CASE STUDY

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Event-Related Potentials Studies of PTSD after infection of SARS-CoV-2 and NeuroCovid-19

Maria Pąchalska[1[A,B,C,D,E,F]], Natalia Nowaczyk[2[A,B,D,E,G]]

[1] Chair of Neuropsychology and Neurorehabilitation, Andrzej Frycz-Modrzewski Krakow University
[2] Institute of Psychology, Adam Mickiewicz Poznan University, Poznań, Poland

SUMMARY

Background: Coronavirus disease 19 (COVID-19) hospitalisation is a potentially traumatic experience, especially in severe cases. Furthermore, the unprecedented context of the SARS-CoV-2 pandemic, with the daily media bombardment about COVID-19 mortality, may have amplified its life-threatening perception also in patients with moderate infection. The purpose of our study was twofold: 1) to evaluate QEEG/ERPs shows of PTSD associated with severe infection SARS-CoV-2, and neuroCOVID-19, 2) to construct a neurofeedback protocol based on these indices to support the psychotherapy of the case study described herein.

Case study: Patient N.C. 49, a frontline healthcare worker in the emergency services (an ambulance driver), became ill with Covid-19 on November 14, 2020. Initially, he lost his sense of smell (anosmia), of taste (ageusia), and had latent blinks (heterophila), headaches, and dizziness. After 10 days of illness, the patient had additionally a dry cough and a shortness of breath and he was hospitalized, sedated and mechanically ventilated for 24 days. After a few months he was diagnosed with PTSD (according to the DSM-5 criteria) and referred to the Reintegration and Training Center of the Polish Neuropsychological Society for further diagnosis and treatment. It was found that the P3 GO and P3 NOGO waves were indeed less in his case ($p < 0.01$) when compared to the ERPs results of a health group of individuals of a similar age ($n = 100$), derived from the normative data bases of the Human Brain Index (HBI) in Switzerland. The ERPs wave pattern in our patient reflects the pattern appearing in patients with PTSD. The patient took part in 20 sessions of individually tailored anodal transcranial direct current stimulation (tDCS), with the excitatory stimulation of the left prefrontal cortex and inhibitory stimulation of the right prefrontal cortex which can reduce anxiety, as was proposed in the subject literature. Also, the neuromarker of PTSD obtained with the use of QEEG/ERPs was helpful in choosing the appropriate tDCS protocol. Neurostimulation with the use of tDCS was administered systematically, every day, 15-20 and 30-40 minutes for each session, for 20 days. He also received individual sessions of psychotherapy every day, 30-40 minutes for each session, for 20 day. After the treatment the patient improved and returned to his previous job as a frontline healthcare worker in the emergency services (an ambulance driver) in the fight against COVID-19.

Conclusions: Detection of the PTSD neuromarker enabled the development of a proper tDCS protocol and the conduct of effective brain neurostimulation of a patient with PTSD. The proposed protocol of treatment, in combination with goal-oriented individual psychotherapy, offered to the patient, was effective in the reduction of PTSD. ERPs can be useful in the diagnosis of PTSD as well as in selecting an appropriate therapy protocol for these patients.

Key words: traumatic event, stress, anxiety, working memory, cognitive control

INTRODUCTION

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causing coronavirus disease 19 (COVID-19), first appeared in December 2019 in the Chinese city of Wuhan, and has rapidly spread around the Word (Zhu et al 2021). This pandemic has adversely affected every aspect of people's lives ranging from the economic, social, and physical to mental health. Since then, knowledge of the effects of COVID-19 on the brain has accumulated rapidly, as reflected in the increasing use of the term "neuro-COVID" (Goldberg et al. 2020: Pąchalska et al. 2021). COVID-19 does not only affect the human brain in the short term. There are likely long-term and very long-term effects of the illness and their implications for cognition. One of the most serious consequences of neuroCOVID-19 is the development of post-traumatic stress disorder (PTSD) (Meli et al. 2019; Righty et al. 2019: Remuzzi & Remuzzi 2020; Qi et al. 2020; Wesemann et al. 2020).

PTSD is a severe but treatable mental disorder that develops after exposure to a life-threatening traumatic event. Clinical manifestations of PTSD include recurrent and intrusive memories, dreams or flashbacks of the trauma, avoidance of trauma-related cues, and a variety of mood and dissociative as well as cognitive symptoms (Tarsitani et al. 2021). In the long term, PTSD is related to alcohol and substance use, mood disorders, suicidality and physical health conditions such as hypertension, obesity and coronary heart disease (McFarlane 2010) The presence of clinically significant PTSD symptoms not fulfilling a full-threshold diagnosis (subthreshold or partial PTSD) has been also related to worse mental and physical health outcomes and a severe reduction in the quality of life (Bergman et al.2015). Importantly, PTSD can be effectively treated with pharmacological or psychological interventions (Bryant 2019).

The first criteria for a diagnosis of PTSD listed in the DSM-5 is **exposure to one or more traumatic event (s)**, which is defined as one that involved death or threatened death, actual or threatened serious injury, or actual or threatened sexual violence. Experiencing the event could be direct, but it does not have to be. And, the DSM-5 has established criteria to show what counts as a traumatic event. In order for a diagnosis to be made, the following criteria has to be met:

Criterion A (at least one symptom)

In order for a PTSD diagnosis to be made, the person has to have been exposed to death. This does not mean that they had to be near death. It means that they need to have been threatened with death or an injury that was serious enough that it could lead to death. This also includes sexual violence.

It is also important to establish that the person does not have to be the one that was in danger. While it could be that they were exposed directly, it could also be witnessing the trauma, finding out about a loved one that was exposed, or being exposed indirectly like those working as first responders.

Criterion B (at least one symptom)

Before someone can be diagnosed, they need to re-experience the event on an on-going basis. This does not mean that they need to be living through the same thing over and over again, but experiencing it through one of the following:

- Nightmares
- Flashbacks
- Involuntary memories
- Emotional distress after being reminded of the trauma
- A physical reaction after being reminded of the trauma

Criterion C (at least one symptom)

The person is displaying avoidance behaviors. This means that they are trying to avoid anything that reminds them of the trauma. This can be through physical reminders or things that make them think about the trauma.

Criterion D (at least two symptoms)

The person experiences negative thoughts and feelings because of the trauma. This can include feeling negative about the world or simply just about themselves, not caring about activities they used to enjoy, isolation, and difficulty in recalling details of the event. This also includes blaming themselves or someone else for the trauma on an exaggerated level.

Criterion E (at least two symptoms)

PTSD diagnosis requires at least two of the following symptoms:

- Increase aggression or irritability
- Hypervigilance (similar to paranoia)
- Participating in risky behavior
- Hard time concentrating
- Problems sleeping
- Increased startle response

Other Criteria

There are a few other criteria that must be present in order for someone to be diagnosed with PTSD. They include:

- Experiencing symptoms for at least one month
- Symptoms impact impairment or distress in normal life such as socially or at work

Subtypes

There are two subtypes that have been specified for PTSD. These are: the Preschool Subtype and the PTSD Dissociated Subtype.

The preschool subtype is for children that are under the age of six-years-old. The Dissociate Subtype is for people that also experience feelings of being detached from their own body or having experiences that make it seem as though the world were not real.

Coronavirus disease 19 (COVID-19) hospitalisation is a potentially traumatic experience, especially in severe cases (Kaseda, Levine 2020). Furthermore, the unprecedented context of the SARS-CoV-2 pandemic, with the daily media bombardment about COVID-19 mortality, may have amplified its life-threatening perception equally in patients with moderate infection. The study by Tarsitani et al. (2021) shows that PTSD and subthreshold PTSD rates in patients hospitalised for COVID-19 are worrying (Bo et al. 2020; Zhu et al. 2020). The female sex and pre-existing mental disorders are established risk factors for PTSD, while the prospective association with obesity needs further investigation (Tarsitani et al. 2021). Therefore clinicians treating COVID-19 should consider screening for PTSD at follow-up assessments in patients discharged from hospital (Zhu et al. 2020).

The purpose of our study was twofold: 1) to evaluate QEEG/ERPs shows of PTSD associated with a severe infection of SARS-CoV-2, and neuroCOVID-19, 2) to construct a neurofeedback protocol based on these indices to support psychotherapy of the case study described herein.

CASE STUDY

Patient N.C. 49, a frontline healthcare worker in the emergency services (an ambulance driver), became ill with Covid-19 on November 14, 2020. Initially, he lost his sense of smell (anosmia), of taste (ageusia), and had latent blinks (heterophila), headaches, and dizziness. After 10 days of illness, the patient had additionally a dry cough and shortness of breath and he was hospitalized, sedated and mechanically ventilated for 24 days. After returning home, the patient was very afraid that he would infect his beloved partner, especially since he had read in the internet that the coronavirus could be excreted in the urine for a month or more after infection. He experienced quite often negative thoughts and feelings about himself, not caring about activities he used to enjoy, isolation, and difficulty recalling details of the event. He was unable to sleep well and was experiencing frequent nightmares. Three months later, flashbacks, involuntary memories and emotional distress appeared after being reminded of the hospitalization period. A primary care physician suspected PTSD and referred him for psychiatric treatment. His health was not good and he could not return to work, therefore he lost economic stability. Despite this, he tried to deal with the symptoms on his own. However the symptoms did not go away and he also experienced chest pains, shortness of breath, and anxiety quite often. So he was referred to a cardiologist, but there were no changes in the EKG and he was given medication for sedation and referred to a neuropsychiatrist. He still refused to be treated psychiatrically and continued to try to cope with the disease himself. Six months later, when the third wave of the Pandemic began in Poland, in which his partner fell ill and died after a few weeks, the patient withdrew from all social contacts, including those with a close friend. When the symptoms grew up and he was no longer able to cope with anything in his daily life, a close friend, who was concerned about his health took him, despite protests, for a neuropsychiatric consultation. He was diagnosed with the use interview and PTSD Checklist for DSM-5 (PCL-5) according to Weathers et al. (2013). Neuropsychiatrist confirmed PTSD and referred to the Reintegration and Training Center of the Polish Neuropsychological Society for a further diagnosis and treatment.

During an interview conducted by a neuropsychologist, the patient complained about intrusive thoughts, anxiety, difficulty falling asleep, problems with concentration, loss of interest. The intrusive thoughts appeared in the patient's memories very often and almost always included the conversation that took place between him and his partner before she went to hospital. The memory was accompanied by a flashback, in which one scene prevailed - the view of the partner appearing in the background of the wall, there was an occasional figure with a face similar to that of the partner, but with a scythe in her hand. The patient presented this vision in the drawing (see Fig. 1). The patient also complained that suicidal thoughts were appearing more and more recently.

Neuropsychological testing

The neuropsychological examination with the WMS-III Word List Test PL[1] is illustrated in Fig. 2. In examination 1 conducted before neurotherapy, a significant decrease of the working memory as compared to the norm was found (total immediate recall = 13/48; long delay recal = 1/12).

It was also found that the patient also have attention problem (trial 5 after distraction with another list to recall the first list of words).

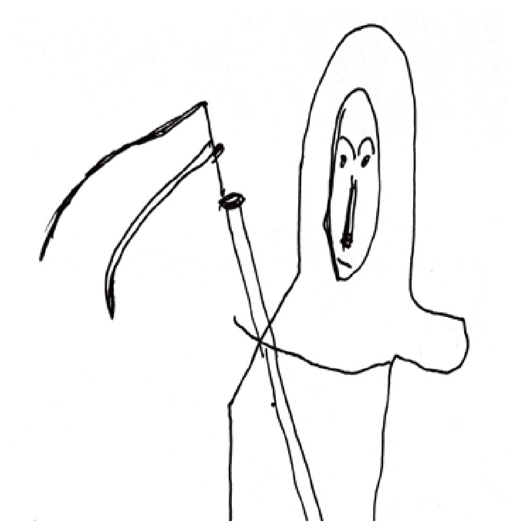

Fig. 1. Patient drawing showing the vision during the experienced flashback
Source: clinical material of M. Pąchalska

[1] Polish version of the Wechsler Memory Scale-III Word List Test (Pąchalska & Lipowska 2006)

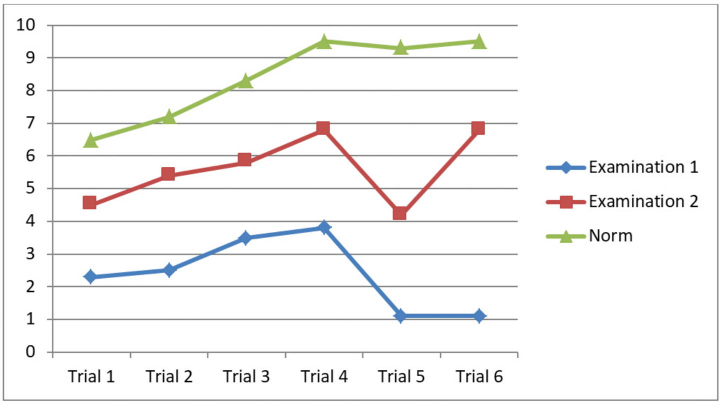

Fig. 2. WMS-III Word List Test before (Examination 1) and after (Examination 2)
Source: clinical material of M. Pąchalska

Neurophysiological testing

To confirm the diagnosis of PTSD made by the neuropsychiatrist, quantitative electroencephalography (qEEG), and event-related potentials (ERPs) were performed.

EEG recording

The electroencephalogram (EEG) was recorded with the Mitsar 21-channel EEG system, with a 19-channel electrode cap with tin electrodes that included Fz, Cz, Pz, Fp1/2, F3/4, F7/8, T3/4, T5/6, C3/4, P3/4, O1/2. The electro-cap was placed on the scalp according to the standard 10-20 system. Electrodes were referenced to linked earlobes (off-line), and the input signals were sampled at a rate of 250 Hz (bandpass 0.5–30 Hz). The ground electrode was on the forehead. Impedance was kept below 5 kΩ. The patient was sitting in a comfortable chair looking at a computer screen (17 inches) 1.5 meters in front of him. All recordings were conducted by the first author of this article. The ERP wave forms were averaged and computed off line, and trials with omission and commission errors were automatically excluded.

Behavioral task

The task consisted of 400 trials which were sequentially presented to the subject every three seconds. Three categories of visual stimuli were used: (1). 20 different images of animals – referred to later as A; (2). 20 different images of plants – P; (3). 20 different images of people of different professions (presented together with an artificial "novel" sound), referred to as H. The trials consisted of presentations of pairs of stimuli with inter-stimulus intervals of 1 s. The duration of stimuli presentation was 100 ms. We used four trial categories : A-A, A-P, P-P, and P-H. In the trials with A-A and P-P pairs, the first and the second stimuli were identical (physically the same). The trials were grouped into four sessions, with 100 trials in each. In each session, a unique set of five A stimuli, five P and five H stimuli was selected. Each session consisted of a pseudo-random presentation of 100 pairs of stimuli, with an equal probability for each category and each trial category (Kropotov 2016). The task was to press a button with the right hand to all the A-A pairs as fast as possible, and to stop pressing in response to other pairs. The patient performed 10 trials without recording to see if he understood the instruction. He rested for a few minutes after completing 100 trials. Stimuli occupied about 3.8° of the visual field around the center of the screen. Visual stimuli (and were selected to have) had similar 2D sizes and luminosities.

Artifact correction procedures

Eyeblink artifacts were corrected by zeroing the activation curves of individual independent components corresponding to eye blinks. These components were obtained by the application of Independent Component Analysis (ICA) to the raw EEG fragments as described in Kropotov (2016). Epochs with excessive amplitude of filtered EEG and/or excessive faster and/or slower frequency activity were automatically marked and excluded from further analysis. The exclusion thresholds were set as follows: (1). 100 μV for non-filtered EEG; (2). 50 μV for slow waves in the 0–1 Hz band; and (3). 35 μV for fast waves filtered in the band 20–35 Hz. In addition, we visually inspected the recordings and excluded the remaining artifacts.

EEG spectra

EEG spectra were computed for Eyes Open, Eyes Closed and the GO/NOGO task conditions separately. The artifact free fragments of EEG were divided into 4 sec epochs with a 50% overlap. The Hanning time window was applied. The EEG spectra were computed for each epoch and averaged. The mean value and standard deviations for each 0.25 Hz bin were computed. For comparison of the EEG spectra pre and before intervention, the t-test was used.

The aim of the research was to detect the PTSD neuromarker, that is the P3 component of cognitive control ERPs in the GO / NOGO task, to determine whether the potential values are lowered in our patient, as it is observed in people with PTSD (cf. Kropotov, Mueller, 2009; Johnson et al., 2013; Kropotov, 2016). The results obtained by the patient are presented in Fig. 3. It can be seen that the P3 GO and P3 NOGO waves were significantly smaller ($p < 0.01$) in comparison with the ERPs results of a group of healthy people of similar age ($n = 100$), derived from the normative database of the Human Brain Index in Switzerland (Human Brain Index, HBI). The ERPs wave patterns in the patient corresponds to those of patients with PTSD (see Johnson et al., 2013; Kropotov, 2016).

The patient took part in 20 sessions of individually tailored anodal transcranial direct current stimulation (tDCS), with the excitatory stimulation of the left prefrontal cortex and inhibitory stimulation of the right prefrontal cortex which can reduce anxiety, as it was proposed in the subject literature (Vicario et al. 2019). Also, the neuromarker of PTSD obtained with the use of QEEG/ERPs was helpful in choosing the appropriate tDCS protocol. Neurostimulation with the use of

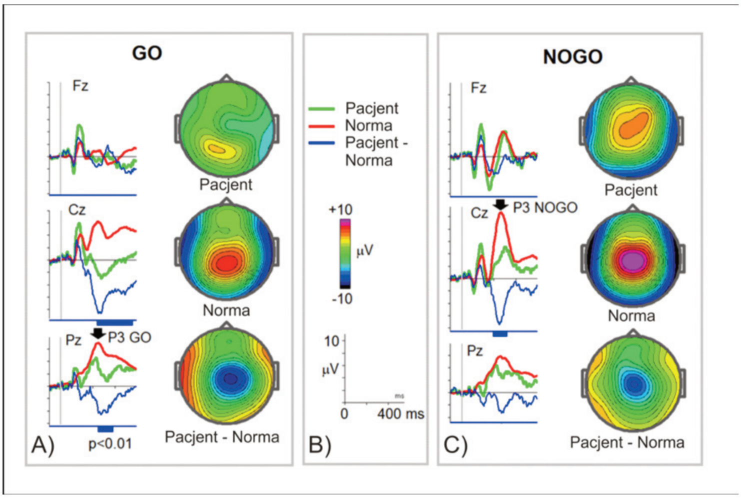

Fig. 3. ERPs in the GO / NOGO task in a patient compared with the ERPs of a group of healthy people (n = 100) from the Human Brain Index (HBI) normative database: A). on the left: ERPs recorded in points Fz, Cz and Pz in the GO samples of the patient (green lines) and the control group of healthy people from the HBI database (red lines) and the differences in ERPs (patient-norm; blue lines) with statistical significance markers (p <0.01) of the difference below the curves; right: maps of ERPs and ERPs differences with a delay corresponding to the P3 GO peak of healthy individuals recorded at Pz; B). scales and line indicators; C). left: ERPs recorded in points Fz, Cz and Pz during the patient's NOGO (green lines) and norm (red lines) and differences in the patient's ERPs compared to the norm (blue lines) with statistical significance (p <0.01) difference below the curves; right: maps of differences ERPs and ERPs with a delay corresponding to the P3 NOGO peak of the control group recorded at point Cz
Source: clinical material of M. Pąchalska

tDCS was administered systematically, every day, 15-20 and 30-40 minutes for each session, for 20 days. He also received individual sessions of psychotherapy every day, 30-40 minutes for each session, for 20 day (see: Pachalska 2008).

It was found that after the treatment in the examination 2 with the WMS-III WLT illustrated in Fig. 2., following neurotherapy, the patient's working memory (also after the distruction) had improved significantly in comparison to the norm (total immediate recall = 35/48; long delay recal = 7/12).

The patient returned to his previous job as a frontline healthcare worker in the emergency services (an ambulance driver) to fight against COVID-19.

DISCUSSION

The patient presented by us in this case study confirms the observations of other authors that the cause of PTSD may be a health condition that puts people at risk of death after infection with SARS-Cov-2, especially if the person is aware that the COVID-19 disease is severe (see: d'Ettorre et al 20021; Sarangi et al. 2021; Chen et al. 2021). The second important reason for the development of PTSD was the fact that the patient we studied was very afraid that he would infect his beloved partner, which could further aggravate his symptoms. Other authors also have similar observations: when patients are concerned about infecting others, especially their loved ones, or are being discriminated against, it leads to a higher possibility of distress (Park et al. 2020; Einvik 2021). Another important reason for the deterioration of the patient's health was the loss of his job and, consequently, economic stability. Economic stability, as it was found by other authors, is protective for excessive distress pertaining to COVID-19,as eqaully is retirement (Park et al. 2020; Lahav 2020). Socially supportive network tiers while maintaining social distance, living with families, and feeling connected contribute to a decreased incidence of COVID-19-related PTSD (Cai et al. 2020; Karatzias et al. 2020; Costantini & Mazzotti 2020). The place of work could also be important (he was a frontline healthcare worker in the emergency services). The importance of this factor is indicated by Rehman et al. (2021). These authors have discussed how the current pandemic has affected people infected with SARS-CoV-2 followed by COVID-19 in various ways depending on their socio-economic status and profession. For instance, a frontline healthcare worker is more fearful than those working from home, such as software engineers, and a person who is economically unstable and has to worry about the daily need of his / her family is more distressed than a person who is stable (Rehman et al. 2021).

People with PTSD are at amplified risk of suicidal ideation, attempts, and even death by suicide compared to the general population; however, they are less likely to seek help because of the fear of stigmatization, belief that symptoms will decrease gradually, and sometimes a lack of enough information about the disease itself (d'Ettorre et al. 2021). Since the whole world is suffering due to the pandemic, irrespective of being exposed to the virus, people might feel anxious about contracting the disease, falling sick, or even dying, leading to feelings of helplessness and PTSD (Sarangi et al. 2021), or even mental breakdown (Roy et al. 2020). Negative or sensational media reports and witnessing the severity of the disease in people all around the globe can stimulate the subconscious perception of threat and induce a subjective experience of fear in people (Chen et al. 2021). With a large number of confirmed cases and death from the coronavirus and its socio-economic consequences worldwide, this has been the most traumatic event compared to all the disease outbreaks of recent times (Marini et al. 2021).

How to help diagnose and treat patients with PTSD?

At the beginning of the 21st century, thanks to the revolution in neuroscience and the introduction of new neurotechnologies, it is possible to search for the PTSD neuromarker (Kropotov 2016). It is also possible to observe the work of the brain in milliseconds, allowing the assessment of neurocognitive and emotional dysfunctions (Pąchalska, Kaczmarek, Kropotov 2021). As a result of the neurodiagnosis, and therefore proper neurotherapy, the patient presented here has decreased P3 GO and P3 NOGO waves, which is associated with cognitive control dysfunction (Kropotov, 2016; Kropotov et al., 2011). Under these conditions, the so-called mnemonic blockade makes the patient unable to cope with intrusive memories that block other positive information. Thus, it is impossible to flexibly activate self-updating because of prospective memory. Thus, disturbances to minimal (working) self appear, are necessary for any proper adaptation. As a result, the patient withdraws from social contacts. These changes, in turn, lead to social isolation, as a result of which the phenomena of "social death" and "cultural death" crept into his life. As we know, significant changes in identity and personality lead to the impoverishment of the social and cultural mind and to the destabilization or even disintegration of the self-system (Pąchalska, Kaczmarek, Bednarek 2020). This situation happened to our patient. When explaining the essence of the problems our patient had to deal with, it should be noted that as a result of the coexistence of late symptoms of neuroCOVID-19 (see Aknin et al. 2021) and PTSD, a mosaic of comorbid and overlapping clinical symptoms could appear.

What does this case teach us?

We confirmed, once again, that the HBI methodology made it possible to detect PTSD neuromarkers (see; Kropotov 2016; Pachalska, Kaczmarek, Bednarek 2020; Pąchalska, Kaczmarek, Kropotov, 2021; Pachalska et al. 2021): this time in a patient who experienced PTSD following neuroCOVID-19. The detection of the PTSD neuromarker was possible thanks to the latest knowledge about the neuroanatomical basis of PTSD, especially regarding the flow of information in the affective system, as illustrated in Fig. 4. The anatomical nodes of the af-

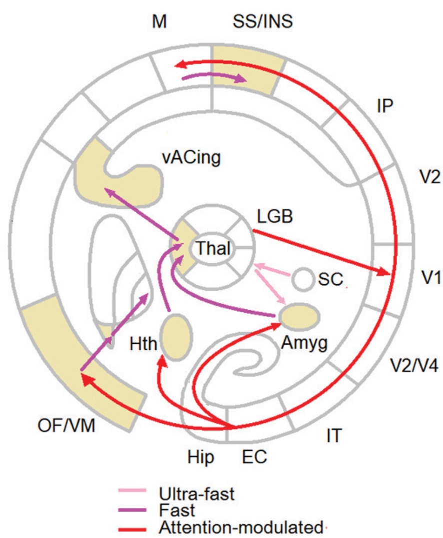

Fig. 4. The flow of information in the affective system. The anatomical nodes of this affective system are the Amygdala (Amyg), anterior hypothalamus (Hth), nucleus accumbens (NAc) and anterior thalamus nucleus, orbitofrontal cortex / prefrontal cortex (OF), ventral part of the anterior cingulate cortex (vACing), cortex islands (INS) and somatosensory cortical regions (SS). Arrows of different colors indicate the flow of information in the ultrafast path, the fast path and the path controlled by attention
Source: Pąchalska, Kaczmarek, Kropotov, 2021

fective system presented here are Amygdala (Amyg), anterior hypothalamus (Hth), nucleus accumbens (NAc) and anterior thalamic nucleus, orbitofrontal cortex / prefrontal cortex (OF), ventral part of the anterior cingulate cortex (vACing), cortex islands (INS) and somatosensory cortical regions (SS).

The persistent stressful situation after the death of a beloved partner additionally led to the strengthening of the patterns of neural network connections underlying anxiety, which intensified the symptoms of PTSD (see also: Trystuła, Zielińska, Półrola et al. 2015; Pąchalska, Kaczmarek and Kropotov 2021). This pattern of connections can be detected by comparing the network of connections observed in the examined patient with data from the normative HBI database (see Kropotov 2009, 2016). Also demonstrated, as noted in his major review, was the effectiveness of tDCS with the excitatory stimulation of the left prefrontal cortex in the reduction of anxiety (Vicario et al. 2019), and therefore PTSD (Kropotov 2016).

It should be stressed that thanks to the HBI methodology, proper diagnosis with the use of neuromarkers of PTSD, proper selection of the tDCS protocol, the patient improved after the treatment and returned to his previous job as a frontline healthcare worker in the emergency services (an ambulance driver) in the fight against COVID-19. The proposed form of diagnosis and therapy is worth considering when the world is struggling with the SARS-CoV-2 and NeuroCOVID-19 pandemic, which causes PTSD in many patients.

CONCLUSIONS

Detection of the PTSD neuromarker enabled the development of a proper tDCS protocol and the conduct of effective brain neurostimulation of a patient with PTSD. The proposed protocol of treatment, in combination with goal-oriented individual psychotherapy, offered to the patient, was effective in the reduction of PTSD. ERPs can be useful in the diagnosis of PTSD as well as in selecting an appropriate therapy protocol for these patients.

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Address for correspondence:
Maria Pąchalska
Chair of Neuropsychology and Neurorehabilitation
Andrzej Frycz Modrzewski Cracow University, Cracow, Poland
Herlinga-Grudzinskiego 1
30-705 Krakow
e-mail: neuropsychologia23@go2.pl