more symptoms joined: loss of smell (anosmia) and loss of taste (ageusia), hearing disorders, shortness of breath and chest pains. The symptoms were associated with SARS-CoV-2 coronavirus infection confirmed by an rt-PCR genetic test. Brain MRI with intravenous paramagnetic contrast medium injection did not show either lesions of acute microischemic significance or areas of pathological enhancement after paramagnetic contrast medium administration. The patient was treated at home. In mid-November 2020, about a month after the infection of SARS-CoV-2 and contracting NeuroCOVID-19, neurocognitive impairment developed and after half a year she was deteriorating and not able to live independently in society because of her condition. She called her problem "brain fog", and was referred for further diagnosis and therapy to the Reintegration and Training Center of the Polish Neuropsychological Society. We diagnosed a range of long-term side effects and introduced neurotherapy (EEG neurofeedback and goal-oriented cognitive training) in the treatment of neurocognitive dysfunctions. It was found that almost all the long-term side effects were reduced in magnitude. The patient improved and she was able to return to work.

Conclusions: EEG neurofeedback and goal-oriented cognitive training might be helpful in the reduction of neurocognitive dysfunctions in patients following the infection of SARS-CoV-2 and long-term side effects after the contraction of COVID-19.

Key words: cognitive control, stress, anxiety, working memory

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is likely to have long-term mental health effects on individuals who have recovered from COVID-19. Rightly, there is a global response for recognition and planning on how to deal with the mental health problems of everyone impacted by the global pandemic (Kumar et al. 2021). Research, since the first confirmed case in Wuhan, China, on December 31, 2019, the novel coronavirus, SARS-CoV-2, has indicated that people contracting the virus and developing coronavirus disease (COVID-19), may suffer not only respiratory and other organ challenges, but also a wide range of neurological (Montalvan et al. 2020; Aknin 2021), neurocognitive (Woo et al. 2020; Pąchalska et al. 2021) and neuropsychiatric manifestation (Mao et al. 2020; Mirfazeli et al., 2020; Rogers et al. 2020;Varatharaj et. 2020).

A recently published study in the journal *The Lancet Psychiatry* says that nearly 34% of individuals studied had some sort of neurological or psychiatric defect, six months after being diagnosed with COVID-19 (Taquet et al. 2021). Their study included over 236 379 people who were diagnosed with SARS-CoV-2, with COVID-19 having increased the risk of neurological and psychiatric outcomes. It was found that risks are greatest in, but not limited to, patients who had severe COVID-19. The authors showed that among the tested patients, those diagnosed with COVID-19, the estimated incidence of a neurological or psychiatric diagnosis in the subsequent 6 months was 33.62% (95% CI 33.17–34.07), with 12.84% (12.36–13.33) receiving their first such diagnosis. Individuals suffering from the long-term side effects of COVID-19 are designated COVID-19 "long-haulers". Most long-haulers deal with symptoms for months after their original COVID-19 diagnosis.

According to Centers for Disease Control and Prevention (CDC), individuals diagnosed with COVID-19 can see a range of long-term side effects (Nuzzo et al. 2201). The CDC says these side effects can last for weeks or even months. They include: (1) tiredness, (2) shortness of breath, (3) coughs, (4) joint pains, (5) chest pains, (6) brain fog, (7) depression, (8) muscle pains, (9) headaches, (10) fevers, (11) heart palpitations, (12) rashes, (13) hair loss, (14) loss of taste/smell, (15) anxiety, and others (Aknin et al 2021). However, we can also find reports of cognitive dysfunctions such as attention, memory and dysexecutive symptoms (Rogers et al., 2020; Varatharaj et al., 2020; Pąchalska et al 2021). Several studies indicate that many patients present symptoms even for a prolonged time after SARS-CoV-2 infection, indicating that the observation of these patients should be maintained [Stueck 2021]. Symptoms that last for weeks or even months after recovery are known as long Covid. Besides fatigue, one of the long Covid symptoms that has been frequently reported is colloquially so-called a brain fog (Varatharaj et al 2020).

While searching PubMed and MedLine we have not been able to find many papers devoted to neurofeedback treatment offers for patients following SARS-CoV-2 infection and the subsequent neuroCOVID-19, especially with regards to so-called brain fog (Rogers et al. 2020). Therefore, we are taking this opportunity to describe just such a case study with the colloquially so-called brain fog in the hope that it will be helpful in understanding and assessing cognitive consequences following long COVID-19. We also hope that our experience in neurotherapy might be helpful for other researchers , as well as possibly being used in the social integration of patients, and in the estimation of effective work capacity, drive, the managing of finances, participation in daily family activities, or the ma king of informed decisions. The information may be also used for planning appropriate neuropsychological rehabilitation to remediate or compensate cognitive deficits in COVID-19 survivors (see also Kumar et al. 2021).

The aim of the study was to evaluate the effectiveness of neurofeedback training in the treatment of cognitive dysfunctions after infection of SARS-CoV-2 and long COVID-19.

CASE STUDY

The 48-year-old woman ZR, an accountant by profession, an employee of the administration of the Municipal Board of Municipal Resources, fell ill on October 13, 2020. The disease began with a very severe burning headache specified on the Visual Analogue Pain Scale (VAS) at 95/100 points, and very severe burning eyeballs pain specified on the VAS Scale at 95/100 points making it difficult to read books or watch TV, and muscle aches specified on the VAS Scale at 90/100 points. Ten days later, on the morning of October 23, 2020, more symptoms joined: loss of smell (anosmia) and loss of taste (ageusia) specified in the Pąchalska Anosmia and Ageusia Test (2021) accordingly for anosmia = 0/10 points and for ageusia = 2/10, and hearing disorders confirmed by tonal audiometry for the right ear 9.3%, left ear 11.1%, binary 10.35%: average for the left ear 25 dB HL, and for the right ear 23dB HL. Late afternoon appeared a shortness of breath and chest pains. She felt "as if her lungs were sinking inwards." Symptoms were associated with SARS-CoV-2 coronavirus infection confirmed on 27.10.2020 by an rt-PCR genetic test. The patient was subjected to brain MRI with intravenous paramagnetic contrast medium injection. There were neither lesions of acute microischemic significance nor areas of pathological enhancement after paramagnetic contrast medium administration. The patient was treated at home. Antibiotic therapy, steroid therapy and oxygen therapy for 7 days and quarantine for 14 days were introduced. Additionally the patient suffered from rheumatoid arthritis, which is a chronic inflammatory disorder that can affect more than just the joints. In some people, the condition can damage a wide variety of body systems, including the skin, eyes, lungs, heart and blood vessels.

In mid-November 2020, about a month after contracting COVID-19, cognitive impairment developed. The first to occur were disorders in understanding speech, which at the beginning were very strong and consisted in perceiving other people's statements as if they were spoken in slow motion. She also had difficulties in naming (word finding problem), and speaking with strange speech prosody (the so-called foreign accent syndrome). Memory problems also appeared: the patient forgot to do the bank transfers which were placed on her desk at work), she did not remember where she had put things, she could not find the car in the parking lot. These disorders persisted for a long time, although their severity decreased.

In April 2021, six months after falling ill, the following intensified: (1) **motor symptoms** (difficulty with walking, chronic fatigue) and (2) **cognitive difficulties**: logical memory disorders (difficulties in reading and understanding the meaning of texts read) and semantic memory disorders (difficulties in understanding the meaning of the names of some subjects) and disturbances in statements about the type of semantic paraphrases, replacing words with other words in spontaneous speech (e.g., the washing machine is spoken of the fridge, and the computer for the phone). She also experienced rapid deterioration in vision: left eye -1.7, right eye -0.5. After vaccination with the 1st dose of the Pfizer/BioNTech vaccine on April 13, 2021, the symptoms of the rheumatoid arthritis, which she had been suffering from since 2019 increased. This mainly involved a tearing pain in the hand muscles (when writing) and legs (when walking), also anxiety (e.g., before entering a store, on the dentist's chair or under the magnetic resonance imaging). Neurocognitive disorders, commonly referred to as "brain fog", were diagnosed after the infection of SARS-CoV-2 and contracting NeuroCOVID-19, and accompanying cognitive problems. She was referred for further diagnosis and therapy to the Reintegration and Training Center of the Polish Neuropsychological Society.

Neuropsychological testing

The neuropsychological testing administered at the Reintegration and Training Center of the Polish Neuropsychological Society is presented in Table 1. It was found that in the 1st examination multiple deficits were displayed. In the 2nd examination, after neurotherapy, ZR's, the verbal and non-verbal IQ increased significantly. The improvement was seen in nearly all cognitive functions, including immediate and delayed logical and visual recall, and the maintaining of attention span. It should be stressed that in the auditory learning task, the patient had forgotten all the words after a 15-minute delay in, and obtained 5 words in recognition; however, in the 2nd examination she remember 2 words after the delay, and managed all the words at recognition.

Neurotherapy

We administered two programs of treatment:

Program A: We administered the most frequently used neurofeedback – frequency/ power neurofeedback with the use of 2 bipolar surface electrodes, called "surface neurofeedback" (Kropotov 2016). We chose theta/beta, SMR training on C3 including (1), strengthening Beta1 and inhibiting Theta + inhibiting Beta 2 as well as (2) for C4 strengthening SMR and inhibiting Theta inhibition + inhibiting Beta, based on the international 10-20 system (Thompson & Thompson 2012) given twice a week for 15 weeks.

Table 1. Neuropsychological testing of the patient ZR in examination 1, and 2

Measure	Exam. 1	Exam. 2
WAIS-R		
IQ – Full	62.5/100	93.5/100
IQ – Verbal	63.5/100	98.5/100
IQ – Nonverbal	58.5/100	87.5/100
Wechsler Memory Scale WMS-III, PL (Pąchalska & Lipowska 2006)		
WMS-III: Attention Spatial Span	3 (1st %ile)	12 (75th %ile)
WAIS-III: Visuospatial Ability Block Design	3 (1st %ile)	8 (25th %ile)
WMS-III Immediate logical memory	11/24	18/24
WMS-III Delayed logical memory	9/24	19/24
WMS-III Immediate visual recall	12/41	36/41
WMS-III Delayed visual recall	6/41	25/41
WMS-III Verbal memory Short Delay Free Recall	0/9(<1st %ile)	2/9 (<1st %ile)
WMS-III Verbal memory Long Free Recall	0/9(<1st %ile)	2/9 (<1st %ile)
WMS-III Verbal memory Long Delay Cue Recall	0/9(<1st %ile)	2/9 (<1st %ile)
TrialMaking Test, TMT		
TMT Executive Functions– Number Sequencing	150 sec (<1st %ile)	54 sec (10th %ile)
TMT Executive Functions – Number Letter Sequencing	Discontinued	150 sec (<1st %ile)
The Stroop Colour and Word Test (SCWT)		
Color	90 sec (<1st %ile)	41 sec (16th %ile)
Word	29 sec (25th %ile)	42 sec (63rd %ile)
Interferences	Discontinued	128 sec (<1th %ile)
Wisconsin Card Sorting Test (WCST)		
Categories	0 (2-5th %ile)	2 (>16th %ile)
Perseverative Errors	46 (<1th %ile)	19 (37th percentile)
Conceptual Level Responses	63 (<19th %ile)	48 (45th%ile)
Fail to Maintain Sets	Discontinued	4 (2-5th %ile)
Authorized Polish Version of the Boston Naming Test (Pąchalska & MacQueen 1998)		
Naming – total number of errors	27/60	6/60
Polish Version of the Token Test (Pachalska 1996)		
Understanding – total number of errors	35/50	7/50

Level of performance corresponding to the percentiles
98-99 %ile = Very Superior
91-97 %ile = Superior
75-90 %ile = High Average
25-74 %ile = Average
9-24 %ile = Low Average
3-8 %ile = Borderline
2nd%ile and below = Impaired

Program B: Goal-oriented Cognitive Training directed toward the reduction of neurocognitive dysfunctions presented by the patient (Pąchalska 2008), given twice a week for 15 weeks. The patient was motivated by different strategies to fight with the consequences of the illness, and she undertook additional activities (see: Table 2).

Table 2. Activities undertaken by the patient

Type of activity	Description of activity
Sleep	She organized conditions for getting good quality sleep.
Exercise	She undertook physical activity beneficial for her heart and lungs, and to boost her brain functioning.
Food	She took a well-balanced, healthy diet to give her body the nourishment needed for good health.
Family contact	She kept in touch with family members and friends via social media and later through real contact to improve her moods, but they also helped her thinking and memories as well.
Other beneficial activities	She read a novel, engaging in cognitively stimulating activities, listening to music, and keeping a positive mental attitude.

Neurocognitive measures

The standard Polish version of the Mindstreams™ Interactive Computer Tests was employed (Pąchalska, Kaczmarek & Kropotov 2014). The neuropsychological functioning as measured by the standard Polish version of the Mindstreams™ Interactive Computer Tests is presented in Fig. 1. In the 1st examination, before neurotherapy, we found disturbances for all tested cognitive functions. The greatest dysfunctions were to occur, however, in the areas of attention, memory and visual-spatial functions. In the 2nd examination, after neurotherapy, it was found that in the standard Polish version of the Mindstreams™ Interactive Computer Tests the patient had improved in almost all the tested cognitive functions. All tested parameters were close to the norm.

After completing the neurotherapy program the patient was glad that she was more independent: she could cook dinner, do the shopping, she knew where she had left her car in the parking lot. She also knows where she has put things, sometimes he forgets where she has placed her glasses or a pen. She is actively looking for a variety of aids in the disease. Recently, she has employed electronic comb therapy, which stopped her hair from falling out. Ten months after the infection of SARS-Cov-2 and developing neuroCOVID-19, she finally returned to work.

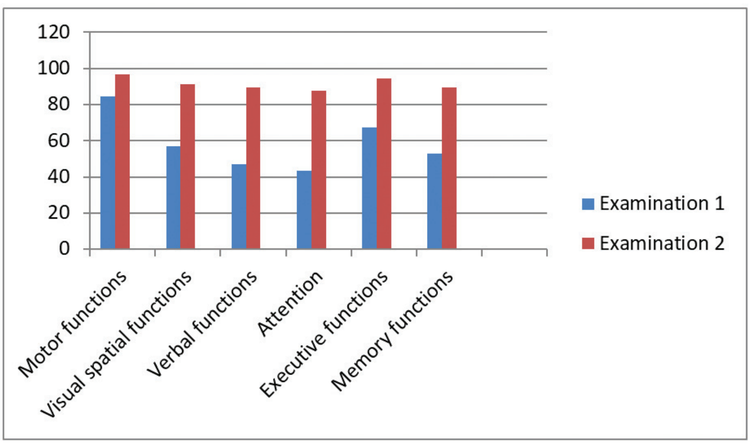

Fig. 1. The effect of the neurofeedback training on the neuropsychological functioning as measured by the standard Polish version of the Mindstreams™ Interactive Computer Tests

DISCUSSION

The patient's improvement may be ascribed to several factors:

EEG-Neurofeedback – a properly selected protocol for the training of the patient's needs. We chose theta/beta, SMR training on C3 included (1), strengthening Beta1 and inhibiting Theta + inhibiting Beta 2 as well as (2) for C4 strengthening SMR and inhibiting Theta inhibition + inhibiting Beta). In the subject literature we can find suggestions that theta/beta, SMR training on C3 may improve neurocognitive functions, the speed of intellectual processes, speech fluency, attention concentration, learning abilities, stimulating of action, increasing the motivation to undertake intellectual effort and work pace, and on C4 may reduce anxiety, agitation and aggression, calm one down, and increase self-control, relaxation spatial orientation and a sense of satisfaction, (Thompson & Thompson 2012; Mohammadi et al. 2015, Aron et al. 2016; Kropotov 2016, Mroczkowska et al. 2018). Neurofeedback is considered as an operant conditioning of neural oscillations, in which the brain is trained to gain control over specific EEG parameters by real-time visual or auditory feedback. The desired brain activity is reinforced and undesired brain activity is inhibited. Several studies supported that neurofeedback training is a promising treatment for various disorders (Thompson & Thompson 2012; Mohammadi et al. 2015, Aron et al. 2016; Kropotov 2016).

Properly selected goal-oriented cognitive training (CT). This is an approach that uses guided practice on structured tasks with the direct aim of improving or maintaining cognitive abilities. CT is probably associated with small to moderate positive effects on global cognition and verbal semantic fluency at the end of treatment, and these benefits appear to be maintained in the medium term (Pąchalska 2008; Bahar-Fuchs et al. 2019).

Adequate motivation of the patient to exercise, who actively searched for various ways of coping with the late effects of SARS-CoV-2 infection and undergoing neuroCOVID-19. Motivation and engagement are important factors associated with therapeutic outcomes in cognitive training (Best et al. 2020; Makransky et al 2007). Besides medical treatment, she practices a healthy lifestyle to improve her situation (cf. Pąchalska 2008).

What made the patient, despite the lack of hospitalization, suffer such severe cognitive impairment?

Rogers et al. (2020) pointed out, that researchers have identified several possible causes of severe cognitive dysfunctions, so-called brain fog, including: (1) lack of oxygen caused by lung damage;(2) inflammation affecting brain cells; (3) an autoimmune disorder that is causing the immune system to attack healthy cells in the body. (4) lack of blood flow caused by swelling of the small blood vessels in the brain; (5) invasion of infectious cells into the brain. In preliminary findings on the basis of a survey conducted among survivors who have returned to the community, more than 50 per cent of respondents reported experiencing brain fog for up to six weeks, about 20 per cent up to 12 weeks, and another 10 per cent up to six months. In our patient the possible coexistence of another illness, that is an autoimmune disorder, may have caused the immune system to attack healthy cells in the body. Currently, it is not clear why some people develop brain fog and others do not. Rogers et al.'s (op. cit.) findings have shown that those with severe disease seem to experience brain fog more often than patients with mild disease, in a way similar to what has been reported elsewhere.

It seems that in our patient the cause of such severe disorders, which lasted many months after the infection of SARS-CoV-2 and neuroCOVID-19, was the overlapping of symptoms related to the invasion of infectious cells into the brain which intensified the symptoms of rheumatoid arthritis. However, more research is needed to understand their aspect.

Why did the patient achieve a relatively large improvement in neurocognitive functions?

The case study presented above shows that neurofeedback may be an additional technique useful in the self-regulation of brain function after SARS-CoV-2 infection and undergoing neuroCOVID-19 when compared to standard neuropsychological therapies.

How to interpret our results?

Microgenetic theory (Brown & Pachalska, 2003) makes it possible to interpret the results we achieved. This theory differs from other theories of brain function, in that it emphasizes:

- process and change, rather than data processors connected to each other by neural "cables," as though the brain were a computer;
- the creative nature of perception, which is not just a passive collection of stimuli, but a process of creating an image of reality;
- understanding the symptom as a segment of normal behavior that is revealed prematurely by pathology, and is not just a deficit, that is, the absence of the correct behavior;
- the development of mental processes that evolve on different scales of time, assuming that the laws of behavior are the laws of evolution expressed on another temporal plane;
- processing of information from whole to part, and not, as in standard theory, from "bits" to "stacks" of information.

The afferent pathways bring impulses received from the sense organs to the brainstem, which constitutes the oldest and most primitive part of the brain. The brainstem reacts with a general activation of the organism, which is transmitted upwards (A), to the limbic system and cerebellum. From these somewhat younger structures the activation signal becomes more complex (B), so that in the cortex it spreads to highly specialized areas. Signals from the cortex then travel by pyramidal pathways back down to the brainstem, and from there by efferent pathways to effectors in the musculoskeletal system (cf. Fig. 2).

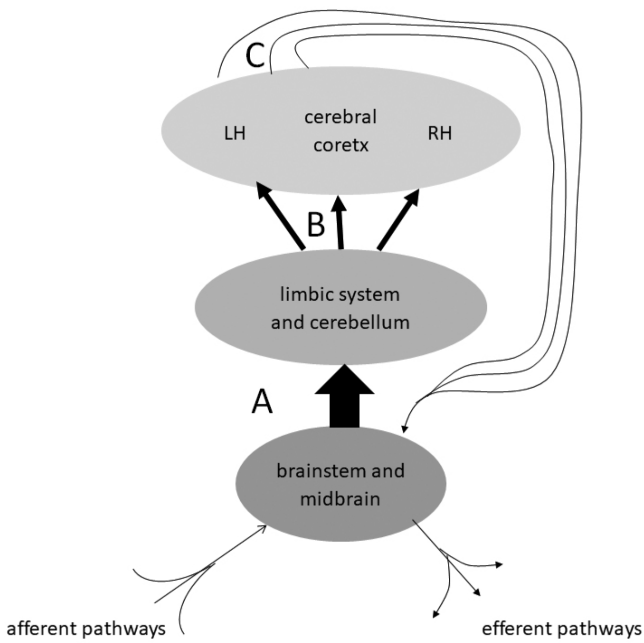

Fig. 2. Schematic diagram of the pathways and brain regions involved in behavior
Source: Pąchalska et al 2021

The process of symptom formation might help us to understand the essence of neurocognitive disturbances after the infection of SARS-CoV 2 and neuro-COVID-19. This process of symptom formation responsible for the heterogeneity and changeability of neurocognitive disturbances in neuroCOVID-19 is explained by Fig. 3. We can see here a bidirectional transition from emotion to perception and action. The state of arousal in the mind, which in a healthy brain can be reinforced or inhibited by the executive functions, cannot be controlled in the brains of the patients after the infection of SARS-CoV 2 and the contraction of neuro-COVID-19. Thus the behavior which a patient exhibits can be diverse, variable, and capricious, depending on a whole range of factors both structural and functional in nature. Therefore, neurotherapy including neurofeedback and cognitive training, which strengthens the control of the frontal lobes over emotions, allowed our patient to achieve significant improvement.

To sum up, we are in agreement with the suggestions of other authors that EEG-neurofeedback training combined with the goal-oriented method of neuropsychological rehabilitation may improve better neurocognitive functioning (cf. Mohammadi et al. 2015). This means that the combined EEG-neurofeedback therapy with goal-oriented cognitive training we used could be more effective than neuropsychological rehabilitation alone.

In response to suggestions by scientists from around the world regarding the future directions of research, something that can be equally supported by our research, work is now under way to modify the diagnostic criteria for cognitive

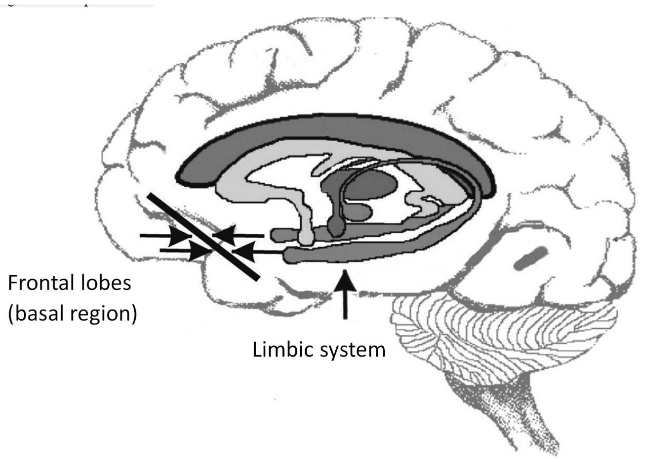

Fig. 3. The bidirectional transition from emotion to mentation and action [frontal lobes, basal region, limbic system].
Source: Pąchalska et al 2021

dysfunctions after the infection of SARS-CoV-2 and neuroCOVID-19. For this purpose, fuller cooperation is necessary between neuropsychologists and psychophysiologists, which will help the latter in understanding the problems of such a person and help the former evaluate the results of new programs of neurotherapy (Aknin 2021; Pąchalska, Kaczmarek, Kropotov 2021).

Neurological, neurocognitive and neuropsychiatric monitoring will enable health care providers to plan adequate health care delivery and allocate resources appropriately. Early intervention for emerging neurocognitive problems will be critical for the independent functioning and improved quality of life of many COVID-19 survivors. However, future studies should take stronger measures to mitigate well-established risks of bias, and should provide long-term follow-up to improve our understanding of the extent to which the observed gains are retained. Future trials should also focus on a direct comparison of EEG neurofeedback versus CT or other alternative treatments.

CONCLUSIONS

EEG neurofeedback and goal-oriented cognitive training might be helpful in the reduction of neurocognitive dysfunctions in patients following the infection of SARS-CoV-2 and long-term side effects after the contraction of COVID-19.

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