CASE STUDY

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EVALUATION OF NEUROTHERAPY PROGRAM FOR A PATIENT WITH CLINICAL SYMPTOMS OF SCHIZOPHRENIA AND SEVERE TBI USING EVENT-RELATED POTENTIALS

Maria Pachalska[1,2(A,B,D,E,F)], Marina V. Pronina[3(A,B,D)], Grzegorz Mańko[4(A,B,D,E)], Marzena Chantsoulis[5(A,B,D,E)], Andrzej Mirski[1(A,B,D,E)], Bożydar Kaczmarek[6(A,B,D,E,F)], Maria Łuckoś[7(A,B,E)], Juri D. Kropotov[3,8(A,B,C,D,E,F)]

[1] Department of Neuropsychology, Andrzej Frycz Modrzewski Krakow University, Krakow, Poland
[2] Center for Cognition and Communication, New York, N.Y., USA
[3] Laboratory for the Neurobiology of Action Programming, Institute of the Human Brain, Russian Academy of Sciences, St. Petersburg, Russia
[4] Department of Ergonomy and Physical Exertion Physiology, Institute of Physiotherapy, Faculty of Health Sciences, Jagiellonian University, Collegium Medicum, Krakow, Poland
[5] Faculty of Physiotherapy, Academy of Physical Education, Wrocław, Poland
[6] University of Economics and Innovation in Lublin, Poland
[7] Reintegrative-Training Centre of the Polish Society of Neuropsychology, Cracow, Poland
[8] Institute of Psychology, Norwegian University for Science and Technology, Trondheim, Norway

SUMMARY

Background: *Despite recent interest in the brain/mind problem and the possible organic correlates of mental disease, relatively few case studies have examined the problem concretely. This article examines the effectiveness of neurotherapy for a 68-year-old male schizophrenic patient whose psychotic symptoms displayed qualitative and quantitative changes after a closed-head injury. We hypothesized that there would be good response to relative beta training applied to regulate the dynamics of brain function.*

Case description: *The patient was diagnosed with schizophrenia in the early 1960s and frequently thereafter hospitalized. Visual hallucinations were the dominant symptom, and art therapy provided some relief, which led to a successful artistic career. In 1989, while actively hallucinating, he suffered a mild TBI in a pedestrian accident. Four years later, he presented with perseveration, hemispatial neglect, and disturbances of working memory. The patient took part in 20 sessions of relative beta training combined with behavioral training. We used standardized neuropsychological testing and ERPs before and after the completion of the program. As hypothesized, there was marked improvement of neurophysiological, neuropsychological, and psychiatric symptoms, as well as executive dysfunction and behavioral disorders. He also began to paint in a completely different style.*

Conclusions: *The case described here shows that the pathomechanisms of schizophrenia and neurobehavioral disturbances resulting from organic brain damage are not unrelated. Microgenetic theory can provide a basis for explaining the course of symptoms in this and similar cases. Relative beta training produced behavioral changes and small physiological changes. ERPs can be used to assess functional brain changes induced by neurotherapeutic programs.*

Key words: *hallucinations, perseveration, neuropsychological rehabilitation, art therapy, traumatic brain injury, ERPs*

INTRODUCTION

Traditional therapies for functional brain recovery in clinically very complicated cases involving schizophrenic patients with a severe traumatic brain injury do not give satisfactory outcomes (Pachalska et al., 2004; Nikolaenko, 2003). The best approach seems to be intensive physical and cognitive therapy (Pąchalska 1999); however, the results are limited and functional gains are often minimal (McAllister 1998; Pachalska et al. 2014). Therefore, supplementary interventions that can augment the response of the brain to the behavioral and cognitive training might be useful to enhance therapy-induced recovery. In this context, neurofeedback self-regulation and noninvasive brain stimulation appear to be options as additional interventions to supplement standard physical therapies (Kaczmarek, 1991; Pachalska, 2007; Pachalska et al., 2011).

CASE DESCRIPTION

The patient to be described here, WW, is a right-handed male, monolingual native speaker of Polish, born in Cracow in 1940. He is single, never married, currently unemployed, on a disability pension, which he supplements by selling his paintings at exhibitions. His father died in the Auschwitz concentration camp at the beginning of the Nazi occupation, and his mother, unable to raise her six children alone, gave her son up to an orphanage. After the war, WW was raised in a series of foster homes and orphanages. He finished vocational school and worked on the railroad. Unfortunately, he fell in with bad company, began to drink, and had several minor scrapes with the law. In 1961, he was accused of a murder he did not commit, and was incarcerated for 6 months until the real murderer was arrested. After this incident WW was arrested several times, and sentenced for short prison terms. He had his first visual hallucination while serving a prison sentence. At that time he began to keep notebooks with extensive verbal descriptions of the visions, sometimes with sketches and drawings, many of which he realized later as paintings.

After being released from prison he spent more time in mental hospitals than at home. It was in the hospital's art therapy workshops, in 1976, that he was able to begin developing his artistic abilities, and became a very prolific painter, winning increasing recognition.

He has been treated pharmacologically with various psychotropic drugs since 1971, and has received psychiatric rehabilitation with kinesitherapy, psychotherapy, sociotherapy, and art therapy. Most of his painting has been done in the graphic arts workshop of the outpatient department at a psychiatric hospital in Cracow, Poland, where he has been treated, recently under the supervision of the first author of the present study. An example of a painting made on the basis of a visual hallucination is shown in Fig. 1. It should be stressed that by his own account WW did not paint while actively hallucinating, but rather from later recollection of the content of the hallucinations (see also Bradford, 2003).

In 1999, while actively hallucinating that he had wings and could fly, he rushed out into traffic to catch a bus, and was struck by a passing automobile. He was thrown 10 meters in the air and suffered a closed-head injury with brain contusion, which resulted in his remaining unconscious for 4-5 hours. He also had a fracture of the femoral cervix. He still has serious problems with locomotion and frequent headaches. He was discharged from the hospital after this accident at his own request, but immediately reported for voluntary psychiatric hospitalization.

In July 2004, WW was referred for a CT-scan, performed by the sixth author of the present study, to ascertain if there were any persistent structural changes resulting from the TBI (an MRI examination could not be done due to the presence of a metal implant in WW's hip). Three interesting images are shown in Fig. 2.

Fig. 1. An example of WW's painting, created on the basis of a visual hallucination
Source: Grochmal-Bach & Pąchalska, 2004

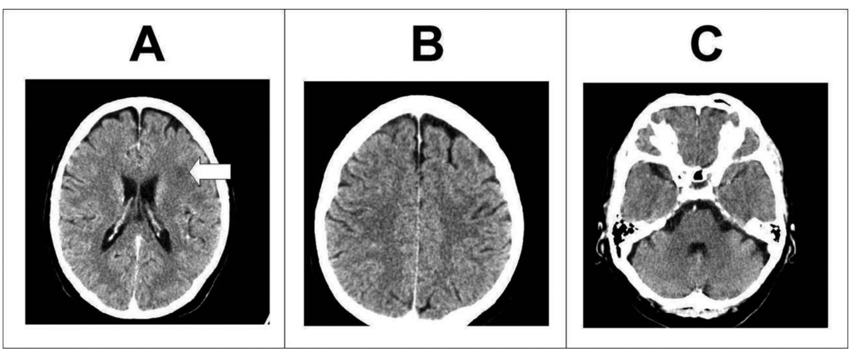

Fig. 2. CT scan of WW's brain, July 2004. A – the white arrow shows a hypodense lesion in the white matter of the left temporal lobe; B – cortical atrophy, especially in the left frontal lobe; C – cortical atrophy in the right temporal lobe and anterior cortex of the cerebellum

In the left frontal lobe, in the white matter on the border of the corona radiata and subcortically, there is a small hypodense zone that may reflect malacial changes consequent to traumatic injury. The administration of contrast had no effect on the image. Apart from this hypodense zone, there are no abnormalities of density in brain tissue. There are, however, features of cortical atrophy, primarily in the frontal regions (more pronounced on the left than on the right), and in the right temporal region. There is also slight cortical atrophy of the cerebellum. The ventricles are symmetrical, slightly enlarged but not displaced. This picture is generally consistent with a mild-to-moderate TBI.

An ophthalmological examination showed normal placement and mobility of the eyeballs. The anterior, medial and posterior segments of both eyeballs were normal. Visual acuity, near and far, was also appropriate for the patient's age and did not require ocular correction. The intraocular pressure was normal, as were the fields of vision in both eyes. This last finding ruled out the possibility that the hemispatial neglect occasionally observed in WW's drawings might be the result of a vision disturbance.

After the accident a change was noticed in his painting style. The hallucinatory content was much reduced, the subject matter became much more traditional, and the color scheme became less garish, dominated by earth tones. Closer analysis of his drawings and paintings from the early part of this period reveal signs of perseveration, rotation, fragmentation, and constructional apraxia.

At the same time he exhibited a strong tendency to perseverate. As shown in Fig. 3, for example, he perseverated heads, which were a favorite topic of his paintings. Moreover, the perseveration also extended to entire pictures, as he began to copy exactly the same picture many times. His works are still highly valued (though some critics his later paintings to be less "interesting"), and he often wins awards at art exhibitions. His works are featured in many catalogs of art by handicapped artists.

It can be noted that each of the four pictures in Fig. 3 contains three heads. The first head depicts a handsome man with dark hair and dark beard (it may be significant that he is similar to the patient himself at a younger age). The sex of the second face is difficult to specify, in that it has the features of both sexes, and seems to be the combination of the first and the third head, since the third is a representation of a young fair-haired woman. Despite the fact that all these pictures depict a single torso with three heads, careful examination reveals differences of colours, contours, background and a number of small details, such as crosses and small figures of people (see Pąchalska et al., 2014). The background of the pictures presented in fig. 3 show navy blue, blue, red, and purple tints. Another feature common to all these pictures is the hole in the torso of the person depicted, which includes small figures of people: four or five in the first picture, and two in the remaining three. Moreover, there is one more head in the above-mentioned hole, looking at the small figures. Yet notable differences in the heads included in the hole can be observed. One head is empty, while in

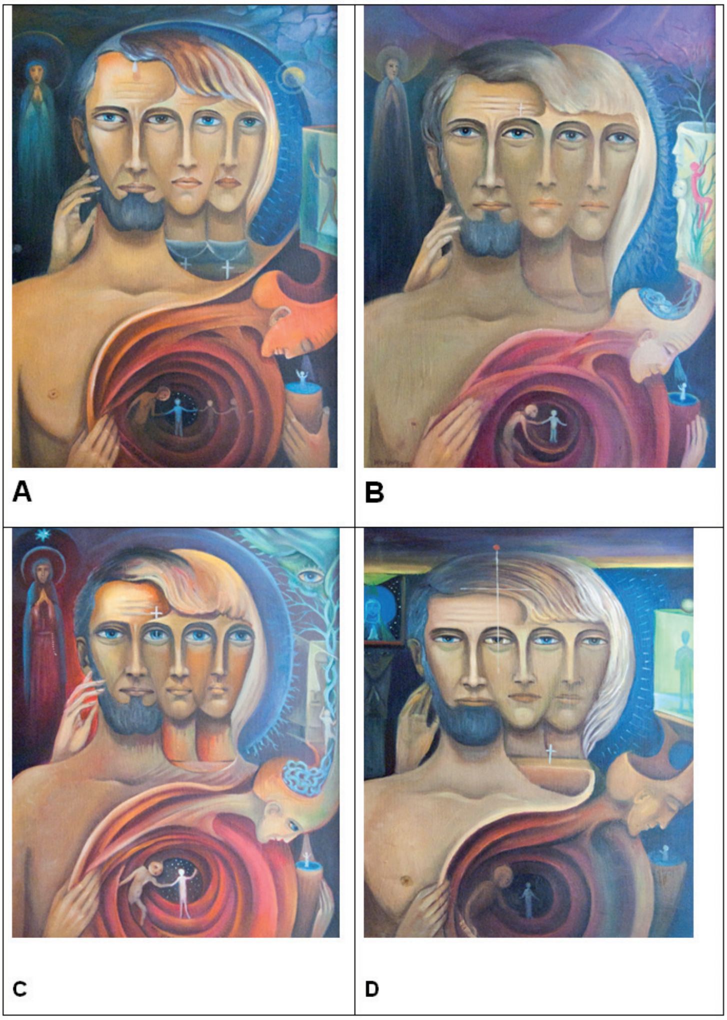

Fig. 3. WW's paintings: perseverated three heads
Source: Private Collection of Prof. Maria Pachalska's Scientific Library

case of the other, various elements emerge from within. It seems the figures closed in the rectangle coming out of the head are trying to get out.

The eyes are characteristic elements of the pictures, and differ in shape, color, and size. In some cases a third eye is depicted that has no connection with any figure. Other characteristic features are crosses and the halo surrounding the head of the first figure. Some critics take this a sign of the deep religious faith of the painter, while others believe it to have no religious references. They presume that the halo of the first figure shows that it rules the other two.

Quite a number of the pictures of three heads have been exhibited all over the world, and have won many prestigious rewards. Most of the many neuropsychologists who have bought one of the copies of this picture are of the opinion that the three heads are a result of tendency to perseverate, typical of dysfunction of executive function, and some of them connected it with posttraumatic depression. The patient says that it is his self-portrait, which suggest that the three-headed figure may be a symbol of his internal dilemmas resulting from difficulties with coping with everyday problems. From this it follows that the figure split into three heads need not reflect perseverations.

It may be helpful at this point to recall the definition given by Code (1989), who states that perseveration means a tendency to continuously repeat a given pattern without taking into consideration the changes occurring in the surroundings or the stimulus itself. Luria (1963) also insisted that as a rule perseverations appear in cases when the patient is not aware that he has already finished the actual activity. Pąchalska (2007) points out that perseveration is a disorder that results from a disruption of a number of functions that require coordination, and so she is inclined to connect the patients' difficulties with executive dysfunctions. This assumption is even more probable due to the fact that most posttraumatic patients do exhibit disorders of executive functions. As a rule, such patients are fully aware of their mistakes and give various explanations of their perseverative actions (MacQueen, 2002; Pąchalska, 2007). The main difficulty is that they are not able to finish one activity and pass to the next one. Hence, it is generally accepted that the ability to inhibit the impulse of activation after the goal of a given action has been attained is disrupted, which results in an inability of the nervous system to adjust to the next action.

The hypothesis of the impairment of an executive function in the patient described here finds further confirmation in the deterioration of his health in November 2011. At that time general negligence could be observed in his behavior. The patient was reluctant to wash, often forgot to eat, and did not throw out his garbage, including apple cores, which resulted in the appearance of swarms of fruit flies in his flat. He also did not pay his rent, and stayed at home all the time. A neuropsychiatric examination revealed a relapse of his schizophrenia, while a neuropsychological assessment pointed to executive dysfunction and posttraumatic depression. This suggested a co-occurrence of two syndromes, which unfortunately is often neglected in traditional medical examinations, and induces physicians and therapists to concentrate only on one illness. As a result the patient is not able to recover fully, since the neglected symptoms prevail and disrupt his life even though they are covered up by the primary diagnosed syndrome.

THE PROGRAM OF NEUROTHERAPY

The patient took part in rehabilitation programs of neurotherapy, with 20 sessions of relative beta training; the goal of the training was to activate the frontal cortex by enhancing beta activity recorded over the frontal electrodes. In more detail, the procedure was as follows: Electrodes were placed at Fz and Cz (bipolar recording). The procedure was to increase the ratio of beta EEG power/EG power in the theta and alpha frequency bands. The beta frequency band was from

13 to 21 Hz. The combined theta and alpha frequency bands were from 4 to 12 Hz. Each session included approximately 20 min. of neurofeedback training.

Cognitive functions

Neuropsychological testing in the first examination showed multiple deficits (see Table 1). Over the course of the entire neurotherapy program, WW's verbal and non-verbal IQ increased significantly (cf. Table 1). Most of his cognitive dysfunctions also resolved, including immediate and delayed logical and visual recall on the WMS-III (cf. Table 1).

In other cognitive functions, WW's results also improved in the follow-up examination. On the auditory learning task, he had forgotten all the words after a 15-minute filled delay at baseline, and got 6 words in recognition; however, in the follow-up examination he remembered 5 words after the delay, and got all the words at recognition. This general pattern was repeated in nearly all neuropsychological testing.

After the completion of the neurotherapy program, the patient was able to paint a picture which departed from the old scheme (see Fig. 4). In accordance with microgenetic theory he is now able to remember his former work precisely as a work completed in the past, and hence to paint a different one (Brown & Pachalska 2003) . Formerly an image of the past had been replaced by an image of the present, since the "pulse awareness," to use William James's term, was restored (see Brown, 2010).

He has worked hard and conscientiously, and his progress has been very gratifying. After 20 sessions of neurofeedback, he independently prepared in September 2013 an exhibition of his works of art in a Krakow art gallery.

EVENT RELATED POTENTIALS [ERPS]

Event related potentials (ERPs) were used before and after neurotherapy to assess functional changes in the patient induced by rehabilitation programs (Kropotov et al., 2013). We used this approach for the following reasons. First, ERPs have a superior temporal resolution (on the order of milliseconds) as compared to other imaging methods, such as fMRI and PET, which have time resolutions of 6 seconds and more (Kropotov, 2009). Secondly, ERPs have been proven to be a powerful tool for detecting changes induced by neurofeedback training in ADHD children (Kropotov, 2009; Kropotov & Mueller, 2009: Kropotov et al., 2005). And finally, in contrast to spontaneous EEG oscillations, ERPs reflect stages of information flow within the brain (Schaffer et al., 1983; Davidson, 1998; Kropotv et al., 2013).

The diagnostic power of ERPs has been enhanced by the recent emergence of new methods of analysis, such as Independent Component Analysis (ICA) and Low Resolution Electromagnetic Tomography (LORETA) (Kropotov 2009).

A modification of the visual two-stimulus GO/NO GO paradigm was used (Fig. 5). Three categories of visual stimuli were selected:

Table 1. Neuropsychological testing of patient WW, baseline and follow-up

Measure	baseline	follow-up
WAIS-R		
IQ – Full	77.5/100	100.5/100
IQ – Verbal	93.5/100	108.5/100
IQ – Nonverbal	61.0/100	92.0/100
Attention		
WMS-III Spatial Span	3 (1^{st} %ile)	12 (75^{th} %ile)
Visuospatial Ability		
WAIS-III Block Design	3 (1^{st} %ile)	8 (25^{th} %ile)
Logical Memory		
WMS-III Immediate logical memory	6/24	21/24
WMS-III Delayed logical memory	3/24	19/24
WMS-III Immediate visual recall	11/41	38/41
WMS-III Delayed visual recall	5/41	29/41
Verbal memory		
CVLT Short Delay Free Recall	0/9(<1^{st} %ile)	2/9 (<1^{st} %ile)
CVLT Long Free Recall	0/9(<1^{st} %ile)	2/9 (<1^{st} %ile)
CVLT Long Delay Cue Recall	0/9(<1^{st} %ile)	2/9 (<1^{st} %ile)
Executive Functions		
TMT– Number Sequencing	Discontinued	54s. (10^{th} %ile)
TMT– Number Letter Sequencing	Discontinued	150s. (<1^{st} %ile)
Stroop		
Color	90 s. (<1^{st} %ile)	41 s. (16^{th} %ile)
Word	29 s. (25^{th} %ile)	42 s. (63^{rd} %ile)
Interferences	Discontinued	128 s. (<1^{th} %ile)
WCST		
Categories	0 (2-5^{th} %ile)	2 (>16^{th} %ile)
Perseverative Errors	46 (<1^{th} %ile)	19 (37^{th} percentile)
Conceptual Level Responses	63 (<19^{th} %ile)	48 (45^{th}%ile)
Failure to Maintain Sets	Discontinued	4 (2-5^{th} %ile)

TMT = TrialMaking Test
Level of performance corresponding to the percentiles
98-99 %ile = Very Superior
91-97 %ile = Superior
75-90 %ile = High Average
25-74 %ile = Average
9-24 %ile = Low Average
3-8 %ile = Borderline
2nd %ile and below = Impaired

Fig. 4. WW's painting after neurotherapy: no more schemes or perseverations of three heads
Source: Private Collection of Prof. Maria Pachalska's Scientific Library

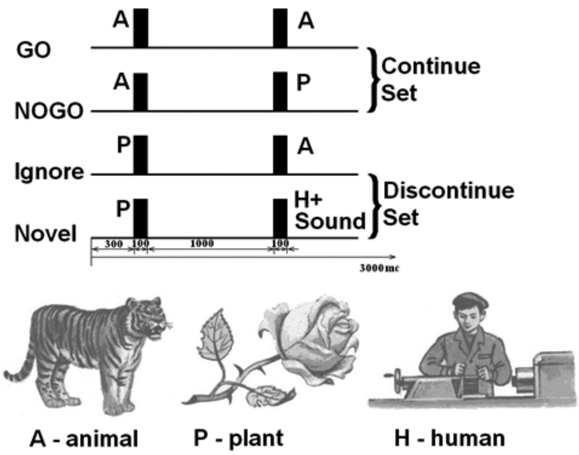

Fig. 5. Schematic representation of the two-stimulus GO/NOGO task. From top to bottom: time dynamics of stimuli in four categories of trials. Abbreviations: A, P, H stimuli are "Animals", "Plants" and "Humans" respectively. GO trials are when A-A stimuli require the subject to press a button. NOGO trials are A-P stimuli, which require suppression of a prepared action. GO and NOGO trials represent "Continue set," in which subjects have to prepare for action after the first stimulus presentation (A). Ignore trials are stimuli pairs beginning with a P, which require no preparation for action. Novel trials are pairs requiring no action, with presentation of a novel sound as the second stimuli. Ignore and Novel trials represent "Discontinue set", in which subjects do not need to prepare for action after the first stimulus presentation. Time intervals are depicted at the bottom

- 20 different images of animals, hereinafter referred to as “A”;
- 20 different images of plants, hereinafter referred to as “P”;
- 20 different images of people of different professions, presented along with an artificial “novel” sound, hereinafter referred to as “H+Sound”.

All visual stimuli were selected to have a similar size and luminosity. The randomly varying novel sounds consisted of five 20-ms fragments filled with tones of different frequencies (500, 1000, 1500, 2000, and 2500 Hz). Each time a new combination of tones was used, while the novel sounds appeared unexpectedly (the probability of appearance was 12.5%).

The trials consisted of presentations of paired stimuli with inter-stimulus intervals of 1 s. The duration of stimuli was 100 ms. Four categories of trials were used (see Fig. 5): A-A, A-P, P-P, and P-(H+Sound). The trials were grouped into four blocks with one hundred trials each. In each block a unique set of five A, five P, and five H stimuli were selected. Participants practiced the task before the recording started.

The patient sat upright in an easy chair looking at a computer screen. The task was to press a button with the right hand in response to all A-A pairs as fast as possible, and to withhold button pressing in response to other pairs: A-P, P-P, P-[H+Sound] (Fig. 5). According to the task design, two preparatory sets were distinguished: a “Continue set,” in which A is presented as the first stimulus and the subject is required to prepare to respond; and a “Discontinue set,” in which P is presented as the first stimulus, and the subject does not need to prepare to respond. In the “Continue set,” A-A pairs will be referred to as “GO trials,” A-P pairs as “NO GO trials.” Averages for response latency and response variance across trials were calculated. Omission errors (failure to respond in GO trials) and commission errors (failure to suppress a response to NO GO trials) were also computed.

EEGs were recorded from 19 scalp sites. The electrodes were applied according to the International 10-20 system. The EEG was recorded referentially to linked ears, allowing computational re-referencing of the data (remontaging).

RESULTS

Behavioral data

The omission, commission errors, reaction time and error in the variance of response are presented below in Table 2. No statistically significant deviations from the average norm were found in either Pre or Post conditions. However, the patient became 56 ms faster in the Post assessment.

Behavioral data (see Table 2) show that the subject has performed within normal limits in all three recordings, including the third recording in which the subject performed worse.

Table 2. Behavioral data

Testing	Omission	Commission	RT1	Var (RT1)
Pre	1%	0%	411	6.8
Post	4%	2%	345	6.0
Norms	4.7%	1.7%	396	7.6

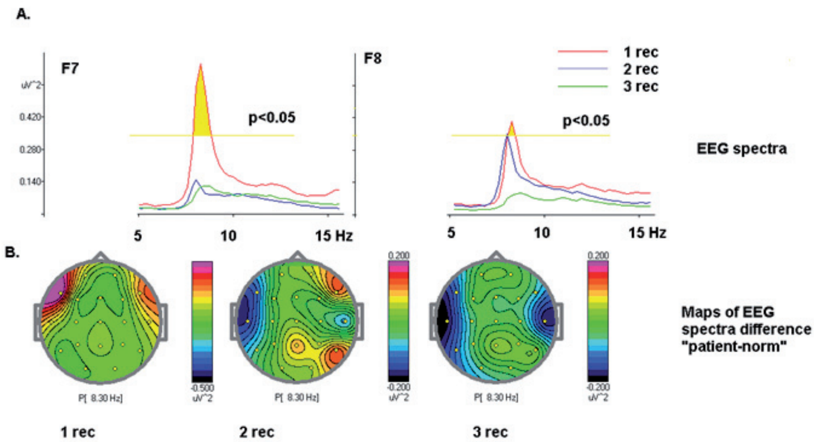

Fig. 6. EEG spectra in the GO/NOGO task at the three recordings
A. EEG spectra at F7 and F8 electrodes, first recording – red, second recording – blue, third recording – green. Note peaks at the spectra in the first recording, corresponding to an alpha rhythm around 8 Hz. Yellow horizontal line – the $p<0.05$ confidence level of the deviation from the normal overall average
B. Maps of EEG spectra at 8.3 Hz at the three recordings

Spectra data

Analysis of spectral data (see Fig. 6) shows that the EEG spectra changed quite dramatically during the period of all three recordings.

Indeed, in the first recording the subject revealed a slow (around 8 Hz) rhythm recorded at F7 and F8. This slow alpha rhythm is reflected in statistically significant deviation from the norms in the EEG spectra. The decomposition of spontaneous EEG during the first recording into independent components revealed two independent components generated correspondingly at the left and right inferior prefrontal cortical areas.

In the second recording the rhythm in the left inferior frontal cortex almost disappeared (Fig. 7 B), whereas the right alpha rhythm disappeared only during the third recording.

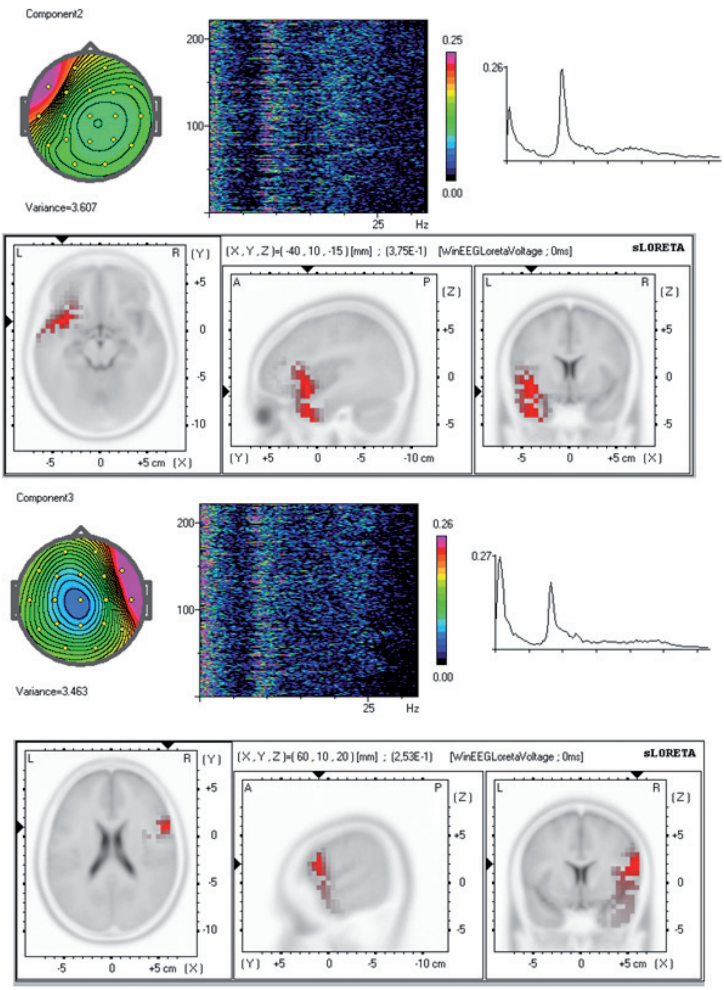

Fig. 7. Independent components extracted from EEG in the first recording
A – independent component generated on the left hemisphere. Top (from left to right) – topography, color coded spectra for 4-second epochs computed for all 20 minutes of recording, averaged spectra of the component. Bottom – sLORETA image of the topography
B – the independent component generated on the right hemisphere. Top (from left to right) – topography, color coded spectra for 4-second epochs computed for all 20 minutes of recording, averaged spectra of the component. Bottom – sLORETA image of the topography

ERP data

From our previous study (Kropotov et al., 2013) we know that a difference in the ERP NOGO-GO wave can be considered to be a sensitive neuromarker of schizophrenia. Fig. 8 A shows the overall average ERP difference waves for a group of healthy subjects and a group of patients with schizophrenia recorded

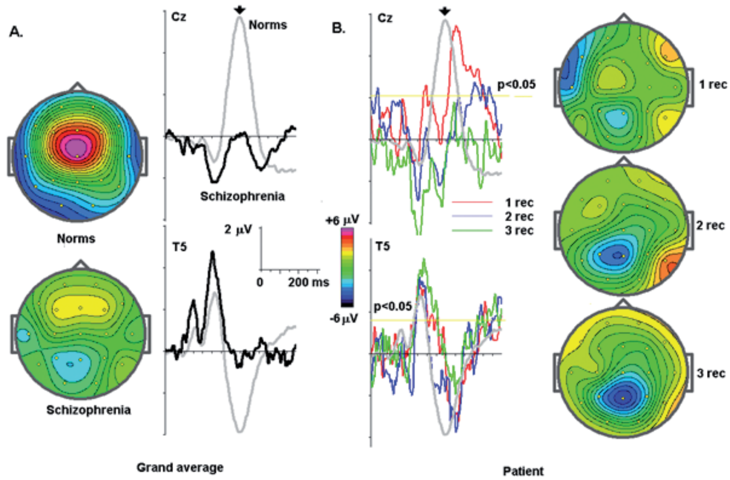

Fig. 8. ERP NOGO-GO difference wave of the patient in comparison with a group of healthy subjects
A. Right – overall average ERP difference wave at Cz and T5 electrodes for a group of healthy subjects (N=61) and a group of patients with schizophrenia (N=28) of comparable age. Left – maps of the difference waves at 390 ms (marked by arrow)
B. Left – individual ERP difference wave for the three recordings at Cz and T5 electrodes. Right – maps of the difference waves at 390 ms (marked by arrow)

at the Psychiatric Clinic in the Institute of the Human Brain at the Russian Academy of Sciences. As one can see, the difference wave at the Cz electrode is dramatically suppressed in the group of patients with schizophrenia.

The patient under study revealed a pattern similar to schizophrenia (Fig 8 B): in all three recordings the difference wave was significantly delayed or reduced, while the positive wave at the T5 electrode was intact.

DISCUSSION

In our methodological approach we are looking for neuromarkers of psychiatric disturbances (Kropotov, 2009; Kropotov et al., 2013). By definition (Williams et al., 2005) the concept of neuromarker is a narrower version of the general concept of biomarker. In EEG-related neuromarkers, the EEG spectra and ERP are considered to be two different windows into brain functioning: spontaneous EEG reflects the mechanisms of cortical self-regulation, whereas ERPs reflect mechanisms of the stages of information flow within the brain.

In the subject under study, two neuromarkers have been detected. The first is associated with frontal alpha asymmetry. According to the Davidson theory, frontal alpha asymmetry (L>R) is associated with depression (Davidson 1998; Gold et al., 2013). This asymmetry is associated with inactivity of the left orbitofrontal cortex and a lack of positive emotions. In this subject, the frontal alpha with the corresponding asymmetry was found only in the first recording. Thus we can conclude that during neurotherapy the subject moved away from a depressed state.

The second neuromarker is associated with a decreased NOGO-GO ERP difference wave. As shown in many studies, including a study done in our lab, this neuromarker is found in a majority of schizophrenic patients. The neurotharapy did not affect this neuromarker. The neurotharapy did not effect this neuromarker. It appears that in this case the effect of neurotherapy was manifested primarily in parameters of cortical self-regulation, but not in parameters of information flow.

CONCLUSIONS

The case described here shows that the pathomechanisms of schizophrenia and neurobehavioral disturbances resulting from organic brain damage are not after all unrelated. Microgenetic theory can provide a basis for explaining the course of symptoms in this and similar cases, as we re-think the brain-mind relationship. The relative beta training produced behavioral changes and small physiological changes. ERPs can be used to assess functional brain changes induced by neurotherapeutical programs.

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Address for correspondence:
Prof. Maria Pąchalska, Ph.D.
Andrzej Frycz Modrzewski Cracow University
Herlinga-Grudzinskiego 1
Cracow, Poland
e-mail: neuropsychologia23@o2.pl