Protocol of a research project

,, Effect of neurofeedback therapy on neurological post-COVID-19 complications,,

Aim of the study:

The aim of this research project was to verify whether neurofeedback can be used as a new therapeutic intervention for treatment of post-COVID-19 related neurological disturbances such as fatigue, depression and anxiety.

The project was based on the comparison of subjectively perceived severity of post-COVID-19 neurological complications before and after 5 sessions of neurofeedback therapy (Othmer method). The study was approved by Ethic Committee of Third Faculty of Medicine, Charles University in Prague, Czech Republic.

Hypotheses:

1. NFB will significantly reduce neurological complications after COVID-19.

2. NFB-related improvement in the aforementioned post-COVID symptoms will persist one week after NFB.

3. NFB-related improvement in the aforementioned in the above post-COVID symptoms will be still evident one month after NFB.

4. Level of fatigue, anxiety and depression will be positively correlated with each other.

5. Reductions in fatigue, anxiety and depression will be positively correlated with each other.

Inclusion and exclusion criteria:

To investigate the effect of neurofeedback therapy, randomly selected patients, (both males and females) were included provided they met the following inclusion criteria: positive anamnesis of COVID-19 ,confirmed by polymerase chain reaction (PCR) antigen test or antibody test, and the presence of at least one of the following neurological complications following SARS-CoV-2 infection: anxiety, fatigue, depression, insomnia, dizziness, seizures, headaches/migraines . The specific symptoms should have been present or persisted for at least 3 months after confirmed SARS-CoV-2 infection and should not have been attributable to any other neurological disease prior to COVID-19. Other inclusion criteria were: being at least 18 years old, being free of neurological/systemic health problems prior to SARS-CoV-2, being medication-free (or medically stable in type and dosage of the drug for at least 3 months prior to neurofeedback experiment), having normal or corrected-to-normal vision and hearing. The exclusion criteria were: being younger than 18 years old, having no positive

anamnesis of SARS-CoV-2 infection, absence of post-COVID complications, the presence of neurological/systemic disorders prior to SARS-CoV-2 infection, impaired hearing and/or vision.

The study was single-blinded open-label non-randomized clinical trial. All participants underwent neurofeedback sessions. The score of the participants, based on standardized medical questionnaires, for the severity of the particular neurological problems was compared and analyzed before and after neurofeedback in within-subject fashion.

Standardized medical questionnaires:

Fatigue Assessment Scale was used for measuring the severity of fatigue.

Beck Anxiety Inventory was used for measuring the severity of anxiety.

Beck Depression Inventory (Second version was used) for measuring the severity of depression.

Dizziness Handicap Inventory was used for measuring the severity of dizziness.

Seizure Severity Questionnaire was used for measuring severity of seizures.

Headache Disability Index was used for measuring the levels of headaches/migraines level.

Insomnia Severity Index was used for measuring the severity of insomnia.

Visual Analogue Scales were used for measuring mood swings plus memory and attention problems. All questionnaires were delivered at baseline, immediately, one week and one month after neurofeedback.

Procedure

NFB training included five NFB sessions which were completed within two weeks. 2 or 3 NFB sessions were held per one week. In order to minimize the possible sources of variability in responses of the participants to neurofeedback therapy stemming from the effects of infradian rhythms, the time for all experimental sessions was supposed to be kept fixed for all 5 NFB sessions with tolerable maximal deviation +/- 3 hours. Time period of one NFB training session was individualized for each participant and ranged between 25–45 minutes. The reason for this time variability was attributed to the process of finding of individual optimal frequency (IOF). This was done in order to end each NFB session with established NFB-rewarded EEG frequency to be as optimal as possible. NFB-rewarded EEG frequency bandwidth was individualized for all participants according to Othmer method. In the first experimental session, the participants got familiarized with neurofeedback therapy and their IOF was being started to be found. Participants were instructed to sit comfortably, relax and

adjust their mental activity to the mental state which is associated with the presence of visual and auditory feedbacks from neurofeedback device. For visual feedbacks, watching the computer screen was required. On the computer screen, there was graph of ongoing EEG activity of the selected neurofeedback-rewarded EEG bandwidth. Online EEG graph was grey when neurofeedback-rewarded selected EEG activity kept below reward threshold. When this EEG activity was at least as high as reward threshold value, EEG graph got blue and this event was associated with auditory feedback as well (so-called,, soft gong sound,, used via neurofeedback software, Deymed Diagnostics, version 11). Certified neurofeedback therapist was involved in manual adjustment of reward threshold therapist to keep frequency of feedbacks as constant as possible. There was an effort to adjust reward threshold to ensure both ‘‘grey” intervals of no feedbacks and ‘‘blue” intervals associated with neurofeedback-related-feedbacks are present. This was done to make brain able to differentiate between the states of being rewarded and the states of not being rewarded by neurofeedback device. In compliance with Othmer method; the starting neurofeedback-rewarded EEG frequency was 12–15 Hz EEG. The first neurofeedback round lasted for 2 minutes.

After finishing each neurofeedback round, participants were asked questions related to their subjective state to find how they felt during the training and whether they experienced some side-effects such as headaches, anxiety, body tension, somnolence, apathy, fatigue and other. Provided that there were reports of anxiety, body tension and headache, neurofeedback-rewarded EEG frequency was lowered 1 Hz. If there came to an occurrence of the feelings of apathy, somnolence or sadness, neurofeedback therapist increased EEG-rewarded frequency 1 Hz. IOF was regularly adjusted for each 5 NFB sessions. The direction of its adjustment consisted in intra-session and inter-session reports of the participants. To verify what were the inter-session effects of neurofeedback like, the participants were regularly asked questions about their sleep, mood, occurrence of headaches and/or the occurrence of other unusual symptoms. Provided that there were reports of symptoms including dizziness, onset insomnia, nightmares, anxiety or headaches, rewarded EEG frequency was lowered 1 Hz. On the other hand, given there were reports of inter-session fatigue, somnolence, sleepiness, sadness, neurofeedback therapist increased rewarded EEG frequency 1 Hz. EEG-rewarded frequency had to meet the following two criteria to be considered as the optimal one: it had to be associated with subjectively calm, relaxed or at least euthymic state during intra-session period of neurofeedback. Any of aforementioned symptoms indicating either high or low arousal were not supposed to be present. Second, regarding inter-session neurofeedback period, at least one positive outcome, for instance, subjective improvement in sleep, mood etc., was supposed to occur.

Neurofeedback training was done in bipolar fashion. Two active electrodes were placed at right and left temporal areas (T3-T4, 10–20 system). Ground electrode was put at right earlobe. Electrodes were filled with Ten 20 Past (Neurodiagnostic Electrode Paste, Weaver and Company, made in USA) used for making electrodes to be fixed at the scalps of

participants. Conductive electrode gel was used for keeping the impedance as low as possible (Sigma gel, Parker laboratories, Fairfield, made in New Jersey, USA).

Statistical analysis:

The repeated measures ANOVA with multiple comparisons with Bonferroni test was used to compare the results obtained before and after neurofeedback therapy. Pearson's correlation coefficients were calculated to find whether the severity of investigated neurological post-COVID-19 symptoms correlate with each other.

Ethical issues:

The study was approved by Ethic Committee of Third Faculty of Medicine, Charles University in Prague, Czech Republic. All the participants, who participated in the study, signed their written informed consent. The study was granted by Programme COOPERATIO of Third Faculty of Medicine, Charles University.