The aim of this study was to test the hypothesis of developing Post-Traumatic Stress Disorder (PTSD) in a major right-hemisphere ischemic brain stroke survivor half a year after CEA revascularization, with the use of Event Related Potentials (ERPs). He was in a serious condition and had limited consciousness. Therefore, the doctor informed the patient’s wife about the possibility of sudden death. The patient heard this information and remembered it, which was one of the main causes of the development of PTSD. On the basis of previous research amplitudes of P3 ERP, components elicited in the cued GO/NOGO tasks have been chosen as the candidate for PTSD neuromarkers.

A 44-year-old patient had a major ischemic brain stroke while sizeable atherosclerotic plaque causing critical stenosis of the internal carotid artery in Angio-CT was discovered. The patient was urgently operated on using CEA. After the operation he had the opportunity to see the removed plaque which had been the cause of his stroke. Despite the positive postoperative recovery, half a year later, the patient began to complain of flashbacks, anxiety, trouble in falling and staying asleep, difficulty in concentration, a loss of interest. For the diagnosis of PTSD we used Checklist Specific for a stressor (PCL-S). Additionally we used Checklist according to the Diagnostic Statistical Manual-5 (DSM-5) classification, and the patient met the PTSD criteria. The cognitive profile of the patient was measured with the use of the Wechsler Memory Test – III (WMS-III). Subsequently, the patient participated in the cued GO/NOGO task (Kropotov, 2009) with a recording 19-channel EEG. The P3 GO and NOGO waves in this task were found to be significantly smaller at p<0.01 in comparison to a group of healthy control subjects of the same age (N=23) taken from the Human Brain Institute (HBI) normative database (https://www.hbimed.com/). The pattern of this neuromarker in our patient corresponds to the ERPs pattern found in PTSD patients.

The ERPs in a GO/NOGO task can be used in the assessment of the functional brain changes induced by chronic PTSD.

Key words: Event-Related Potentials (ERPs), cued GO/NOGO task, information processing, functional neuromarkers
INTRODUCTION

Strokes constitute the third leading cause of death in the United States (Goldfinger, Edmondson, Kronish et al. 2013) and the leading cause of long-term disability (Roger, Go, Lloyd-Jones et al. 2012) mainly caused by motor, neurocognitive and/or psychological disorders. The psychological consequences of a stroke include mainly depression in 29-33% (Hackett, Yapa Parag et al. 2005), anxiety in 36-71% (Pachalska 2014), but PTSD may also occur (Merriman, Norman, Barton 2007).

PTSD, in accordance with the DSM-5 classification (see: American Psychiatric Association, 2013) is considered to be a form of anxiety disorder connected with the short- or long-term exposure to a traumatic event which possesses features that are exclusively threatening or that are catastrophic in nature, ones that exceed the limits of human endurance. Traumatic events of this magnitude are considered to be:

- participation in front-line fighting;
- being the victim/or witness of bombardment, torture in concentration camps, and finally acts of terrorism [so-called man-made disorders];
- being the victim and/or witness of a transport catastrophe,
- being the victim and/or witness of flooding, particularly when personal loss is involved
- a tragic accident in which someone closed has died
- being the victim of rape, sexual harassment, or an attack with violence.

It is known that PTSD occurs after exposure to combat or other life threatening events, (Polusny, Erbes, Murdoch 2011), but can also develop as a result of a life-threatening health condition putting the patient in danger of death (especially if he/she is aware of this fact). This conditions as varied as TBI (Półrola, Kaczmarek, Góral-Półrola et al. 2016), acute coronary syndromes (Edmondson, Rieckmann, Shaffer et al. 2011; Edmondson, Richardson, Falzon et al. 2013) and ischemic strokes (Merriman, Norman, Barton 2007; Bruggimann, Annoni, Staub et al. 2006; Field, Norman, Barton 2008; Wang, Chung, Hyland et al. 2011).

A review of the Medline databases for the period of twenty years (1998-2018) show the absence of any description of the impact of a major ischemic stroke operated on by means of the CEA method on the development of PTSD; therefore, the correlates and causes have not been well described (Goldfinger, Edmondson, Kronish et al. 2013).

One of the most effective ways to diagnose the presence of PTSD and to help in the administration of appropriate rehabilitation, and therefore to improve the patient’s quality of life is the implementation of new neurotechnologies, e.g., Event Related Potentials (ERPs) (Chrapusta, Kropotov & Pachalska, 2017).

The aim of this study was to test the hypothesis of developing Post-Traumatic Stress Disorder (PTSD), as a result of a life-threatening health condition which puts the patient in danger of death, after a major right-hemisphere ischemic brain stroke half a year after CEA revascularization, with the use of Event Related Po-
tentials (ERPs). On the basis of the previous research amplitudes of P3 ERP, the components elicited in the cued GO/NOGO tasks have been chosen as candidate for being PTSD neuromarkers.

CASE STUDY

A 44-year-old patient had a major right-hemisphere ischemic brain stroke caused by critical carotid artery stenosis, confirmed by a Doppler Ultrasound Exam and MRI examination. He was in a serious condition and had limited consciousness. Therefore, the doctor informed the patient’s wife about the possibility of sudden death. The patient heard this information and remembered it, which was one of the main causes of the development of PTSD.

Two weeks later he was qualified for the CEA revascularization method in accordance with the International Guidelines of the European Society of Cardiology in cooperation with the European Vascular Surgery Society 2017 (Aboyans, Ricco, Bartelink, 2017) and repeatedly operated on at the Department of Vascular Surgery and Endovascular Procedures of the John Paul II Hospital in Krakow using CEA methodology.

The operation was performed in a new operating theatre with a hybrid room at the John Paul II Hospital, Kraków, and involved the application of modern endovascular equipment (see: Fig. 1).

This is a high volume centre with a large number of patients classified for vascular operations, including revascularisation in the case of a major stroke (Pieniazek, Musialek, Kablak-Ziembicka et al 2008).

Fig. 1. The new operating theatre with hybrid room at the John Paul II Hospital in Cracow
Source: photo M. Trystula
The patient underwent endarterectomy of the right internal carotid artery (Carotid Artery Endarterectomy, CEA) under general anaesthesia with the use of brain protection (a shunt). The treatment lasted 1.5 hours, without intra- and postoperative complications. Awoken without a problem. The successive stages of the revascularization procedure of the right internal carotid artery are shown in Fig. 2 A, B, C, D.

The sizeable atherosclerotic plaque which had been the cause of the stroke was removed and the patient had the opportunity to see it after surgery (see: Fig. 3).

Fig. 2. Right the internal carotid artery after opening: A - visible the atherosclerotic plaque in the bottom; B – the state following shunt introduction; C – the state after the removal of the atherosclerotic plaque; D – the state after the reconstruction of the internal, external and common carotid artery wall

Fig. 3. Atherosclerotic plaque, removed during the CEA from the right carotid internal artery, which had caused the stroke
Source: own material
On the 4th day after the operation, following neuropsychological testing, the patient was discharged from the hospital in a good state both as a whole and localised. The neck wound was healing extremely well. The stitches were removed on the 16th day after the operation. The rehabilitation lasted 3 months lasting from 2 to 5 hours daily. Despite the severity of the illness and operation no major complications (second stroke / heart attack / death) appeared, and he recovered. However, half a year later, he returned to the unit, and complained of flashbacks of conversation held in his presence between the doctor and the patient’s wife with a concomitant vision of death manifesting itself as a person dressed in white and hold a scythe. The flashback was accompanied by panic fear. The patient presented it in picture form (see Fig. 4).

Additionally he complained of other symptoms, especially anxiety, trouble in falling or staying asleep, difficulty in concentration, a loss of interest.

**Ethics statement**

The patient was informed in detail about the whole procedure and provided written consent for his participation in the experiment (according to the guidelines of the Helsinki Declaration, 2008). The study protocols received ethical approval from the Ethical Committee of the Regional Medical Chamber (KB6/16).

**Neuropsychological examination**

The neuropsychological examination included the PTSD Checklist Specific for a stressor (PCL-S), in which the patient was asked to report on whether he had each of the symptoms of PTSD, as a result of his stroke or of the whole treatment procedure (Weathers, Litz, Herman et al. 1993). The PCL-S is a validated 17-item scale that corresponds to the DSM-IV criteria for PTSD, with high internal consistency and test-retest reliability (Kelley, Weathers, McDevitt-Murphy et al. 2009; Conybeare, Behar, Solomon et al. 2012). In the analysis of the results

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*Fig. 4. A drawing of the flashback*
*Source: own material*
we used the more specific cutoff of 50, which was recommended by the authors of the scale and corresponds to a sensitivity of 0.60 to 0.78 and a specificity of 0.86 to 0.99 in relation to a clinical diagnosis of PTSD (Andrykowski, Cordova, Studts, et al. 1998). Analysis of the results showed that the patient scored 64 points, which means the occurrence of PTSD (a PCL-S score of greater than 50 points). Additionally we used the Checklist according to the Diagnostic Statistical Manual-5 (DSM-5) classification and the patient met the PTSD criteria.

The cognitive profile of the patient was measured with the use of the Wechsler Memory Test – III (WMS-III). In Test 1 (four days after the CEA) disturbances of selectivity and attention concentration, the dynamics of working memory and logical and verbal memory were observed both in the testing immediately after the presentation of material for learning as well as after a 30-minute delay. This means that the patient was unable to learn new material. In addition, there were noted marked disturbances in the executive functions.

Table 1. The results of neuropsychological testing in Test 1 (four days after the CEA) and Test 2 (half a year after the CEA)

<table>
<thead>
<tr>
<th>Method</th>
<th>Test 1</th>
<th>Test 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>WAIS-R</td>
<td></td>
<td></td>
</tr>
<tr>
<td>l.l. – total</td>
<td>93/100</td>
<td>execution interrupted</td>
</tr>
<tr>
<td>l.l. – verbal</td>
<td>88/100</td>
<td>execution interrupted</td>
</tr>
<tr>
<td>l.l. – non-verbal</td>
<td>77/100</td>
<td>execution interrupted</td>
</tr>
<tr>
<td>WMS – III</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtest of attention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WMS-III spatial subtest</td>
<td>12 (75th%)</td>
<td>execution interrupted</td>
</tr>
<tr>
<td>sight-spatial tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WAIS-III building blocks subtest</td>
<td>8 (25th%)</td>
<td>execution interrupted</td>
</tr>
<tr>
<td>Logical memory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WMS-III logical memory (direct)</td>
<td>11/24</td>
<td>execution interrupted</td>
</tr>
<tr>
<td>WMS-III logical memory (with a 30-minute delay)</td>
<td>8/24</td>
<td>execution interrupted</td>
</tr>
<tr>
<td>Verbal memory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVLT reconstruction after a short break</td>
<td>2/9 (&lt;1st%)</td>
<td>0/9 (&lt;1st%)</td>
</tr>
<tr>
<td>CVLT reconstruction after a long break</td>
<td>2/9 (&lt;1st%)</td>
<td>execution interrupted</td>
</tr>
<tr>
<td>CVLT reconstruction after a long break with a clue/prompt</td>
<td>2/9 (&lt;1st%)</td>
<td>execution interrupted</td>
</tr>
<tr>
<td>EXECUTIVE FUNCTIONS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trail Marking Test (TMT)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>number sequences</td>
<td>150 seq. (&lt;1st%)</td>
<td>execution interrupted</td>
</tr>
<tr>
<td>number and letter sequences</td>
<td>150 seq. (&lt;1st%)</td>
<td>execution interrupted</td>
</tr>
<tr>
<td>Wisconsin Card Sorting Test [WCST]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Categories</td>
<td>2 (&gt;16th%)</td>
<td>execution interrupted</td>
</tr>
<tr>
<td>perseveration errors</td>
<td>19 (37th%)</td>
<td>execution interrupted</td>
</tr>
<tr>
<td>errors in classification</td>
<td>63 (&lt;19th%)</td>
<td>execution interrupted</td>
</tr>
<tr>
<td>errors in the transfer to particular categories</td>
<td>execution interrupted</td>
<td>execution interrupted</td>
</tr>
</tbody>
</table>

*TMT- Trail Marking Test

Level of execution (in seq.) corresponds with the percentiles:
98-99% – very high,
91-97% – high,
75-90% – averagely high,
25-74% – average,
9-24% – low average,
3-8% – on the border with low,
2% and lower – weak.
Of special note are the results obtained in Test 2 (half a year after CEA), which in the neuropsychological tests not only failed to improve but in point of fact deteriorated significantly. The patient in practice was unable to perform any test task for almost the entirety of the tested neuropsychological parameters. This fact meant that cognitive control underwent a marked deterioration.

**Neurophysiological examination**

The patient participated in the cued GO/NOGO task (Kropotov 2009). The EEG was recorded using a 19-channel electroencephalographic PC-controlled system, the “Mitsar-201” (CE 0537) manufactured by Mitsar Co., Ltd., according to the 10-20 system. Electrodes were applied using caps manufactured by Electro-Cap International, Inc. Referential electrodes were linked to both ears, allowing for the computational re-referencing of the data (re-montaging). The EEG computationally was re-referenced to the common average montage. The tin recessed electrodes were attached to the scalp using ECI ELECTRO-GE. Quantitative data were obtained using WinEEG software (Kropotov & Ponomarev 2009).

**Event related potentials (ERPs) study**

**Cued GO/NOGO task**

To test the brain correlates of the cognitive control a specific variant of the cued GO/NOGO task was used (Kropotov & Ponomarev, 2009; Kropotov, Ponomarev, Hollup et al., 2011). In this task, images of animal (a) and plant (p) categories served as the relevant stimuli. The trials consisted of the presentations of paired stimuli s1-s2 with inter-stimulus intervals of 1000 ms and inter-trial intervals of 3000 ms. Four categories of trials were used: a-a, a-p, p-p and p-h+novel sound, where h is an image of a human. The duration of the stimuli was 100 ms. The patient’s task was to respond by pressing a button with the right hand to a-a trials (GO trials) and to withhold from responding in a-p trials (NOGO trials).

The pictures were selected in such a way that the overall luminance and the image sizes of the animals and plants were approximately equal. To avoid any habituation to the repeating stimuli, 20 different images of animals, plants and humans were randomly presented in various combinations. To maintain a certain level of alertness, novel sounds were occasionally presented simultaneously with the images of a human in ignore trials. They produced an orientation reaction, confirmed by the elicitation of the P3 novelty ERP wave.

The trials were grouped into four blocks of one hundred trials each. In each block a unique set of five a, five p, and five h stimuli were selected. Each block consisted of a pseudo-random presentation (requiring an equal number of trials in four categories) of 400 trials with 100 trials within each trial category. The patient practiced the task before the recording started. He sat upright in a comfortable chair looking at a computer screen. Stimuli were presented on 17-inch CRT computer screens which were positioned 1.5 meters in front of the patient and occupied 3.8° of the visual field. He rested for a few minutes after each 200 trials.
Data recording

The patient responses were recorded in a separate channel. The average for response latency as well as its standard deviation were calculated. Omission errors (failure to respond in GO trials) and commission errors (failure to suppress a response to NOGO trials) were also computed. The EEG was bandpass-filtered between 0.3 and 50 Hz, and digitized at a rate of 250 samples per second per channel (see: Kropotov 2009).

Artifact correction

Eye blink 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 (see: Vigário, 1997; Jung, Makeig, Humphries 2000). A comparison of the method applied in our study with an EOG regression technique is described in Tereshchenko, Ponomarev, Kropotov, & Muller (2009). In addition, epochs with an 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 follow: (1) 100 µV for non-filtered EEG; (2) 50 µV for slow waves in 0-1 Hz band; and (3) 35 µV for fast waves filtered in the band 20-35 Hz (see: Kropotov 2016).

RESULTS

Behavioural data

The parameters of the patient performance in the cued GO/NOGO task in comparison to the normative data are presented in Table 2. The normative data have been obtained from a group of healthy subjects (N=23) selected from the Human Brain Index (HBI) normative database (see description of the database in Kropotov, 2009, 2016). Note the statistically significant (p<0.01) increase of reaction time while the other parameters do not deviate from the normative data.

ERPs

Figure 5 depicts ERPs in the cued GO/NOGO task in the patient in comparison to the grand averaged ERP for the group of healthy control subjects [(HC) (N=23)]. It was found that P3 GO and P3 NOGO waves in this task were significantly smaller at p<0.01 in our patient in comparison to a group of healthy control subjects of the corresponding age taken from the HBI normative database. This

<table>
<thead>
<tr>
<th>Data</th>
<th>Omission errors</th>
<th>Commission errors</th>
<th>Reaction time (RT)</th>
<th>Standard deviation of RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>4</td>
<td>0</td>
<td>559</td>
<td>119</td>
</tr>
<tr>
<td>Norm</td>
<td>2.5</td>
<td>0.7</td>
<td>377</td>
<td>78</td>
</tr>
<tr>
<td>p-value</td>
<td>0.63</td>
<td>0.52</td>
<td>0.01</td>
<td>0.08</td>
</tr>
</tbody>
</table>
observed pattern of ERP waves in the patient corresponds to the ERP pattern found in PTSD patients (see also Kropotov 2016). At the same time, the maps of the P3 waves show the P3 NOGO – anteriorization as a neurophysiological standard-index for the cognitive response control to be quite similar to that found in healthy controls.

**DISCUSSION**

The patient after the major right-hemisphere ischemic brain stroke described here, developed half a year after a successful CEA revascularization, PTSD with flashback. He was in a serious condition and had limited consciousness. Therefore, the doctor informed the patient’s wife about the possibility of sudden death. The patient heard this information and remembered it, which was one of the main causes of the development of PTSD.

In neuropsychological testing we found disturbances in the selectivity and concentration of attention, the dynamics of working memory and logical and verbal memory which was reflected by the fact that he was unable to learn new material (see also: Misterska and Głowacki 2013).
In this study we tested the hypothesis as to whether the P3 components of cognitive control in the cued GO/NOGO task are impaired in our patient. The dysfunction of cognitive control is reflected in a decrease of P3-like ERP components in PTSD patients (for a review see: Johnson, Allana, Medlin et al., 2013). The cued GO/NOGO task is designed specifically to measure the P3 - like components of cognitive control (Kropotov & Ponomarev, 2009; Kropotov, Ponomarev, Hollup et al., 2011, Kropotov, 2016).

The patient performed well in the cued GO/NOGO task while 19-channel EEG. He was attentive as much as he could be. However, his reaction time was shown to be statistically longer in comparison to a group of healthy control subjects of the same age (N=23) taken from the HBI database. Omission and commission errors were similar to those found in the healthy control subjects, indicating no behavioral correlates of impaired cognitive control.

However, a different pattern was found in his ERP measures extracted from the EEG. In particular, the P3 GO and NOGO were found to be significantly smaller at p<0.01 than in the group of healthy controls from the HBI database. A similar pattern were also found by other authors in different PTSD patients (see also: Araki, Kasai, Yamasue et al 2005; Kropotov 2009; 2016). Our finding supports the initial hypothesis of the presence of PTSD in the patient.

The case study of the patient presented herein is unique in nature in terms of the multidiscipline diagnosis and treatment employed. The application of CEA revascularization after a stroke and the ERP measures of PTSD after this operation is applied in a pioneering fashion in the world. It support the observations of other authors that an extensive ischemic stroke and its consequences, as well as the removal of the sclerotic plaque which was the cause of the stroke, as well as the operation itself may be the main reason for the development of PTSD.

The time that elapsed from the stroke itself through transportation to the hospital, waiting for confirmation of acceptance to the neurological ward, neurological treatment, the transferring to the vascular surgery ward, preparing for the operation and finally awakening after the operation(s) itself all additionally increase the stress. The days following a stroke to the operation itself, a period perceived as relatively short for the surgeon, is for the patient an incomparably longer period of stress and uncertainty. Similarly, the several days of the post-operation period, when there is still no guarantee of procedural success without major complications (myocardial infarction / postoperative stroke / death). As a result the patient may also develop PTSD (Trystuła 2018).

Particularly dangerous for the development of PTSD following an ischemic stroke may be the fact that the patient heard, at some stage of the treatment, from someone in a white coat that the prognosis is bad, even with the possibility of death (Pąchalska & Grochmal-Bach 2003). The major ischemic stroke in our patient was additionally influenced by shocking information about the possibility of his sudden death. The strong impact of this event is supported by the fact that it occurred in recurring, intrusive violent thoughts (flashback). In this case, a mnemo-
nomic interlock (Williams, Barnhofer, Crane et al. 2007) may occur, which will cause uncontrolled flashback, which is just an axial symptom of PTSD.

Patients with PTSD show dysfunction of cognitive control (Vasterling, Brailey, Constans et al., 1998; Koso & Hansen, 2006; Leskin & White, 2007) and if a mnemonic interlock occurs, in this situation the patient cannot cope with this problem with negative memory recurrence blocking other positive information. This situation happened to our patient. In such a case it is essential to help the patients with proper diagnosis and treatment.

The study shows that the ERP measures in the cued GO/NOGO task could serve as reliable functional neuromarkers for detecting cognitive control dysfunction, and therefore to help in the diagnosis of PTSD, as well as focusing on further treatment. It should be mentioned that the patient was referred for rehabilitation to the Rehabilitation Center, especially for neurofeedback (cognitive protocol). The whole complex procedure described here improved - in the patient opinion - his quality of life, which is finally a long-term index of treatment well-understood.

CONCLUSIONS

The ERPs in a GO/NOGO task can be used in the assessment of the functional brain changes induced by chronic PTSD.

REFERENCES


Trystula et al., Neuromarkers of PTSD


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