Psychiatr. Pol. 2019; 53(6): 1261–1273
PL ISSN 0033-2674 (PRINT), ISSN 2391-5854 (ONLINE)
www.psychiatriapolska.pl
DOI: https://doi.org/10.12740/PP/OnlineFirst/102622

Evaluation of cognitive deficits in schizophrenia using event-related potentials and rehabilitation influences using EEG Biofeedback in patients diagnosed with schizophrenia

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Summary

Cognitive deficits in schizophrenia patients have a chronic and negative effect on patients' social functioning. Antipsychotic drugs do not sufficiently improve cognitive functions. In this study, an analysis of previous studies on cognitive functions using event-related potentials in schizophrenia patients was conducted on the basis of available publications (Pubmed, Scopus). The studies indicate numerous deviations at various stages of information processing in patients diagnosed with schizophrenia when compared to healthy subjects, and this justifies the need for the development of new methods influencing the bioelectric brain activity in cognitive rehabilitation of these patients. EEG Biofeedback is a method which could be used for rehabilitation of cognitive functions in schizophrenia patients. Despite it being used in practice, the importance of EEG Biofeedback as a rehabilitation influence on cognitive functions in schizophrenia has not been fully ascertained. This paper analyses the results of previous studies on the effect of EEG Biofeedback therapy on cognitive functions as a possible method to be used in the rehabilitation of schizophrenia patients. Currently, the body of research that may prove the value of this method in the rehabilitation of patients with schizophrenia appears to be insufficient, and there is no scientific evidence from randomized studies for the usefulness of EEG Biofeedback in schizophrenia treatment. At the moment, the recommendation of this method in the cognitive rehabilitation of patients is a therapeutic experiment. The researchers, on the basis of an analysis of clinical cases, currently propose that EEG Biofeedback is conducted in patients diagnosed with schizophrenia by experienced practitioners, paying particular attention to strengthening alpha in the right parietal region.

Key words: schizophrenia, rehabilitation

Introduction

Cognitive deficits in schizophrenic patients have a chronic and negative effect on patients' academic, professional and social functions [1–6]. The studies indicate that cognitive deficits are present in schizophrenic patients regardless of the illness phase. Patients experiencing the first psychotic episode present with deficits indicating disrupted functions of the frontal and temporal lobes. They are manifested as deficits in attention, sensory processing, executive functions, verbal fluency, verbal memory, as well as learning abilities [7–14].

Dysfunctions in the prefrontal region contribute to disorders in cognitive processes associated with working memory, selectiveness and sustaining of attention, processing of information, and action planning, i.e., those that significantly influence patient's functioning and quality of life [7–24]. It was Kraepelin who noticed the importance of disruptions in cognitive functions in the clinical picture of schizophrenia [1]; he even considered them to be characteristic signs of that illness, with its psychotic symptoms being secondary. Kahn sums up the importance of cognitive disorders in schizophrenia, and emphasizes a significant influence of a low intelligence level as associated with a risk of the illness. The failure to achieve the expected level of intelligence precedes the occurrence of psychosis by several years, and a reduction in cognitive functions occurs only after an episode of psychosis. A degree of deterioration in cognitive functions is considered to be an important prognostic factor for the course of schizophrenia [1].

When evaluating cognitive functions, the researchers analyze event-related potentials (ERP), which are changes in the brain bioelectrical activity related to information processing processes [17, 23, 24]. In the ERP response, we distinguish components corresponding to stimulus processing stages. Early components are potentials of medium latency (exogenous), whose parameters are directly associated with the physical parameters of a stimulus. They reflect the automatic sensory analysis and are subject to modulation associated with capturing the stimuli of expected physical parameters [23, 24].

Other components reflect a bioelectrical activity of a brain of an examined person during purposeful cognitive decisions in response to processed stimuli. Morphology of endogenous ERP does not directly depend on the stimulus type; it rather depends on the properties of processed information and the importance assigned by the subject to experienced stimuli. Endogenous ERP is influenced by psychological factors and the mental condition of the subject. Processes activated at the moment of recognizing a different stimulus are mainly associated with an intellectual analysis of that stimulus, manifested as late endogenous components (including P3a, P3b, MMN (mismatch – negativity) N2, N4, N6) [17, 23, 24].

Numerous studies focus on the P300/P3 component; this potential is characterized by two waves: P3a and P3b [17, 23, 24]. P3a has shorter latency (250–350 ms), and its maximum amplitude is registered in the frontal-central leads. P3b appears after 350–700 ms, and its maximum amplitude occurs in the central-parietal region [24]. Alternatively, P3 potential can be described as P3b.

N400/N4 is a negative evoked potential of long latency, and it is associated with the reaction to an unexpected end of a task or a semantic change [25].

Endogenous potentials are also generated while waiting for a stimulus to occur and are described as a contingent negative variation (CNV) or *Bereitschalts potential* (BP) [24]. CNV/BP reflects focusing of the attention required to perform the signalized activity [23]. Many authors are of the opinion that CNV is the best physiological indicator for selective attention [23, 25].

Event-related potentials (ERP) in patients diagnosed with schizophrenia

Studies on event-related potentials in schizophrenia patients are conducted to gain knowledge on pathophysiological and genetic susceptibility markers [26, 27]. The susceptibility marker, or endophenotype, is a heritable trait associated with a causative pathophysiological factor in inherited disease [27]. The susceptibility marker can form a basis for a decision on disorder classification and on a treatment method based on knowledge on causative factors of the disorder.

Some of the waves, P50, N100, MMN, P300, and N400 in particular, have been proposed as schizophrenia biomarkers [28]. Markers can either be a marker of a condition (episodic, associated with symptoms) or a trait (episodic, not related to clinical condition) [29]. Based on the study results, it has been proposed to use visual P300 potentials as a marker of the clinical status of schizophrenia (the study results indicate, amongst others, that the visual P300 potentials are an indicator of the severity of clinical symptoms) [30–32], while auditory P300 potentials could be used as a marker of a trait or susceptibility to schizophrenia [33].

Studies on event-related potentials are conducted both in patients diagnosed with schizophrenia and in clinically healthy members of families of schizophrenia patients. In many (though not all) studies on auditory P300 potentials, differences in this wave are observed in clinically healthy people from families of schizophrenia patients at high risk of schizophrenia, versus healthy people [34]. Differences in parameters of visual and auditory P300 waves versus a control group of healthy people are not a parameter characterizing only schizophrenic patients, as they are also observed in patients diagnosed with bipolar affective disorder, ADHD, or substance abuse [35, 36].

Concerning the waves with latency shorter than P300, many studies confirm deviations involving the amplitude of the wave P50 in patients diagnosed with schizophrenia; in these patients, a stronger P50 reply to the second click of the pair was also observed in stimulation with auditory stimuli, and this also refers to the gating deficit and a sensory overload of the cognitive fragmentation. In healthy members of families of schizophrenia patients, a weaker P50 suppression was also found, and this is considered as related to the genetic susceptibility to schizophrenia [37]. The researchers point towards the hippocampus as the structure responsible for the sensory gating process. The stimulus inhibition is disrupted by glutamate release, controlled by GABAnergic interneurons. Medicines reversing the inhibition of GABAnergic neurones improve sensory gating in schizophrenia patients. Also, the prefrontal cortex plays a role in sensory gating. Some researchers indicate that while the temporal cortex is of key

importance in generating P50, the prefrontal cortex is mainly responsible for the gating process (reduction in the P50 amplitude) [38]. In the study, statistically significant differences were observed between the P50 suppression deficit and greater problems with attention, poorer working memory, and reduced information processing rate [39].

The researchers evaluated relations between P50, and S1 and S2 amplitudes, and the cognitive functions in the studied schizophrenia patients. The results of this study indicate there are relationships between the results of the tests evaluating the cognitive functions of the subjects and P50, as well as between continuous attention and the S2 amplitude [40]. An attempt was made to correlate the P50 results with results of the cognitive tests in pharmacologically naive schizophrenia patients. No significant correlations were found [41]. A meta-analysis conducted by Ferreira-Santos et al. [42] shows that a rare stimulus causes a higher P2 amplitude and longer latency of that wave in studied patients diagnosed with schizophrenia than in a control group of healthy people. A meta-analysis conducted by McCleery et al. [43], concerning an analysis of face processing by patients diagnosed with schizophrenia, shows that the results strongly support the observed N170 and N250 differences versus the healthy people under analysis, this being a neurophysiological manifestation of disrupted face processing by people diagnosed with schizophrenia. The results of a systematic review of studies on face processing in schizophrenia confirm that the P100 amplitude in response to faces shown is lower in schizophrenia patients versus a control group of healthy people, and this indicates that disruption of socially important visual stimuli begins at earlier stages of processing than it was previously assumed. These studies also show emotional characteristics of deficits specific to patients [44]. Further studies also confirm a disrupted perception of faces expressing fear, and differences in P100 versus a control group of healthy people [45]. The language processing in patients diagnosed with schizophrenia is also characterized by imprecise associations within semantic networks, reflected in the studies as the reduced N400 amplitude [46].

Currently, MMN is considered as a possible marker for psychosis development in people at high risk of developing schizophrenia, and as an exceptional candidate for a biomarker which is characteristic and specific for that illness [47, 48]. Identification of a marker for susceptibility to psychosis in this population is of great importance for possible implementations of early interventions in the illness course [49, 50].

Bodatsch et al. [51] studied people from a group at a high risk for development of psychosis, and compared MMN in people in whom psychotic symptoms were not observed with MMN of people who developed schizophrenia. In people who developed schizophrenia, the MMN amplitude was lower already on the day of inclusion into the study, similar to the results in a group of people with a history of the first psychotic episode. The amplitude in people who did not develop the illness was similar as in a control group of healthy people. The studies show that MMN could be an indicator of a time for a transition into psychosis in people from the high risk group with more pronounced differences in MMN versus a control group of healthy people [51].

Studies conducted by Näätänen et al. [47, 48] show that MMN/P3 examinations repeated at certain intervals can provide more important information on schizophrenia progress in a subject from the high-risk group than either of these tests alone [52].

MMN/P3 amplitudes are reduced already at the prodromal stage of schizophrenia, and MMN indicates a relationship with disruptions in cognitive functions and functional disability already at this stage of the illness [53]. MMN was examined in hospitalized patients diagnosed with schizophrenia, experiencing auditory hallucinations. Significant differences were found versus a control group of healthy people concerning reduction in the amplitude in the studied group [54].

To this date, the number of studies evaluating the influence of the cognitive training on the brain bioelectrical function in schizophrenia patients is scarce. Kariofillis et al. [55] studied an effect of cognitive training (auditory or visual-spatial) on evoked potentials in patients diagnosed with schizophrenia. The computer training took 2 weeks. Evoked potentials were studied under the odd–ball paradigm before training, after 2 weeks of training, and 2 months after training. In both studied groups, a reduction in the P2 latency was observed after the training and in the follow-up study. An increased P2 amplitude was associated with positive symptoms and deteriorated functioning, while the longer latency was associated with more intense stereotypic thinking. The effects of the visual-spatial training associated with P2 latency lasted longer than in the event of the auditory training; however, this can mean that deficits of auditory discrimination in schizophrenic patients require more intense training to achieve a stable change [55]. In the study of Popov et al. [56], the researchers compared the memory training and the auditory training with the standard cognitive rehabilitation program. Both types of training influenced the normalization of M50 (magnetoencephalographic version of P50) during the four weeks of the study; however, this study was not continued and the length of this improvement remains unknown.

Rass et al. [57] studied the effect of visual and auditory rehabilitation exercises with a computer; they did not find a significant improvement in auditory P300 neither in the examination immediately after the applied influence, nor in the long-term follow-up.

The results of the studies on event-related potentials in patients diagnosed with schizophrenia indicate numerous deviations in the bioelectric brain activity during information processing, when compared to subjects with no mental disorders. Antipsychotic medicines do not improve cognitive functions in patients diagnosed with schizophrenia to a clinically satisfactory extent [4, 18–22]. This justifies the need for studies on non-pharmacological methods of brain neuromodulation and neurostimulation in these patients. Rehabilitation influences which would improve the cognitive functions in schizophrenia patients in a non-pharmacological way include transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS) and EEG Biofeedback. EEG Biofeedback enables targeted modulation of the brain activity in brain regions of a small volume. It has certain advantages over other neuromodulation techniques, such as transcranial magnetic stimulation, because people in whom EEG Biofeedback is conducted, learn to modulate their brain bioelectric activity as required without a need to use external stimulating equipment, and certain studies confirm that the effects of such influences are maintained for a long time [58]. The studies of the influence of the computer cognitive training indicate a possibility of the modification of the brain bioelectric activity in patients diagnosed with schizophrenia by applying the training. The encouraging results of tests on the influence of computer cognitive

training on the morphology of the event-related potentials in patients diagnosed with schizophrenia prompt further research on the possible rehabilitation influence of EEG Biofeedback on cognitive functions in these patients.

EEG Biofeedback-based rehabilitation in patients diagnosed with schizophrenia

Despite it being used in practice, the importance of EEG Biofeedback as a rehabilitation influence on cognitive functions in schizophrenia has not been fully ascertained.

EEG Biofeedback is based on concepts of instrumental conditioning, on assumptions that the brain bioelectrical function can be modulated by conditioning stimuli [35, 59]. This was demonstrated for the first time in the 1930s and 1940s by means of electroencephalography for alpha rhythm blocking [17, 59]. In the studies, auditory stimuli were associated with light stimuli, and the alpha rhythm was slowly trained to block after auditory stimulation. Subsequent studies conducted in the 1960s confirmed that a conditional block of the alpha rhythm is possible, as well as modulation of EEG synchronization, when using operant conditioning [17].

In the 1960s, it was demonstrated that neurotherapy can teach patients to promote the normal bioelectrical function of the brain by normalizing dysfunctional brain waves characterized by excessive activity of slow waves. Vialatt and Regan studies show that repeatable stimulation has a positive influence on components of response to a stimulus, changes in the strength of interneuronal connections and an increase in the number of synaptic connections [59–62].

Synchronic oscillations are correlated with cognitive functions: perception, attention and memory. A relationship was demonstrated between the theta rhythm and the processes of learning and memory; this rhythm can induce neuroplastic changes at the synaptic level as a long-term synaptic potentiation or depression, and this, in turn, is associated with the development or disappearance of engrams and long-term memory [62]. A rehabilitating potential of these influences is based on neuronal plasticity and learning of behaviors to improve cognitive functions [63–65]. Recommendations for patients diagnosed with schizophrenia, based on clinical experience, but not on randomized studies, include strengthening of the alpha activity in the right parietal region, a 2–5 Hz reduction in the activity in the left frontal region, as well as a reduction in the fast theta function in all regions in which the training was conducted [66]. Gruzelier [67] suggests that conducting an appropriate and long-term training may significantly clinically improve the functioning of patients diagnosed with chronic schizophrenia. The use of EEG Biofeedback is particularly interesting due to the development of connectomics and understanding of the brain as a network of interconnected elements, in which changes (modulations) in one region may have a significant impact on distant regions located away from the source of modulation.

The researchers evaluated a way in which the brain dynamically activates various regions, depending on the task difficulty. For the analysis, machine learning was used. A typical neurofeedback study using these tools could be performed in the following way: it would train a statistical model discriminating patterns of the brain activation

in response to various stimuli, presenting to the subject a stimulus, asking a person subjected to that influence to perform a mental operation based on that stimulus, uncoding of a changed pattern of the brain activation on the basis of the statistical model, adapting the stimulus on the basis of the new brain status, and asking the subject to repeat the mental operation.

An ability to transform the behavioral states on the basis of the underlying brain dynamisms is currently very useful in studies on mechanisms of attention [25]. Trousselard et al. used EEG Biofeedback to decrease experienced fear by controlling and visualizing pulse and heart rate variability, as well as synchronization of the respiratory rate and the heart rate in patients with clinically stable schizophrenia. The use of this form of influence did not induce hallucinations or other psychotic symptoms, instead it improved the emotional functioning of patients; however, it did not influence cognitive functions [68].

A case report describes a case of a 21-year-old man diagnosed with undifferentiated schizophrenia, treated with aripiprazole for 18 months from the illness onset and undergoing intense EEG Biofeedback training. In the quantitative EEG analysis, statistically significant disruptions of coherence were identified, occurring with the illness duration. Both influences led to a significant improvement in the patient's functioning [69].

In the study covering 51 drug-naive patients diagnosed with schizophrenia, QEEG was evaluated, and deviations in QEEG z-scores were verified versus the standards; this was used as a basis for determining EEG Biofeedback protocols. The aim was to reduce hypercoherences (areas showing increased coherency versus standard values). These areas were determined by analyzing QEEG in sequences for all brain regions.

Hypercoherency is understood as a lack of differentiation in brain function or a reduction in functional 'flexibility'. The improvement in the PANSS scale exceeded 20% and was statistically significant; it concerned both positive and negative symptoms. The analysis of the results of baseline QEEG justified the qualification of the brain bioelectrical function of all subjects in the studied group as similar to that in patients with chronic schizophrenia. After the EEG Biofeedback protocol was applied, the brain bioelectrical function of 19 patients differed significantly from the function in patients diagnosed with chronic schizophrenia [70].

rt-fMRI was used for the first time in 1995 [71], while evidence for a possibility to use this method for neurorehabilitation was provided in 2005 [72]. Changes in the fMRI response following EEG Biofeedback in targeted neural networks were already observed after a single 30-minute session [73], and in specific circumstances related to symptoms, after numerous sessions [74]. rt-fMRI and EEG Biofeedback can be used simultaneously, and this is when the spatial resolution of fMRI and the temporal resolution of EEG are used in the recording and analysis [75].

In 2013, Ruiz et al. [76] conducted rtf-MRI EEG Biofeedback training of the frontal insular cortex, bilaterally, in patients diagnosed with schizophrenia, and studied the influence of that training on recognizing facial emotions. They demonstrated an improvement in recognizing disgust, and it was correlated with the level of self-activation of the right insula. The training also led to an increase in the number of inputs

and outputs of the frontal insula. This study was the first to demonstrate the ability of teaching patients diagnosed with schizophrenia the volitional regulation of brain activity by using rt-fMRI EEG Biofeedback, changing the perception of emotions, as well as modulating connections in the network [76]. Cordes et al. [77] conducted a study in which an attempt was made to improve cognitive functions in studied patients diagnosed with schizophrenia by using the rt-fMRI EEG Biofeedback training. They specified the frontal part of the cingulate gyrus as a structure strongly involved in cognitive functions in the study on the rt-fMRI training. EEG Biofeedback resulted in the activation of the dorsal part of the frontal cingulate gyrus in the studied subjects diagnosed with schizophrenia, while in the studied subjects from the control group it activated its ventral part. Functionally, the dorsal part of the frontal cingulate gyrus is strongly activated in cognitive tasks, while the ventral part is activated in emotional processes. The authors of the study emphasize that rt-fMRI Biofeedback offers an opportunity to directly influence the targeted neural networks, with simultaneous monitoring of the effects of that influence [77].

Recapitulation

Cognitive disorders significantly undermine schizophrenia patients' ability to continue with professional work or studies. Antipsychotic medications show no significant improvement of cognitive functions [16]. Therefore, non-pharmacological forms of rehabilitation must be researched. The previous studies indicate numerous deviations at various stages of information processing in patients diagnosed with schizophrenia when compared to healthy subjects, and this justifies the need for the development of new methods influencing the bioelectric brain activity in cognitive rehabilitation of these patients. EEF Biofeedback is a method which could be used for rehabilitation of cognitive functions in schizophrenia patients. Despite it being widely used in practice, the effectiveness of EEG Biofeedback as a rehabilitation influence on cognitive functions in schizophrenia has not been fully ascertained. Currently, the number of studies evaluating the effect of EEG Biofeedback therapies on the event-related potential as a neurophysiological reflection of cognitive functions in schizophrenia patients is very scarce. Researchers' recommendations for patients diagnosed with schizophrenia, based on clinical experience, include the strengthening of the alpha activity in the right parietal region, a 2–5 Hz reduction in the activity in the left frontal region, as well as a reduction in the fast theta function in all regions in which the training is conducted. Conducting an appropriate and long-term training may significantly clinically improve the functioning of patients diagnosed with chronic schizophrenia.

The determination of the best protocols for EEG Biofeedback in persons diagnosed with schizophrenia requires further research. The duration of the improvement in cognitive functions, achieved by this method, should also be evaluated. The modern methods for data analysis and connectomics concepts create a potential field for new therapeutic protocols.

The widely applied EEG Biofeedback is a possible tool for such influences, while the body of research studies that may show the value of this method in the rehabili-

tation of patients with schizophrenia currently appears to be insufficient, and there is no scientific evidence from randomized studies for EEG Biofeedback usefulness in schizophrenia treatment. There is a need for randomized studies in patients diagnosed with schizophrenia, with QEEG or fMRI conducted before and after EEG Biofeedback, as well as a long-term follow-up comparing EEG Biofeedback to the standard pharmacotherapy. At the moment, Bolea [66] proposes for EEG Biofeedback in patients diagnosed with schizophrenia to be conducted by experienced practitioners, paying particular attention to the strengthening of alpha in the right parietal region. At the moment, the recommendation of this method in the cognitive rehabilitation of patients is a therapeutic experiment.

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