Personalized Psychiatry and Neurology

Case Report

Transcranial Magnetic Stimulation for Catatonia: Cases Serie

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Citation: Zakharova, N.V., Mamedova, G.S., Shkurinova, M.A., Kartashov, S.I., Zaborin, A., Orlov, V.A., Kholodny, Yu.I. Transcranial Magnetic Stimulation for Catatonia: Cases Serie. *Personalized Psychiatry and Neurology* **2023**, *3 (1)*: 66-78. https://doi.org/10.52667/2712-9179-2023-3-1-66-78

Chief Editor: Nikolaj G. Neznanov, D Med Sci, Professor

Received: 20 April 2023
Accepted: 08 May 2023
Published: 15 May 2023

Publisher's Note: V.M. Bekhterev NMRC PN stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Abstract: The article presents the results of transcranial magnetic stimulation of dorsolateral prefrontal cortex (DLPFC) in four patients with catatonia. The uniqueness of these observations arises from three factors. First, rehabilitation neuromodulation of catatonia was used in a personalized course of exposure to magnetic pulses, considering the intensity of regional cerebral blood flow (rCBF) in the affected area. Secondly, the entire course of treatment was carried out on an outpatient basis. Thirdly, the content of Gamma-aminobutyric-acid (GABA) and glutamate in the cerebral cortex was additionally studied before and after the course of transcranial magnetic stimulation (TMS). All four patients were diagnosed with catatonia as part of schizophrenia spectrum disorders in three cases and in one case within the structure of recurrent depression phase. All patients took monotherapy with atypical antipsychotics as the main psychopharmacotherapy, were compliant and gave informed voluntary consent. The effectiveness of TMS was recorded in three cases. There were no adverse events or complications in all 20 sessions.

Keywords: *catatonia; transcranial magnetic stimulation; neurostimulation; magnetic resonance spectroscopy.*

Introduction

Catatonia is diagnosed in 5–43% of patients with various mental disorders [1,2], characterizing the clinical picture of acute psychotic episodes and persisting on subsyndromal level during remission [3–5], thus actualizing the problem of elaborating therapeutic interventions for catatonia on an outpatient basis. Although the current experience in application of transcranial magnetic stimulation (TMS) in catatonia is limited, it provides promising data on positive effect of dorsolateral prefrontal cortex (DLPFC) stimulation in a series of clinical observations, summarized in the article "Catatonia with schizophrenia: From ECT to rTMS" [6] and a systematic review [7]. According to the available data, TMS shows comparable efficacy with electroconvulsive therapy, but unlike it is safe and does not require general anesthesia in intensive care unit.

Here we present a series of four cases of catatonia treatment using TMS. Patients have been examined since April 2021 till February 2022 on an outpatient basis within the first psychotic episode at the stage as follow-up treatment of past psychosis.

The stimulation protocol was chosen based on the intensity of regional cerebral blood flow (rCBF). The information about dynamics of neurotransmitter level in brain gray matter was additionally collected using MR spectroscopy, which is a promising neurovisualization method for assessment of TMS efficacy [8–10]. Bimodal analysis of TMS action on functional parameters of GABA and glutamate is one of the most perspective methods of neurophysiological brain imaging in different mental disorders [11,12].

Case Descriptions

Patient 1: Male, 23 Years Old

Symptoms as first visit: substupor, staring, rigidity, negativism, waxy flexibility, withdrawal into himself, muscle resistance, grasp reflex, autonomic disorders, compulsions, emotional lability, and blunted affective responses.

He lives alone in a separate apartment, but at his parents' expense, is helpless in household, does not work or study for the past five years.

It is known that his family history is positive for suicides, alcoholism, and affective disorders in both parental lines. He was born from complicated birth and suffered hypoxia. His early development was normal, he grew as a lively, active, and naughty child with demonstrative behavior and emotional lability typical for B cluster.

The prodromal phase was characterized by cognitive deficit without motor abnormalities or affective disorders. Since the age of 14 years, the periods of poor performance at school have occurred due to short span of attention, fatigability, difficulty focusing and memorizing. Such periods lasted from six to eight weeks and were not accompanied by mood changes or anxiety, though caused dysadaptation at school and inability to learn professionally.

The disease manifested from severe akinesia and abulia. Since the age of 21 years, he has not left his house, played computer games, ignored personal hygiene, and slept with his clothes on.

Frank psychosis was characterized by psychomotor agitation, severe disorganization of thoughts and behavior with catatonia: since 23 years old he became irritable and rudely reacted to his mother's comments. He has been speaking to himself for a month, shouted for no reason, laughed, danced, stuck his tongue out, and grimaced. He went out at the staircase naked, stood for hours staring at the same spot. For several hours a day he was stereotypically twisting his hands, tapped on his thighs, repeated the same phrase with different volume. He did not sleep or eat for a week and was therefore admitted to a mental hospital, where he was observed for six weeks with the diagnosis acute polymorphic psychotic disorder (F23.1). However, no signs of mood disorders, symptoms of hallucinatory-delusional symptoms were detected. In the acute care department, he was treated with aminazine, risperidone, and clozapine in therapeutic doses with no observable effect, which was followed by 10 sessions of ECT resulting in incomplete remission. As an outpatient he administered risperidone 4 mg/day, clozapine 75 mg/day, valproic acid 300 mg/day, and trihexyphenidyl 2 mg/day.

In this condition he was accepted to receive a neuromodulation course using TMS.

Patient 2: Male, 18 Years Old

Symptoms as first visit: substupor, mutism, staring, catalepsy, stereotypies, manneriism, verbigerations, waxy flexibility, withdrawal into himself, ambitendency, autonomic disorders, compulsions, emotional lability, and blunted affective responses, episodes of unmotivated aggressiveness, anxiety, and ambivalence.

He lives with his mother and at her expense, studies in a grammar school with poor performance.

The family history is positive for schizophrenia in paternal grandfather.

He was born with asphyxia with triple cord entanglement and underweight. Until two years old he was restless, whiney, did not eat or sleep well. He had permanent fears of either darkness, or insects, demanding from his mother to stay beside him. He was uncommunicative and shy, self-conscious, and self-inconfident, typical for C cluster. He went to school at 7 years old and was studying well.

In the previous history he suffered from distinct psychogenic depression with abulia, since he was separated from his mother because of the long-term treatment in the orthopedic department at the age of 12. He was dreary, introspective, and silent, ate too much

sweets with no control over the amount of food intaken and gained over 10 kg for 3 months. The depression did not require correction after hospital discharge.

The disease manifested from difficulties in simple habitual actions intention: since the age of 14 he noticed psychomotor disorders in form of complications of action initiation with long pauses even in everyday activities. The necessity to take a shower was postponed for a day, then spent 2–3 h in the bathtub under water streams. He became impulsive, irritated from minor misfortunes or disappointments and expressed aggressiveness in breaking or crashing things uncontrollably. He relied on his mother in problem solution and followed her instructions. He did not control his nutrition, weighed over 110 kg by the age of 17. He barely left his house apart from school lessons and hardly spoke to anyone.

Frank psychosis was characterized by gradual progression of hallucinatory-delusional syndrome with the background anxious affect and development of catatonia at the top of psychosis. At the age of 18 he causelessly felt an approaching disaster, stopped sleeping, the sound of his own thoughts seemed unfamiliar and beyond his control, slowly transforming into the voices inside his head that at first only commented the events, then started to threaten and offend him. That was a reason for him to visit the mental hospital, where he was treated inpatient for two months with the diagnosis of paranoid schizophrenia, observation period less than a year (F20.0) with no substantial effect and the development of adverse events. Haloperidol at a dose of 5 mg/day in tablets provoked akatisia, hand tremor, muscle rigidity, and positive cogwheel sign. After management of neurolepsy with anticholinergic drugs, risperidone was prescribed at a dose of 4 mg/day, providing the reduction of hallucinatory-delusional symptoms and catatonic phenomena came to the fore. In this condition he was included to receive a neuromodulation course using TMS.

Patient 3: Female, 25 Years Old

Symptoms as first visit: substupor, staring, catalepsy, waxy flexibility, withdrawal to himself, ambitendency, and grasp reflex.

She lives alone, professionally adapted.

The family history is unremarkable. She was born at the seventh month of pregnancy and weighed 2150 g. Early ontogenesis was normal. She grew confident, stenic, but at the same time distanced from the others, scrupulous in questions of justice, did not tolerate refusals, suspicious to strangers, typical for A cluster. She went to school at 6 years old and was an excellent student, spent all her time learning.

Noteworthy features of her previous history include certain accentuation of her personal traits seen in childhood at the age of 13: her mother had tragically died, but she did not express emotional reactions, though became even more introspective ever since, cocooned in her own thoughts, distrustful to others, and had problems in understanding the nuances of social interaction. She noticed a sensation of opposing herself to the outside world, wanted to always prove her point, considering her ideas correct, while other people were «shallow and malicious».

She studied finance and worked as a tax inspector, where she had a reputation of a principled and stenic person. She did not express much interest to men, however, considered herself engaged since 20 years with a young man in the absence of proposal or any other signs of attention from him).

Frank psychosis was preceded by a short prodromal phase characterized by anxious affect in form of interchanging interpretative delusions and fantastic ideas, psychomotor agitation, and catatonia at the top of psychosis, i.e., changes in mental status were provoked at the age of 25 after she accidentally found out about the wedding of her beloved one. She felt offended and disappointed in her whole life, replayed in her memory the events involving him, considered herself miserable and emotionally ruined. She noticed causeless and subjectless anxiety, feeling of approaching trouble, and slept badly with no signs of depression. Two weeks after breakup she was not thinking about the man anymore. She tried to distract herself with hard work and went for a business trip to check

financial activity of a large company. There she noticed surveillance and suspicious cars from the first days after arrival, saw illegal monitoring devices in the tax office. With increasing anxiety, she concluded that the company management covered the majority of income, despite the absence of proofs and clues. Back in Moscow she could not stop recalling what had happened to her, with increasing anxiety she decided that she facilitated the violation of law by her actions but without her own intention, rather mysteriously influenced or affected by a secret organization capable of controlling her mind and behavior. A week later she felt that she developed special powers, such as predicting events, hearing the thoughts of other people and affecting them. Her sister reported that she was talking indistinctly in that period, used short phrases that suggested she thought of herself as the head of good and bad forces and could «make everyone kind». She did not sleep at night and felt fear that forced her to freeze for several hours. Sometimes she began to walk around the room unstoppably, stereotypically touching things. She froze, did not react to addressing speech and stayed in uncomfortable positions motionless for about one hour. In this condition she was admitted to the acute hospital department. After two months after manifestation of psychosis she was admitted to Mental-health Clinic, where she stayed for about one month and discharged with a diagnosis of paranoid schizophrenia, observation period less than a year (F20.0094), establishment of pharmacological remission. She was treated with risperidone up to 8 mg/day and clozapine up to 150 mg/day with positive effect and lytic reversal of paranoia, accompanied by minor extrapyramidal symptoms. She was recommended to take risperidone at a dose of 6 mg/day as outpatient therapy. In this condition he was included to receive a neuromodulation course using TMS.

Patient 4: Male, 20 Years Old

Symptoms as first visit: substupor, staring, catalepsy, stereotypies, verbigerations, rigidity, withdrawal into himself, grasp reflex, and autonomic disorders.

He lives with his parents and at their expense, studies at the university behind of study program.

The family history is remarkable for multiple hospitalizations to a mental hospital of his father's blood brother, who later committed suicide.

He was born with signs of congenital torticollis. He could not stand stuffy rooms and often fainted. He grew as a naughty, whining child, frail under his mother’s overprotection, with prevailing personal traits of C cluster. He has been suffering from logoneurosis until present, as well as fear of darkness, water, and open spaces. At school, he was an outcast and an object of derision for his peers, spent his free time at home playing violin and clarinet with his mother.

During prodromal phase he demonstrated vital, or melancholic depression with signs of motor retardation. Pronounced changes of mental status established at the age of 15 with autochthonous low mood, substernal feeling of grief, somnolence (slept up to 20 h a day), cognitive deterioration, asthenia, and suicidal thoughts. The depressive episode lasted about half a year and relieved without treatment. He later suffered at least three episodes of depression with similar symptoms, aggravating each time and characterized by progression of stupor, withdrawal into himself, detachment from the outside world, and feeling of derealization. Depressive episodes were separated by periods of remission, when he returned to his normal life, continued to study, and helped about the house.

There was no frank psychosis and the reason for doctor visit was catatonic depression. Three months before the doctor examination he refrained from food, was crying a lot, had troubles sleeping, ignored hygienic procedures, could sit in an empty bathtub for hours under streams of water. In this condition he was admitted to Mental-health Clinic, where he spent three weeks with the diagnosis of major depressive disorder, recurrent, severe with psychotic symptoms (F33.3). He was treated with fluvoxamine 100 mg/day, risperidone 4 mg/day, diazepam 5 mg/day and a course of TMS after the stabilization of condition.

Diagnostic Procedures

All patients were right-handed, were thoroughly examined before TMS application involving specialized doctors to exclude the risks of CNS and internal disease decompensation, as well as screened for absolute and relative contraindications against MRI and magnetic field neuromodulation. In addition, before the beginning of any interventions in all cases patients signed an informed consent. Psychopathological examination (clinical interviewing, physical examination, and battery of psychometric tests, including PANSS, SAS, NSA-4, BFCRS, NCRS, and BACS) was performed twice: at first visit (V1), a diagnostic stage before TMS initiation, and at the second visit (V2), a final analysis of efficacy of 20 TMS sessions.

For differential diagnosis and reduction of risk of phenomenological overlap between catatonia and negative disorders or extrapyramidal complications of antipsychotic treatment, the results of psychometric evaluation were assessed using PANSS, SAS, and NSA-4. The results are presented in Table 1.

Table 1. Sociodemographic, clinical-dynamic, and psychometric characteristics of patients prior to TMS treatment.

Characteristics	P1	P2	P3	P4
Sex	m	m	f	m
Age	23	18	26	20
Family history	positive	positive	negative	positive
Family status	single	single	single	single
Work status	unemployed	student	employed	student
Years of education	11	10	15	12
Personality cluster	B	C	A	C
Age of onset of mental disorder, years	14	12	13	14
Cardinal syndrome at onset	D-D	D-D	P. D	D-D
Age of frank psychosis, years	21	18	25	20
Cardinal syndrome of frank psychosis	D	D-D	P. D	—
Duration of catatonia, months	7	2	6	1
Dreatment duration, months	6	1	5	1
Number of ECTs	10	0	0	0
SAS, total score	2**	0	0	1**
NSA-4 speech quantity	2	2	2	2
NSA-4 reduced range of emotion	2	4	4	3
NSA-4 reduced social drive	1	4	3	2
NSA-4 reduced interests	1	3	3	2
NSA-4 total score	2	3	3	3
ICD-10 diagnosis	F23.1	F20.0	F20.094	F33.3

Note: *P1 patient showed stiffness of elbow joints and increased blinking when tapped on the glabella; wrist rigidity was found in P4. D — disorganization, D-D — delusional depression, P.D. — paranoid delusion. Scales and questionnaires for assessing pain characteristics in patients with back pain

Neurovisualization was conducted twice using MAGNETOM Verio (Siemens, Germany) MR tomograph with the magnetic field of 3.0 T before and after TMS course in the following regimes:

T1 weighted scans to construct a 3D reference structural image.

The method of arterial spin labeling (ASL) MR perfusion without contrast was applied to assess rCBF in DLPFC bilaterally as a replication of one of the clinical TMS trials [13].

MEGA PRESS sequences were used for GABA scanning with the following parameters: TE = 28 ms, TR = 1000 ms, averages = 8, magnetic field gradient = 20 mT/m, volume element sizes 25 mm * 25 mm * 50 mm voxel for PRESS protocol and TE = 68 ms, TR = 2500 ms, averages = 128, magnetic field gradient = 22 mT/m, 25 mm * 25 mm * 50 mm voxel size for GABA+ and GABA- protocols. Gannet Masters in Matlab software was used for data processing of GABAa concentration. The concentration in institutional units (i.u.) demonstrating the absolute concentration in mmol/L calculated per pure water concentration of 55.556 mmol/L was determined according to the formula: [GABA]=SGABA/SH2O*(0.78*fGM*RGM+0.65*fWM*RWM++0.97*fCSF*RCSF)/(1-fCSF)*[H2O]/(RGABA*eff)

VAPOR protocol was used for glutamate scanning with the following parameters: TR = 4000 ms, TE = 35 ms with the incremental step of 10 ms in the transition to the next measure up to 185 ms at sixteenth measure, averages = 10, magnetic field gradient = 20 mT/m, 20 mm * 20 mm * 20 mm voxel size. Data processing was performed in JMRUI software.

Spectroscopy of GABA and glutamate neurotransmitters was executed in gray matter of frontal lobes in the interhemispheric fissure (Figure 1).

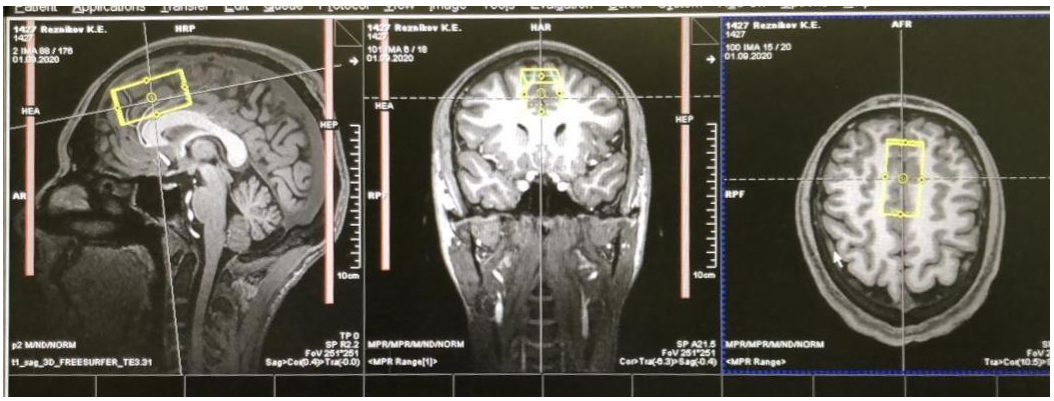

Figure 1. Projection of MR spectroscopy with highlighted area of GABA and glutamate concentration analysis

Therapeutic Intervention

All patients continued the anti-relapse treatment with atypical neuroleptics (clozapine or risperidone) that showed the highest efficiency and safety during inpatient treatment, combined with mood stabilizers in two cases.

TMS course consisted of 20 daily morning sessions (Table 2) on weekdays with the weekend breaks. The stimulation protocol corresponded to the international guidelines on good laboratory TMS practice [14].

Personalized choice of stimulation protocol referred to the preliminary results of randomized placebo controlled clinical TMS trial in catatonia [13], where the TMS regime was determined by rCBF lateralization in DLPFC reflecting the neuronal activity in that region.

TMS treatment was performed using Neuro-MS/D (Neurosoft) magnetic stimulator with angular figure-of-eight coil. Craniometry was used to identify DLPFC region.

P1, P2, and P4 underwent 10 sessions of high-frequency stimulation at the frequency of 20 Hz with the amplitude of 120% MT in the projection of left DLPFC consisting of 1600 pulses per session (procedure duration of ~15 min).

P3 underwent 20 sessions of low-frequency stimulation at the frequency of 1 Hz with the amplitude of 120% MT in the projection of left DLPFC consisting of 1600 pulses per session (procedure duration of ~27 min).

Treatment regimens have not been changed in any of the cases.

Table 2. Therapeutic approach for each studied patient.

ID	daily drug doses, mg/day	rCBF lateralization in DLPFC	TMS protocol
P1	clozapine 75, valproic acid 300	equal	high-frequency stimulation
P2	risperidone 4	equal	high-frequency stimulation
P3	clozapine 75	left	low-frequency stimulation
P4	risperidone 4	equal	high-frequency stimulation

Therapeutic Effect and Outcome

Safety evaluation was performed daily during TMS sessions. None of participants reported any adverse events at high compliance.

The efficacy was estimated during the V2 by the following criteria:

- positive clinical response: decline of BFCRS and NCRS scores by 70% from the primary evaluation;
- achievement symptomatic remission (total BFCRS and NCRS score 3 and less).

Positive clinical response was detected in two patients (P1, P3) according to both scales, and additionally in P4 according to only BFCRS.

Symptomatic remission was formed in three patients (P1, P3, P4) referring to BFCRS, whereas the analysis of catatonia dynamics by NCRS suggested that symptomatic remission was not achieved in any participant (Table 3).

Table 3. Dynamics of catatonia symptoms in studied patients

Patient number	NCRS M		NCRS A		NCRS B		NCRS total		BFCRS	
	V1	V2	V1	V2	V1	V2	V1	V2	V1	V2
P1	9	1	6	2	11	1	26	4*	18	2* **
P2	9	5	11	9	8	4	28	18	20	8
P3	5	1	10	2	8	3	23	6*	17	2* **
P4	5	1	6	4	6	3	17	7	15	3* **

Note: * positive clinical response; ** achievement of symptomatic remission

In addition, the dynamics of cognitive parameters was assessed in patients referring to BACS battery of tests (Table 4) and neurotransmitter concentration measured with brain spectroscopy (Table 5).

Table 4. Dynamics of cognitive indices in studied patients.

Patient number (sex)	Working memory		Motor dexterity		Executive functions		Verbal learning		Verbal fluency		Processing speed	
R**	19 :16		65 : 59		16 : 16		43 : 43		49 : 40		54 : 60	
	V1	V2	V1	V2	V1	V2	V1	V2	V1	V2	V1	V2
P1 (m)	17*	23*	41	56	3	4	23	40	32	44*	47	54
P2 (m)	17*	24*	25	40	1	6	25	39	32	45*	30	47
P3 (f)	20*	23*	35	48	2	5	29	34	34	42	47	55*
P4 (m)	19*	24*	26	28	1	5	33	35	41*	42*	35	47

Note: * Correspondence to normal values; ** R - reference values in the age group younger than 30 years (f : m) [15].

Table 5. Dynamics of neurotransmitter concentration according to brain spectroscopy in studied patients

Patient number	Glu (mmol/L)		Glu/NAA		GABA (mmol/L)	
			0,15*		4,02*	
	V1	V2	V1	V2	V1	V2
P1	37.08	13.00	0.54	0.19	4.12	3.27
P2	10.61	11.28	0.17	0.17	4.37	5.56
P3	14.40	10.19	0.22	0.16	4.74	4.72
P4	5.19	10.71	0.08	0.17	4.16	3.88

Note: Glu - glutamate concentration, Glu/NAA - Na-acetyl aspartate (NAA) glutamate (Glu) ratio; GABA - gamma-aminobutyric acid; * Reference values.

Discussion

There are several individual reports of TMS efficacy for treating catatonia in patients admitted to acute care departments [6,16–24], and a single study of TMS outpatient application [25], although the neuromodulating techniques are actively used in patients with remission [26].

Features of Comorbid Catatonic Ponditions in patients

Regarding the clinical characteristics of patients, it can be noted that symptomatic, syndrome, and nosological profiles are generally similar to the ones described in literature. The condition of P2, an 18-year-old man with depressive paranoid psychosis was comparable with the description of a 16-year-old girl presented by Sharma et al. [24]. The case of P3 was comparable with the observations published in 2002 by Saba G. et al. [17], showing the successful treatment of catatonia on top of psychosis overlapping with hallucinatory-delusional symptoms. Symptoms of depression complicated with catatonic stupor in P4 resembled the clinical picture of a 17-year-old teenager described by Marei A. and Rached H. in 2017 [27], however, the effect in our case developed gradually.

In case of P1 it is noteworthy that despite a single previous ECT session the catatonic symptoms persisted pronounced and reduced under the influence of TMS with resulting symptomatic remission.

Features of the Study Design

The elaboration of study design referred to the preliminary results of randomized placebo-controlled clinical trial of TMS in catatonia [13], where the personalization was based on the MR visualization of blood supply intensity, i.e., the increase or decrease of rCBF in the intended area of magnetic exposure. Such methodology seemed reasonable since the parameters of rCBF in our patients were heterogeneous, therefore requiring different types of TMS (high- or low-frequency).

In addition to the clinical and psychometric evaluation of the condition dynamics, changes in cognitive functions were analyzed using BACS test battery. This instrument allowed assessing the short-term verbal memory, working memory, motor functions, processing speed, semantic and verbal fluency, and problem-solving behavior.

Measurement of GABA and glutamate levels using MR spectroscopy in catatonia is one of the most novel methods applicable in assessing TMS action [28], especially due to potentially higher significance as a biomarker of catatonia [29,30]. These presumptions are based on several factors. Firstly, the cognitive control of negative emotions is modulated by GABA-A receptors in prefrontal regions (orbitofrontal and medial prefrontal cortices [31,32], which induces psychosis given the inhibition of GABAergic neurotransmission in these areas accompanied by hyperactive dopaminergic neurotransmission [33,34]. Moreover, the depression of inhibitory processes provokes hyperkinesis or symptoms of disorganization (mannerism, echophenomena, perseverations etc.), whereas excessive suppression of this network causes hypokinetic catatonia with rigidity, catalepsy, mutism, and stupor [35]. It should be emphasized that abovementioned ideas about aberrations of the neurotransmitter activity in catatonia are speculative since the diagnostic value of these biomarkers has not yet been proven [36].

Efficiency and Safety Evaluation

TMS was effective in three out of four patients when assessing the clinical condition using BFCRS, demonstrating clinical improvement and achievement of symptomatic remission (total score did not exceed 3 points by the end of 20 sessions), whereas the NCRS assessment provided less optimistic results, particularly, symptomatic remission was not shown in any of the observations and clinical improvement was reached only by two patients.

It is interesting to review the case of P2, for whom TMS course was ineffective. A potential reason for that lies in phenomenological overlap between catatonic and negative symptoms at the moment of examination, supported by the follow-up data after six months from TMS course (see "patients' opinions"). To summarize, the negative symptoms with prominent apato-abulic component were predominant in P4, progressing and resistant to correction.

As shown in results section, adverse effects or TMS complications did not develop in any patient, which is in line with the literature data on relative safety of method for catatonic patients of different age groups [18], including those with epileptiform brain activity [19] or heart disease [21].

Assessment of Dynamics in Cognitive Functions

The analysis of changes in the parameters of cognitive functions showed significant differences in their dynamics using BACS battery of tests (Table 4). According to the subtests, P1 demonstrated substantial changes in the cognitive profile compared to the first assessment. Subtests "Verbal learning" and "Processing speed" showed the largest gain of test scores of all subjects. The lowest dynamics in comparison with P1 was found in P4, whose cognitive parameters augmented insignificantly compared to the primary assessment. However, "Processing speed" and "Working memory" subtests were characterized by the highest gain from the primary score.

Comparison of dynamical data with reference values discovered the absence of substantial improvement in "Motor fluency", "Processing speed", "Executive functions", and "Verbal learning" domains. In the first case, the execution of test was complicated by prevailing psychomotor disturbance of subjects. Therefore, we should refer to the positive dynamics of improvement, rather than an attempt to reach normal values. As for the processing speed, the patients with schizophrenia suffer from impaired volition, directly affecting the will to perform a higher number of tasks for limited time.

Evaluation of Neurotransmitter Concentration

The results interpretation of MR spectroscopy of brain tissue represented by absolute metabolite concentrations can be inaccurate and is prone to errors. Normally the comparable specificity parameters of MR spectroscopy can be obtained by using the metabolite ratio, rather than the absolute values of their concentrations (e.g., Glu/NAA).

To receive relevant data for spectroscopy processing, patients are obliged to lie still for quite a long time, which is not always easy for them. Results of international studies do not always consistent with each other, including the reports on elevation, absence of differences, and decrease in different brain regions of patient groups. Such discrepancy can be associated with the regional effects, methodological differences of proton MR spectroscopy, stage, disease severity or antipsychotic drug effect.

Both patients P1 and P3 showed a trend towards the reduction of both absolute and relative glutamate concentration, i.e., the parameter approached the reference value of 0.15. On the contrary, an opposite trend to minor elevation was seen in P4, thus also approaching the normal value. The results of P2 were challenging to interpret hence the concentration slightly above norm and remains stable throughout the treatment course. The clinical correlation shows no positive effect of TMS in P2, whereas P1, P3, and P4 had a marked positive dynamic in BFCRS (P1, P3, and P4) and NCRS (P1 and P3) tests.

After the TMS course GABA concentration diminished in all cases but P2, in whom the elevation of GABA level was registered.

At this stage it is hard to make a definite conclusion reflecting how concentrations of neurotransmitters change during TMS treatment and their association with clinical characteristics of patients. We hope that future research might clarify the correlations.

Study Advantages

- TMS for treatment of catatonia in outpatient conditions;
- monotherapy with contemporary etiotropic drugs (antipsychotic or antidepressant) in combination with necessary additional substances (mood stabilizers or anticholinergic drugs);
- residual catatonic symptoms in the mental status at the moment of study entry;
- bimodal MRI approach (rCBF and MR spectroscopy);
- personalized stimulation procedure;
- consideration of the dynamics of both psychometric deficiencies using BFCRS and NCRS, and cognitive functions with BACS.

Study Limitations

Described series of clinical cases of successful TMS application in treatment of catatonia represented in this article are considered as the lowest level of evidence according to the paradigm of evidence-based medicine. The absence of control group, placebo control (shame TMS), blinding, and randomization complicate the potential certainty of result interpretation. In other words, placebo effect cannot be excluded as a leading contributing factor of patients' improvement, which could be further facilitated by daily communication of subjects and TMS operators able to serve as a psychological support. Other events and conditions unrelated to treatment could have also made a major impact.

Another limitation of this study was the absence of specific scales that assess depression, which does not allow to exclude the intersection of psychomotor and depressive symptoms.

Rationale of Conclusions

- the method is safe in a short-term period

The present study did not detect any adverse events, which is consistent with the world experience of TMS application in managing mental disorders. Considering the study limitations of follow-up period for six months after the treatment course, allows to convincingly suggest a short-term safety of this method.

- ambiguous efficacy results

Referring to the achievement of symptomatic remission as the main criterion of treatment efficacy, we ended up with controversial results. Depending on the applied scale of catatonia evaluation (BFCRS or NCRS), remission was achieved by a different number of subjects, thus emphasizing the importance of choosing a specific psychometric instrument. Furthermore, it should be noted that positive clinical effect was registered in 2-3 out of 4 patients.

Comparison of our results with predominantly positive clinical outcomes in literature reports yet does not allow to convincingly infer the efficacy of TMS in catatonia management. Therefore, further research is required to determine the reason of non-response and specify psychometric instruments for results assessment.

Catamnesis

After six months after TMS course all patients underwent follow-up examination. None of them reported any side effects of TMS treatment. P1 informed us that he found a job but intended to change it since the conflict situations and was socially active. P3 and P4 returned to work and studies with no household difficulties, remained socially active and continued the drug administration. P2 returned to studies, though reported difficulties in learning, unwillingness to study, and absence of motivation. His mother controlled the visits to psychoneurological center, she mentioned that he missed university classes, did not help about the house, lay in bed for too long, and did not communicate with anyone.

Conclusions

TMS potentially activates metabolic processes in brain tissues, thus promoting deceleration of pathological mechanisms and potentiating neuroplasticity with procognitive effect, expressed primarily in the increase of processing speed and response to it, as well as in the improvement of working memory. To summarize, the influence of TMS on local brain regions makes it possible to achieve a positive clinical effect in treatment of catatonia.

In our opinion, TMS is a well-tolerable method that is not associated with severe adverse events, therefore presenting a favorable safety profile, especially comparing to ECT commonly used in catatonia management.

No strong and unequivocal results were received for the efficacy of TMS in treatment of catatonia. A positive clinical effect was seen, however, insufficient for achieving remission in most subjects. Placebo-controlled trial of protocol efficacy on a larger sampling is the future direction.

Author Contributions: Conceptualization, N.V.Z.; methodology, G.S.M; investigation, M.A.S., S.I.K..; data curation, A.Z.; writing—original draft preparation, V.A.O; writing—review and editing, Yu.I.K.; project administration, N.V.Z. All authors have read and agreed to the published version of the manuscript.

Informed consent: All patients signed the necessary informed consents in accordance with the requirements of Good clinical practice.

Conflicts of Interest: The authors declare no conflict of interest.

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