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Article

Application of Transcranial Magnetic Stimulation for the Treatment of Residual Catatonia

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Abstract: Catatonia is a common syndrome among psychiatric patients, diagnosed in 20-43% of cases. Treatment methods for patients with catatonia are limited to the use of benzodiazepines and ECT in the acute period, and the problem of anti-relapse and maintenance therapy remains one of the most difficult. Currently, transcranial magnetic stimulation is a promising approach in the treatment of catatonia. The purpose of the study was to evaluate the possibility of using the method of transcranial magnetic stimulation of the brain in patients with schizophrenia in remission with residual catatonic symptoms. Material and methods. 50 patients diagnosed with schizophrenia and residual catatonic symptoms were examined by clinical and psychometric methods and divided into 2 groups (therapeutic and comparison groups) to prospectively evaluate the effectiveness of transcranial magnetic stimulation for 4 weeks. Results. Transcranial magnetic stimulation of the DLPFC on the left in patients with residual catatonia TMS turned out to be effective and safe - a tendency was revealed to reduce psychomotor impairments that made up the clinical picture before the start of stimulation, along with an improvement in basic cognitive functions. Conclusions. Augmentation of standard psychopharmacotherapy protocols with TMS is effective for the correction of psychomotor symptoms.

Keywords: *schizophrenia, catatonia, transcranial magnetic stimulation.*

1. Introduction

Transcranial magnetic stimulation (TMS) is a safe, non-invasive method of changing neuronal activity in local areas of the cerebral cortex through a magnetic field. This is a promising and actively developing therapeutic technique that has found wide application in psychiatry. In Russia, TMS as an additional method of treatment is being actively introduced into psychiatric practice [1–4].

The biophysical mechanisms underlying the effectiveness of TMS are based on changes in the excitability of neurons and their metabolic electrophysiological activity [5–7] , optimization of plasticity and functional connectivity between brain regions [8–11] , which is reflected in the proven effectiveness of this method in the treatment of depression [5–7] , schizophrenia and other primary psychotic disorders, in particular, negative symptoms [12–14] and auditory hallucinations [13,15–18] and overcoming resistance [19] , including catatonic symptoms [20].

The use of TMS for the treatment of catatonia is relevant in several aspects. On the one hand, this syndrome is widespread among psychiatric patients in a wide range: from 5-10% [21], according to the results of a meta-analysis of clinical and epidemiological studies, to 20-43% when assessing the condition using psychometric scales [22,23]. Such indicators may be due to the fact that catatonia is removed from the category of the schizophrenia spectrum in modern diagnostic manuals and is considered as a transnosological construct [24,25], largely due to the clinical pathomorphism of this syndrome. A tendency

has been established towards the manifestation of catatonia with "atypical, structurally unformed symptom complexes that do not have a single dynamic developmental stereotype" [26] and a decrease in the severity of psychopathological manifestations to a subsyndromal level [27]. Persistence of symptoms of catatonia at the threshold level for diagnosis persists even at the stage of remission after urgent states that occur with gross disorganization of thinking and behavior [28,29]. It is worth mentioning that, according to modern concepts, remission is a stage of the disease at which important symptoms may not be completely reduced, but persist at a subsyndromal level. The authors in one of the previous publications noted the possibility of establishing remissions in schizophrenia with residual catatonic symptoms [30]. On the other hand, treatment and rehabilitation methods for patients with catatonic psychomotor disorders are limited to the use of benzodiazepines and ECT in the acute period without recommendations for anti-relapse or maintenance therapy.

Based on the results of neuroimaging studies, it has been established that the characteristic manifestations of catatonia correlate with dysfunction of the lateral part of the orbitofrontal cortex [31,32], which is almost impossible to influence using TMS. However, the possibility of neuromodulation with magnetic impulses on the DLPFC, rather than the OFC, in catatonia is advisable due to the close connectivity of these areas and the availability of the DLPFC for stimulation. The intensification of metabolic processes in brain tissue helps not only to slow down pathological mechanisms, but also mediates the processes of neuroplasticity, which together has a beneficial clinical effect.

The existing world experience in the use of TMS for catatonia, according to the scientific literature, is small and contains information about the positive effect of high-frequency stimulation on the DLPFC in a series of clinical observations (see Appendix 1), which is summarized in the article "Catatonia with schizophrenia: From ECT to rTMS" [20] and in a systematic review [33].

According to our hypothesis, therapy for catatonia as psychomotor abnormalities is possible with stimulation of the dorsolateral prefrontal zone cerebral cortex.

Objective

The purpose of the study was to evaluate the possibility of using the method of transcranial magnetic stimulation of the brain in patients with schizophrenia in remission with residual catatonic symptoms.

2. Materials and Methods

The study sample included 50 patients (30 men and 20 women, average age 31.5 ± 9.5 years) meeting the criteria for schizophrenia according to ICD-10, examined during the period of convalescence after acute psychotic episodes that occurred with catatonia.

Inclusion criteria: diagnosis of schizophrenia; the presence of catatonic symptoms; Bush-Francis Catatonia Scale (BFCRS) total score >5; age from 18 to 55 years; informed consent to participate in the study.

Non-inclusion criteria: somatic or neurological disease; the presence of absolute and relative contraindications for neuromodulation with a magnetic field; period of pregnancy and lactation in women; alcohol and substance abuse.

The study was carried out in 2 stages (visits):

Stage 1: upon inclusion in the study (visit 1): clinical-psychopathological (clinical interview, filling out an individual card) and psychometric assessment of the state (PANSS scale, Bush-Francis catatonia scale BFCRS)

Stage 2: after 4 weeks (visit 2): psychometric assessment of the state (PANSS scale, Bush-Francis catatonia scale BFCRS) over time

Efficacy was assessed at the time of visit 2 according to the following criteria: the therapeutic response was regarded as positive when individual scores on the PANSS scale were reduced by 25% from the original; We additionally analyzed the dynamics of the

reduction of scores on the BFCRS scale. Achieving symptomatic remission was defined as an almost complete reduction in the severity of symptoms (with a decrease in individual PANSS symptoms to a level of no more than 3 points).

All patients in the sample were offered treatment with the TMS method, but 30 people did not undergo the TMS course due to contraindications (5 people), or remote residence from the hospital and the inconvenience of daily sessions (11 people), or refused without explanation or for delusional reasons (14 people). Moreover, all 30 patients agreed to 2 visits (upon inclusion in the study and a month later) and formed a comparison group when assessing the effectiveness of TMS. 20 patients who completely completed the course of treatment with this method made up the therapeutic group.

TMS therapeutic group - 20 patients (13 men and 7 women; average age 29.4 ± 7.7 years) underwent a course of transcranial magnetic stimulation as an augmentation of standard antipsychotic therapy; comparison group without TMS - 30 patients (17 men and 13 women; average age 33 ± 10.5 years) received only standard antipsychotic therapy.

The assessment of mental pathology was carried out using a clinical method (psychopathological examination with the mandatory use of objective data obtained from relatives and from medical documentation).

A formalized assessment of the condition was carried out using psychometric techniques: Positive and Negative Syndrome Scale (PANSS) [35]; Bush-Francis catatonia rating scale (BFCRS) [36].

The assessment of the possibility of using the transcranial magnetic stimulation method was carried out in accordance with the requirements for description and reproduction of the intervention (TIDiR) [37]. Safety and effectiveness were assessed during a naturalistic observational study of two groups - patients who, as a measure of augmentation of standard antipsychotic therapy, completed a course of 20 sessions of non-invasive TMS intervention (n = 20) and patients who continued to take standard antipsychotic therapy without any additional effects (n=30). In the present study, treatment with transcranial magnetic stimulation fully complies with the ethical standards and safety regulations for the use of TMS in mental disorders, effective in 1998 [38] with subsequent revisions in 2008, 2014, 2018 and 2021. [39]. These ethical and safety standards are the basic principles for the development of clinical trial designs, basic research experiments and practical guidelines for the application of the method [40].

2.1. Methodology of Transcranial Magnetic Stimulation

High frequency neuromodulation course TMS therapy was performed using a Neuro-MS/D magnetic stimulator (Neurosoft) with a figure-of-eight angular inductor. The incentive regulations were consistent with international guidelines on good TMS practice [40].

2.1.1. Rationale for Choosing a Stimulation Protocol

The development of a protocol for high-frequency stimulation of the left DLPFC was based on the results of fundamental research. It has been established that an important link in the pathogenesis of catatonia is structural (reduced gray matter volume) and functional (reduced restraining state activity) disturbances in the frontoparietal network [31] , also known as the central executive network, including the superior, middle, medial and inferior frontal cortex with a key connectivity hub in the orbitofrontal cortex (OFC). The OFC exerts cognitive control over emotional processing and is closely connected to cortical and subcortical structures. Impaired connectivity of OFC neurons is clinically expressed in the inability of cognitive control of the expression of emotions and the implementation of behavioral acts [41] . It is believed that in catatonia, communication disruption occurs primarily due to structural and functional aberrations of the OFC and dorso-

lateral prefrontal cortex (DLPFC) [31,32] , leading to an imbalance of the connectome between the cortical areas regulating decision-making processes, control of emotions and behavior with the amygdala, hippocampus, thalamus [42,43] .

2.1.2. Preparatory and Diagnostic Procedures

All right-handed patients were comprehensively examined by specialists before starting treatment with TMS to exclude the risk of decompensation from the central nervous system or internal organs. Before starting the course, everyone was screened for the presence of absolute and relative contraindications for magnetic field neuromodulation. In some cases, the maintenance therapy regimen was adjusted - drugs that increase the threshold of convulsive activity were discontinued [44].

The projection of the dorsolateral prefrontal cortex (DLPFC) on the left was chosen as the stimulation zone, which can be determined by the craniometric method, focusing on the external anatomical formations of the head.

2.1.3. Therapeutic Team

Sessions of transcranial magnetic stimulation were conducted by psychiatrists - employees of the Laboratory of Fundamental Research Methods of the National Scientific Research Center for Neuropsychiatry of the State Budgetary Institution of Healthcare "PKB 1 DZM" under the guidance of Ph.D. Zakharova N.V., who has a valid advanced training certificate for providing medical care using the TMS method.

2.1.4. Therapeutic Effect

The main property of rhythmic TMS, which generates a series of pulses with a frequency of 10 Hz, is the modulation of the level of cortical excitability: low-frequency exposure with a frequency of less than 1 Hz reduces the excitability of the motor cortex, while an increase in frequency of more than 5 Hz increases cortical excitability [45]. The neurophysiological mechanism for implementing the method is the generation of an electric field in neuronal tissue with instantaneous depolarization of membranes, leading to the emergence and instantaneous propagation of an action potential and electrical signal transmission between neurons. The neurophysiological basis of the action of a magnetic pulse during TMS is a change in interneuronal connections and the activity of neurotransmitters in the affected area, which is reflected in increased regional blood flow identified by neuroimaging of the cerebral cortex during studies of the effect of TMS [46].

2.1.5. Conditions for TMS

TMS was carried out in the premises of the Laboratory of Fundamental Research Methods of the National Scientific Research Center for Neuropsychiatry of the State Budgetary Healthcare Institution “PKB 1 DZM”, equipped to implement this method of non-invasive intervention, located in one of the hospital’s medical buildings with the ability to provide the entire volume of emergency care in the event of the development of adverse events. All procedures were carried out in accordance with current sanitary standards and regulations.

2.1.6. Features of Non-InvasiveIintervention

The TMS course consisted of 20 sessions conducted daily in the morning hours of weekdays with breaks on weekends. A protocol of high-frequency (10 Hz) rhythmic stimulation of the left dorsolateral prefrontal cortex with an amplitude of 80% of the motor response threshold was chosen as a therapeutic intervention. In one session, 1600 magnetic pulses were applied for 15.5 minutes.

2.1.7. Personalization and Titration of Stimulation Intensity

The motor response threshold (MRT), an important diagnostic characteristic of stimulation intensity, represents the minimum magnetic induction force at which a motor response occurs in muscle tissue. To determine it, the coil is placed on the surface of the head in the projection of the center of innervation of the muscles of the thumb (m. abductor pollicis brevis), and the minimum amplitude of the magnetic field is applied. By increasing the amplitude by 5% in one step, the strength of the magnetic pulse is found at which a motor response occurs (involuntary contraction of the finger muscles).

PMO was measured every 3–5 sessions, since the indicator is dynamic and depends on many factors.

2.1.8. Assessment of Method Safety and Compliance

The patients were seated in a comfortable chair while ensuring maximum head immobility to reduce the risk of displacement of the coil fixed in a special bracket.

Before each session, the TMS physician verified the correct functioning of the coil by producing single pulses to assess the quality of auditory and tactile artifacts.

Throughout the session, the TMS doctor was next to the patient, observing his condition, and at the end of the procedure he asked about his well-being and sensations.

All patients who participated in this study received recommended and maximum daily doses of antipsychotics in accordance with current international standards for psychiatric care. In some patients, the treatment regimen included several drugs from different pharmacological groups, which is quite acceptable in combination with TMS. It has been established that magnetic stimulation is not only not dangerous in cases of polypharmacy (2 antidepressants, a mood stabilizer, an atypical antipsychotic), but also helps to overcome the pharmacoresistance of symptoms [47] and by increasing the effectiveness of basic psychopharmacological drugs without the development of characteristic adverse effects [48–50] .

2.2. Medications

All patients included in the study continued to take the medications prescribed by their attending physicians without changing the treatment regimen for 2-4 weeks before the start of the TMS course, which made it possible to evaluate the effect of neuromodulation, reducing the likelihood of the drugs influencing the dynamics of the condition [44]. During the course of 20 sessions conducted over four weeks, no cancellation or dosage adjustment occurred in any observation. None of the patients reported any adverse events with a high level of compliance.

2.3. Statistical Analysis

Statistical processing was carried out in the Jamovi program. Of the descriptive statistics parameters, medians and quartiles were used. Indicators of psychometric scales and clinical and dynamic characteristics were analyzed using the t-test method indicating the degree of freedom (df), test parameter t (t) and 95% confidence interval (95% CI). The association between indicators was assessed using Pearson's $\chi 2$ test. In all tests, data were considered statistically significant at a two-sided $p < 0.05$.

3. Results

Table 1 shows some sociodemographic and clinical dynamic parameters of the patients included in the study. It is worth noting that no statistically significant differences were found when comparing these indicators, which allows us to adequately assess the effectiveness of the TMS technique, taking into account the relative homogeneity of clinical and psychometric indicators in patients in the follow-up sample (Table 2).

Table 1. Sociodemographic and clinical-dynamic indicators of the therapeutic sample

Indicators	**TMS Group n=20**	**Group without TMS n=30**	**χ 2 (p)**
	N (%)		
Men	13(65)	17(56.7)	0.67(0.431)
Women	7(35)	13(43.3)	
	M±SD	M±SD	Me [Q1; Q3]
Average age at the time of examination, years	29.4 ± 7.7 29[18;50]	33 ± 10.5 31[19;52]	29.1 (0.215)
Average age of manifestation of psychosis, years	22.5 ± 5 23[13;36]	24.4 ± 6.8 23[12;39]	19.0(0.328)
Duration of illness from the manifesto	6.9 ± 5.9 5[0;20]	8.6 ± 7.2 7[0;24]	18.8(0.401)
	N (%)		
Disability	13(65)	17(56.7)	0.54(0.851)

Table 2. Results of psychometric research on the PANSS and BFCRS scales of patients in the examined groups before treatment (average value ± standard deviation, Me [Q1; Q3])

Scale	TMS Group n=20	Group without TMS n=30	p [95% CI]
PANSS general	81 ± 6.9 80 [77; 85]	81.2 ± 7.3 81[75; 87]	1,000 [-5.00; 4.00]
PANSS P	11.7 ± 1.5 11 [11; 12]	12.7 ± 1.9 13 [12; 13]	0.014 [-2.00; -1.000]
PANSS N	30.9 ± 3.8 31 [28; 34]	29.7 ± 4.5 30 [27; 32]	0.305 [-1.00; 4.00]
PANSS G	37.2 ± 3.7 37 [35; 39]	38.2 ± 3.1 37 [35; 40]	0.695 [-3.00; 2.00]
BFCRS general	9 ± 6.9 9 [3;13]	7.7 ± 6.8 6 [3;7]	0.49 [-2.00; 6.000]

Statistically significant differences were recorded between the therapeutic and comparison groups in terms of the average total score of the PANSS-P positive symptoms subscale (p = 0.014), although in all patients the symptoms were defined as threshold.

The results of the psychometric assessment of the state using the PANSS scale before and after the use of TMS are presented in Table 3. Significant differences were revealed

on all points ($p<0.05$). Taking into account the chosen protocol and the dynamics of the decrease in the average score, the first thing that draws attention is a significant decrease in the severity of anxiety (G2), tension (G4) and motor retardation (G7), which were reduced by slightly less than 50% after augmentation of the standard TMS therapy protocol. Also, it is important to note an increase in poor attention (G11) in this group, as well as a decrease in the level of conceptual disorganization (P2), which indicates an indirect effect of TMS on cognitive functions.

Table 3. Results of a psychometric study on the PANSS scale of patients in the TMS group before and after treatment, (average value ± standard deviation, Me [Q1; Q3])

Scale	TMS Group (n=20) (1 visit)	TMS Group (n=20) (2 visit)	p [95% CI]
PANSS general	81 ± 6.9	71.3 ± 5.3	<0.001
	80 [77; 85]	69 [68; 76]	[8.09; 11.1]
PANSS P	11.7 ± 1.5	9.9 ± 1	<0.001
	11 [11; 12]	10 [9; 10]	[1.42; 2.30]
P1 (delusions)	1.9 ± 0.7	1.6 ± 0.5	0.005
	2 [2; 2]	2 [1; 2]	[0.113; 0.553]
P2 (conceptual disorganization)	2.4 ± 0.6	1.7 ± 0.5	<0.001
	2 [2; 2]	2 [1; 2]	[0.447; 0.887]
P3 (hallucinatory behavior)	1.7 ± 0.6	1.5 ± 0.5	0.043
	2 [1; 2]	2 [1; 2]	[0.007; 0.374]
PANSS N	30.9 ± 3.8	30.5 ± 3.6	0.008
	31 [28; 34]	31 [28; 34]	[0.113; 0.649]
PANSS G	37.2 ± 3.7	31 ± 2.7	<0.001
	37 [35; 39]	30 [29; 32]	[6.02; 8.74]
G2 (anxiety)	2.2 ± 0.6	1.3 ± 0.5	<0.001
	2 [2; 3]	eleven; 2]	[0.659; 1.15]
G4 (tension)	2.5 ± 0.7	1.4 ± 0.5	<0.001
	3 [2; 3]	eleven; 2]	[0.729; 1.56]
G7 (motor retardation)	2.4 ± 1	1.3 ± 0.5	<0.001
	2 [1; 4]	eleven; 2]	[0.582; 1.51]
G9 (unusual thought content)	2.1 ± 0.4	1.6 ± 0.6	<0.001
	2 [2; 2]	2 [1; 2]	[0.243; 0.709]
G11 (poor attention)	3.9 ± 0.6	2.6 ± 0.5	<0.001

	4 [4; 4]	3 [2; 3]	[0.875; 1.70]
G13 (disturbance of volition)	3.9 ± 0.7	3.3 ± 0.5	0.001
	4 [3; 4]	3 [3; 4]	[0.282; 0.956]
G15 (preoccupation)	3.9 ± 0.6	3.4 ± 0.5	<0.001
	4 [4; 4]	3 [3; 4]	[0.243; 0.709]

The dynamics of the condition of patients who did not undergo a course of TMS (only standard antipsychotic therapy), analyzed in a similar way, can be judged by the indicators of symptom severity presented in Table 4. Let us note some differences in the change in the mental state of patients in the comparison group. The severity of motor disturbances, the persistence of thoughts with unusual content and the level of preoccupation with one's own experiences remained stable during the month of observation, with a slight decrease (by less than 20%) in anxiety and tension. However, the average total score of negative symptoms increased statistically significantly, which may be due to a general reduction in positive symptoms, which previously leveled out the formed deficiency manifestations.

Table 4. Results of a psychometric study on the PANSS scale of patients in the group without TMS before and after treatment (average value ± standard deviation, Me [Q1; Q3])

Scale	Group without TMS (n=30) (3 visit)	Group without TMS (n=30) (4 visit)	p [95% CI]
PANSS general	81.2 ± 7.3	76.8 ± 6.7	<0.001
	81[75; 87]	76 [72; 81]	[1.83; 3.62]
PANSS P	12.7 ± 1.9	10.3 ± 1.4	<0.001
	13 [12; 13]	11 [9; 11]	[1.26; 2.19]
P1 (delusions)	2.4 ± 0.6	1.9 ± 0.6	<0.001
	2 [2; 3]	2 [2; 2]	[0.264; 0.701]
P2 (conceptual disorganization)	2.1 ± 0.3	1.6 ± 0.5	<0.001
	2 [2; 2]	2 [1; 2]	[0.289; 0.676]
P3 (hallucinatory behavior)	2.2 ± 0.6	1.6 ± 0.5	<0.001
	2 [2; 3]	2 [1; 2]	[0.407; 0.834]
PANSS N	29.7 ± 4.5	29.9 ± 4.7	0.012
	30 [27; 32]	30 [27; 33]	[-0.364; -0.05]

PANSS G	38.2 ± 3.1	36.6 ± 2.8	0.001
	37 [35; 40]	36 [35; 38]	[0.53; 1.88]
G2 (anxiety)	2.1 ± 0.5	2 ± 0.6	0.033
	2 [2; 2]	2 [2; 2]	[0.020; 0.394]
G4 (tension)	2.4 ± 0.5	2 ± 0.7	0.003
	2 [2; 3]	2 [2; 2]	[0.184; 0.781]
G7 (motor retardation)	1.1 ± 0.3	1.1 ± 0.4	0.326
	1[1; 1]	1[1; 1]	[-0.105; 0.036]
G9 (unusual thought content)	1.8 ± 0.5	1.8 ± 0.4	0.083
	2 [1; 2]	2 [2; 2]	[-0.22; 0.01]
G11 (poor attention)	3.8 ± 0.7	3.5 ± 0.6	0.001
	4 [3; 4]	4 [3; 4]	[0.131; 0.489]
G13 (disturbance of volition)	4.2 ± 0.6	4 ± 0.5	0.012
	4 [4; 5]	4 [4; 4]	[0.050; 0.364]
G15 (preoccupation)	4.1 ± 0.6	4.1 ± 0.6	0.161
	4 [4; 4]	4 [4; 4]	[-0.167; 0.029]

To assess the effect of TMS on the reduction of individual symptoms, we compared the dynamics of the condition in patients in the TMS group and the comparison group with statistical analysis of the delta scores for some PANSS subscales (Fig. 1).

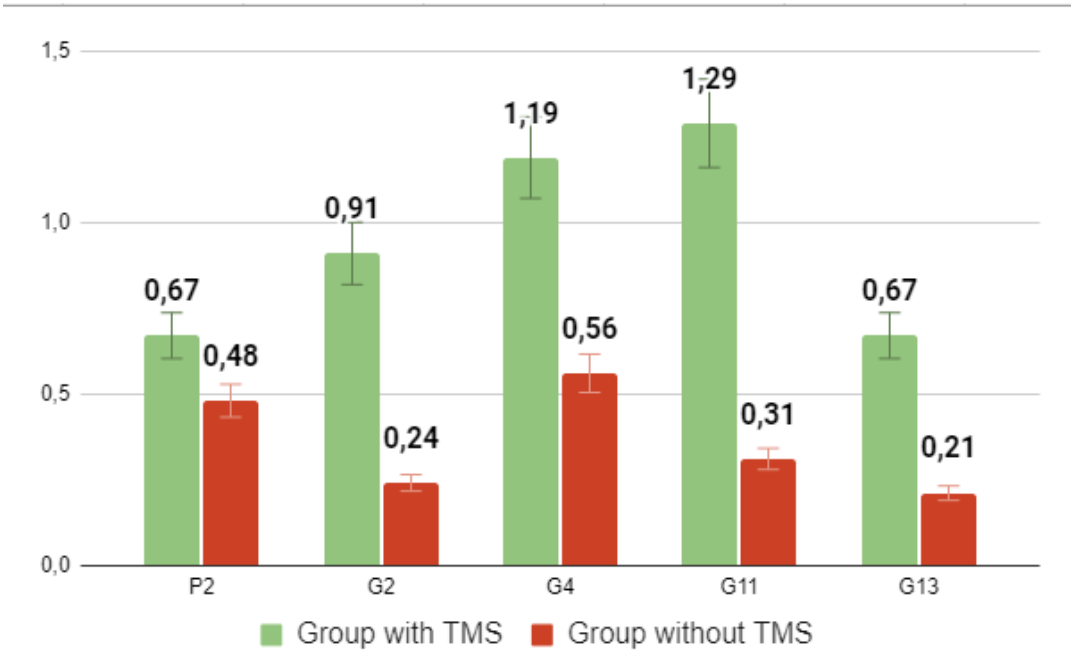

Figure 1. Difference (delta) between TMS and no-TMS groups on selected PANSS subscales

A significant difference in delta was found for all subscales presented ($p<0.05$), except for conceptual disorganization ($p=0.205$). Thus, it can be assumed that, despite the overall significance of the decrease in scores, positive dynamics are expressed in patients of the therapeutic group, which can be explained by the beneficial effect of TMS.

To assess psychomotor impairment, it was decided to use the Bush-Francis Scale (BFCRS). Table 5 shows changes in the total score and individual symptoms in patients in the therapeutic group before and after a course of 20 sessions of high-frequency TMS. Significant differences were found in most symptoms, for example: excitement, stupor, mutism, staring, posturing/catalepsy, echo phenomena, rigidity, negativism, waxy flexibility, withdrawal and muscle resistance.

Table 5. Results of a psychometric study on the BFCRS scale of patients in the TMS group before and after treatment (average value ± standard deviation, Me [Q1; Q3])

Scale	TMS Group (n=20) (1 visit)	TMS Group (n=20) (2 visit)	p [95% CI]
BFCRS general	9.1 ± 6.9	3.6 ± 2.8	<0.001
	9 [0;25]	3 [0;11]	[3.24; 7.71]
Excitement	0.7 ± 1.5	0.2 ± 0.4	<0.001
	0 [0;1]	0 [0;0]	[0.25; 0.798]
Immobility/stupor:	0.6 ± 0.9	0	0.010
	0 [0;2]		[0.150; 0.993]
Mutism	0.7 ± 1	0	0.003
	0 [0;2]		[0.279; 1.15]
Staring	0.7 ± 0.8	0.2 ± 0.4	<0.001
	1 [0;1]	0 [0;0]	[0.291; 0.757]
Posturing/catalepsy	0.6 ± 0.9	0	0.004
	0 [0; 1]		[0.225; 1.01]
Grimacing	0.4 ± 0.7	0.3 ± 0.5	0.083
	0 [0; 1]	0 [0; 1]	[-0.02; 0.306]
Echopraxia/echolalia	0.5 ± 0.7	0.1 ± 0.3	0.002
	0 [0;1]	0 [0;0]	[0.154; 0.607]
Stereotypy	0.6 ± 0.6	0.5 ± 0.5	0.083
	1 [0;1]	1 [0;1]	[-0.02; 0.306]
Mannerisms	0.7 ± 0.7	0.9 ± 0.9	0.329
	1 [0;1]	1 [0;2]	[-0.05; 0.147]
Verbigeration	0.2 ± 0.5	0.2 ± 0.5	0.162
	0 [0;0]	0 [0;0]	[-0.041; 0.232]
Rigidity	0.4 ± 0.6	0	0.008
	0 [0;1]		[0.113; 0.649]
Negativism	0.6 ± 0.7	0.3 ± 0.5	0.030

	1 [0;1]	0 [0;1]	[0.030; 0.541]
Waxy flexibility	0.5 ± 0.8	0	0.014
	0 [0;1]		[0.106; 0.847]
Withdrawal	0.8 ± 0.8	0.4 ± 0.5	0.031
	1 [0;1]	0 [0;1]	[0.033; 0.633]
Impulsivity	0.5 ± 0.7	0.4 ± 0.5	0.162
	0 [0;1]	0 [0;1]	[-0.041; 0.232]
Automatic obedience	0.1±0.2	0	0.329
	0 [0;0]		[-0.147; 0.051]
Gegenhalten	0.1±0.2	0.05 ± 0.2	0.042
	0 [0;0]	0 [0;0]	[0.007; 0.374]
Aggressiveness	0.4 ± 0.6	0.2 ± 0.5	0.104
	0 [0;1]	0 [0;1]	[-0.042; 0.423]

In patients in the comparison group who continued to take standard antipsychotic therapy, no significant changes were found in either the sum of scores or individual symptoms on the BFCRS scale (Table 6).

Table 6. Results of a psychometric study on the BFCRS scale of patients in the group without TMS before and after treatment, (average value ± standard deviation, Me [Q1; Q3])

scale	Group without TMS (n=30) (3 visit)	Group without TMS (n=30) (4 visit)	p [95% CI]
BFCRS general	7.7 ± 6.8	7.6 ± 6	0.928
	6[3;7]	6[3;9]	[-0.736; 0.805]
Excitement	0.7 ± 0.8	0.6 ± 0.8	0.326
	0 [0; 1]	0 [0; 1]	[-0.036; 0.105]
Immobility/stupor:	0.4 ± 0.8	0.4 ± 0.7	0.713
	0 [0;0]	0 [0;1]	[-0.233; 0.161]
Mutism	0.4 ± 0.7	0.3 ± 0.6	0.161
	0 [0;1]	0 [0;1]	[-0.029; 0.167]
Staring	0.9 ± 0.8	0.8 ± 0.8	0.326
	1 [0;1]	0 [0;1]	[-0.036; 0.105]
Posturing/catalepsy	0.3 ± 0.5	0.4 ± 0.5	0.326
	0 [0;1]	0 [0;1]	[-0.034; 0.035]
Grimacing	0.2 ± 0.5	0.2 ± 0.4	1.00
	0 [0;0]	0 [0;0]	[-0.102; 0.102]
Echopraxia/echolalia	0.1±0.4	0.2 ± 0.4	0.161

	0 [0;0]	0 [0;0]	[-0.167; 0.029]
Stereotypy	0.3 ± 0.5	0.2 ± 0.4	0.184
	0 [0;1]	0 [0;0]	[-0.052; 0.259]
Mannerisms	0.6 ± 0.9	0.5 ± 0.7	0.103
	0 [0;2]	0 [0;1]	[-0.029; 0.306]
Verbigeration	0.2 ± 0.5	0.2 ± 0.4	1.00
	0 [0;0]	0 [0;0]	[-0.102; 0.102]
Rigidity	0.5 ± 0.7	0.4 ± 0.6	0.424
	0 [0;1]	0 [0;1]	[-0.105; 0.243]
Negativism	0.3 ± 0.6	0.3 ± 0.5	0.573
	0 [0;0]	0 [0;1]	[-0.158; 0.089]
Waxy flexibility	0.2 ± 0.6	0.3 ± 0.6	0.424
	0 [0;0]	0 [0;0]	[-0.243; 0.105]
Withdrawal	1.2 ± 0.9	1.3 ± 0.8	0.489
	1 [0;2]	1 [1;2]	[-0.273; 0.133]
Impulsivity	0.4 ± 0.6	0.5 ± 0.7	0.184
	0 [0;1]	0 [0;1]	[-0.259; 0.076]
Automatic obedience	0.3 ± 0.7	0.2 ± 0.6	0.103
	0 [0;0]	0 [0;0]	[-0.029; 0.306]
Gegenhalten	0.2 ± 0.6	0.1 ± 0.3	0.083
	0 [0;0]	0 [0;0]	[-0.014; 0.221]
Aggressiveness	0.2 ± 0.4	0.1 ± 0.3	0.161
	0 [0;0]	0 [0;0]	[-0.167; 0.029]

The severity of catatonia symptoms at the time of visit in patients of both groups did not show significant differences ($p = 0.49$), however, at visit 2, the difference in the average total score on the BFCRS scale was determined to be significant ($p = 0.006$).

4. Discussion

The hypothesis about the possibility of treating psychomotor abnormalities and cognitive impairment accompanying catatonia was confirmed. High-frequency stimulation of the left DLPFC has an activating effect with a decrease in the manifestations of bradyphrenia. Thus, when exposed to the left DLPFC, high-frequency stimulation with a frequency of 10 Hz with an amplitude of 80% of the PMO in order to activate the pathological hypofunction of the region had an activating effect with a decrease in the manifestations of bradyphrenia and bradykinesia, which can be considered confirmation of the hypothesis about the possibility of treating catatonia.

During 20 sessions of high-frequency 10 Hz with an amplitude of 80% PMO stimulation of the DLPFC on the left to twenty patients with residual catatonia, TMS was effective and safe - a tendency was revealed to reduce psychomotor disorders that made up the clinical picture before the start of stimulation, along with an improvement in basic cognitive functions in combination with the absence of unwanted phenomena or complications of neuromodulation with magnetic pulses. This confirms the hypothesis about the

possibility of stimulation of the dorsolateral prefrontal zone of the cerebral cortex due to the pathomorphism of neurophysiology in this area to achieve a therapeutic effect in the treatment of catatonia.

The results of this study replicate information from scientific publications about the successful experience of using TMS in the projection of the dorsolateral prefrontal cortex [20,51–58], however, the method and protocols have some features.

It is worth noting that 14 out of 20 patients (70%) who completed the TMS course simultaneously participated in socio-psychological rehabilitation programs - psychoeducation, cognitive training, group psychotherapy, combined with TMS. Such a multimodal approach, implemented by a multiprofessional team, may lead to more pronounced positive effects [59–61].

Of course, age-related, clinical-dynamic and genetic factors can change the biophysical and clinical effects of TMS. In particular, still rather poorly understood genetic differences contribute to individual responsibility for TMS-induced synaptic events and form an additional potential source of variation in therapeutic response. Thus, it may be difficult to know whether the failure of a TMS protocol in a study is due to the therapeutic ineffectiveness of the protocol or to the inclusion of nonresponders to the protocol.

5. Conclusions

Augmentation of standard protocols for psychopharmacotherapy of residual catatonia in patients with schizophrenia using TMS is effective for the correction of psychomotor symptoms, as evidenced by a significant reduction in the severity of motor disorders on the BFCRS catatonia scale (average score before treatment 9.1 ± 6.9 and after treatment 3.6 ± 2 ,8) in the TMS group.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Independent Interdisciplinary Committee for Ethical Review of Medical Research (extract from protocol No. 12 dated July 14, 2017).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

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