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EEG Microstate Analysis and the EEG Inverse Problem Solution as a Tool for Diagnosing Cognitive Dysfunctions in Individuals Who Have Had a Mild Form of COVID-19

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Abstract—The term "postcovid syndrome" is firmly entrenched in medical terminology, however, many aspects of its clinical manifestations are not well understood. The aim of this work was to find the causes of the development of cognitive dysfunctions in individuals who had a mild form of SARS-CoV-2 using high-density EEG technology and solving an inverse neurophysiological problem. A dynamic study was conducted of 38 people who had COVID-19 and returned to work. Neurophysiological studies were carried out using the EGI-GES-300 system (128 channels). The descriptive characteristics of electroencephalograms were built on the method of studying the spectral density of the EEG signal on the surface of the scalp, and the dynamic characteristics of the signal were studied by fixing EEG microstates, using the method of D. Lehmann and T. Koenig (2018). In the study, a relatively new diagnostic technique for studying cognitive impairments based on the analysis of EEG microstates was implemented, which made it possible to identify signs of functional restructuring of the neuronal macronetworks of the brain and trace the characteristic adaptation of a person during the period of convalescence. The results obtained made it possible to detect a violation of the implementation of the speech function, as a violation of the perception system (ventral information flow system), as well as the connection between the fields of Wernicke's center and Broca's center (dorsal information flow system), leading to the development of communicative dysfunctions that cause characteristic clinical symptoms due to impaired perception of new information and difficulties in implementing the solution. Thus, the survey showed that SARS-Co-V2 causes objective changes in the functional activity of the brain, which are manifested by the syndrome of cognitive dysfunction and require the development of more sensitive clinical tests than currently used.

Keywords: new coronavirus infection, electroencephalography, EEG-microstates, recovery, brain activity

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The "post-covid syndrome" term is firmly entrenched in medical terminology, but many aspects of its clinical manifestations are not well understood. Of particular interest is the nature of the possible impact of SARS-CoV-2 on the central nervous system and the patterns of formation of various disorders of its functions, including cognitive ones, during the period of convalescence.

According to emerging ideas, the impact of the new SARS-CoV-2 coronavirus infection on the central nervous system (*CNS*) is beyond doubt, while it is believed that SARS-CoV-2, like other coronaviruses, can enter the *CNS* in two ways—hematogenous and neuronal—but is quickly neutralized, and therefore clinically significant lesions of the medulla and its membranes are usually not observed [1, 2]. At the same time, descriptions of neurological manifestations in SARS-CoV-2 Roy, Gosh, and co-authors [3] indicate that most often with SARS-CoV-2 there are cerebral symptoms, such as headache and dizziness (13.1–16.8% of cases), as well as anosmia and hypogeusia/ageusia—up to 83% of cases. Cerebrovascular events are recorded with a frequency of 2 to 17%, seizures, in 1% of cases (which does not exceed their frequency in the population). This allowed us to suggest their secondary genesis due to hypoxic and electrolyte disorders, as well as exposure to immune response products.

In their work on rodents and cell cultures of human nerve cells, Song and co-authors [4] demonstrated the invasion of viral RNA into cells and the subsequent mass death of neurons. But, clinical reports of direct damage to the brain substance in the form of meningoencephalitis are rare [5–7]. Clinical manifestations of encephalopathy in COVID-19 according to Helms and co-authors, in 40% of cases [8] autopsies that died from a new coronavirus infection [9–11] revealed viral

RNA transcripts in the tissue of cranial nerves, as well as viral proteins in olfactory endothelial cells.

As follows from the above, the main neurological manifestations of SARS-Cov-2 are characterized by cerebral neurological symptoms and (or) damage to individual cranial nerves; structural changes in the brain tissue, even if they are present, require the exclusion of other causes.

The genesis of the neuropsychological disorders observed in SARS-CoV-2 infection in approximately 25% of patients remains unclear (According to a systematic review by Rogers and co-authors [12], it was stated that anxiety-phobic disorders occur in most cases (8.5–28.8%) and depressive (9.5–16.5%) spectrum, however, in severe SARS-CoV-2, their causes are most often not the effect of the virus itself, but a stressful state associated with the fact of the disease, isolation, staying in the intensive care unit, fear of death or the development of various complications in the future.

In these circumstances, diagnostic methods are of particular interest that can objectify clinical manifestations from the point of view of functional changes in the central nervous system and especially the cortical structures of the brain, but according to a meta-analysis of 12 EEG studies covering 308 patients. In patients with a new coronavirus infection, in the overwhelming majority of cases, nonspecific changes were recorded, paroxysmal activity was recorded in 20.3% of cases, and electroencephalographically confirmed convulsions and status epilepticus—in 2.05% of cases [13].

Approximately the same conclusions were reached by Petrescu, Taussig, and Bouilleret who explained the appearance of specific EEG changes by the severity of the condition, general ischemia—hypoxia and the development, in connection with the above, of secondary neurological pathology [14].

Consequently, neurophysiological studies conducted earlier confirmed the absence of specific and focal changes in the bioelectrical activity of cortical structures in patients with a new coronavirus infection. Such results are quite expected, since the impact of SARS-CoV-2, despite the presence of direct routes of penetration into the nervous tissue, is characterized by diffuse processes without focal destruction of nerve cells, which is probably accompanied by general changes in the bioelectrical activity of the brain corresponding to various neuropsychological syndromes. The objectivization of such "general brain" changes require the use of somewhat different methodological approaches.

One of the promising objective methods for isolating and recording the aforementioned processes is the analysis of quasi-stable processes of change—EEG microstates, proposed by Lehmann and co-authors [15]. EEG microstates are defined as short (100 ms) periods of stability of the topographic characteristics of the distribution of rhythmic EEG activity over the scalp, with rapid activity changes without transitional options. Their functional interpretation is based on the concept of generation of a stable EEG state by the coordinated activity of individual neural networks that perform the same or similar functions. The duration of a single microstate reflects the preservation of the structure of a single neural network, and the change from one microstate to another reflects the transfer of activity between individual neural networks.

Michel, Koenig, and co-authors [16] came to the conclusion that the duration of a microstate can be interpreted as a reflection of the safety and stability of the functioning of the underlying neural assembly, and the frequency of registration is the activity (activation) of the underlying neural generators during the execution of a separate brain function.

At present, the sequence of EEG microstates is considered by many researchers as a direct reflection of the state of the basic mechanisms for the implementation of higher nervous functions, which changes with lesions and diseases [17]. The technique can be used to detect signs of cognitive dysfunctions that have developed, in particular, after COVID-19, but its main provisions still need to be further researched, especially using methods for solving the EEG inverse problem — research.

The purpose of this work was to find the causes of the development of cognitive dysfunctions in individuals who had a mild form of SARS-CoV-2 using high-density EEG technology and solving an inverse neurophysiological problem.

MATERIALS AND METHODS

Core Study Group

A dynamic study was conducted of 38 COVID-19 survivors returning to work. All examined were right-handed, with no history of severe traumatic brain injury or mental illness (mean age was 38.6 ± 2 years).

All participants were health care workers who received appropriate special education. Neuropsychological testing was carried out using the *Montreal Cognitive Assessment* (*MoCA*), Table 1. Its choice was due to the largest coverage of various cognitive functions and its greater sensitivity compared to other scales in detecting mild and moderate cognitive impairment [18].

The MRI study using T1, T2 imaging protocols, suppression and diffusion modes revealed changes in only two participants—5% of all cases. The detected changes in the first case were represented by chronic thrombosis of the venous sinuses, and in the second—by small vessel disease. Both findings were not associated with previous SARS-CoV-2 infection.

Almost all participants in the study were characterized as people in a state of recovery who did not have clinical manifestations of the underlying disease, and therefore had no contraindications to perform their

Table 1. Neuropsychological study results of the main group of patients

Value	*MoCA*-score
Mean	26
Range	3
Min	25
Max	28

— Absence of cognitive disorders, 25–26 points and above
— Mild cognitive impairment, 24–22 points
— Moderate cognitive disorders, 22–16 points
— Severe cognitive impairment, less than 16 points

work duties. This choice was due to the exclusion of the possible development of secondary CNS damage caused by prolonged ischemia-hypoxia, the development of thromboembolic complications, as well as distress syndrome caused by staying in the intensive care unit.

Main Group of Comparison

This group consisted of 33 practically healthy people who volunteered to participate in the experiment. Their age range was from 19 to 60 years, the average age was 32.37 ± 9.44 years, which generally corresponded to the indicators of the main group. The education of the volunteers also corresponded to that of the participants in the main group; at the time of the study, 35 people (87%) were employed. The majority of volunteers lived in the family, 37 (93%). The study participants had no disability. Most of the subjects were right-handed, 38 (92.7%) people.

General characteristics of methods The EEG was recorded in a darkened room with relative sound insulation, in a state of relaxed wakefulness with eyes closed. EEG was recorded using the original 128-channel *Hydrocel-128 system* (USA) with an averaged reference. Recording, switching and hardware filtering of the bioelectrical EEG signal was carried out using an *EGI-GES-300* bioamplifier (*Magstim*, USA). The received signal was converted into digital form by sampling at a Nyquist's frequency of 500 Hz, which made it possible to exclude signal distortion at frequencies from 1 to 250 Hz. The bandwidth of the signal ranged from 0.5 to 70 Hz. with the inclusion of a notch network filter of 50 Hz, which included the main ranges of interest. During the first minute after connecting the volunteer to the device, no recording was made to exclude artifact activity associated with disadaptation and the need to get used to the study.

The total resistance of the neurointerface electrodes, impedance, was controlled within the limits of 10 kOm and was constantly checked during the entire study according to the recommendations of the manufacturer.

The pool of stress tests included an EEG study in a state of passive relaxed wakefulness with eyes closed, which was considered as a state of background bioelectrical activity, and a study under auditory-speech load, in the form of listening to a short story in the native language.

Such a load made it possible to obtain conditions of an altered environment comparable to the state of passive relaxed wakefulness in terms of general characteristics, but determined by the activation of only one cognitive function with a relatively well-known architecture of the cortical analyzer, according to the provisions of the model, two streams [19].

The subsequent acquisition, processing and analysis of the obtained results were carried out in several stages. At the first stage, artifact signals were minimized, for which third-party electrical devices that created parasitic electromagnetic fields were turned off, the interface impedance was controlled, the temperature in the room was regulated, and parasitic muscle movements were minimized. At the second stage, the obtained data pool was filtered using a broadband filter 1–70 Hz, standardization of the basic assembly into a single electrode space, and the procedure for extracting independent signal components, which made it possible to purify the EEG signal from various artifacts of a physical and biological nature that were not eliminated on the first stage. At the third stage, the segmentation of the EEG signal was carried out with the selection of individual EEG microstates using the K-means clustering method or the adhesion-spray method with the allocation of 6 classes of individual microstates, taking into account the variability of classes 5 and 6. The final stage of the study included analysis of the localization of the source of activity of each of the selected EEG classes, microstates, according to the method of Pascual-Marqui, using the algorithm for solving the inverse EEG problem implemented in the application software package—*sLORETA* [20, 21].

The result provided information about the characteristics of the bioelectrical activity of the brain both at rest and under load, including data on 6 separate EEG classes, microstates, the component of the character-

Table 2. Dynamics of clinical and EEG changes in patients with SARS-CoV-2, depending on the period of convalescence

Clinical and EEG changes	1 m	2 m	3 m	4 m	5 m	*p*
Complaints	100%	100%	88%	75%	20%	*
Fast activity (>14 Hz, smoothness of zonal differences, arrhythmic)	100%	50%	25%	25%	7%	*
Slow activity (Less than 7 Hz)	0%	17%	0%	0%	7%	*
Preservation of the EEG pattern (10 Hz—average alpha of the activity range, preservation of zonal differences)	25%	50%	75%	75%	93%	*
Other rhythms (10–15 Hz)	25%	50%	25%	0%	27%	*

* $0.01 < p < 0.05$ (χ^2-*test*).

istics of 1, their microstate lifetime (duration) in seconds; 2, the frequency of its registration in 1 s (occurrence); the volume of the contribution of the EEG microstate to the overall structure of the spectral characteristic of the total energy of the scalp field or the percentage of EEG coverage, microstate (coverage), as well as information about the localization of the main cortical field that forms the EEG microstate, according to the atlas of Brodman.

Statistical Processing of the Obtained Results

Statistical analysis of the obtained results was carried out using the statistical package *GNU-PSPP* under *Linux Mate 10.10.* The general structure of the statistical analysis included the following steps. Checking the data for reliability and consistency of the obtained data using the Cronbach method (0.5 < alpha), after which the factor analysis method was used to highlight the leading factors for further analysis. To compare the results, *t*-comparison methods were used to determine the significance of changes in one observation group depending on the effect of the selected factor, and the one-way *ANOVA* test was used to establish the influence of individual factors on different comparison groups. Pearson's χ^2 method was also used to assess group changes, with results as qualitative measures. All calculations used one degree of freedom, the level of evidence was taken as alpha > 0.05. Recommendations [22] were used to develop a general methodology for statistical analysis.

RESULTS

Analysis of the Background EEG—Records in Patients Who Have Undergone SARS-Cov-2 in a State of Passive Relaxed Wakefulness

Factor analysis of the primary data made it possible to identify three main independent values: 1, convalescence time (in months); 2, changes in EEG activity (fast β-range and slow lower α/θ range); 3, age. Other indicators, such as the nature of MRI changes and the results of neuropsychological testing of *MoCa* did not show a difference with those in healthy subjects, therefore they were not considered as influencing quantities.

An analysis of the time factor and clinical manifestations showed that in the first month in 100% of cases, cerebral neurological symptoms were recorded in the form of weakness, fatigue, impaired attention and memory, however, the neuropsychological examination performed using scales did not reveal significant deviations from the norm, which was probably associated with the clinical orientation of these methods and their focus on the registration of changes associated with disability.

Characteristics of bioelectrical activity in the first month of convalescence, in 100% of cases, had changes in the overall EEG pattern in the form of disturbances in zonal differences and the predominance of fast forms (more than 14 Hz) of bioelectrical activity. Later they regressed within 4–5 months (Table 2).

By the 5th month, there was a regression of clinical manifestations and normalization of the overall EEG pattern. At the same time, slow (7 Hz or less) activity (as an indicator of the structural reorganization of the nervous tissue) was not characteristic of patients who underwent a new coronavirus infection, and the detection of other rhythmic patterns did not correlate with changes in clinical characteristics.

The obtained comparisons confirmed the presence of non-specific diffuse changes in brain activity in people who had SARS-CoV-2 infection, not associated with structural changes in the cortical structures of the brain, so the functional mechanism of the occurrence of these disorders was of undoubted interest, which we tried to analyze using the study of changes in EEG characteristics.-microstates.

EEG microstates in SARS-CoV-2 survivors. Characteristics of EEG microstates in people who recovered from a new coronavirus infection were compared with similar indicators obtained from participants in the control group (Tables 3–5).

As can be seen from the presented results, the transferred novel coronavirus infection caused changes in the lifetime of all classes of EEG microstates ($0.001 < p < 0.01$) and the frequency of their reg-

Table 3. Comparative characteristics of the lifetime of the EEG-microstates of classes 1–6 in seconds in those who have recovered from a new coronavirus infection and in the control group, who are in a state of passive relaxed wakefulness

Group	Class I		Class II		Class III		Class IV		Class V		Class VI	
	mean	dev	mean	dev	mean	dev	mean	dev	mean	dev	mean	dev
Recovered	0.04	0.02	0.04	0.02	0.04	0.01	0.05	0.02	0.04	0.02	0.05	0.01
Healthy	0.02	0.01	0.02	0.01	0.03	0.01	0.02	0.01	0.03	0.01	0.02	0.01
p-ANOVA	<0.001		<0.001		<0.001		<0.001		0.01		<0.001	

Table 4. Comparative characteristics of the frequency of EEG registration-microstates of classes 1–6 per 1 s in patients who have recovered from a new coronavirus infection and participants in the control group who are in a state of passive relaxed wakefulness

Group	Class I		Class II		Class III		Class IV		Class V		Class VI	
	mean	dev	mean	dev	mean	dev	mean	dev	mean	dev	mean	dev
Recovered	3.88	0.00	6.18	3.43	3.88	0.01	6.57	3.48	3.88	0.00	5.65	3.91
Healthy	6.18	3.43	6.57	3.48	5.65	3.91	5.65	3.91	5.71	4.09	5.71	4.09
p-ANOVA	0.00		0.00		0.03		0.03		0.03		0.03	

istration ($0.001 < p < 0.03$). At the same time, the coverage indicator, which characterizes the volume of neuronal structures involved in the implementation of the EEG microstate, did not show significant differences both in SARS-CoV-2 survivors and in the control group ($0.2 < p < 1$), except for class 6 EEG-microstates ($p < 0.001$).

Comparative Characteristics of the EEG Microstates Recorded During the Implementation of the Speech Function

A comparative analysis of the characteristics of EEG microstates during a functional load in the form of a comparison of the state of passive relaxed wakefulness and listening to a text in the native language, carried out using a *paired t-test*, showed that the participants in the control group had all three main indicators—duration of existence, frequency of occurrence and percentage of coverage—significantly ($p < 0.05$) different during listening or active speech production from the state of passive relaxed wakefulness (Tables 6–11).

At the same time, in persons who recovered from SARS-CoV-2, such differences between the characteristics of bioelectrical activity in the state of passive relaxed wakefulness and during auditory and speech loading were not observed. In the vast majority of comparisons, the differences were not significant (with a p-value > 0.3). Only in the study of the coverage index, statistically significant ($p = 0.02$) differences were recorded in the 5th class of the EEG-microstates.

Analysis of the Source of Microstate Activity by Solving the Inverse EEG Problem

Based on the clustering and division of the overall EEG record into separate classes of EEG-microstates, a study was made of the sources of formation of their activity using the algorithm for solving the inverse EEG problem.

But since the algorithms for solving the EEG inverse problem are based on the principles of dipole localization of the source, which is based on the power values of the scalp EEG signal calculated using the fast

Table 5. Comparative characteristics of the percentage of EEG coverage—microstates of classes 1–6 per 1 s in patients who have recovered from a new coronavirus infection and participants in the control group who are in a state of passive relaxed wakefulness

Group	Class I		Class II		Class III		Class IV		Class V		Class VI	
	mean	dev	mean	dev	mean	dev	mean	dev	mean	dev	mean	dev
Recovered	16.5%	6.7%	15.4%	6.6%	16.7%	5.7%	17.3%	6.3%	16.0%	6.4%	18.1%	5.6%
Healthy	16.6%	13.9%	18.8%	13.2%	17.0%	14.0%	16.3%	14.9%	18.1%	15.7%	13.2%	12%
p-ANOVA	0.96		0.24		0.96		0.75		0.53		<0.001	

Table 6. Comparative characteristics of the EEG lifetime-microstates of classes 1–6 in a state of passive relaxed wakefulness and during auditory-speech load in participants in the control group

Test	Class I		Class II		Class III		Class IV		Class V		Class VI	
	mean	dev	mean	dev	mean	dev	mean	dev	mean	dev	mean	dev
Rest	0.02	0.01	0.02	0.01	0.03	0.01	0.02	0.01	0.03	0.01	0.02	0.01
Stimulation	0.04	0.01	0.04	0.01	0.04	0.01	0.04	0.01	0.05	0.01	0.04	0.01
p-t-test	<0.001		<0.001		<0.001		<0.001		<0.001		<0.001	

Table 7. Comparative characteristics of the EEG lifetime-microstates of classes 1–6 in a state of passive relaxed wakefulness and during auditory-speech load in people who have recovered from a new coronavirus infection

Test	Class I		Class II		Class III		Class IV		Class V		Class VI	
	mean	dev	mean	dev	mean	dev	mean	dev	mean	dev	mean	dev
Rest	0.04	0.02	0.04	0.02	0.04	0.01	0.05	0.02	0.04	0.02	0.05	0.01
Stimulation	0.04	0.02	0.04	0.02	0.04	0.01	0.04	0.01	0.05	0.01	0.04	0.02
p-t-test	>0.5		0.4		>0.5		>0.5		0.02		>0.1	

Fourier transform method, the potential power of the areas of the cerebral cortex that produce rhythmic activity turns out to be higher than that of excited areas with disorganized activity. Thus, when solving the inverse problem of the EEG, it is not the region of the functionally active nervous tissue that is singled out, but the regions that are in the state of maximum rhythmic synchronization in the range of 10–24 Hz (maximally covering the μ-band rhythms, according to the recommendations [16], which was taken into account in the context assessment of the overall work of brain structures, therefore, in our study, the general term "rhythmic activity" was used, reflecting the area of interest of the algorithm used for solving the EEG inverse problem, based on the change in periods of activity, but not equivalent to the term "excitation of nervous tissue." This made it possible to identify two main sequences characteristic of cortical structures that produce rhythmic activity both for the state of passive relaxed wakefulness and for auditory-speech load and to localize the data obtained in accordance with the atlas of cortical fields by Brodmann (Figs. 1 and 2).

The obtained results showed that in the participants of the control group who did not have SARS-CoV-2 in a state of passive relaxed wakefulness, the solution of the inverse EEG problem does not highlight the Brodmann fields that form the cortical representation of the speech analyzer (39, 40 and 44, 45), however, in all of the EEG classes, microstates, there is a component of rhythmic activity 47 of the Brodmann field, which is responsible for the perception and realization of music.

The auditory load was characterized by the selection of fields 22 (grade 2), 23 (grade 6), 37 (grades 3,4,5 and 6), 39,40 (grades 3,4,5,6), 44 (grades 3, 4 and 6). classes), 45 (grade 6) and 47 (grade 5), which form the noise perception center, Wernicke's area, Broca's area and the music perception center, which corresponded to the accepted ideas about the implementation of the speech function through the dorsal stream of the two-stream model of the speech analyzer.

However, in people who recovered from a new coronavirus infection, the appearance of other sequences for solving the EEG inverse problem (Fig. 2) was observed in the form of a decrease in the

Table 8. Comparative characteristics of the frequency of EEG registration-microstates of classes 1–6 in a state of passive relaxed wakefulness and during auditory-speech load in participants in the control group

Test	Class I		Class II		Class III		Class IV		Class V		Class VI	
	mean	dev	mean	dev	mean	dev	mean	dev	mean	dev	mean	dev
Rest	6.18	3.43	6.57	3.48	5.65	3.91	5.66	3.93	5.71	4.09	5.40	3.80
Stimulation	3.88	0.00	3.88	0.00	3.88	0.00	3.88	0.00	3.87	0.01	3.88	0.00
p-t-test	<0.001		<0.001		0.01		0.01		0.01		0.02	

Table 9. Comparative characteristics of the frequency of EEG registration-microstates of classes 1–6 in a state of passive relaxed wakefulness and during auditory-speech load in persons who have recovered from SARS-CoV-2

Test	Class I		Class II		Class III		Class IV		Class V		Class VI	
	mean	dev	mean	dev	mean	dev	mean	dev	mean	dev	mean	dev
Rest	3.88	0.00	3.88	0.01	3.88	0.00	3.88	0.00	3.88	0.00	3.88	0.01
Stimulation	3.88	0.01	3.88	0.00	3.88	0.00	3.88	0.01	3.88	0.01	3.63	0.95
p-t-test	>0.5		0.4		>0.5		>0.5		0.4		0.2	

Table 10. Comparative characteristics of the percentage of coverage, microstates of 1–6 classes in a state of passive relaxed wakefulness and during auditory-speech load in participants in the control group

Test	Class I		Class II		Class III		Class IV		Class V		Class VI	
	mean	dev	mean	dev	mean	dev	mean	dev	mean	dev	mean	dev
Rest	17%	14%	19%	13%	17%	14%	16%	15%	18%	16%	13%	12%
Stimulation	17%	3%	17%	4%	16%	3%	17%	3%	18%	4%	16%	4%
p-t-test	0.8		0.4		0.6		0.9		0.9		0.2	

total number of EEG microstates involved in the implementation of the speech function.

Thus, in the state of passive relaxed wakefulness, there was no release of Brodmann's field 47, which is characteristic of the participants in the control group. At the same time, field 22 (classes 1,5,6), and field 37 (class 3), as well as fields 39, 40 (all EEG classes, microstates) were recorded. With auditory-speech load, field 37 (grades 1 and 3) and 39 (grades 4, 5, 6) and 41 (grade 6) were distinguished.

DISCUSSION

The study of changes in the bioelectrical activity of the brain, through the use of systems for isolating EEG, microstates, in combination with a system for localizing the cortical source of activity, made it possible to significantly expand the capabilities of the routine EEG method and improve the accuracy of its results, especially when using a multichannel EEG system of high recording density. The use of EEG technology as a base technology made it possible to register the processes of dynamic changes in the activity of brain neural networks, which is currently not available for methods based on functional MRI technology.

A comparative analysis of changes in the characteristics of EEG microstates also confirmed the presence of functional changes in bioelectrical activity, which were based not on structural changes in neural formations, but on changes in the organization of sequences of activities of individual neuronal groups that form the structural basis of a functional connectome. Thus, the absence of significant changes in the percentage of EEG coverage, microstates, in healthy people and persons who had recovered from SARS-CoV-2 demonstrated the preservation of the volumes of neural structures involved in functional implementation, while the lifetime and frequency of occurrence of individual EEG classes, microstates, differed.

Neurophysiological examination proved to be the most sensitive method for studying the dynamic processes of brain activity and even at the level of routine EEG, was able to detect certain changes in the characteristics of the bioelectrical activity of the brain in comparison with healthy people with similar physical and psycho-emotional stress, which were characterized by diffuse and nonspecific changes in bioelectri-

Table 11. Comparative characteristics of the percentage of coverage, microstates, of classes 1–6 in a state of passive relaxed wakefulness and during auditory-speech load in patients who have recovered from a new coronavirus infection

Test	Class I		Class II		Class III		Class IV		Class V		Class VI	
	mean	dev	mean	dev	mean	dev	mean	dev	mean	dev	mean	dev
Rest	17%	7%	15%	7%	17%	6%	17%	6%	16%	6%	18%	6%
Stimulation	15%	6%	17%	7%	17%	5%	16%	8%	20%	3%	15%	7%
p-t-test	>0.5		>0.4		>0.5		>0.5		0.02		0.1	

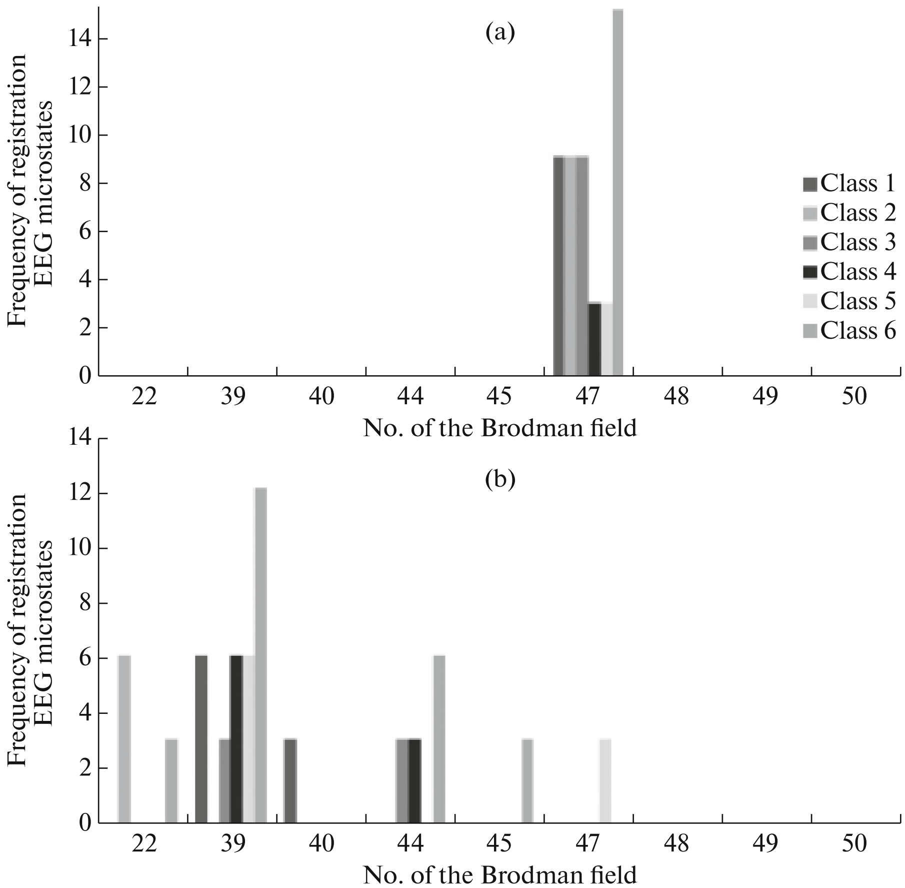

Fig. 1. The frequency of registration of Brodmann field activity (according to *sLORETA* data) in participants of the control group in a state of passive relaxed wakefulness or rest condition (a) and during auditory-speech stress (b); $0.01 < p < 0.05$ (χ^2-*test*).

cal activity brain structures in the form of a predominance of fast forms and disturbances in the normal spatial distribution of rhythms, which, according to some authors, reflected a mismatch in the joint work of individual neural networks [14].

Further expansion of the scope of the study to include the method of EEG analysis, microstates, and methods for determining the source of bioelectrical activity in the case of SARS-CoV-2 revealed changes that can be interpreted as a functional restructuring of individual neuronal networks, without pronounced structural damage, which was assessed by the absence of changes in indicators of the percentage of coverage each class of EEG microstates, but in combination with an increase in the lifetime of each EEG microstate, and a decrease in the frequency of their registration in a limited period of time. Of particular interest was the almost complete regression of the variability of the EEG recording frequency indicator, microstates, in people who had recovered from a new coronavirus infection, determined in all selected classes. This phenomenon was regarded by us as gross manifestations of low compensatory abilities in such people, caused by the disease.

However, the most complete characterization of bioelectrical changes in SARS-CoV-2 survivors was demonstrated by solving the inverse EEG problem, which made it possible to establish a violation of the sequences of registration of rhythmic activity in the mu-range of frequencies over the cortical structures of the brain in their association with the Brodmann field atlas.

The identification of rhythmic activity in the mu band, found in our study, confirms the ideas presented in [23] about the cortical nature of rhythmic phenomena associated with the activity of individual cortical macronetworks, a large number of neurons of which form the rhythmic activity of the mu band. This suggests the presence of individual rhythms characteristic of individual cortical representations of cortical analyzers, including auditory-speech, within the mu-range of frequencies. Unfortunately, such a study is beyond the scope of the presented study design and requires a separate scientific work.

The solution of the EEG inverse problem made it possible to detect a violation of the implementation of the speech function, both a violation of the perception system (the system of the ventral information flow),

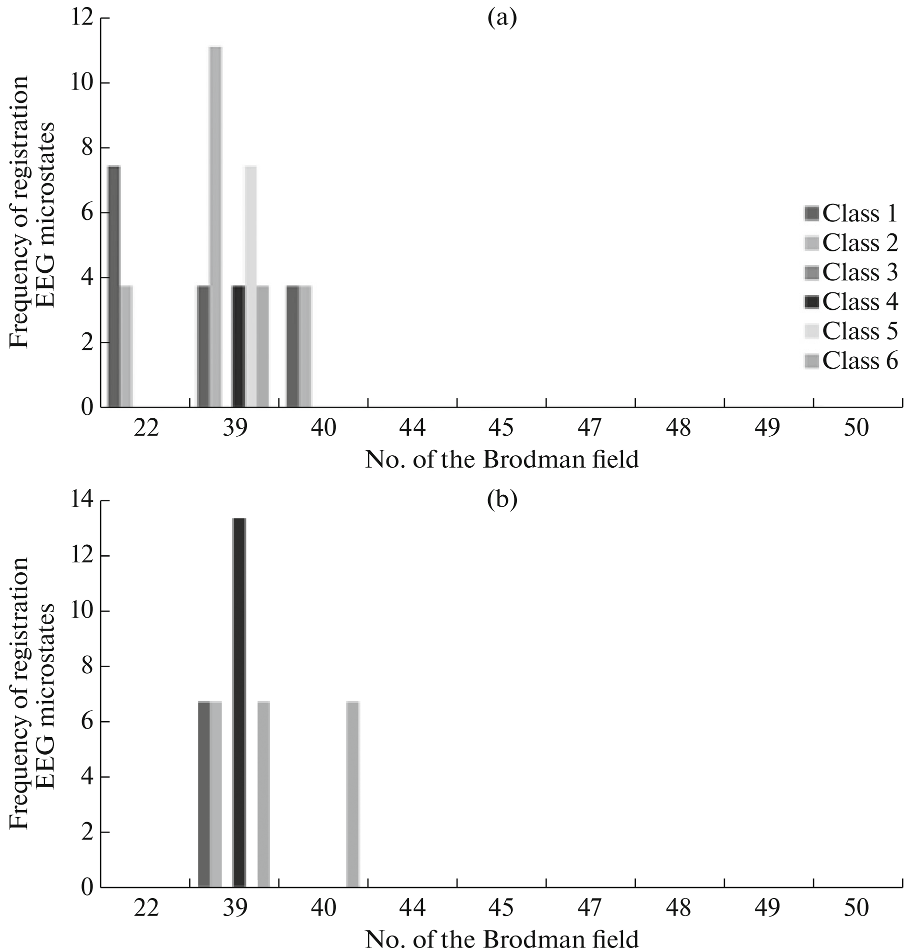

Fig. 2. The frequency of registration of Brodmann field activity (according to *sLORETA* data) in accordance with the Brodmann field number in people who have recovered from a new coronavirus infection in a state of passive relaxed wakefulness or rest condition (a) and during auditory-speech stress (b); $p < 0.05$ (χ^2-*test*).

and the connection between the fields of Wernicke's center and the Broca's center (the system of the dorsal information flow), leading to the development of communication dysfunctions that cause characteristic clinical symptoms due to a violation of the perception of new information and difficulties in implementing the solution. This is probably due to the effects of the SARS-CoV-2 infectious agent on neuronal structures, which were previously described in experimental works [24], including indirectly through immunopathochemical processes.

However, in the course of the study, it was found that the recorded rhythmic EEG activity, which forms the indicators of the activity of the general scalp potential, under the conditions of studying physiological processes, was not associated with the processes of excitation of neurons, but characterized with the states preceding excitation [20].

This did not allow using the fMRI method as a confirmation of the results obtained by changing the characteristics of the *BOLD* signal, which is also confirmed by the literature data [21, 24, 25], indicating the difficulties in obtaining independent confirmation of EEG data.

The study made it possible to come to the following conclusions:

(1) Persons who have undergone forms of a new coronavirus infection and returned to work after convalescence retain not only subjective symptoms that form a "post-covid" syndrome within the framework of general asthenic manifestations that do not have clear clinical diagnostic criteria, but also have objective changes in the bioelectrical activity of the brain brain.

These changes are associated not only with the development of psychological distress caused by SARS-CoV-2 as a new infection with a very serious prognosis, but also with the still unexplored mechanisms for the development of functional damage to the activation sequences of various neural networks involved in the implementation of higher nervous functions, possibly from—due to the peculiarities of the impact of the SARS-CoV-2 virus or the products of the immune response on the nervous tissue.

(2) Recovery of general EEG characteristics in patients with SARS-CoV-2 is observed over a long period of time (at least six months), which probably represents the basis of general brain dysfunctions, united by the general term post-COVID syndrome. Under these conditions, in order to objectify the observed picture, it is necessary to conduct further multimodal neurophysiological examinations of such patients aimed at objectively identifying subclinical symptoms of cognitive impairment in order to create an optimal and complete program for their rehabilitation.

(3) Analysis of changes in the characteristics of the spectral field of the scalp in the studied classes of EEG-microstates, showed that the basis for the formation of a separate class is the production of EEG rhythmic phenomena fixed in time in the neural networks of a separate Brodmann field, however, this fact excludes the use of the fMRI technique to confirm the results of an EEG study, since these changes in the recorded signal are associated with the period of preparation and “waiting” of neural structures, which represent processes different from the period of activity of the nervous tissue, while fMRI registers processes associated with metabolic changes in functionally active cortical areas.

(4) The results of solving the inverse problem of the EEG showed that in people who have recovered from a new coronavirus infection, changes in the implementation of speech function are recorded, in the form of a disorganization of the sequence of switching on the main speech centers, especially in a state of passive relaxed wakefulness.

CONCLUSIONS

The study shows that people who have had a new coronavirus infection for a long time (up to 6 months) have cognitive impairments that make it difficult to recover from professional skills.

These disorders are difficult to differentiate only on the basis of clinical or neuroimaging techniques, since they are based not on the structural reorganization of the nervous tissue in response to the direct action of an infectious factor, but on functional changes in the sequences of excitation, inhibition, and functional “waiting” of the neural networks of the brain.

To register and verify these processes, it is necessary to develop methods for effective neurophysiological analysis that allow diagnosing and localizing processes with rapid dynamics and obtaining information about the nature and structure of functional, including cognitive impairments.

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COMPLIANCE WITH ETHICAL STANDARDS

All studies were carried out in accordance with the principles of biomedical ethics formulated in the Declaration of Helsinki of 1964 and its subsequent updates and approved by the local ethics committee of the Federal Center for Brain and Neurotechnologies of the Federal Medical and Biological Agency of Russia (Moscow).

Informed Consent

Each participant in the study provided a voluntary written informed consent signed by him after explaining to him the potential risks and benefits, as well as the nature of the upcoming study.

Conflict of Interests

The authors declare the absence of obvious and potential conflicts of interest related to the publication of this article.

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