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ANALYSIS AND MODELING OF COMPLEX LIVING SYSTEMS

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Frequency, time, and spatial electroencephalogram changes after COVID-19 during a simple speech task

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We found a predominance of α-rhythm patterns in the left hemisphere in healthy people compared to people with COVID-19 history. Moreover, we observe a significant decrease in the left hemisphere contribution to the speech center area in people who have undergone COVID-19 when performing speech tasks.

Our findings show that the signal in healthy subjects is more spatially localized and synchronized between hemispheres when performing tasks compared to people who recovered from COVID-19. We also observed a decrease in low frequencies in both hemispheres after COVID-19.

EEG-patterns of COVID-19 are detectable in an unusual frequency domain. What is usually considered noise in electroencephalographic (EEG) data carries information that can be used to determine whether or not a person has had COVID-19. These patterns can be interpreted as signs of hemispheric desynchronization, premature brain ageing, and more significant brain strain when performing simple tasks compared to people who did not have COVID-19.

In our work, we have shown the applicability of neural networks in helping to detect the long-term effects of COVID-19 on EEG-data. Furthermore, our data following other studies supported the hypothesis of the severity of the long-term effects of COVID-19 detected on the EEG-data of EEG-based BCI. The presented findings of functional activity of the brain–computer interface make it possible to use machine learning methods on simple, non-invasive brain–computer interfaces to detect post-COVID syndrome and develop progress in neurorehabilitation.

Keywords: COVID-19, brain–computer interface, EEG, frequency patterns, brain ageing, neurorehabilitation, post-COVID syndrome, deep learning

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АНАЛИЗ И МОДЕЛИРОВАНИЕ СЛОЖНЫХ ЖИВЫХ СИСТЕМ

УДК: 004.5, 519.6, 519.7

Частотные, временные и пространственные изменения электроэнцефалограммы после COVID-19 при выполнении простого речевого задания

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Используя анализ данных и применение нейронных сетей в нашей работе, мы выявили закономерности электрической активности мозга, характеризующие COVID-19. Нас интересовали частотные, временные и пространственные паттерны электрической активности у людей, перенесших COVID-19. Мы обнаружили преобладание паттернов α-ритма в левом полушарии у здоровых людей по сравнению с людьми, переболевшими COVID-19. Более того, мы наблюдаем значительное снижение вклада левого полушария в области речевого центра у людей, перенесших COVID-19, при выполнении речевых заданий. Наши результаты показывают, что сигнал у здоровых людей более пространственно локализован и синхронизирован между полушариями при выполнении задач по сравнению с людьми, перенесшими COVID-19. Мы также наблюдали снижение низких частот в обоих полушариях после COVID-19. Электроэнцефалографические (ЭЭГ) паттерны COVID-19 обнаруживаются в необычной частотной области. То, что обычно считается шумом в ЭЭГ-данных, несет в себе информацию, по которой можно определить, переболел ли человек COVID-19. Эти паттерны можно интерпретировать как признаки десинхронизации полушарий, преждевременного старения мозга и стресса при выполнении простых задач по сравнению с людьми без COVID-19 в анамнезе. В нашей работе мы показали применимость нейронных сетей для выявления долгосрочных последствий COVID-19 на данные ЭЭГ. Кроме того, наши данные подтвердили гипотезу о тяжести последствий COVID-19, обнаруженных по ЭЭГ-данным. Представленные результаты функциональной активности мозга позволяют использовать методы машинного обучения на простых неинвазивных интерфейсах «мозг–компьютер» для выявления пост-COVID-синдрома и прогресса в нейрореабилитации.

Ключевые слова: COVID-19, интерфейс «мозг–компьютер», ЭЭГ, частотные паттерны, строение мозга, нейрореабилитация, постковидный синдром, глубокое обучение

Introduction

In recent years brain–computer interface (BCI) has been gaining more and more popularity as a way to augment human capabilities by providing a new interaction link with the outside world. It can be used in virtual assistant applications, ambient technologies, and education. The ability to monitor brain activity with continuous temporal resolution allows BCI devices to be useful for different healthcare applications, such as an aid for disabled or senior people and the development of rehabilitative and restorative therapies for stroke, traumatic brain injuries, and neurodegenerative diseases [Velasco-Álvarez et al., 2021; Kosmyna et al., 2016; Millán et al., 2010; Portillo-Lara et al., 2021].

While developing an EEG-based BCI, we found a significant inhomogeneity of the EEG-data [Zubov, Isaeva, Bernadotte, 2021; Vorontsova et al., 2021; Mazurin, Bernadotte, 2021; Bernadotte, 2022a; Bernadotte, 2022b]. Given the COVID-19 situation with more than 500 million confirmed cases worldwide and more than 6 million deaths, we hypothesized that this heterogeneity might be related to the neurological consequences of COVID-19 [WHO, 2021].

In 2022, there were seven Human coronaviruses; some was associated with severe respiratory diseases, mainly: Middle East respiratory syndrome CoV (MERS-CoV), SARS-CoV-1, SARS-CoV-2; while the others were associated with neurological complications: CoV-229E, HCoV-OC43, SARS-CoV-1, and SARS-CoV-2 (COVID-19).

HCoV-229E and HCoV-OC43 RNA were shown to be detected significantly more frequently in brain tissue autopsied from Multiple Sclerosis (MS) patients than in the brain of the donors who had no obvious clinical symptoms of MS [Arbour et al., 2000; Salmi et al., 1982].

The scientific community saw the first published data regarding neurological complications linked to SARS-CoV-2 (COVID-19) in 2020. Neuronal damage appears to be caused by direct, virus-mediated, and non-virus-mediated injury. There are acute lesions, such as CNS demyelinating events, encephalitis, meningitis and myelitis, Guillain – Barre' syndrome, Bell's palsy, myasthenic disorders, hemorrhagic stroke, multiple ischemic infarcts, epileptic status [Arbour et al., 2000; Patone et al., 2021; Murray et al., 1992; Karpenko et al., 2018; Bernadotte, Mikhelson, Spivak, 2016; Aarsland, Bernadotte, 2015; Bernadotte et al., 2014] — all these diseases and signs of aging are associated with inflammation, which, in terms of morphological and functional features, are very similar to the consequences of SARS.

Although many research groups are studying the EEG data of post-COVID patients confirming that COVID-19 causes long-term consequences, such as executive and psycho-affective deficits and EEG abnormalities, there is only one study on classifying the post-COVID consequences using neuropsychological assessments and classic machine learning algorithms. Matias-Guiu and colleagues were able to classify 75 % of patients not affected by the post-COVID syndrome. However, their overall results were considered too low to establish a quality classification of fatigue levels in patients [Rubega et al., 2022; Cecchetti et al., 2022; Appelt et al., 2022; Matias-Guiu et al., 2022].

Previously, we showed that despite the noisy signal, the EEG-data reveals patterns characteristic of the internal pronunciation of word-movement commands [Vorontsova et al., 2021]. That is, despite the prejudice against the noisiness of the EEG-signal, this signal provides meaningful data about very subtle processes of mental functioning.

In another paper, we presented a binary classifier based on a convolutional and recurrent neural network [Zubov, Isaeva, Bernadotte, 2021], which showed accuracy equal to 60 % on average, with a maximum value of 78.9 % when classifying EEG-data from people who have undergone SARS-CoV-2 (COVID-19), and people who did not meet the SARS criteria.

It is known that the alpha rhythm (α-rhythm) of the brain's electrical activity with a frequency of 8 to 14 Hz is best expressed in the occipital areas of the brain. This α-rhythm has the highest amplitude in wakefulness, especially with eyes closed in a darkened room. Decreased α-rhythm is characteristic of concentration (mainly visual) or mental activity [Ossadtchi et al., 2017]. We wondered whether there were changes in α-rhythm in people who had undergone COVID-19. We were also interested in other frequency, time, and space domains. EEG-data make it possible to analyze a noisy signal presented from different brain parts in different frequency domains over a relatively long time period (one recording lasts about one hour).

An exciting frequency domain in the EEG-data is the signal with a frequency greater than 50 Hz. In the classical approach to EEG analysis, this frequency range is not of interest; however, data is showing that the contribution of this signal (> 50 Hz) to the frequency patterns of EEG-data increases with age and may indicate neurological changes [Voytek et al., 2015]. We hypothesized that this increased presence of high frequencies might characterize the neurological consequences of COVID-19. In addition, we were interested in detecting spatial features of the brain's electrical activity after COVID-19.

Methods

Collecting the EEG-data

The dataset we used for the study consisted of 32-channel recordings of EEG-signal made at 250 Hz during several silent and vocalized speech sessions of 105 subjects. The dry plastic electrodes (Datwyler's SoftPulseTM Medium, brush type electrode) were placed according to the traditional 10–20 scheme. The "Afz"-channel was used as a reference electrode. The word presentation signal was also captured with a light sensor and included in data files as a mark. Each experiment lasted 5 to 14 sessions, depending on the subject's condition. Each session consisted of ten words from the training dictionary in random order, with repetitions allowed. During each session, the subjects were asked to pronounce the words shown on the screen aloud (verbalized speech) or silently (imaginary speech) without removing the EEG equipment.

We selected 22 individuals who were diagnosed with COVID-19 during the six months prior to the experiment (10 female, 12 male, age 23–44, mean 33, higher education: all, six months between positive PCR test and data acquiring on average) and balanced it with 21 individual who with non-COVID-19 history (7 female, 14 male, age 20–47, mean 31, higher education: 19).

All subjects had reached the age of majority, were in good health, and voluntarily signed a consent to participate in the study. The EEG is considered a safe procedure. However, the subjects could interrupt the study at any time without giving a reason. The exclusion criteria for the study were a history of head trauma, alcohol or other intoxication, and epilepsy.

Eye Noise Filtering

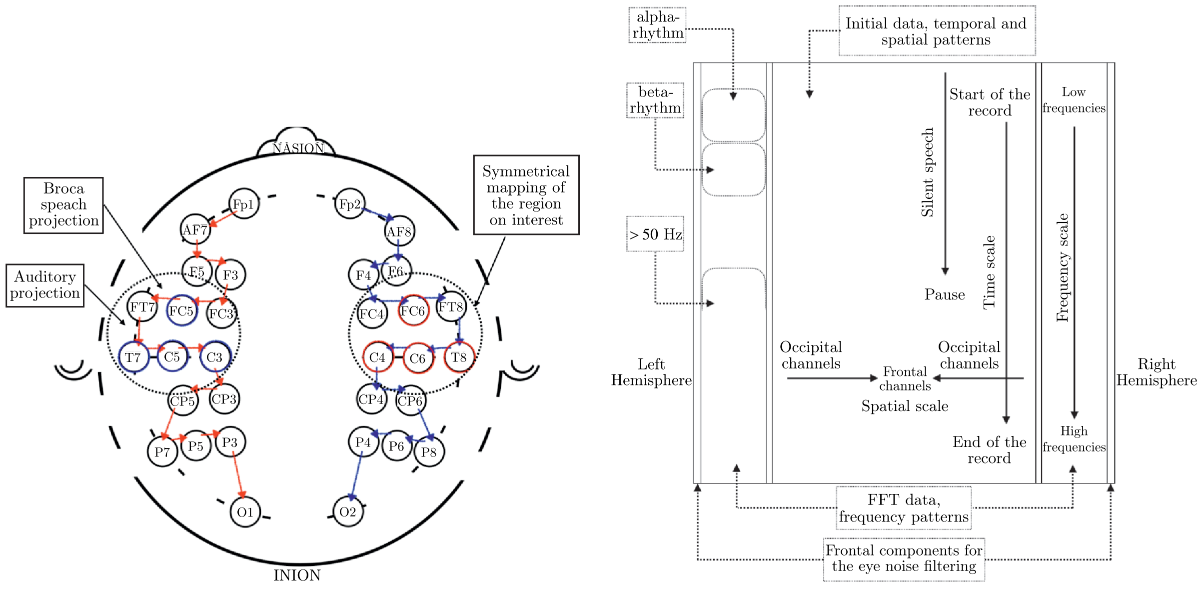
We used the eye noise filtering based on a three-step algorithm presented earlier [Vorontsova et al., 2021] that includes performing an ICA decomposition of selected frontal lobe channels and extracting the eye noise component using Fast Fourier transform (FFT) and the Savitsky – Galey filter. We decided to consider eye noise independently of brain activity for our study.

Separation of Electrodes Into Left and Right Hemispheres

The separation of the electrodes into the left and right hemispheres was performed considering the spatial balance between the hemispheres, and can be seen in Figure 1.

Downsampling

The sampling rate was downsampled using index masks on the original EEG-data. For example, when we performed downsampling from 250 Hz to 125 Hz, the first array contained elements with even indices and the second, with odd indices. When lowering the frequency to 62.5 Hz, the indices were selected according to the remainder when divided by 4.



(a) (b)

Figure 1. Separation of electrodes into the left and right hemispheres (a). Resulting vector after the preprocessing technique (b)

Presenting the EEG-data as a Two-Dimensional Vector

First, we cut the EEG-data into 2D vectors — 1024 long (about 4 s, considering the that sampling rate is equal to 250 Hz) and 32 wide (the number of EEG-channels).

Second, we duplicated eight channels (Fp1, Af7, F5, F3, Fp26, Af8, F6, F8).

Third, using the downsampling algorithms presented above, the sampling rate was downsampled from 250 Hz to 125 Hz, and the data were split into two separate samples (let us call them “Sample 01” and “Sample 02”) with dimensions of 40×512.

Fourth, using the downsampling algorithms presented above, we downsampled “Sample 01” (“Sample 02” separately) from 250 Hz to 125 Hz and packed the resulting samples into a 2D vector (80×512) and cut the first half into a 2D vector (80×256) each. In parallel, the sampling rate was downsampled from 125 Hz to 62.5 Hz for “Sample 01” (“Sample 02” separately), and the resulting samples were packed into a 2D vector (160×256).

Fifth, in parallel, using the Eye Noise Filtering presented above, we obtained six components of eye noise (6×256) from six groups of channels from “Sample 01” (“Sample 02”). The sampling rate was downsampled using index masks on the original EEG-data. For example, when we performed downsampling from 250 Hz to 125 Hz, the first array contained elements with even indices and the second — with odd indices. When lowering the frequency to 62.5 Hz, the indices were selected according to the remainder when divided by 4.

Sixth, considering the separation of electrodes into the left and right hemispheres, we combined vectors into a 2D vector (256×256). All the obtained vectors were combined according to the following order: eye noise of the left hemisphere, downsampled tensors from the left hemisphere, median from “Fc5” and “C5” channels, downsampled tensors from the left and right hemispheres, respectively, median from “Fc6” and “C6” channels, downsampled tensors from the right hemisphere, eye noise of the right hemisphere.

Using such an approach made it possible to represent the data in the form of a square containing fairly evenly distributed information about the signal without any information losses. Thus, the resulting (256×256) tensor contains preprocessed data, additional features, and data with minimal processing,

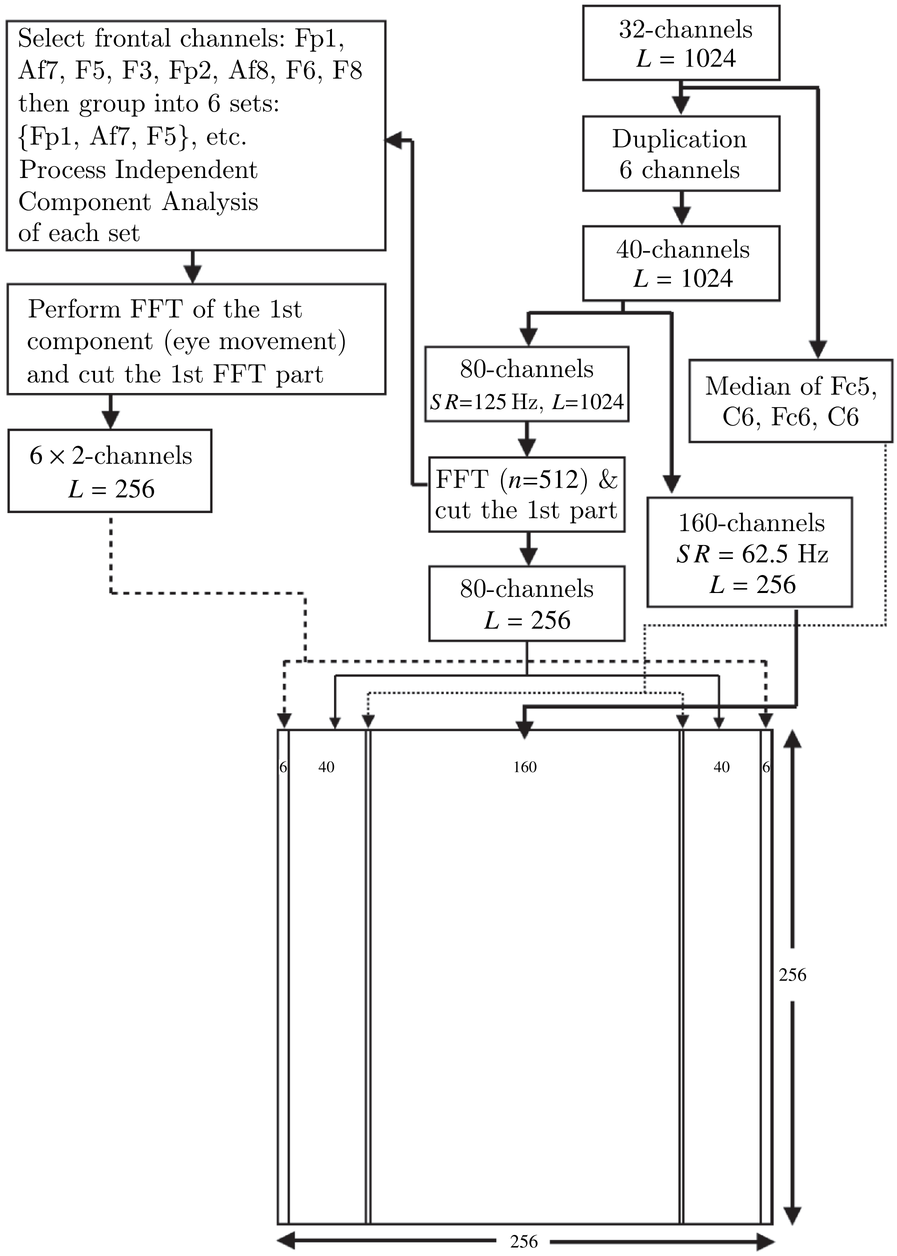


Figure 2. Presenting EEG-data as two-dimensional vectors

which can help the neural network identify patterns. The preliminary data processing considers not only the presence of noise, but also the peculiarities of their location.

The complete preprocessing scheme can be seen in Figure 2. The resulting (256×256) tensor can be seen in Figure 1, *b*.

Neural Networks

We used two models: the first was based on convolutional neural networks ResNet and two layers of controlled recurrent units — Gated Recurrent Unit (GRU) [He et al., 2016; Vorontsova et al., 2021], and the second model was based on DenseNet121 [Huang, Liu, Weinberger, 2018]. Both models were selected due to their performance in our previous research.

The collected dataset was split into three parts for the training and evaluation. First, the set of all the individuals who provided EEG recordings for our study was split to form two disjoint groups of different sizes. The data recordings corresponding to the smaller one formed the test dataset, which consisted of 10 % of the total dataset. A larger group of recordings was mixed and split to form training (70 % of the initial data) and validation datasets (20 %). In other words, the train and validation datasets were constructed classically, while the test part of the dataset was formed using an out-of-sample approach.

Detection of a pattern of Neural Networks perception through the nullifying kernel

For the 2D vector (256×256), we applied a nullifying kernel of size (32×32) with a stride equal to 12 and a padding equal to 0.

In applied machine learning, the problem of sample heterogeneity is often encountered. For example, the sample heterogeneity leads to serious difficulties in solving the problem of brain electrical activity pattern recognition when developing a brain–computer interface for people of different social characteristics. We used a criterion of clustering quality based on the features selection [Mazurin, Bernadotte, 2021], which has low computing needs and is based not on the proximity/remoteness of the sampled objects, but on the ability of an algorithm to recognize hidden patterns, that is, to select groups that are similar in features.

The function applied to the kernel was the accuracy of the binary classification of the trained neural network obtained on the test dataset when this section of each 2D vector (256×256) was zeroed on the test dataset. Thus, we obtained the contribution of a particular area of a 2D vector (256×256) (frequency, temporal, and spatial domain patterns) to the accuracy of binary classification (data from participants with diagnosed COVID-19 history vs data from participants without such a diagnosis). The resulting vector was a 16×16 square.

Results

Using the two presented neural networks to classify EEG-data, we obtained the following results: binary ResNet18+2GRU classification accuracy reached 66 %, and DenseNet — 63 % on average. More details can be seen in Table 1. We see that the presented neural networks classifiers can, with an accuracy of more than 63 %, separate EEG-data after COVID-19 from data that did not meet the COVID-19 criteria.

Table 1. Statistical data of ResNet18+2GRU and DenseNet121 neural networks

Statistics	Model name	
	DenseNet121	ResNet18+2GRU
best train accuracy	0.99	0.76
best val accuracy	0.52	0.72
best train loss	0.0006	0.517
best val loss	2.231	0.567
Class 0 test accuracy*	0.641	0.656
Class 0 test loss*	2.2713	0.645
Class 1 test accuracy**	0.619	0.663
Class 1 test loss**	2.248	0.626

* Class 0 — subjects who have undergone COVID-19.
** Class 1 — subjects who haven’t has COVID-19.

Using pattern detection by Neural Networks perception through the nullifying kernel, we obtained a (16×16) vector, which can be seen in Figure 3. The obtained data demonstrate the “attention” of the neural network to specific patterns from the spatial, frequency, and temporal domains. We see a difference in perception ("attention") when assigning EEG-data to one of the classes: COVID-19 and non-COVID-19. This difference in perception suggests that a combination of patterns is essential for classification.

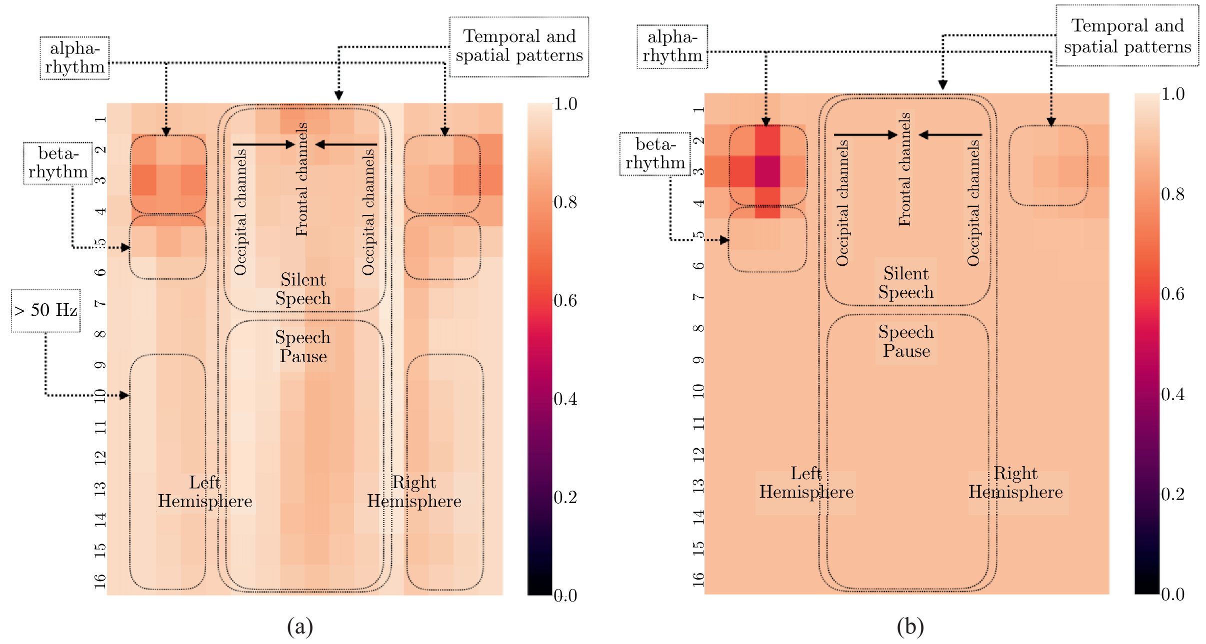


Figure 3. Patterns in time, space and frequency of healthy people and participants with diagnosed COVID-19 history: the darker the color, the higher the contribution of this pattern to the binary classification accuracy of the DenseNet121 (a) and of the ResNet18+2GRU network (b)

Representing the signals from 32 EEG-channels as a set of frequency and time domain features, we found a predominance of α-rhythm patterns in the left hemisphere in healthy people compared with people with COVID-19 history. We see a significant decrease in the contribution of the α-rhythm in the EEG-signal in both hemispheres in people who have undergone COVID-19.

Moreover, we observe a significant decrease in the contribution of the left hemisphere in the area of the speech center in people who have had COVID-19 when performing speech tasks. Usually, the loss of α-rhythm indicates brain overstrain during a task.

The data show that the signal in healthy people is more spatially localized and synchronized between the hemispheres when performing tasks than in people who have undergone COVID-19. There is no frequency synchronization of the hemispheres, and there is a decrease in low frequencies in the activity of both hemispheres in people who have had COVID-19.

We observe a significant increase in the contribution of high frequencies (> 50 Hz) to the EEG-signal in the right hemisphere in people who have had COVID-19.

Discussion

According to other studies, even after up to 10 months after COVID-19 resolution, cognitive impairment, detected by tests, and functional impairment, determined by EEG and MRI, are observed [Cecchetti et al., 2022]. Also, even six months after suffering COVID-19, 18F-FDG-PET/CT shows signs of hypometabolism and elevated levels of cytokines in the blood and cerebrospinal fluid [Kas et al., 2021]. This data supports the hypothesis of the severity of the long-term effects of COVID-19 and the results of our study.

A significant decrease in the α-rhythm in both hemispheres in people with COVID-19 history can be interpreted as signs of severe brain tension when solving simple tasks.

Healthy people have more spatially localized and synchronized signals between the hemispheres when performing simple tasks, while people who have had COVID-19 have no hemispheric synchronization and decreased low frequencies amplitudes. This pattern can renew the remaining data on hemispheric desynchronization and signs of demyelination.

A significant increase in the contribution of the right hemispheric high frequencies (> 50 Hz) in people who have had COVID-19 may indicate signs of premature brain aging [Voytek et al., 2015]. Thus, what is commonly considered noise in EEG-data carries information that can be used to determine if a person has had a COVID-19 or not.

In addition, we see that it is crucial to choose the optimal neural network to identify COVID consequences. The two networks presented focus differently on the temporal, spatial, and frequency patterns. Furthermore, the deeper neural network (DensNet121) can “isolate” more subtle patterns. However, at the same time (expectedly), it overfits faster, and for a given task and a given dataset, the size could be more optimal in terms of classification accuracy.

When presenting certain data with selected features, such as frequencies, the spatial organization of the signal, and task features, neural networks can focus on the selected features. We see that networks “look” at different features with different “attention”. This allows us to conclude the different frequency, time, and space range contributions. This indirectly indicates that changes in a certain frequency and spatial range characterize the post-COVID state.

Conclusion

In our work, we have shown the applicability of neural networks in helping to detect the long-term effects of COVID-19 on EEG-data. Furthermore, in accordance with other studies, our data supported the hypothesis of the severity of the long-term effects of COVID-19 detected on the EEG-data of EEG-based BCI.

We have demonstrated that EEG-patterns in the temporal, spatial, and frequency domains differ in people who did not meet the COVID-19 criteria and those who have undergone COVID-19.

These patterns can be interpreted as signs of hemispheric desynchronization, premature brain aging, and more brain stress when solving simple speech tasks compared to people who did not have COVID-19.

However, the overall accuracy of the data with the existing preprocessing can be increased further with additional data preprocessing, such as discrete wavelet-transform and extraction of specific features or brain waves, or by increasing the dataset size. Future studies using advanced preprocessing protocols could be of interest to further disentangle the relationships between post-COVID and brain functions in the context of brain–computer interaction.

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