Activity of BDNF and MMP-9 in Structural Synaptic Modulation in Patients with Schizophrenia Undergoing Rehabilitation

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Abstract

The aim of the study was to evaluate the levels of brain derived neurotrophic factor (BDNF) and matrix metalloproteinase-9 (MMP-9) in two groups of schizophrenic patients receiving rehabilitation and to find out whether there existed relationships between the levels of these biomarkers and the severity of psychopathological symptoms, changes in event-related potentials (ERP), and quantitative EEG parameters. The study involved two groups of patients diagnosed with schizophrenia in remission who participated in a 12-week conventional rehabilitation program (Group 1) or Biofeedback training (Group 2). The following parameters were assessed: BDNF levels, MMP-9 levels, ERP, QEEG, and psychopathological symptoms (PANSS). (1) The magnitude of changes in the investigated parameters was similar in both groups. (2) Comparable therapy outcomes were obtained for all the dependent variables except for BDNF, whose levels were higher in the GSR-BF patients. GSR Biofeedback can be used as a new alternative to conventional rehabilitation. BDNF can be used as a target in the evaluation of the effectiveness of various rehabilitation modalities, in contrast to MMP-9, which, despite its role in neuromodulation, cannot be treated as a marker of treatment outcomes.

Introduction

Schizophrenia is a mental disorder with a multi-factorial aetiology [1]. Because of its chronic nature, it leads to numerous limitations in the activities of daily living of patients in professional, family and social settings. These limitations are due to the progressively deteriorating cognitive functions, such as concentration, attention, working memory, emotions, and executive functions [1–10].

The deepening dysfunctions are associated with disturbances in the activity of various brain regions, mainly the frontal and temporal regions, limbic and midline brain structures and basal ganglia [2–9]. They can be alleviated by systematic pharmacological treatment and rehabilitation.

Among the various methods that can be effectively used in the rehabilitation of patients suffering from schizophrenia, the most commonly mentioned ones are transcranial magnetic stimulation (TMS), transcranial direct current stimulation (t-DCs) and Biofeedback [11, 12].

The therapeutic effect of these methods is based on a stimulation mechanism that leads to the restructuring of neuronal connections [11–14] by inducing changes in the bioelectric activity of the brain and activating the glutamate receptors NMDA (an excitatory neurotransmitter), AMPA (an ionotropic transmembrane receptor) and BDNF (brain derived neurotrophic factor, a member of the nerve growth factor family of proteins) [15–22].

The anatomical reorganization of neural circuits depends on biochemical changes and the accompanying changes in the action potentials in dendritic spines (sprouting) [12, 13], which increase neurotransmitter release, allowing the formation of new connections based on long-term potentiation (LTP) [23–26].

There are many biomarkers that participate in these biochemical structural changes. One of them is extracellular matrix metalloproteinase-9 (MMP-9), which is necessary for the transformation of pro-BDNF (a glycosylated precursor protein) into mature BDNF (a non-glycosylated protein) [16, 18, 27–33].

MMP-9, as an extracellular catalyst of metabolism plays an essential role in the cycle of changes associated with the activation of BDNF (a dopaminergic neurotransmitter protein), which is responsible, among others, for the improvement of cognitive function [34, 35]. Abnormal MMP-9 levels inhibit BDNF activity and lead to the so-called deficit syndrome (negative symptoms, cognitive deficits) which characterizes individuals diagnosed with schizophrenia [30, 35–39].

The deficit symptoms caused by disease-induced changes in the brain's bioelectric activity [40] can be confirmed in studies using modern neuroimaging techniques (magnetoencephalography MEG, positron emission tomography PET, functional magnetic resonance fMRI) as well as studies of qualitative (EEG) and quantitative (QEEG) changes in brain activity [41, 42] and changes in event related potentials (ERP) [40, 43]. These methods and the physiological markers associated with signalling and reorganization may also turn out to be effective in assessing the outcomes of rehabilitation therapy [42, 44–46].

This present study is an attempt to assess the role of BDNF and MMP-9 in structural synaptic modulation in people with schizophrenia following two different rehabilitation programs and to find out whether there exists a relationship between the rehabilitation interventions used and changes in the investigated parameters. The aim of the experiment was to compare two groups of male patients with a clinical diagnosis of schizophrenia, in the remission period, recruited according to inclusion criteria. Group 1 were men who

followed a standard rehabilitation program and Group 2 were men who received galvanic skin response (GSR) Biofeedback training (GSR-BF).

The working hypothesis was that GSR-BF training should improve the cognitive functions of schizophrenic patients with an efficiency similar to or higher than that of standard rehabilitation interventions, as demonstrated by:

- a reduction in cognitive deficits (changes in ERP),
- a reduction in the severity of psychopathological symptoms (PANSS scale),
- quantitative changes in the EEG (attention – theta/beta ratio, concentration – theta/SMR ratio),
- changes in blood serum levels of BDNF and MMP.

Subjects, Materials And Methods

Participants

Forty-four male patients with schizophrenia in remission were recruited for the study. The time of remission before the study was at least four months in both groups. All patients were qualified for tests according to the inclusion criteria, which prohibited the inclusion of patients with mental retardation. The following study inclusion criteria were used: a patient's informed consent, a clinical diagnosis of schizophrenia (DSM-V), age (18–50 years), right-handedness, no history of neurological diseases, and exclusion of mental impairment, dementia and addiction to alcohol. Group 1 (26 individuals) included patients who followed a conventional rehabilitation program and Group 2 (18 individuals) was comprised of patients receiving GSR-BF training.

A comparative analysis showed that there were no significant differences between the groups in terms of age, education, place of residence, outpatient treatment, medication regimes, and suicide attempts. The mean age of Group 1 subjects was 36 years (M = 36.38; SD = 8.87) and those in Group 2–37 years (M = 37.22; SD = 6.38). In Group 2, four patients had primary education, 5 had vocational education, and 9 had secondary education. In Group 1, one patient had primary education, 6 had vocational education, 13 had secondary education, and 5 had tertiary education. Most of the patients (14) in Group 2 lived in large cities of over 100,000 inhabitants, two lived in smaller towns (below 100,000 inhabitants), and two were country-dwellers. In Group 1, four patients were inhabitants of large cities, 10 lived in smaller towns, and 11 lived in the countryside. All subjects received atypical neuroleptics; in three patients from Group 1, they were administered via the IM route. Patients in both groups reported irregular treatment in outpatient clinics (Group 2–6 men and Group 1–16 men) and admitted to no suicide (Group 2–11 men vs. Group 1 – 17 men).

Small differences between the groups were found with regard to marital status, number of children, number of hospital admissions, employment, household composition, and family history of mental illness. There were 15 single men in Group 2, and 23 in Group 1. Similar numbers of patients in both groups reported having no children (Group 2–16 persons and Group 1–23 persons). The mean number of hospital admissions was also similar for the two groups (Group 2–6.8 and Group 1–8). The patients received their income from a disability pension (Group 1–16 persons and Group 2–12 persons), odd jobs (Group 1–5 persons and Group 2–1 person) and social security (Group 2–4 persons and Group 1–2 persons). Similar numbers of respondents reported living with their parents (Group 2–13 persons and Group 1–21 persons). Also, similar numbers of patients had no family history of mental illness on the mother's side (Group 2–17 persons and Group 1–24 persons) or on the father's side (Group 2–16 persons and Group 1–18 persons).

In line with the experimental design, the patients recruited for the study were examined twice. The first (baseline) examination was associated with recruitment and obtaining the patient's informed consent; the second (follow-up) examination was conducted three months after inclusion in the programme (approval of the Bioethics Committee KE-0254/35/2019). The conventional rehabilitation program (Group 1) realized daily and systematically, involved various forms of training: personal hygiene, managing medications, personal finance and budgeting, practical skills, social skills, communication skills, as well as sports, art and social activity classes, and psychological counselling. Each patient's rehabilitation schedule was based on the type of deficits the patient had, and daily plans were drawn up by ward staff (doctor, psychologist, nurse). All patients were obliged to take an active part in the entire series of rehabilitation sessions and follow the rehabilitation schedule. GSR-BF trainings (Group 2) included exercises in three training modules, which were tailored to address the deficits reported by the patients, mainly in the areas of concentration, relaxation and self-regulation. The standard rehabilitation program (Group 1) and GSR-BF training (Group 2) were used as independent variables.

Dependent variables

To evaluate the effect of the two types of rehabilitation interventions, we measured symptom severity using the PANSS scale, took blood samples to assess serum concentrations of BDNF and MMP-9 concentration, and recorded event-related potentials (ERP) and quantitative EEG (QEEG) before and after therapy. All these parameters were included in the analysis as dependent variables.

Apparatus

The GSR-BF training sessions were performed using an Elmiko Digi-Track apparatus in the following training modules: *CENTER* (relaxation), *BALANCE* (concentration) and *INSECTS* (self-regulation). Exercises were conducted twice a week for 3 months. Twenty-four measurements in three modules (72 measurements in total) were obtained for each participant. The study was carried out in accordance with the adopted plan: the training sessions were held in a quiet room, at a scheduled time, after a morning meal. The patients had not drunk coffee or smoked cigarettes for one hour before the test. Exosomatic DC (direct current) measurements were made using electrodes attached to the index and ring fingers of the left hand and coupled to a device which displayed the training modules one by one. The training tasks in each module were displayed on a monitor screen, and the patient did the exercises following the instructions. The training time was determined by a computer program, and the subject's results were recorded graphically at the end of each session. In total, 1,296 measurements were obtained (72 measurements for each patient).

ERPs were recorded using a Cognitrace amplifier. Twenty one cup electrodes (Fpz, Fz, Cz, Pz, Oz, Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, T6), two ear electrodes A1 and A2, and a GND electrode were mounted on the patients' head. The patient was seated in a separate, darkened room. They were instructed to keep their eyes closed and were wearing headphones, through which acoustic stimuli were presented to them according to the oddball paradigm (a series of tones of different frequencies [1000 Hz and 2000 Hz]] and a volume of about 70 dB presented in a random order over a time of 100 ms). The P300 test, which measures the endogenous cognitive potential, was performed twice. One trial lasted 3 min and 20 s and contained 80% of frequent stimuli and 20% of rare (meaningful) stimuli to (the latter of) which the patient responded by pressing the button. Measurements were performed twice in each group.

Quantitative EEG (QEEG) was performed using the Elmiko Digi-Track apparatus. Two electrodes were placed on the patient's head at Fz and Cz to record the activity of the brain in these regions, and the Fast Fourier Transform algorithm (FFT) was used to transform the raw EEG frequency signal into a QEEG power spectrum. Rhythms from the selected regions were evaluated twice in both groups: at the beginning of the experiment and at a 3-month follow-up [47].

Reagents

Fasting BDNF and MMP-9 tests were performed using native blood samples collected by the non-contact method. Blood serum concentrations of BDNF were measured by ELISA according to the Human BDNF ELISA Kit user manual (R&D Systems), and the concentrations of MMP-9 in serum were tested using a Human MMP-9 ELISA Kit (Biorbyt).

The tests were performed twice in each group, at the beginning and at the end of the experiment.

Statistical analyses

The results were analysed statistically using STATISICA software (Statsoft), and the significance of differences was assessed with the non-parametric Mann-Whitney U test and Spearman’s rank correlation coefficient.

Results

To verify the assumptions of the study and assess the effectiveness of GSR-BF therapy and standard rehabilitation in patients with schizophrenia, a comparative analysis of the results was performed. Table 1 presents measurements of serum levels BDNF and MMP-9 as well as other measurements which differed statistically significantly between groups. The remaining results, which were not statistically significant, are not shown.

Table 1
Variables for which statistically significant differences were obtained between baseline and follow-up measurements in both groups (Group 1, Group 2)

Variable	Group	Examination I (baseline)		Examination II (follow-up)		Difference	Significance of differences		Confidence level	
		M	SD	M	SD		T	P	-95%	+ 95%
BDNF (ng/ml)	**2**	44.78	10.69	55.50	10.76	10.72	-6.185	< 0001	7.06	14.38
	1	50.16	11.38	52.96	10.70	2.80	-1.575	0.128	0.87	6.47
MMP9 (ng/ml)	**2**	698.06	366.01	796.94	395.77	98.88	-1.51	0.15	-39.28	237.03
	1	687.41	211.12	775.84	385.89	88.43	-1.46	0.16	-36,71	213.57
PANSS-POS	**2**	9.06	2.04	7.50	2.23	-1.56	10.719	< .001	-1.86	-1.25
	1	9.28	2.01	8.24	2.01	-1.04	6.186	< .001	-1.39	-0.69
PANSS-NEG	**2**	13.94	3.92	11.83	4.48	-2.11	8.304	< .001	-2.65	-1.57
	1	15.16	3.51	14.08	4.47	-1.08	2.596	0.016	-1.94	-0.22
PANSS-GEN	**2**	24.83	3.35	22.61	3.71	-2.22	10.736	< .001	-2.66	-1.79
	1	27.44	3.31	25.88	4.20	-1.56	2.742	0.011	-2.73	-0.39
PANSS-TOT	**2**	47.83	8.49	41.94	9.64	-5.89	11.834	< .001	-6.94	-4.84
	1	51.92	7.22	48.20	9.36	-3.72	3.375	0.003	-6.00	-1.45
F- z N1 (amplitude)	**2**	-3.95	2.53	-5.36	1.93	-1.41	2.588	0.020	-2.57	-0.26
	1	-5.29	3.93	-6.58	3.44	-1.30	1.263	0.219	-3.42	0.83
C- z P2 (latency)	**2**	208.82	14.81	196.06	18.27	-12.77	2.643	0.018	-23.01	-2.52
	1	203.92	23.94	205.04	21.70	1.13	-0.185	0.855	-11.43	13.68
QEEG C-z theta/beta	**2**	1.92	0.57	2.29	0.88	0.37	-2.632	0.018	0.07	0.67
	1	2.35	0.94	2.49	0.82	0.14	-1.453	0.159	-0.06	0.34
QEEG C-z theta/SMR	**2**	2.07	0.64	2.37	0.80	0.30	-2.358	0.031	0.03	0.57
	1	2.49	1.00	2.60	0.83	0.10	-1.013	0.321	-0.10	0.31

M – mean; SD – standard deviation; T – Student's t-test; P – level of significance, Group 1 – patients following a standard rehabilitation program, Group 2 – patients participating in GSR-BF training sessions; PANSS-POS – total positive items, PANSS-NEG – total negative items, PANSS-GEN – total general items, PANSS-TOT – total score; F-z – frontal brain region; C-z – central brain region.

The analyses show that both forms of therapy, conventional rehabilitation interventions (Group 1) and GSR-BF-based interventions (Group 2), reduced the severity of psychopathological symptoms in the examined patients. The two groups differed clearly in BDNF levels and ERP and QEEG parameters. GSR-BF patients showed an improvement in concentration (theta/beta and theta/SMR ratios) and initial stimulus analysis (N1 amplitude, P2 latency). This finding corroborates the significant increase in BDNF levels.

Because the effect of a therapeutic intervention is indicative of changes in diagnostic parameters, in the further part of the study an attempt was made to determine which form of therapy was more effective. To this end, analyses were carried out to show differences between the interventions (groups) in the magnitude of changes from baseline to follow-up measurements and correlations between the values of these changes for each group. The results are shown in Tables 2–4. A statistically significant difference in the magnitude of change was only observed for BDNF. The results for MMP-9 measured in blood were not significant and neither were the results for other parameters not shown in Table 2.

Table 2
Statistically significant difference between groups in the magnitude of change from baseline to follow-up measurements

Biomarkers	**Group 1**		**Group 2**		**Comparison between groups**	
(difference in the magnitude of change)	**M**	**SD**	**M**	**SD**	**T**	**P**
BDNF (brain derived neurotrophic factor**) [ng/ml]**	**2.80**	**8.89**	**10.72**	**7.35**	**-3.093**	**0.004**
MMP-9 (matrix metalloproteinase-9) [ng/ml]	88.43	309.82	98.88	277.82	-0.115	0.909
M – mean; SD – standard deviation; T – Student's t-test; P – level of significance						

In the case of BDNF, a statistically significant difference between measurements was observed in the GSR-BF patients (Group 2: M = 10.72; SD = 7.35 vs. Group 1 M = 2.80; SD = 8.9). In the case of other variables, no statistically significant differences in the magnitude of change in measurements were observed – the changes were similar in both groups.

Table 3
Correlations between the magnitude of changes from baseline to follow-up measurements in the group of patients following a standard rehabilitation program (Group 1)

Variable	**Group 1 (standard rehabilitation program)**									
	PANSS POS	**PANSS NEG**	**PANSS GEN**	**PANSS TOT**	**BDNF (ng/ml)**	**QEEG theta/beta**	**QEEG theta/SMR**	**N1 ampl.**	**P2 latency**	**MMP9 (ng/ml)**
PANSS POS	–	*0.315*	*0.588**	*0.712**	*−0.211*	*0.034*	*0.078*	*0.193*	*−0.405*	*0.393*
PANSS NEG	*0.315*	–	*0.568**	*0.799**	*−0.343*	*0.388*	*0.399*	*−0.028*	*−0.100*	*−0.202*
PANSS GEN	*0.588**	*0.568**	–	*0.880**	*−0.085*	*0.038*	*0.042*	*0.272*	*−0.030*	*0.212*
PANSS TOT	*0.712**	*0.799**	*0.880**	–	*−0.221*	*0.147*	*0.168*	*0.192*	*−0.174*	*0.150*
BDNF(ng/m)	*−0.211*	*−0.343*	*−0.085*	*−0.221*	–	0.101	0.140	0.433	−0.117	−0.011
QEEG theta/beta	*0.034*	*0.388*	*0.038*	*0.147*	0.101	–	0.904*	0.007	−0.498*	−0.099
QEEG theta/SMR	*0.078*	*0.399*	*0.042*	*0.168*	0.14	0.904*	–	0.181	−0.488*	−0.248
N1 (amplitude)	*0.193*	*−0.028*	*0.272*	*0.192*	0.433	0.007	0.181	–	−0.555*	−0.027
P2 (latency)	*−0.405*	*−0.100*	*−0.030*	*−0.174*	−0.117	−0.498*	−0.488*	−0.555*	–	0.123
MMP-9 (ng/ml)	*0.393*	*−0.202*	*0.212*	*0.150*	−0.011	−0.099	−0.248	−0.027	0.123	–
Legend: correlations were assessed using Spearman's rank correlation coefficients (*italics*) and Pearson's r; statistically significant correlations ($p < 0.050$) are marked with an asterisk (*)										

Correlation analysis showed that in Group 1, the standard rehabilitation exercises reduced the severity of positive and negative symptoms measured on the PANSS scale and improved attention and concentration (QEEG), as confirmed by the shortened P2 latency.

Table 4
Correlations between the magnitude of changes from baseline to follow-up measurements in the group of patients participating in GSR-BF training sessions (Group 2)

Variable	Group 2 (Biofeedback training program)									
	PANSS POS	PANSS NEG	PANSS GEN	PANSS TOT	BDNF (ng/ml)	QEEG theta/beta	QEEG theta/SMR	N1 ampl.	P2 latency	MMP9 (ng/ml)
PANSS POS	–	*0.737**	*0.851**	*0.877**	*−0.770**	*0.171*	*0.274*	*−0.106*	*0.074*	*−0.002*
PANSS NEG	*0.737**	–	*0.846**	*0.920**	*−0.857**	*0.004*	*0.018*	*−0.228*	*−0.061*	*−0.047*
PANSS GEN	*0.851**	*0.846**	–	*0.956**	*−0.804**	*0.112*	*0.169*	*−0.103*	*0.172*	*−0.202*
PANSS TOT	*0.877**	*0.920**	*0.956**	–	*−0.832**	*0.149*	*0.209*	*−0.166*	*0.061*	*−0.112*
BDNF(ng/ml)	*−0.770**	*−0.857**	*−0.804**	*−0.832**	–	0.123	0.057	0.153	0.296	0.016
QEEG theta/beta	*0.171*	*0.004*	*0.112*	*0.149*	0.123	–	0.875*	−0.161	−0.127	0.137
QEEG theta/SMR	*0.274*	*0.018*	*0.169*	*0.209*	0.057	0.875*	–	−0.298	−0.297	0.177
N1 (amplitude)	*−0.106*	*−0.228*	*−0.103*	*−0.166*	0.153	−0.161	−0.298	–	0.035	−0.066
P2 (latency)	*0.074*	*−0.061*	*0.172*	*0.061*	0.296	−0.127	−0.297	0.035	–	−0.411*
MMP-9 (ng/ml)	*−0.002*	*−0.047*	*−0.202*	*−0.112*	0.016	0.137	0.177	−0.066	−0.411*	–

Legend: correlations were assessed using Spearman's rank correlation coefficients (*italics*) and Pearson's r; statistically significant correlations ($p < 0.050$) are marked with an asterisk (*)

Correlation analysis conducted in Group 1 showed that Biofeedback training reduced the severity of positive and negative symptoms measured on the PANSS scale, increased BDNF levels, improved attention and concentration (QEEG), shortened P2 latency, and increased MMP-9 levels.

Discussion

The increase in BDNF levels observed in patients who received GSR-BF may support the superiority of this type of medical intervention. BDNF is not only a growth factor for neurons in the prenatal period. In adults, BDNF attenuates neuronal degeneration, is responsible for neural (synaptic) plasticity, and affects the development of serotoninergic, cholinergic, noradrenergic and dopaminergic neurons [48]. BDNF is expressed most robustly in the hippocampus and cerebral cortex, which is reflected in the fact that it is involved in the interactions of the human body with the environment [49]. What makes these interactions possible are the processes of learning and memory, associated with the hippocampus, in which a vital role is played by long-term potentiation (LTP) and long-term depression (LTD) of synaptic transmission [50, 51]. Bearing in mind that the pathogenesis of schizophrenia is associated with dopaminergic, glutamatergic, GABA-ergic and serotonergic systems, mainly within the hippocampus and frontal lobes, it is likely that BDNF plays a key role in brain adaptation processes in schizophrenic patients undergoing rehabilitation. On the one hand, then, disturbances in the brain levels of BDNF may play an aetiologic role in the development of schizophrenia-type disorders, and on the other, the concentration of BDNF may be a measure of the effectiveness of a rehabilitation procedure. Reduced cortical and hippocampal BDNF expression has been recorded in post-mortem studies of schizophrenic patients. The number of TrkB receptors, which are the primary molecular targets of BDNF action, was also reduced in those patients [48, 52]. A decrease in the levels of this factor has been associated with impaired brain plasticity accompanied by neuronal atrophy and increased neuronal apoptosis. Restoration of the BDNF-dependent ability of the brain to adapt to environmental conditions always requires appropriate stimulation, e.g. physical and mental exercises which involves increasing intraplanar transmission of information in accordance with the so-called stimulus effect [53].

Such stimulation, for instance GSR-BF stimulation, induces changes in intracellular transmission, resulting in an altered expression of genes and proteins. At the molecular level, this is manifested by induction of long-term potentiation (LTP) of hippocampal cells, which

is primarily dependent on the glutamatergic receptors AMPA and NMDA [54]. The functional and structural changes within synapses, which underpin neural plasticity, are initiated by the activation of a synaptic terminal, which results in the opening of AMPA-receptor ion channels and the influx of sodium ions into the cell. The increase in intracellular sodium levels results in the removal of magnesium ions which block NMDA receptors and a secondary influx of calcium ions (in the presence of glutamate) through NMDA receptor-coupled ion channels. The early phase of LTP begins about 10–20 minutes after stimulation and lasts for about 2 hours. During this time, calcium ions present in the cell activate calcium/calmodulin-dependent protein kinase (CAMKII), protein kinase C (PKC) and tyrosine kinases [55]. Under their influence, the proteins responsible for synaptic transmission become modified. Maintenance of LTP, which may persist for days and weeks (or even months), requires changes in the expression of genes and synthesis of proteins that control the internal neuronal mechanisms in unison with extraneuronal, glial signalling [56–58]. These changes lead to alterations in presynaptic and postsynaptic architecture, manifested by the formation of local protein aggregates, an increase in glutamate receptor density and, at the functional level, transfer of short-term memories from the hippocampus to the cortex.

An important role in brain plasticity is also played by a process opposite to LTP, namely, long-term synaptic depression (LTD). LTD involves BDNF as a factor that affects the activity of NMDA receptors involved in LTD. The study of the role of BDNF as a marker of schizophrenia and the effectiveness of its treatment would require measurement of the concentrations of this factor in the individual parts of the brain, because blood BDNF levels are a sum of the concentrations of this factor in the CNS and at the periphery. Research so far, however, has shown that there exists a significant correlation between brain and blood BDNF levels [52, 59], which entails that the BDNF levels measured in our study reflect the concentrations of this factor in the brains of schizophrenic patients undergoing different forms of rehabilitation. This is confirmed by our results, which demonstrate that there exists a relationship between the activity of the neurotransmission system and neuroplastic reorganization at the synaptic level. These processes give rise to changes in the cognitive system that are associated with the generation of the theta rhythm and an increase in the amplitude of the N1 wave and prolongation of P2 wave latency [60–62]. The occurrence of such changes is indicative of improvement in information reception and initial stimulus analysis and points to a reduction in the participants' levels of positive and negative symptoms.

A second potential marker of schizophrenia and the effectiveness of its treatment analyzed in this study was serum level MMP-9. A growing number of reports indicate that enzymes from the group of metalloproteinases (MMPs) are involved in the development of diseases of the CNS [30]. Like BDNF, MMPs play an important role in neural (synaptic) plasticity. Other functions of MMP in the CNS include regulation of the permeability of the blood–brain barrier and participation in the regeneration of myelin sheaths. The "central" effects of MMP have been most fully characterized for MMP-9 [63]. Its most important role is in the processes of modification of the structure of synapses during LTP. Local transformation of synapses as a result of LTP involves, on the one hand, the formation of local protein aggregates, and on the other – the activity of proteolytic enzymes from the MMP family. Their activity leads, among others, to the formation of new dendritic spines and changes in the density of the glutamate receptors (AMPA, NMDA) which mediate LTP and LTD. Similarly to BDNF, MMPs, and especially MMP-9, are postulated to be implicated in the pathogenesis and progression of schizophrenia [64]. This hypothesis is confirmed by studies in which increased expression of MMP-9 was observed upon stimulation of glutamatergic neurons. In the present study, statistically significant differences in serum MMP-9 levels were found between patients receiving conventional rehabilitation and those treated using GSR-BF. Analogous results have been obtained by other researchers who investigated the problem of the role of MMP in the progression of schizophrenia. Like BDNF, MMP-9, despite participating in various processes (inflammation, cancer, oxidative stress), reflects changes in the CNS. Our study shows that the markers presented can be indicators of the effect of rehabilitation interventions.

Conclusions

Comparable therapy outcomes were obtained for all the dependent variables except for BDNF, which levels were higher in the GSR-BF patients. GSR Biofeedback may be considered as a new alternative to conventional rehabilitation. Both BDNF and MMP-9 can be used as targets in the evaluation of the effectiveness of various rehabilitation modalities.

Declarations

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The authors declare no conflict of interest.

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Author Contributions:

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