DYNAMICS OF EEG REACTIONS UNDER COMBINATION OF RESONANCE SCANNING AND ADAPTIVE NEUROSTIMULATION IN PATIENTS WITH POST-COVID SYNDROME

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Abstract. The dynamics of electroencephalographic (EEG) reactions were analyzed under a combination of resonance scanning and EEG-guided adaptive neurostimulation in the process of the cognitive rehabilitation of patients with post-COVID syndrome (PCS). It has been shown that the introduction of resonant scanning before adaptive neurostimulation makes it possible to observe the dynamics of resonant EEG reactions, provides activation of potential EEG oscillators of the brain, and increases the responsiveness of the brain to subsequent adaptive neurostimulation. Complex treatment procedures, due to the progressive involvement of resonant and adaptive mechanisms and mechanisms of neuroplasticity, contribute to the cognitive rehabilitation of patients with PCS, which manifests itself in the normalization of the EEG, a decrease in stress levels, and an improvement in emotional state and mood of the patients.

Keywords: resonance scanning, adaptive neurostimulation, cognitive rehabilitation, dynamics of resonant EEG reactions, resonant activation of potential oscillators, adaptation mechanisms, mechanisms of neuroplasticity, post-COVID syndrome.

List of Abbreviations

EEG – electroencephalogram
PCS – post-COVID syndrome

Introduction

As the COVID-19 pandemic develops, the problem of analyzing the pathophysiological consequences of the disease becomes highly actual and is reflected in the ascertaining of presence of the so-called "post-COVID syndrome" (PCS). It is now known that PCS can develop in all patients who have had COVID-19, regardless of the severity of the disease (Bogolepova *et al.*, 2021). PCS is included in the International Classification of Diseases (ICD-10) as a "Post-COVID-19 condition" under the code of U09.9 and includes a large list of symptoms lasting over 12 weeks (Glazachev & Kryzhanovskaya, 2021). The clinical picture of PCS is very diverse, but the most common mental disorders are asthenia, cognitive impairment, anxiety-depressive and stress disorders (Mosolov, 2021). The presence of mental disorders, characteristic of PCD, negatively affects the cognitive functions of patients and significantly slows down the process of body recovery after COVID-19 (Golovacheva *et al.*, 2021). That is why new effective technologies for the cognitive rehabilitation of patients with PCS are now highly required (Glazachev & Kryzhanovskaya, 2021).

One of such technologies was previously developed and successfully tested for the correction of the functional state in patients with signs of post-traumatic stress disorder and professional burnout syndrome (Fedotchev, Parin & Polevaya, 2021), as well as in the cognitive rehabilitation of patients with acute cerebrovascular accident (Mukhina *et al.*, 2021). We are talking about the technology of adaptive neurostimulation with double feedback from the electroencephalogram (EEG) of the patient. As shown in a recent review, this technology demonstrates increased efficiency due to the resonant interaction of rhythmic sensory stimuli with bioelectrical processes in the human brain

(Fedotchev *et al.*, 2021). The technology involves the presentation of therapeutic light and music stimuli, automatically modulated by feedback signals from the rhythmic components of the human EEG. As a result of treatment, patients show normalization of the activity of the cardiovascular system and the cognitive-emotional sphere, accompanied by a decrease in the level of maladjustment and stress, as well as a significant increase in assessments of well-being and mood (Fedotchev *et al.*, 2022).

Despite the positive results of the studies undertaken, they did not analyze the dynamics of EEG reactions during therapeutic interventions. To analyze it, stimulation should have the dynamic nature. This can be achieved by modifying stimulation procedures by performing resonance scanning just prior to adaptive neurostimulation. The method of resonance scanning consists in dynamic spectral analysis of the EEG upon presentation of rhythmic light stimuli with a stepwise increasing frequency in the range of the main EEG rhythms (Fedotchev, 1997). This approach makes it possible to observe the dynamics of reactions of individual frequency components in the EEG spectrum during stimulation with varying frequency (Salansky *et al.*, 1998; Fedotchev, 2001), which makes it possible to assess the dynamics of the involvement of the systemic mechanisms of the brain in the observed processes (Savchuk *et al.*, 2022).

In this work, the task was to analyze the dynamics of EEG responses during the cognitive rehabilitation of patients with PCS using a combination of resonance scanning and EEG-guided adaptive neurostimulation.

Materials and Methods

The study involved 19 subjects aged 45 to 72 who were admitted to the Volga District Medical Center with post-COVID pneumonia and showed clear signs of PCS, such as asthenia, anxiety, depression and stress, as well as a combination of gloomy mood and irritability. Each patient underwent 2 to 4 treatment procedures of cognitive rehabilitation; the total number of observations was 39.

The study was carried out in accordance with the Declaration of Helsinki (2013) and approved by the Ethics Committee of the Lobachevsky State University of Nizhny Novgorod. After clarifying the potential risks, benefits and nature of the upcoming study, each participant provided voluntary written informed consent to participate in the survey.

Before the treatment procedures, the subjects were fitted with EEG sensors (an active electrode in the Cz lead, a reference and ground electrode on the earlobes), as well as stereo headphones (Philips SBC HL140) and glasses with red LEDs with a power not exceeding 100 μW mounted in their tinted lenses. The subjects were not given any task, but were asked to sit still with their eyes closed during all examinations.

Treatment procedures began with a 60-second recording of the background electrical activity of the brain with an EEG filtering range of 2–32 Hz and a signal sampling rate of 100 Hz, during which, using an original modification of dynamic spectral analysis based on fast Fourier transforms (Fedotchev *et al.*, 2016), the dominant narrow-frequency (0.4-0.6 Hz) spectral component in the alpha-rhythm range (8–13 Hz) was determined in each person, that is the alpha-EEG oscillator of the patient.

After recording the background, resonance scanning was performed by presenting rhythmic light stimuli according to a special program. It consisted of presenting a series of flashes with a stepwise increasing frequency in the range from 4.0 Hz to 14.0 Hz with a step of 0.15 Hz. The duration of stimulation at each step with a fixed frequency was 5 s, and the total duration of photostimulation was 360 s.

Then the subjects were simultaneously presented with music-like stimuli formed on the basis of the alpha EEG oscillator, and rhythmic light stimulation controlled by the total EEG of the subject. This was achieved by normalizing the digitized EEG values, in which the largest negative value of the EEG signal corresponded to the minimum, and the largest positive value corresponded to the maximum luminescence of the LEDs.

At the end of stimulation, EEG recording continued for 30 seconds to measure the after-effects, and then the subjects were asked about their feelings during treatment sessions.

When processing the obtained EEG records, the presence of photic driving reactions (resonant EEG reactions at the stimulation frequency), the presence of nonlinear reactions at multiple frequencies, or multiplication reactions (resonant EEG reactions at the frequency of harmonics) were taken into account, as well as the powers of the EEG in the frequency ranges: theta (4-8 Hz), alpha (8-13 Hz), beta (13–21 Hz).

Statistical processing of the results was carried out using the SigmaPlot 11.0 software package. When assessing the normality of distribution, the Shapiro–Wilk test was used. Since all samples followed a normal distribution, we calculated the mean values of the indicators (M) and standard errors (m). To determine the EEG effects of stimulation, the levels of significance of shifts (with a sign) of the parameters under exposure relative to the background were assessed using a paired Student's t-test. Differences were considered statistically significant at $p \leq 0.05$.

Results

Individual features of EEG responses were analyzed by successive calculation of EEG and stimulation spectra during each examination, which made it possible to visually compare their dynamics. Below is a typical example of such spectral dynamics for one of the subjects (Fig. 1).

In Fig. 1, one can see that before the start of photostimulation, the pronounced spectral peaks in the range of the alpha rhythm with a frequency of about 9 Hz are recorded. At the very beginning of the resonant scanning, a short-term suppression of alpha activity is observed. Then, as the stimulation frequency increases, resonant spectral peaks are observed in the EEG spectra, exactly coinciding in frequency with the current stimulation frequency (resonant EEG reactions at the stimulation frequency). In addition, resonant spectral peaks are also observed at the frequency of the second harmonic of stimulation (rhythm multiplication reaction). These spectral peaks form oblique straight lines on the left side of the figure, reflecting the resonant activation of the EEG at the stimulation frequency and its harmonic.

It can also be seen that after a short pause, the process of adaptive neurostimulation begins, in which the local resonance peaks on the spectral EEG curves resemble the spectral peaks recorded for the dynamics of stimulation. One can also see a significant increase in the power of the EEG alpha range both during adaptive neurostimulation and after its completion.

The effects of resonance scanning were quantitatively assessed in each experiment by comparing the powers of EEG rhythms in the background and during photostimulation. In order to determine the dynamics of the power of EEG rhythms during repeated examinations, the average values for the initial and final treatment procedures were calculated (Fig. 2).

In Fig. 2, it can be seen that under the influence of resonant scanning, resonant activation of all EEG rhythms is observed already in the initial examination, which is especially pronounced and significant for the EEG alpha range. When examinations are repeated, the power of all rhythms increases both in the background and during resonant scanning. A significant ($P < 0.01$) increase in power was noted for the EEG alpha rhythm.

Quantitative EEG characteristics recorded at the end of the initial and final treatment sessions were also compared (Table 1).

Table 1 data show that as the sessions of complex therapeutic stimulation are repeated, the frequency of rhythm acquisition and rhythm multiplication EEG reactions significantly increases. There is also an increase in the power of all EEG rhythms relative to the background. However, a significant power increase under treatment is noted only for the EEG alpha rhythm.

Questioning the subjects about their subjective feelings in the course of treatment revealed that most of them rated the conducted treatment sessions positively and found the performed procedures pleasant and calming. All subjects

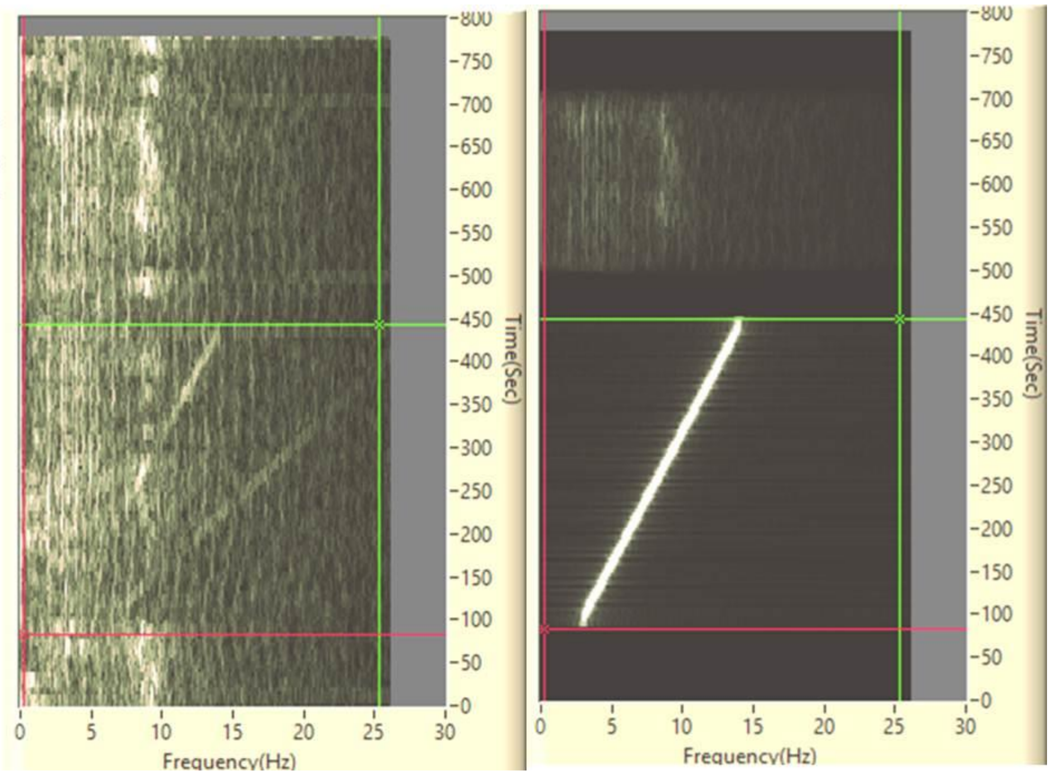

Fig. 1. Dynamics of the EEG (left) and stimulation (right) spectra during the treatment procedure with subject No. 04: X-axis – the frequency of the spectrum, Hz; Y-axis – the time of the experiment, sec.; Z-axis is the spectral density reflected in the color intensity

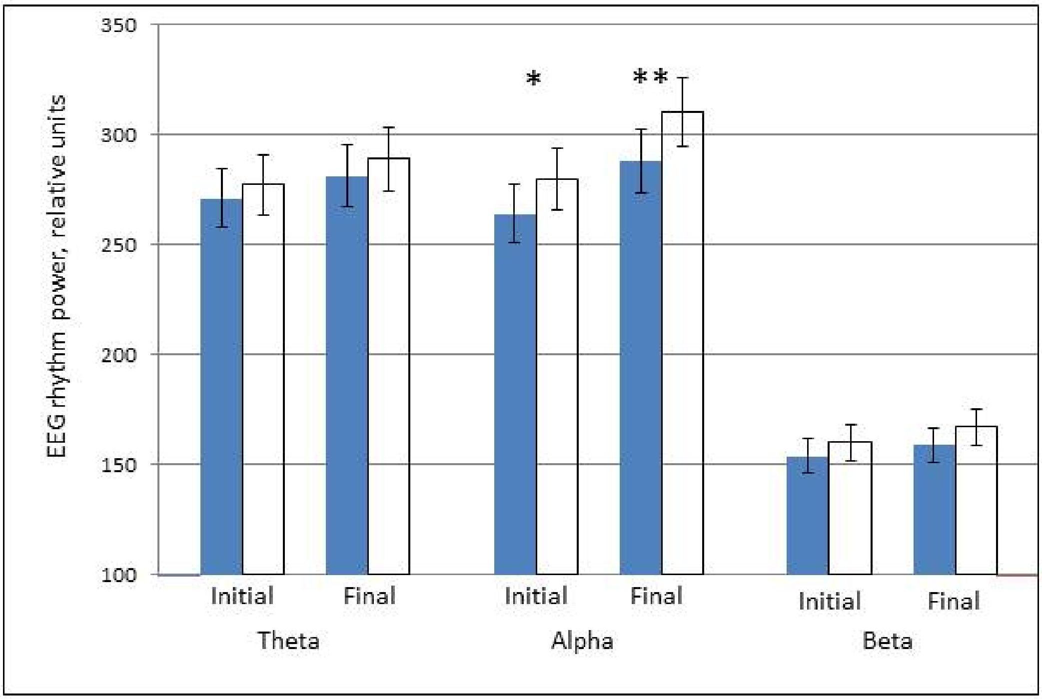

Fig. 2. EEG theta-, alpha-, beta-rhythm powers before (dark columns) and after (light columns) treatment in the initial and final session
Note: * - P < 0.05; ** - P < 0.01

Table 1

Occurrence of EEG rhythm driving and EEG rhythm multiplication reactions, as well as the power shifts of the EEG rhythms under stimulation in the initial and final treatment procedure

EEG indicator	Initial session	Final session	Difference P value
EEG rhythm driving reaction (%)	**47.4 ± 11.8**	**80.0 ± 9.1**	**0.034**
EEG rhythm multiplication reaction (%)	**21.1 ± 9.6**	**60.0 ± 11.2**	**0.015**
Theta EEG power shift (relative units)	7.3 ± 5.6	10.0 ± 4.9	0.728
Alpha EEG power shift (relative units)	**20.9 ± 5.2**	**44.0 ± 8.4**	**0.023**
Beta EEG power shift (relative units)	8.4 ± 2.6	19.0 ± 6.9	0.172

Note: the values with difference levels P < 0.05 are shown in bold

reported a decrease in stress level and an improvement in their emotional state.

Discussion

An analysis of the dynamics of EEG reactions during resonance scanning made it possible to obtain a number of new data on the EEG effects of therapeutic interventions. It has been established that under the influence of photostimulation with increasing frequency the resonant activation of potential EEG oscillators of the brain occurs, which is especially pronounced for the EEG alpha range. With the repetition of therapeutic procedures, the resonant activation of the EEG is enhanced, indicating the participation of learning and training processes in increasing the responsiveness of the brain to subsequent adaptive neurostimulation.

It has also been shown that resonance scanning makes it possible to observe the dynamics of resonant EEG responses at the stimulation frequency (rhythm acquisition) and at the frequency of harmonics (rhythm multiplication), which reflect the degree of functional lability, adaptive potential, and non-linear brain reactions due to the mechanisms of neuroplasticity (Spiegler *et al.*, 2011; Coelli *et al.*, 2019). The magnitude of these EEG reactions significantly increases with the repetition of treatment sessions, indicating the progressive involvement of adaptive mechanisms and mechanisms of neuroplasticity in the treatment process. In fact, the combination of resonance scanning with adaptive neurostimulation is a variant of guided neuroplasticity (Naryshkin *et al.*, 2020) and multisensory stimulation (Yang *et al.*, 2021) procedures, which are considered to be the most effective non-drug treatments for cognitive disorders.

It is important to emphasize that under the influence of medical procedures, predominant resonant activation is noted for the alpha range of the EEG and is accompanied by a decrease in the level of stress, an improvement in the emotional state and mood. These data indicate that in the process of stimulation procedures, the patients demonstrate gradually forming the so called “alpha state” (Frederick, 2012) and the signs of elimination the markers of cognitive decline known from the literature (Lejko *et al.*, 2020).

Conclusion

The presented data convincingly indicate that the introduction of resonance scanning procedure before the EEG-guided adaptive neurostimulation provides additional opportunities for improving the efficiency of cognitive rehabilitation of patients with PCS. Resonance scanning makes it possible to observe the dynamics of resonant EEG responses, provides activation of potential brain oscillators and increases the brain's responsiveness to subsequent adaptive neurostimulation, acting as the treatment efficiency enhancer. Complex treatment procedures, due to progressive involvement of resonant and adaptive mechanisms and mechanisms of neuroplasticity, contribute to the cognitive rehabilitation of patients with PCS, which manifests itself in the normaliza-tion of the EEG, a decrease in stress levels, and an improvement in emotional state and mood.

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References

BOGOLEPOVA A.N., OSINOVSKAYA N.A., KOVALENKO E.A. & MAKHNOVICH E.V. (2021): Fatigue and cognitive impairment in post-COVID syndrome: possible treatment approaches. *Nevrologiya, Neiropsikhiatriya, Ppsikhosomatika* **13**(4), 88–93.

COELLI S., TACCHINO G., VISANI E., PANZICA F., FRANCESCHETTI S. & BIANCHI A.M. (2019): Higher order spectral analysis of scalp EEG activity reveals non-linear behavior during rhythmic visual stimulation. *J. Neural Eng.* **16**(5), 056028.

FEDOTCHEV A.I. (1997): Application of EEG resonance responses for improvement of sensory stimulation efficiency. *Human Physiology* **23**(4). 491–496.

FEDOTCHEV A.I. (2001): Photoinduced resonance phenomena in the human electroencephalogram as a function of frequency, intensity, and duration of stimulation. *Biophysics* **46**(1), 112–117.

FEDOTCHEV A.I., BONDAR A.T., BAKHCHINA A.V., GRIGORIEVA V.N., KATAYEV A.A., PARIN S.B., RADCHENKO G.S. & POLEVAYA S.A. (2016): Transformation of Patient's EEG Oscillators into Music-like Signals for Correction of Stress-Induced Functional States. *Sovremennye tehnologii v medicine* **8**(1), 93–98.

FEDOTCHEV A.I., PARIN S.B. & POLEVAYA S.A. (2021): Adaptive neurostimulation methods in correcting posttraumatic stress disorder and professional burnout syndrome. *Opera Med. Physiol.* **8**(2), 68–74.

FEDOTCHEV A.I., PARIN S.B., POLEVAYA S.A. & ZEMLYANAYA A.A. (2021): Human endogenous rhythms in the development of non-invasive methods of closed-loop adaptive neurostimulation. *J. Pers. Med*. **11**, 437.

FEDOTCHEV A.I., PARIN S.B., POLEVAYA S.A. & ZEMLYANAYA A.A. (2022): EEG-based musical neurointerfaces in the correction of stress-induced states. *Brain-Computer Interfaces* **9**(1), 1–6.

FREDERICK J.A. (2012): Psychophysics of EEG alpha state discrimination. *Conscious Cogn.* **21**(3), 1345–1354.

GLAZACHEV O.S. & KRYZHANOVSKAYA S.Yu. (2021): Prospects for Adaptive Medicine Techniques in the Era of the New Coronavirus Pandemic. *Vestnik Mezhdunarodnoi Akademii Nauk (Russian Section)* **1**(23), 58-63.

GOLOVACHEVA V.A., TABEEVA G.R. & KUZNETSOV I.V. (2021): Cognitive impairment in COVID-19: associations, pathogenesis and treat-ment questions. *Nevrologiya,Neiropsikhiatriya,Psikhosomatika* **13**(2): 123–129.

LEJKO N., LARABI D.I., HERRMANN C.S., ALEMAN A. & ĆURCIC-BLAKE B. (2020): Alpha Power and Functional Connectivity in Cognitive Decline: A Systematic Review and Meta-Analysis. *J. Alzheimers Dis.* **78**(3), 1047–1088.

MOSOLOV S.N. (2021): Long-term psychiatric sequelae of SARS-CoV-2 infection. *Sovremennaya Terapia Psihicheskih Rasstoistv* **3**, 2–23.

MUKHINA E.A, POLEVAYA S.A., PARIN S.B. & FEDOTCHEV A.I. (2021): Cognitive rehabilitation of patients with acute cerebrovascular accident using EEG-guided adaptive neurostimulation. *Opera Med. Physiol*. **8**(4), 90–96.

NARYSHKIN A.G., GALANIN I.V. & EGOROV A.Yu. (2020): Controlled neuroplasticity. *Human Physiology* **46**(2), 112–120.

SALANSKY N., FEDOTCHEV A. & BONDAR A. (1998): Responses of the Nervous System to Low Frequency Stimulation and EEG Rhythms: Clinical Implications. *Neurosci. Biobehav. Rev.* **22**(3), 395–409.

SAVCHUK L.V., POLEVAYA S.A., PARIN S.B., BONDAR A.T. & FEDOTCHEV A.I. (2022): Resonance Scanning and Analysis of the Electroencephalogram in Determining the Maturity of Cortical Rhythms in Younger Schoolchildren. *Biophysics* **67**(2), 1–8.

SPIEGLER A., KNOSCHE T.R., SCHWAB K., HAUEISEN J. & ATAY F.M. (2011): Modeling brain resonance phenomena using a neural mass model. *PLoS Comput Biol*. **7**(12), e1002298.

YANG H., LUO Y., HU Q., TIAN X. & WEN H. (2021): Benefits in Alzheimer's Disease of Sensory and Multisensory Stimulation. *J Alzheimers Dis*. **82**(2), 463–484.