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Changes in frontal cortex hemodynamic activity in a patient with schizophrenia undergoing electroconvulsive therapy – case analysis using functional near-infrared spectroscopy (fNIRS)

Piotr Ziemecki[1] ABCDEF https://orcid.org/0000-0002-4753-3993,
Agnieszka Permoda-Pachuta[2] AE, https://orcid.org/0000-0003-3413-5723,
Paweł Krukow[3] BC, https://orcid.org/0000-0001-9497-2713,
Natalia Kopiś-Posiej[3] BC https://orcid.org/0000-0001-9163-4591,
Hanna Karakuła-Juchnowicz[2] D, https://orcid.org/0000-0002-5971-795X,

[1]Doctoral School of the Medical University of Lublin, Poland
[2]I Deparment of Psychiatry, Psychotherapy and Early Intervention, Medical University of Lublin, Poland
[3]Department of Clinical Neuropsychiatry, Medical University of Lublin, Poland

Abstract

Introduction: In recent years, one of the most interesting areas of research is the change in hemodynamic response of the prefrontal cortex as a predictor of response to electroconvulsive treatments (ECT). Near-infrared spectroscopy (fNIRS) is non -invasive functional neuroimaging technique that allows the assessment of neuronal activity in frontotemporal regions. The goal of our study was to verify feasibility of fNIRS method to monitor potential changes in frontal cortex hemodynamic activity as a response to ECT treatment.

Material and method: The 30 years old, patient with schizophrenia was admitted to the Department of Psychiatry, Psychotherapy and Early Intervention in Lublin for psychiatric treatment. Due to the incomplete therapeutic effect, after using clozapine and electroconvulsive therapy was performed. To monitor the activity of the brain functional fNIRS technique was used. The hemodynamic response of the frontal cortex during performance was assessed: verbal and non-verbal fluency tasks. The Positive and Negative Symptoms Scale was used twice before and after ECT.

Results: As a result of pharmacotherapy and electroconvulsive treatment, clinical improvement was achieved, but full remission was not achieved. Evaluation of HbO and Hb fluctuations from one channel showed that the hemodynamic activity of the frontal cortex was opposite to the standard at the time of task initiation. After a series of treatments, the pattern of activity reversed in a more normative direction for figural fluency.

Discussion: It appears that the data provided indicate that fNIRS neuroimaging may be a useful tool in monitoring changes in cortical activity patterns in response to therapeutic stimulation such as ECT.

Keywords: ECT, fNIRS, schizophrenia

Streszczenie

Wstęp: W ostatnich latach jednym z najbardziej interesujących obszarów badań jest zmiana odpowiedzi hemodynamicznej kory przedczołowej jako predyktor odpowiedzi na leczenie elektrowstrząsowe (ECT). Spektroskopia w bliskiej podczerwieni (fNIRS) jest nieinwazyjną techniką neuroobrazowania, która pozwala na ocenę aktywności neuronalnej w obszarach czołowo-skroniowych kory mózgowej. Celem naszego badania była weryfikacja uzyteczności metody fNIRS do monitorowania potencjalnych zmian w aktywności hemodynamicznej kory czołowej w odpowiedzi na leczenie ECT.

Materiał i metoda: Pacjent lat 30 z rozpoznaniem schizofrenii został przyjęty do Kliniki Psychiatrii, Psychoterapii i Wczesnej Interwencji w Lublinie w celu leczenia psychiatrycznego. Ze względu na niepełny efekt terapeutyczny po zastosowaniu farmakoterapii w tym i leczenia klozapiną , przeprowadzono zabiegi elektrowstrząsowe. Do monitorowania aktywności czynnościowej mózgu wykorzystano technikę fNIRS. Oceniano odpowiedź hemodynamiczną

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kory czołowej podczas wykonywania: werbalnych i niewerbalnych zadań fluencji. Skalę PANSS zastosowano dwukrotnie przed i po leczeniu ECT.

Dyskusja: W wyniku farmakoterapii i leczenia elektrowstrząsami uzyskano poprawę kliniczną, ale nie osiągnięto pełnej remisji. Ocena fluktuacji HbO i Hb z jednego kanału wykazała, że aktywność hemodynamiczna kory czołowej była przeciwna do normy w momencie rozpoczęcia zadania. Po serii zabiegów wzorzec aktywności odwrócił się w kierunku bardziej normatywnym.

Wnioski: Wydaje się, że dostarczone dane wskazują, że neuroobrazowanie fNIRS może być użytecznym narzędziem w monitorowaniu zmian we wzorcach aktywności korowej w odpowiedzi na zabiegi elektrowstrząsowe.

Słowa kluczowe: zabiegi elektrowstrząsowe, fNIRS, schizofrenia

Introduction

Schizophrenia is a global mental illness and affects approximately 24 million people (0.32%) worldwide [1]. It is one of the most severe health condition [2].

Many people with schizophrenia do not achieve full remission, and among those with good outcomes, the diagnosis changes their lives [3].

Despite many years of development of the concept of schizophrenia, not all the factors responsible for the pathogenesis of this disease have been identified.

There is a search for factors that can objectify the diagnosis of schizophrenia, as well as those that will be indicators of remission of this disease or will be predictors of clinical response to the form of treatment used. The prevalence of treatment-resistant schizophrenia (TRS) ranged from 22% in first episode to 39.5% in multiple-episode samples [4]. Clozapine is considered the gold standard for patients with TRS. Despite optimal treatment, a subgroup of TRS patients fails to respond for clozapine. In these cases, electroconvulsive therapy (ECT) is used as an augmenter [5]. ECT is an effective [6] treatment for schizophrenia and drug-resistant depression that has been known for several decades [7]. The study's findings suggested the effectiveness of clozapine and ECT in the management of TRS [8,9,10]. Despite many years of ECT use, its mechanisms of action are still not fully elucidated. A search for markers correlating with the effectiveness of electroconvulsive therapy (ECT) is still a challenge for modern psychiatry.

Predictors of good clinical response include biological [11,12] and genetic markers [13].

Changes in fMRI or PET imaging [14] in frontal cortex hemodynamic activity are also observed.

Frontal functions such as working memory, attention, judgment are thought to be impaired in schizophrenic patients [15]. Prefrontal cortex is an area stimulated by electrical treatments [16]. Studies using methods such as PET or Doppler indicate a change in perfusion of the prefrontal area of the brain during ECT treatment.

Near-infrared spectroscopy (NIRS) is a functional neuroimaging technique that allows the assessment of neuronal activity in frontotemporal regions. It is used for non-invasive monitoring of adult brain function in a wide variety of tasks [17]. This technique detects changes in the cortical oxygenation levels of hemoglobin.

The advantages of using fNIRS are that it is a relatively inexpensive procedure, portable and it may be repeated multiple times for patients [18].

In recent years, one of the most interesting areas of research is the change in hemodynamic response of the prefrontal cortex as a predictor of response to electroconvulsive treatments [19,20,21].

Therefore, fNIRS may be useful as a diagnostic method and in monitoring the effectiveness of treatment in patients with schizophrenia [22]. The goal of our study was to verify feasibility of fNIRS method to monitor potential changes in frontal cortex hemodynamic activity as a response to ECT treatment.

Materials and methods

Literature review was carried out using electronic databases: PubMed, Google Scholar, using the following keywords: ECT, fNIRS, frontal activation, schizophrenia. Publications in English were used. The patient's medical records, results of laboratory and imaging tests were used to describe the case.

The Positive and Negative Syndrome Scale (PANSS) was used to measure the severity of schizophrenia symptoms. This scale was published in 1987 by Stanley Kay, Lewis Opler and Abraham Fiszbein and it is widely used in psychopharmacological therapy research [23].

To monitor the activity of the brain by measuring the level of oxygenated hemoglobin within the frontal cortex microvasculature an fNIRS device was used.

The study was performed using the Photon Cap C20 system (Cortivision sp. z o.o., Lublin, Poland) device with 32 channel montage covering forehead regions of participants' heads. This device allows non-invasive monitoring of the activity of selected areas of the cerebral cortex and measuring the hemodynamic response of the

brain. The hemodynamic response of the frontal cortex during performance was stimulated by two cognitive tasks: initial letter verbal fluency and non-verbal fluency tasks. Non-verbal fluency test was based on digitalized design fluency task used previously in clinical groups comprising patients with schizophrenia and bipolar disorder [24,25].

The verbal fluency test consisted of generating as many words as possible beginning with a letter given by the experimenter (e.g., 'K'), within a limited time (60 sec.).

Digitalized nonverbal fluency test [26] is a measure consisting of five parts, each containing a different stimulus pattern. Participants are instructed to draw as many unique patterns as possible by connecting at least two dots forming a five-point matrix. Nonverbal fluency is considered to be the total number of unique patterns drawn within 60 seconds. A tablet application was used to test nonverbal fluency [24].

Data sampled at 5 Hz were analyzed in CortiPrism software, version 6.12 (Cortivision sp. z o.o., Lublin, Poland). The data were first converted to optical value. Then the motion artifact correction function [27] and band-pass filtering from 0 Hz to 0.2 Hz were applied. Correction was applied for short channels. The data were then converted to hemoglobin concentration using a modified Beer-Lambert law. For block averaging of hemoglobin concentration data, 15-second segments of excerpts (0-15 ---T1; 15-30 -- T2; 30-45 -- T3; 45-60 -- T4) were selected for the verbal fluency task and for the non-verbal fluency task. Data on oxygenated hemoglobin (oxy-HB) and deoxygenated hemoglobin (deoxy-HB) concentrations were analyzed.

Electroconvulsive therapy was performed using the Thymatron System IV device. This apparatus delivers a charge in the form of a short electrical pulse, the maximum charge it can deliver is 504 mC . The current parameters were selected according to the half age method [28]. Bilateral positioning was used, with the same electrode array covering frontal and temporal areas. Brain activity was monitored with an electroencephalogram (EEG).

The study was approved by the Bioethical Committee of the Medical University of Lublin (No.KE-0254/171/06/2022). Written consent for the study was obtained.

Study case and description

Patient, 30 years old, single with secondary education, childless lives with family. Family history was without psychiatric burden. He was born from first pregnancy uncomplicated, without perinatal complications. Consecutive Apgar scale scores 10/10 [29]. The patient denied head injuries with loss of consciousness and epilepsy. He had smoked marijuana regularly for several years, had taken cocaine several times in his life, and drank alcohol occasionally. In 2019, he began to isolate socially, felt fear of contact with other people, also described a sense of being stalked – he felt followed. The patient discontinued his college studies. Since 2020, symptoms of disorganization, bizarre and maladaptive behavior had been present, and he began to take an interest in religious topics and collected religious objects.

He also began to utter delusional content of a grandiose and religious nature and was convinced of possessing special abilities sent by higher forces (healing the sick, telepathic communication), periodically became agitated and aggressive.

He first attended an outpatient psychiatric appointment at the urging of his family in 2022. He was referred to the Psychiatric Hospital for further diagnosis and treatment. The patient consented to psychiatric hospitalization. On admission to the psychiatric hospital, he was auto and allopsychically oriented, in behavior he was calm, resonant, bizarre, there were pseudo-philosophical, religiously oriented statements, he uttered numerous delusional contents.

During hospitalization, the patient remained in a slightly depressed mood and psychomotor drive, was ambivalent, resonating affective inadequacy. Impaired abstract thinking was observed concentrating thinking and functioning around overvalued ideas about religion and quantum interactions. He spent most of his time in the patient's room, praying surrounded by religious objects, uttered numerous delusional contents with religious and pseudo-philosophical themes regarding abilities to communicate with others through thoughts and quantum interactions.

He established good relations with other patients willingly attended occupational therapy, presented a complete lack of insight into the illness at the same time agreeing to the proposed forms of treatment. Pharmacotherapy was changed several times during hospitalization.

Before starting ECT, olanzapine aripiprazole and risperidone were used, with no significant therapeutic effect. Due to the incomplete therapeutic effect, clozapine was included, and then electroconvulsive therapy was administered. The patient developed episodes of uncontrolled urination, the dose of clozapine was reduced from 375mg/day to 150mg/day, and aripiprazole was restarted. After a series of treatments, the patient was observed to have a decrease in mood, and antidepressant treatment was included (duloxetine).

Electroshock treatments were carried out twice a week under general anesthesia and relaxation. Propofol at a dose of 100mg was used for anesthesia. Gradual

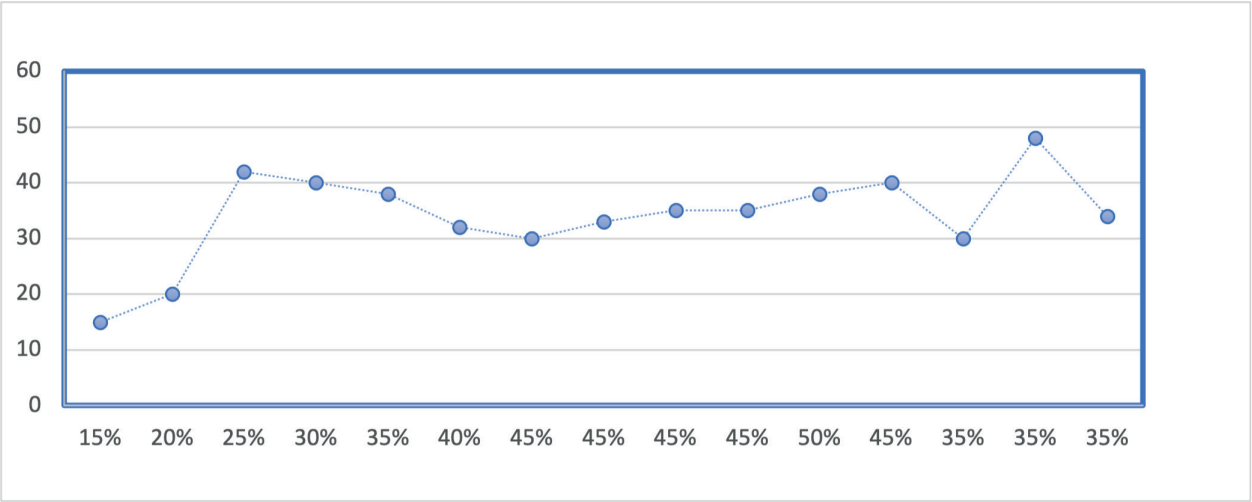

Figure. 1. The graph shows the relationship between seizure duration in seconds and the percentage of maximum output power charge applied.

improvement in mental status occurred after the 6th electroshock treatment. A total of 15 procedures were carried out, their course was without complications.

As a result of the treatment, the patient's mental state improved, he became partially critical of the delusional content uttered so far, distanced himself from the pathological pattern of functioning, his mood and psychomotor drive equalized, and his abstract thinking improved. On the day of discharge, the patient was oriented in clear consciousness leveled mood and psychomotor drive effect was modulated in a limited range, delusional contents were not uttered, hallucinations were denied and his behavior did not indicate that he was experiencing them. Overvalued ideas with religious themes persisted. Suicidal thoughts and tendencies were not present. The patient declared himself motivated to continue pharmacotherapy and psychotherapy on an outpatient basis.

To measure the prevalence of positive and negative syndromes PANNS was used twice before and after ECT.

Table 1. PANNS scores before and after ECT.

Positive and Negative Syndrome Scale (PANSS)	Score before ECT therapy	Score after ECT therapy
Positive Subscale Score	32	18
Negative Subscale Score	31	23
General Psychopathology Subscale Score	61	42
Total PANSS score	124	83

The patient underwent fNIRS-assessment twice, before and after a series of electroconvulsive treatments.

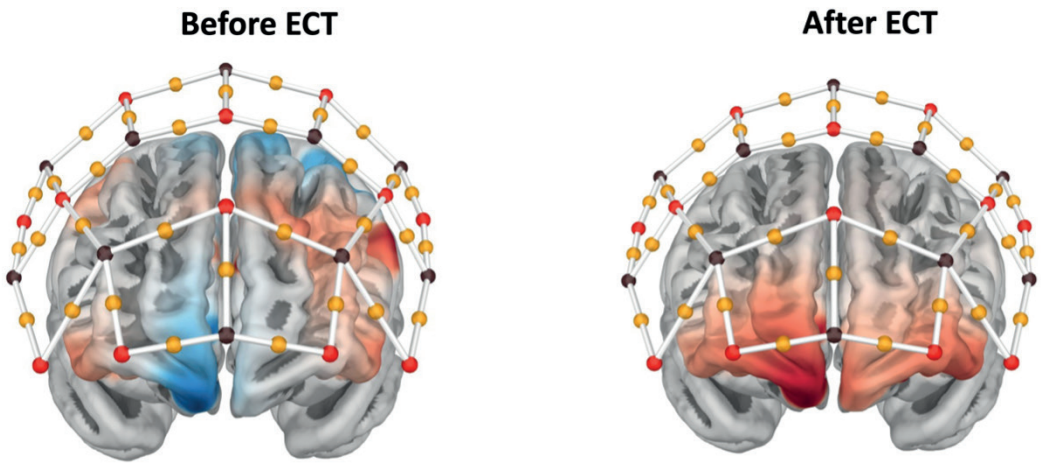

Fig.2. Activity in the first 15 seconds (verbal fluency).

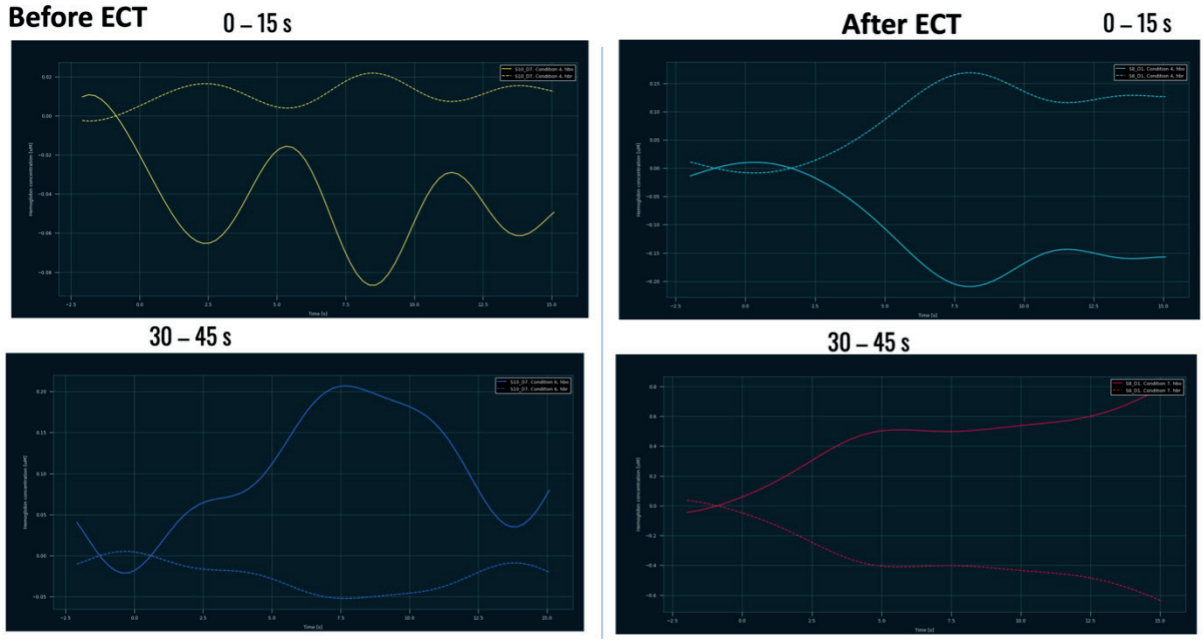

Fig.3. Curves show oxygenated (solid line) and deoxygenated hemoglobin (dashed line) levels during verbal fluency test.

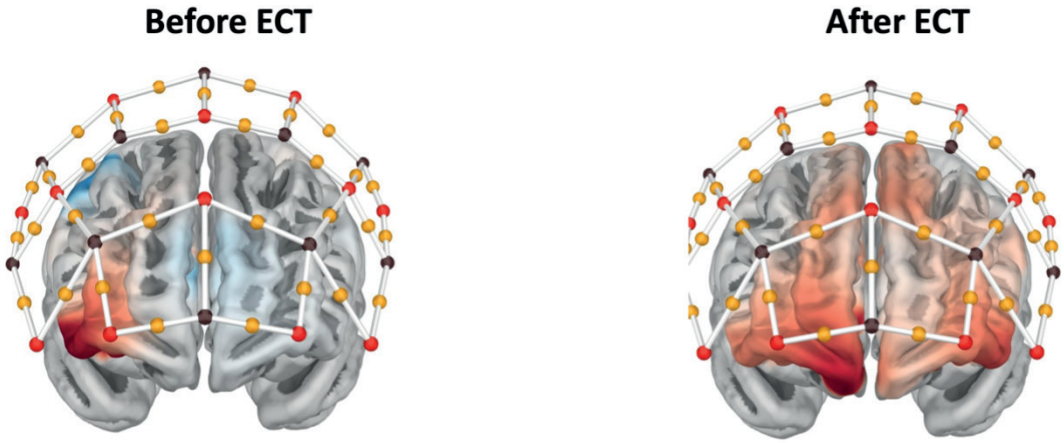

Fig.4. Activity during the first 15 seconds of the nonverbal fluency test (Ruff Figural Fluency Test -RFFT).

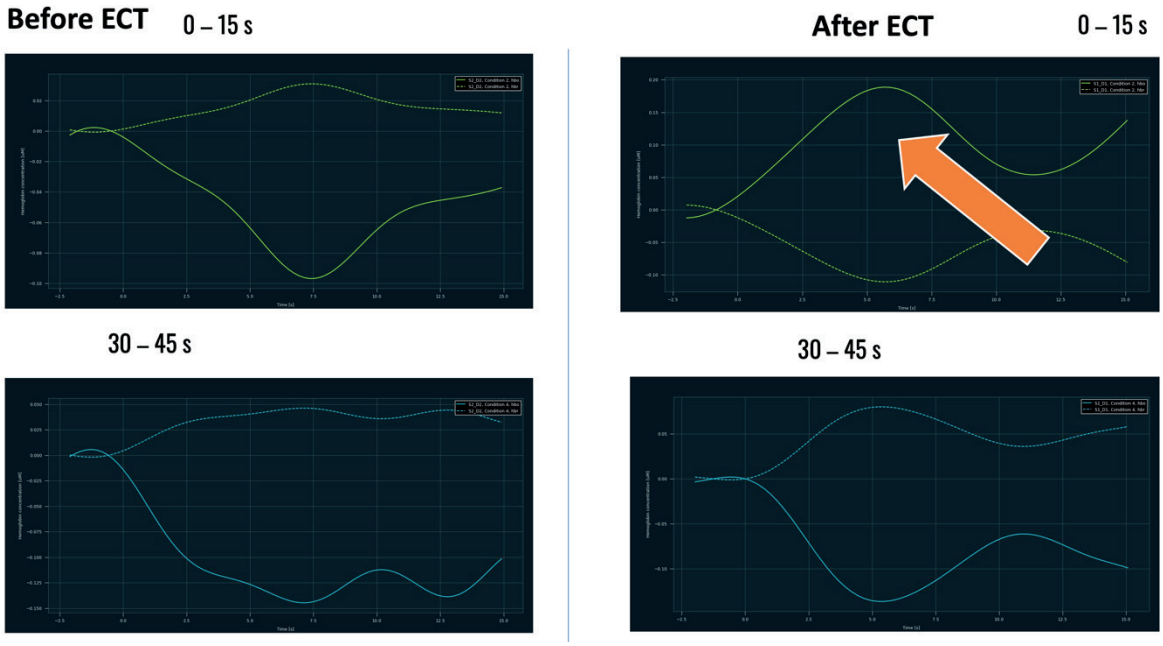

Fig.5. Curves show oxygenated hemoglobin (solid line) and deoxygenated hemoglobin levels (dashed line during nonverbal fluency test).

In our study, reductions in frontal cortex activity were observed before the start of ECT treatments. Atypical patterns of functional asymmetry were evident, with pattern activity of the prefrontal cortex being opposite to the pattern at the start of the task.

This corresponds with reports of changes in cortical activity in individuals with a diagnosis of schizophrenia available from the literature [30,31].

Discussion

There are reports in the literature [32] about the possibility of using the fNIRS method as an auxiliary tool for the differential diagnosis of schizophrenia.

It was noted that the most significant differences between the control group and the group of patients with schizophrenia were related to the fNIRS results during the verbal fluency test [32,33] and occurred mainly in the prefrontal cortex area. Prefrontal cortex area is a region whose dysfunction occurs in diseases such as schizophrenia or mood disorders in the course of unipolar or bipolar affective disorder.

After a series of 15 ECTs, an increase in the contribution of the prefrontal cortex to the initiation of information processing was observed as well as the pattern of activity reversed in the normative direction.

Studies indicate [34,35] that antipsychotics can improve prefrontal cortex function, especially when pharmacological intervention is in the early stages of psychosis.

Meta-analyses [36,37] also confirm effectiveness of combining clozapine with ECT in treatment-resistant schizophrenia patients. In the present case, in view of the lack of improvement after the applied pharmacotherapy and the finding of drug resistance in the patient, ECT was applied. Clinical improvement was noted, confirmed by a reduction in symptoms on the PANSS.

Conclusions

As a result of the electroconvulsive treatment administered, clinical improvement was achieved, but full remission was not achieved. Maps of hemodynamic activity of the frontal cortex indicate that before ECT, the activity recorded during cognitive tasks was significantly reduced, with atypical patterns of functional asymmetry, with absent or even inhibited activity of prefrontal regions. The change in activity after the treatments consisted primarily of an increase in the involvement of the prefrontal cortex in initiating information processing. Evaluation of HbO and Hb fluctuations from one channel showed that the hemodynamic activity of the frontal cortex was opposite to the standard at the time of task initiation. After a series of treatments, the pattern of activity reversed in a more normative direction for figural fluency. It appears that the data provided indicate that fNIRS neuroimaging may be a useful tool in monitoring changes in cortical activity patterns in response to therapeutic stimulation such as ECT.

Conflict of interest

The authors have declared no conflict of interest.

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Corresponding author

Piotr Ziemecki
e-mail: piotr.ziemecki@gmail.com
Doctoral School of the Medical University of Lublin, Poland

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