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Changes in EEG Measures of a Recipient of the mRNA COVID-19 Vaccine – A Case Study *

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***Abstract:*— The current study is aimed to evaluate the effect of COVID-19 vaccine on human EEG and the persistence of the effect. Within a one-year-long resting EEG study period, the healthy male subject was administered two Comirnaty doses three weeks apart to prevent COVID-19. Fourteen recordings were acquired from the subject in one year: twelve reference and two post-vaccination recordings after administrating the second dose of Comirnaty. The changes in absolute powers of EEG frequency bands, EEG spectral asymmetry index (SASI), and Higuchi's fractal dimension (HFD) were analyzed. The results indicated a statistically significant increase in absolute gamma power, SASI and HFD values on the fifth day after the vaccination, while the EEG had restored its normal character on the twelfth day after vaccination. These measures seem to have higher sensitivity for the detection of the effects of the vaccine**

***Clinical Relevance* – This is the first study evaluating COVID-19 vaccine effect on healthy human EEG. The study indicated that the vaccine disturbs EEG, but the impact is not long-lasting.**

I. Introduction

COVID-19, caused by a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become a worldwide pandemic illness. In addition to respiratory system disorders, a significant part (36.4%) of COVID-19 patients had acute neurological expressions [1]. Acute neurological syndromes can be caused by a viral infection of the brain or by disease-related hypoxia and inflammation.

Today, the potential effects of COVID-19 on the central nervous system are put forward, but we do not have the information if and how COVID-19 vaccines affect the brain. Some studies have been conducted to analyze neurological complications by COVID-19 vaccines [2], [3]. However, the complications are rare and not always directly associated with vaccination. Still, to the best of our knowledge, the before-and-after study of the effects of COVID-19 vaccines on the healthy brain has not been performed.

Vaccines introduce antigens to our immune system, followed by our body's immune response that later helps to identify the pathogens when infected and counteract the invaders more effectively. COVID-19 vaccines have mild side effects similar to those seen with COVID-19, including neurological symptoms such as headaches and fatigue [1], [4], [5]. On the other hand, the brain can also be affected by stress caused by the vaccines' side effects. Stress can also affect the central nervous system and cause alterations in the brain's physiology.

Brain bioelectrical activity can be measured by electroencephalography (EEG) – a non-invasive and cost-effective method used to detect changes in brain function. Several EEG measures have shown changes during stressful situations. Studies using different tests of stress, theta and alpha band power indicated a decrease [6], [7], while in higher frequency rhythms, like beta and gamma, an increase was detected [7], [8]. The spectral asymmetry index (SASI), characterizing the balance between EEG higher and lower band powers, has been shown effective to detect the effect of different stressors: a physical stressor, microwave radiation [9], a chemical stressor, coffee intake [10], and occupational stress [8]. In addition, SASI distinguished between major depressive disorder and healthy groups [11], [12]. Still, not all information can be collected by linear methods; the nonlinear Higuchi's fractal dimension (HFD) describes the EEG signal's self-similarity and characterizes the signal's complexity. It has been shown that the complexity of the EEG signal raises in the case of depression and under stress conditions [8], [11].

Although the EEG measures can be considered as stable markers [13], [14], each EEG measure has a normal variability which is in turn individual [15] and usually unknown. We hypothesize that in the conditions of the impact by vaccine or increased stress due to the immunization, the EEG will be disturbed compared to the normal state. Thus, to evaluate the effects of a stressor, we need to know the subject's normal variability of the EEG measures of interest. The EEG and the sensitivity to vaccination are individual; therefore, a more detailed study on a single subject would provide clearer preliminary results on the effects of the vaccine.

The present study aims to investigate the effects of the COVID-19 vaccine on the central nervous system and the durability of the effect. For this purpose, the normal variability of the EEG measures, including spectral band power, SASI, and HFD, for a selected subject were evaluated over a year. The alterations in the measures after administration of Comirnaty (BioNTech Manufacturing GmbH) second dose were compared to the average levels of variability of the measures in normal conditions.

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II. METHODS

A. Subject

The EEG data were repeatedly recorded from a healthy right-handed 49(50)-year-old male. The subject had no history of mental disorders or head traumas. He was a nonsmoker, did not consume narcotic or psychotropic substances. The study was conducted following the Declaration of Helsinki and was formally approved by the Research Ethics Committee of the National Institute for Health Development. Participation in the study was voluntary and the subject signed written informed consent.

B. Comirnaty Administration and Side Effects

During the one-year-long study period, the subject got two Comirnaty injections three weeks apart. Comirnaty contains a molecule called messenger RNA (mRNA) with instructions for producing a spike protein from SARS-CoV-2, the virus that causes COVID-19. After the first Comirnaty injection, the side effects were limited to pain at the injection site and left upper limb where the injection was administered and lasted for a few days. After the second injection, the side effects were pain in the left upper limb, headache, muscle aches, tiredness, fever, and fogginess. Fogginess lasted for about a week, with other side effects resolved by the fourth day after vaccination.

C. Collection of EEG Data

Fourteen recordings were acquired from the subject in one year: twelve reference (r1-r12) and two post-vaccination recordings after the second Comirnaty administration (p1, p2). The intervals between recordings were usually four weeks, except for post-vaccination recordings (5 and 12 days after vaccination), which were deliberately shorter. The interval between the first dose of vaccine and the subsequent EEG recording was 19 days. Due to the extensive time interval, we treated the corresponding recording (r7) as a reference recording.

To minimize the impact of the environment and the impact of the subject's activities on the EEG data, we used a routine where all recordings were acquired on the same day of the week and at the same time (Wednesday 7:30). The subject was instructed to abstain from alcohol and simulating drinks (coffee, tea, energy drinks, etc.) 24 hours before recording. The subject came to the recording without eating or drinking (excluding water) to avoid the effect of different breakfasts on the EEG. After arriving at the research laboratory, the subject completed the health data form and mental health questionnaires before each recording. The EEG data were recorded using Neuroscan Synamps2 acquisition system and a 32 channel Quick-Cap (Compumedics, NC, USA) with a sampling rate of 1000 Hz. EEG electrodes were positioned according to the extended international 10/20 system with linked mastoids as reference. The subject was lying in a relaxed supine position in a dimly lit laboratory room during the recording procedure. Ten minutes of eyes-closed and five minutes of eyes-open EEG data were acquired in 30 channels and vertical and horizontal electrooculograms to monitor eye movements in two channels. The impedance of EEG electrodes was kept below ten kΩ to achieve good conductivity between the skin and the electrode.

D. EEG Data Preprocessing

The data were processed using MATLAB software (The Mathworks, Inc.). EEG data were re-referenced using the reference electrode standardization technique (REST) [16]. Previous studies have shown that the REST reference is suitable for low-density EEG montage and is a good reference technique for comparing the results across laboratories [17], [18]. Parks-McClellan low and high-pass forward-backward filters were applied to the EEG signals to remove baseline fluctuations and high-frequency noise; frequency bandwidth of 2 to 47 Hz remained for further processing. The first 3 minutes from each recording were used for the following processing and were divided into nine nonoverlapping 20.48-second long segments. According to [19], stress affects the brain's (pre)frontal region the most; therefore, channel Fz was chosen for further processing and analysis. Next, theta, alpha, beta, gamma frequency band powers, SASI, and HFD values were calculated for all nine segments and a median value over those segments was found.

E. Frequency Band Power

We decomposed EEG data into classical frequency bands, such as theta (4-8 Hz), alpha (8-12 Hz), beta (12-30 Hz), and gamma (30-47 Hz) frequency bands. Each frequency band was first obtained using high and low pass Parks-McClellan forward-backward filter. The bandwidth power P for the filtered signal S with the length N was calculated as in

$$P = \sum_{i=1}^{N} S(i)^2. \qquad (1)$$

F. Spectral Asymmetry Index

First, power spectrum density was estimated by means of Welch's averaged periodogram method (Hanning window with the length of 1024 samples, 50% overlap). Next, powers for predefined lower frequency band P_{low} (4 to 7 Hz) and higher P_{high} frequency band (14 to 38 Hz) were calculated as described in [11], [12] and SASI was calculated as in

$$SASI = \frac{P_{high} - P_{low}}{P_{high} + P_{low}}. \qquad (2)$$

G. Higuchi's Fractal Dimension

Fractal dimension is a very sensitive nonlinear method for finding information about the physiological signal. Fractal dimension estimate HFD is a fast method calculated in the time domain, which does not need long signal segments. HFD is based on a measure of length *(k)* of the curve that represents the considered time series while using a segment of k samples as a unit if $L(k)$ scales like $L(k) \sim k^{-FD}$. To calculate HFD, the EEG data were first downsampled to 200 Hz and the value of fractal dimension FD with a parameter k_{max}=8 was calculated according to the algorithm presented by Higuchi [20].

H. Statistics

We used two-sample t-test to control the hypothesis that EEG measures' values from post-vaccination recordings come from the same distribution as the reference recordings. The initial significance level was chosen $\alpha = 0.05$. As we had six different measures, we conducted statistical tests multiple times (6), therefore p-values were adjusted applying modified Bonferroni correction.

III. Results

The main results of this study are presented in Fig. 1 and Table I. Theta, alpha, beta, and gamma frequency band absolute powers, SASI, and HFD values for each recording in channel Fz are presented in Fig.1. The mean and standard deviation values over 12 reference recordings, i.e., regular variation, are presented in Table I and shown with straight and dashed lines, respectively, in Fig.1. There is more or less change in all frequency bands except beta in the first post-vaccine recording. The absolute power in the theta and alpha frequency band are somewhat lower after vaccination, being more noticeable in the alpha band. After vaccination, a statistically significant change can be seen in the gamma band power (Bonferroni corrected $p<0.0084$). SASI measure value also reveals a statistically significant change after vaccination being noticeably higher than in reference recordings (Bonferroni corrected $p<0.0125$). HFD also shows a statistically significant increase in complexity (Bonferroni corrected $p<0.01$). Five days after vaccination, there is a significant change in spectral power/ power asymmetry (gamma band, SASI) and in the signal complexity. However, it can be seen that a week later, on the twelfth day after vaccination, there is no longer any significant deviation in the bands' powers, asymmetry, or fractal dimension, and the values are again in the normal range.

IV. Discussion

Deviation of EEG measure values outside the usual range could characterize an effect of a prominent stressor. After the vaccination, the subject in this study experienced mild but still disturbing side effects from Comirnaty, such as fever, headache, and fogginess. Although fogginess had almost entirely resolved by day five, the changes in EEG measures

TABLE I. Subject's Usual EEG Measure values and values after Administrating Comirnaty (BioNTech Manufacturing GmbH) vaccine in Channel Fz

Measure	***Mean[a]***	***SD***	***5 days post-vac.***	***12 days post-vac.***
Theta power[b] (10^5)	3.03	0,86	1.63	3.79
Alpha power (10^6)	1.00	0.20	0.47	1.14
Beta power (10^5)	1.38	0.15	1.32	1.29
Gamma power (10^3)	7.32	0.75	10.81*	6.27
SASI	0.034	0.055	0.214*	0.041
HFD	1.194	0.027	1.288*	1.170

a. Mean and standard deviation are calculated over 12 EEG reference recordings, excluding post-vaccination recordings.

b. Power values are presented in μV^2.

* Statistically significant difference after applying modified Bonferroni correction

were still strongly evident. Therefore, the alterations in EEG were related rather to the effect of vaccine than to the stress related to side effects.

The subject had somewhat decreased theta and alpha rhythm powers, which is consistent with the results of [6], [7], where responses to acute stress had a similar effect. However, the difference was not statistically significant after Bonferroni correction. There was no change from the usual absolute power deviation in the beta band. Still, it is possible that if lower and higher frequency beta bands had been used separately, a significant change would have been revealed. The relative power of the gamma band is often used to assess stress [8], an increase in the absolute gamma power is also evident in this study. SASI, combining besides beta and theta, also a

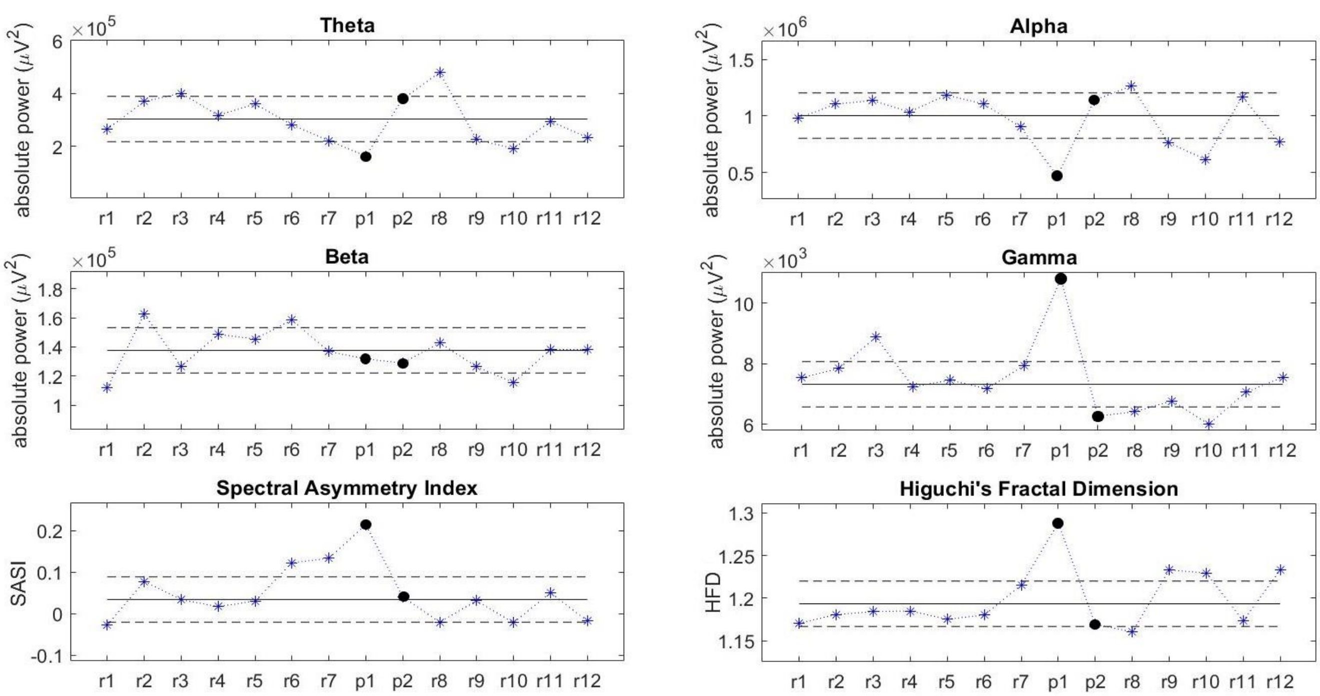

Figure 1. Results of the absolute powers of the EEG theta, alpha, beta, gamma frequency band, spectral asymmetry index, and Higuchi's fractal dimension during one year for one subject. Asterisks indicate reference recordings (r1-r12) that were acquired four weeks apart on regular basis. The dots (p1, p2) show the values on the fifth and twelfth days after vaccination with Comirnaty COVID-19 vaccine. Straight and dashed lines represent the mean and standard deviation values of the twelve reference recordings.

part of gamma band, noteworthy highlighted the increase in its value. In the previous studies, SASI has been shown to be able to highlight the effects of different stressors [8], [9], [10], [11], [12]. The current results are consistent with the results reported in the studies cited above. Therefore, vaccines might be considered a biological stressor to the central nervous system.

Twelve days after vaccination, all EEG measure values have returned to their normal range, indicating a temporary effect. Unfortunately, this study does not answer whether the impact on the EEG is directly due to the reaction caused by the vaccine or the discomfort caused by the symptoms.

The present study illustrates that EEG absolute gamma power, SASI, and HFD are the methods of sufficient sensitivity to detect the changes in brain physiology related to vaccination.

Although the study presents changes in only one person, those are consistent with the results of previous studies on stress and stressors. Thus, temporary abnormalities in EEG signals after vaccination may occur to a greater or lesser extent also in other persons.

V. Conclusion

The results of this preliminary study performed on a single subject indicated clearly that the COVID-19 vaccine caused a response in the brain detectable by the EEG measures. The statistically significant increases in the EEG absolute gamma power, spectral asymmetry index, and Higuchi’s fractal dimension illustrated the high sensitivity of these measures to detect the effects caused by the vaccine. The impact of the vaccine was short-term; by the twelfth day after the vaccination, the brain had restored normal activity and the EEG measures were back to their normal levels. Further investigation on larger numbers of subjects is needed to support the conclusions.

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