PROTOCOL OF A SCIENTIFIC PROJECT

To evaluate the effectiveness of rehabilitation in patients with schizophrenia using neurofeedback, clinical scales and tests, brain-derived neurotrophic factor (BDNF) and electrophysiological markers (ERPs, mapping, QEEG)

Aim of the study

The aim of the scientific project was to verify if neurofeedback can be a new form of therapeutic / rehabilitation intervention for people with schizophrenia. The project involved comparing the existing form of standard rehabilitation with a new galvanic skin response neurofeedback (GSR-NF) therapy. The experimental project was approved by the Bioethics Committee of the Medical University of Lublin (Poland), number KE-0254/35/2016.

Hypothesis

Neurofeedback training improves clinical, cognitive and psychosocial functioning of people with schizophrenia to a greater extent than standard rehabilitation alone.

Inclusion and Exclusion Criteria

To demonstrate the effect of different forms of therapy, randomly selected patients, males, with a diagnosis of schizophrenia, in remission for ≥1.5 years, were included in the study. The inclusion criteria: patient's consent, clinical diagnosis of schizophrenia (DSM-5), adults 18-65y, right-handedness. The exclusion criteria: no current neurological diseases, mental disability, alcohol neither psychoactive substances addiction.

All patients were randomly assigned to three groups:

A- Gr. 1 consisted of patients who did not receive standard rehabilitation interventions (N=18),
B- Gr.2 consisted of patients who received a standard rehabilitation program according to an established schedule (N=26),
C- Gr. 3 consisted of patients undergoing GSR-NF training (N=19).

Tests, scales, biochemical and electrophysiological markers

To determine the effect of therapy in the clinical, cognitive and psychosocial domains, all patients were examined twice at an interval of 3 months based on selected tests, scales, biochemical and electrophysiological markers (clinical- PANSS, cognitive - CTT, d2, psychosocial - BCIS, AIS, GSES, biochemical – BDNF, and electrophysiological – ERPs, QEEG:

1. Positive and Negative Syndrome Scale (PANSS); for measuring symptoms, syndromes and general severity of schizophrenia;

2. Color Trails Test, CTT; part 1 (CTT-1) to assess visual performance and psychomotor speed, when connecting numbers in a string from 1 to 25 and part 2 (CTT-2) to assess performance skills and working memory, when connecting numbers with simultaneous selection of a colour sequence in a string from 1 to 25;

3. D2 test of attention, d2; to measure processing speed (amount of material processed in a specific time), quality of work (accuracy and the errors made) and persistence as an indicator of features of behaviour manifested during work (irritation, stability of work or lack of it, discouragement, fatigue); the level of concentration was a result of the interaction of these behaviours, and a product of the stimulus and control coordination;

4. Beck Cognitive Insight Scale, BCIS; to evaluate patients' self-reflectiveness and their self-certainty in their interpretations of their experiences;

5. Acceptance of Illness Scale, AIS; to estimate limitations imposed by the illness, lack of independence due to the illness, and reduction of self-esteem;

6. General Self-Efficacy Scale, GSES; to check patients' ability to cope with stressful or challenging social demands, relying on their self-efficacy;

8. Brain-derived neurotrophic factor, BDNF; serum level of BDNF was determined following blood sampling into a clot tube using a non-contact method; laboratory levels were determined immunoenzymatically with ELISA technique;

7. Quantitative Electroencephalography - Neurofeedback, QEEG-NF; to map and statistically meta-analyze EEG recordings in relation to neurofeedback stimulation.

Procedures and equipment

The GSR-NF training sessions were held twice a week for three months. The training scheme assumed the gradation of task difficulty, taking into account the individual progress of the workshops. The galvanic skin response (GSR) has two components, the general tonic-level electrodermal component (*skin conductance level, SCL*) and the phasic component (*skin conductance responses, SCRs*), which are indispensable diagnostic parameters in the management of mental disorders. They can be used as reference in GSR-NF to modulate the patient's emotional state depending on the current needs. The GSR-NF training sessions were conducted in the CENTER (relaxation), BALANCE (concentration), and INSECTS (self-control) modules using a Digi-Track apparatus (EEG-DigiTrack Biofeedback- EEG + SpO2 + HR). NF trainings were performed in accordance with the approved schedule; training was conducted in a sound-proof room always at a specified time, mainly after the breakfast. Patients were requested not to drink coffee or smoke for one hour before the training. The measurements

were made by the exosomatic method with DC (*direct current*) using electrodes placed on the index and ring fingers of the left hand and connected to the device displaying the successive training modules. The training exercises in the individual modules were presented on the monitor screen, and the patient performed them in accordance with the instruction. The task of the subjects performing the CENTER exercise, in which they had to bring bubbles appearing on the screen into a circle in the centre of the screen, was to achieve relaxation, especially by controlling/modulating their breath and heart rate. The greater the relaxation, the faster the patient performed the task and went to the next level of the module. Training in the BALANCE module was designed to improve concentration. The subjects' task was to achieve a state of maximum concentration, as they placed and balanced a ball in the middle of a tilting board. The task in the INSECT module was to reach a state of internal balance between cognitive and executive functions. The subjects had to recognize moving and hidden insects on the monitor screen and click on them with the mouse. The slow movement of the insects reflected gradual achievement of internal balance during training, which made it easier for the patient to complete the task. The GSR apparatus registered the neurophysiological changes which determined the subjects' psychophysical condition, on the basis of their skin resistance. The training time was set by the computer program and was 5 min for the CENTER and BALANCE modules and 10 min for the INSECT module. At the end of each session, the patient's results were recorded graphically. Prior to NF training and after 3-month program the level of clinical, cognitive and social deficits was assessed.

The standard rehabilitation consisted in enriching the daily routine with social activities that building up team competences, playing social roles, personal acceptance, and growing own independence. At least one teamwork session was offered daily.

The EEG potentials were tested using a Cognitrace apparatus. Twenty one cup electrodes (an international 10–20 Electroencephalogram system with ear electrodes (ground and reference)) – Fp-z, F-z, C-z, P-z, O-z, Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, T6, two ear electrodes A1 and A2, and GND, were attached to the patient's head. The patient stayed in a separate, dark room. The test was performed with the subject in a sitting position, with eyes closed, and wearing earphones through which the acoustic stimuli were delivered in accordance with the oddball paradigm (a series of tones with frequencies in the range from 1000 Hz to 2000 Hz of ca. 70 dB were presented for ca. 100 ms in a random sequence). The P300 test, determining exogenous cognitive potential, was performed twice. One test lasted 3 min and 20 sec and contained 80% of frequent stimuli and 20% of rare (important) stimuli. The subject was required to respond to the rare stimuli by pressing the button. The measurements were performed twice. QEEG was performed in each patient, three months apart, before and after program. QEEG NF, in which the amplitudes and frequencies of the individual waves were performed using the Digi-Track apparatus. The patients had two electrodes placed on their heads, in the F-z and C-z regions, and the Fast Fourier Transform (FFT) algorithm transformed the raw EEG recording into frequencies for statistical processing (the so-called QEEG power spectrum). In the studied group, the brain rhythm from the two selected areas was evaluated twice.

Primary outcome measures

Neurofeedback training improves the functioning of people with schizophrenia to a greater extent than standard rehabilitation alone, what can be demonstrated by:

1. reduction of the severity of psychopathological symptoms (scale: PANSS),
2. improvement in cognitive and psychosocial performance (scales: BCIS, CTT-1, CTT-2, d2, AIS and GSES),

   which correspond to biochemical and electrophysiological markers:

3. serum level of BDNF (brain derived neurotrophic factor),
4. event-related potentials (ERP) and Quantitative Electroencephalography – Neurofeedback-dependent (QEEG-NF).

Secondary outcome measures

The neurofeedback training can strengthen and extend the scope of clinical, cognitive and psychosocial rehabilitation of schizophrenia patients, what can be demonstrated comparing pre- and post-therapy markers.

Statistical Analyzes

The values of the investigated variables were presented as means and standard deviations. The sociological and demographic parameters were presented as numbers and percentages. The results were compared using Student's t-test for dependent samples, non-parametric Mann-Whitney U-test and Spearman's rank correlation coefficient. Differences were considered to be statistically significant at $p < 0.05$. Analyzes were performed using Statistica 13.3.

Ethical Issues

The study protocol was approved by the local Bioethics Committee – approval no. KE-0254/35/2016. All the patients invited to take part in the study gave their written informed consent. The study was granted by Medical University of Lublin.