

RATIONALE FOR THE EFFICIENCY OF TRANSCRANIAL MAGNETIC STIMULATION IN MULTIPLE SCLEROSIS

Petro Gaponov

*Clinical department of vascular pathology of the brain and rehabilitation
State Institution «Institute of Neurology, Psychiatry and Narcology
of the National Academy of Medical Sciences of Ukraine»*

46 Ac. Pavlova str., Kharkiv, Ukraine, 61068;

*Department of Medical rehabilitation, sports medicine and medical physical education
Kharkiv Medical Academy of Postgraduate Education*

58 Amosova str., Kharkiv, Ukraine, 61176

gaponov.petya@gmail.com

Abstract

The aim. Based on the analysis and comprehensive clinical and neurological evaluation of the results to substantiate the effectiveness of transcranial magnetic stimulation (TMS) in the treatment and rehabilitation of patients with multiple sclerosis (MS).

Methods. A total of 110 MS patients were included in the study. The control group consisted of 30 patients who received pathogenetic therapy and 80 patients who underwent a course of rhythmic transcranial magnetic stimulation (rTMS) together with pathogenetic therapy.

Results. The results obtained during the study indicate the complex multifactorial nature of fatigue and its significant impact on the clinical manifestations of MS. Also, the use of rTMS reduced the severity of the main neurological symptoms of MS. The improvement in the overall EDSS scale in the group of patients receiving rTMS was statistically significant: from 5.0 ± 1.9 points to 4.5 ± 2.0 points ($p < 0.01$), in the comparison group ($p > 0.05$). Under the influence of TMS, gait function improved, but these indicators were statistically insignificant ($p > 0.05$). The greatest effect of rTMS was obtained on the manifestations of fatigue and also extended to its cognitive and psychosocial components. The obtained patterns are confirmed in the analysis of indicators on the SCA and FS scales. Involvement in the treatment of patients with MS rTMS allowed to achieve a significant reduction in the manifestations of all components of fatigue: from 76.0 ± 20.9 points to 75.5 ± 20.5 points ($p < 0.05$).

The data obtained during the study confirm the effectiveness, safety and viability of non-invasive neuromodulation by rTMS in the treatment and rehabilitation of patients with MS.

Conclusions. The use of rTMS has a positive effect on the manifestations of fatigue, both motor and cognitive, in patients with MS at all types of course and at different stages of progression. Non-invasiveness, safety and ease of use, the possibility of differentiated use allow the use of rTMS in the clinic of rehabilitation treatment and become an important component of active drug and non-drug rehabilitation of patients with MS.

Keywords: multiple sclerosis, type of multiple sclerosis, fatigue, transcranial magnetic stimulation, non-invasive stimulation.

DOI: 10.21303/2504-5679.2021.001992

1. Introduction

Multiple sclerosis is a complex, heterogeneous disease associated with increasing disability. According to the WHO, among neurological diseases, multiple sclerosis is one of the main causes of persistent disability of young people [1].

Despite the presence of advanced treatments that modify the disease, as well as symptomatic treatments that can reduce the activity and progression of the disease, there is a need for comprehensive rehabilitation measures to improve quality of life [2, 3]. In recent years, in addition to improving the existing arsenal of neurorehabilitation methods (exercise therapy, kinesiotherapy, physiotherapy), there are new techniques that can improve the patient's recovery [4, 5]. Recent methods include non-invasive neuromodulation methods, such as rhythmic transcranial magnetic stimulation (rTMS) [6, 7]. A feature of the rTMS method is its non-invasiveness, safety and ease of use [8, 9]. All these qualities and the possibility of differentiated use allow the use of rTMS in the clinic of rehabilitation treatment and become an important component of active

drug and non-drug rehabilitation of patients [10, 11]. In this regard, the TMS method can act as a tool for local individual modulator of certain areas of the cortex (activation or inhibition) in the mode required for a particular patient and have a positive effect on certain symptoms and syndromes [12, 13].

MS has a wide range of clinical manifestations [14, 15]. Fatigue is one of the leading syndromes observed in this category of patients and which has two components in its structure – motor and non-motor [16, 17]. All objective methods are aimed at quantifying each of them [18].

The aim of the research. Based on the analysis and comprehensive clinical and neurological evaluation of the results to substantiate the effectiveness of TMS in the treatment and rehabilitation of patients with MS.

2. Materials and methods

The study was conducted from 2019 to 2021 in the Department of Autoimmune and Degenerative Diseases of the Nervous System on the basis of the State Institution «Institute of Neurology, Psychiatry and Narcology of NAMS of Ukraine». The study involved 110 patients diagnosed with MS. The diagnosis was made according to the criteria of McDonald et al., 2017.

All procedures in this study are in line with the ethical standards of the 1975 Helsinki Declaration, as revised in 2008, and national legislation. Informed consent to participate in the study was discussed and signed by all study participants. Meeting of the Commission on Ethics and Deontology (minutes No. 7B of July 19, 2019) of the «Institute of Neurology, Psychiatry and Narcology of NAMS of Ukraine».

All patients received disease-modifying therapy drugs – drugs of the 1st (interferon beta 1- β , interferon beta 1- α , glatiramer acetate, teriflunomide) or 2nd line (mitoxantrone, ocrelizumab, alemtuzumab, cladribine) in combination with pulse therapy with methylprednisolone in case of exacerbation of the disease.

The study was performed in two stages. The first stage included the study of clinical and neurological features depending on the type of course, taking into account the motor and cognitive components of fatigue in patients with MS. The second stage was devoted to assessing the impact of rTMS on the components of fatigue.

According to the aim of the study, all patients were randomly divided into two groups: I – 80 (72.7 %) patients who underwent TMS, and II (comparison group) – 30 (27.3 %) patients who received only pathogenetic therapy.

The neurological status of patients was studied according to generally accepted criteria and included mental status, condition of cranial nerves, motor system, muscular strength, gait, statics and coordination of movements, sensitivity, state of reflex system, autonomic nervous system.

Clinical and neurological examination of patients with MS was performed using the FS and EDSS scales (Definitions for a standardized, quantified neurological examination and assessment of Kurtzke's Functional Systems and Expanded. Disability Status Scale in Multiple Sclerosis, 1983). The severity of the effect of fatigue was assessed by the scales MFIS (Modified Fatigue Scale Impad, 1998), FSS (Krupp et al., 1989), SCA.

RTMS was used for non-invasive neuromodulation during treatment and rehabilitation. The course of treatment was performed on a MagVenture, MagPro X100 and an 8-shaped inductor (coil). All patients were tested using a safety questionnaire and selected according to the indications and contraindications of rTMS [9]. Depending on the leading clinical manifestations, different protocols for rTMS were used. Protocols with high-frequency stimulation of DLPFC zones and primary motor cortex, M1 zone (D, S) with frequency 10 Hz, amplitude 90–100 % of WWII, duration of 10 sessions, from 1600 to 2000 stimuli per session were selected [19].

Statistical analysis of the data was performed using the licensed application package Statistica 13. Assessment of the nature of the distribution of quantitative characteristics was performed using the Shapiro-Wilk test. Intergroup analysis of differences was performed using the nonparametric Mann-Whitney test for quantitative traits and using Fisher's exact test for categorized traits. Correlation analysis was performed using Spearman's rank correlation method. The level of statistical significance of differences and correlations $p < 0.05$ was considered acceptable.

3. Result

Among patients with MS, women dominated: 66.4 % vs. 33.6 % of men; the largest proportion of women was found in the remitting type – 74.6 %, the smallest – in the initially progressive (50.0 %), however, gender differences between different types of MS are not statistically significant ($p > 0.05$) (Table 1).

Table 1

Gender structure of the studied contingent

Sex	Primarily progressive		Secondarily progressive		Remitting		Total	
	abs.	M±m	abs.	M±m	abs.	M±m	abs.	M±m
Men	7	50.0±13.4	15	40.5±8.1	15	25.4±5.7	37	33.6±4.5
Women	7	50.0±13.4	22	59.5±8.1	44	74.6±5.7	73	66.4±4.5
Total	14	100.0	37	100.0	59	100.0	110	100.0

The mean age of the examined patients at the time of the study was 39.7 ± 9.2 years; the oldest were patients with primary progressive type of course (42.7 ± 7.4 years), slightly younger – with secondary progressive (40.1 ± 11.1 years), and the youngest – with remitting type (38.7 ± 8.3 years), although the differences between the groups are statistically insignificant ($p > 0.05$).

The average duration of MS in the examined patients was 6.7 ± 4.2 years; the largest – in patients with primary progressive type (11.1 ± 4.7 years), insignificant ($p > 0.05$) smaller – in patients with secondary progressive type (8.8 ± 3.8 years), and significant $p < 0.05$ less – in patients with remitting type (4.4 ± 2.7 points).

In 54.5 % the process was active at the time of the survey, in 45.5 % – inactive. The largest proportion of patients with active process was in the secondary-progressive type (70.3 %), and the smallest – in the primary-progressive (21.4 %)

The nature of MS in most subjects was monosyndromic (73.6 %); the proportion of polysyndromic variants differed slightly in different types and was the largest in the primary progressive variant (35.7 %), and the smallest – in the secondary – progressive (21.6 %) (Fig. 1).

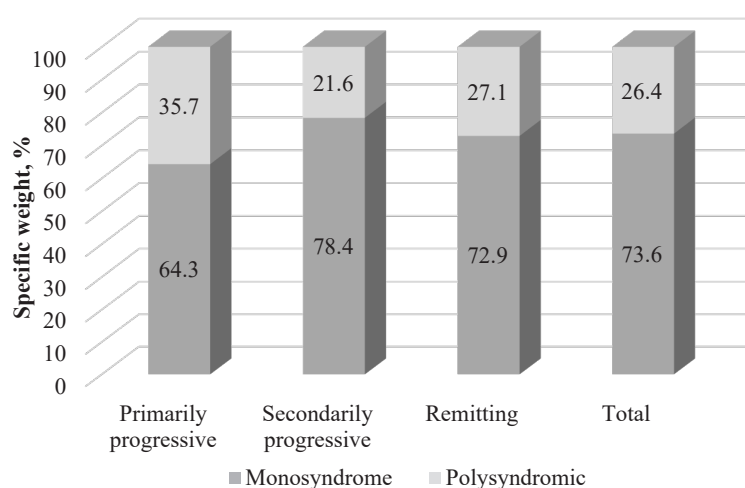


Fig. 1. The nature of MS in the examined patients

Analysis of lateralization revealed a predominance of left-sided lesions (43.6 %), somewhat less often found right-handed (30.9 %) and rarely symmetrical (25.5 %). Left-sided lesions dominated in patients with secondary-progressive type (67.6 %), and right-sided and symmetrical – in patients with primary progressive type (42.9 %) (Fig. 2).

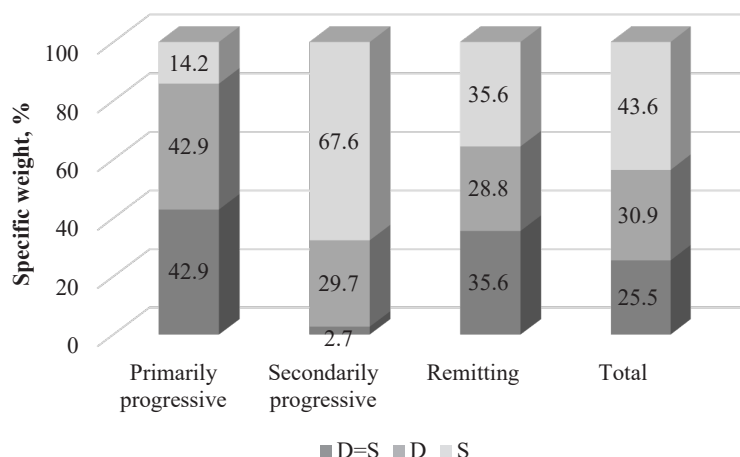


Fig. 2. Features of lateralization of the process in the examined patients

The peculiarities of fatigue manifestations in MS were studied in detail. Our data allow us to consider fatigue in MS as a separate clinical and socio-medical phenomenon, characterized by certain clinical and phenomenological features, characteristics of functioning and quality of life of patients, as well as the mutual influence of various clinical factors.

When analyzing the severity of fatigue in MS according to the MFIS scale, fairly high values were found for all subscales (**Fig. 3**). Thus, the index on the physical subscale in all patients was 16.5 ± 11.2 points, on the cognitive subscale – 23.8 ± 10.1 points, on the psychosocial subscale – 4.0 ± 2.1 points. The overall MFIS score in the examined patients was 44.3 ± 23.0 points. At the same time, there is a clear tendency to significantly more pronounced fatigue in patients with primary progressive type of MS, less – in patients with secondary progressive type, and the least – in patients with remitting type.

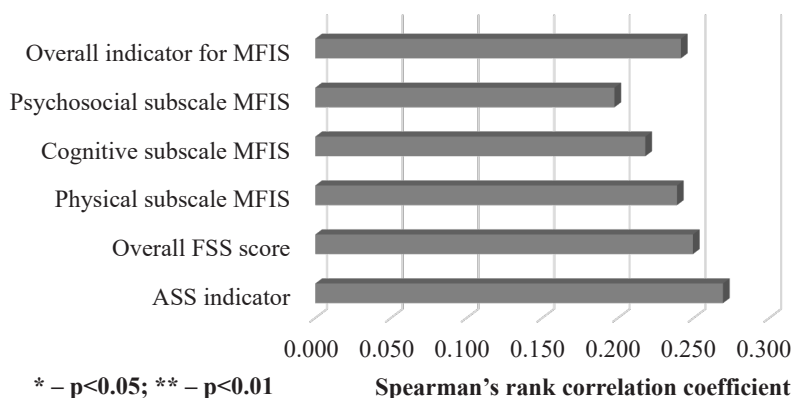


Fig. 3. Correlations between fatigue rates and the overall severity of MS symptoms on the EDSS scale

Similarly, the indicators on the FS and ASS scales reflected the same trends (**Fig. 3**). Thus, the overall score on the FSS scale in all patients was 40.7 ± 13.7 points, in patients with primary progressive type – 52.6 ± 9.9 points, with secondary progressive type – 49.8 ± 8.7 points, with remitting type – 32.1 ± 11.1 points. The indicator on the ASS scale in all examined patients was 76.1 ± 20.9 points, in patients with primary progressive type – 96.9 ± 13.4 points, with secondary progressive type – 89.4 ± 13.1 points, and when remitting type – 62.9 ± 16.7 points.

At the same time, the clinical and pathogenetic mechanisms of fatigue in MS are complex and multifactorial [20]. This was confirmed by the results of non-parametric correlation analysis. Thus, none of the indicators of the severity of clinical symptoms of MS on the FS scale (optic nerve damage, cranial nerve disorders, pyramidal pathway symptoms, incoordination,

impaired sensitivity, pelvic dysfunction and intelligence) did not show significant correlations with fatigue ($p > 0.05$). In this case, the overall severity of the EDSS scale was associated with a direct correlation with the severity of fatigue according to all scales used in our study (**Fig. 3**).

As the general indicator on the EDSS scale is defined mainly by indications of loss of gait function, especially at heavy forms of a disease, the inverse correlations between preservation of gait function (distance which the patient can pass) and indicators of expressiveness of fatigue are natural (**Fig. 4**).

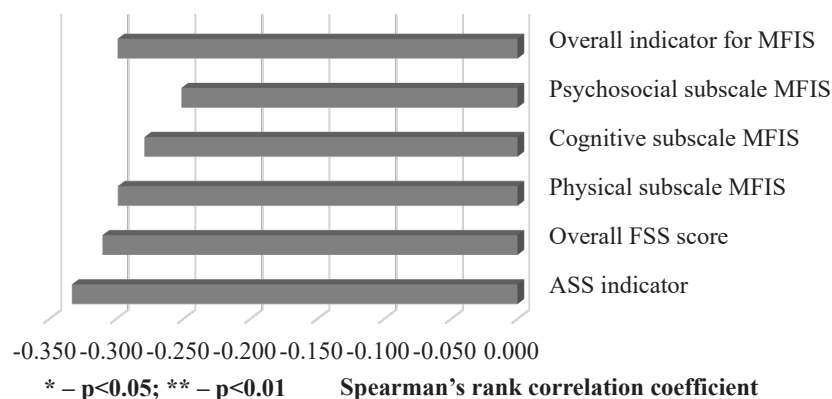


Fig. 4. Correlations between gait function and fatigue rates

In addition, significant correlations were found between the duration of the disease and the severity of fatigue, but primarily due to the cognitive component (**Fig. 5**). The correlations between age and fatigue rates were not statistically significant ($p > 0.05$), indicating a lack of relationship between these factors.

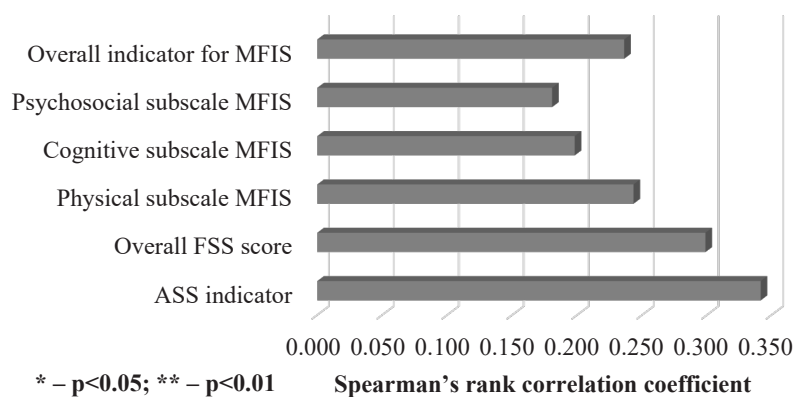


Fig. 5. Correlations between fatigue and disease duration

It should be noted that the correlations are mostly weak (except for ASS), which indicates a complex multifactorial nature of fatigue in MS and the inability to explain it only by the formal characteristics of the severity of neurological symptoms.

The introduction of TMS in the complex of treatment and rehabilitation measures for MS has improved the overall condition of patients and achieved significant changes in some important areas.

The use of TMS allowed to some extent reduce the severity of the main neurological symptoms of MS, although the dynamics here was ambiguous and not very pronounced (**Table 2**).

Neither traditional nor the proposed therapy did not affect the optic nerve damage: the indicators did not change under the influence of treatment. Symptoms of cranial nerve disorders in the comparison group during therapy slightly worsened: from 1.9 ± 1.1 points to 2.0 ± 1.0 points ($p > 0.05$), and in the group receiving TMS, slightly decreased: from 1.5 ± 1.0 points

to 1.4 ± 1.0 points ($p > 0.05$). Symptoms of pyramidal pathway damage in the comparison group decreased slightly: from 4.1 ± 1.1 points to 3.5 ± 1.3 points ($p > 0.05$), while in the intervention group the improvement was significant: from 3.6 ± 1.4 points to 3.3 ± 1.3 points ($p < 0.01$). Traditional therapy was significantly effective against coordination disorders, where the FS scale decreased from 3.8 ± 1.2 points to 3.3 ± 1.2 points ($p < 0.05$), a similar effect was achieved in the intervention group, where the indicator decreased from 3.1 ± 1.4 points to 2.8 ± 1.3 points ($p < 0.05$). Dynamics in the symptoms of pelvic disorders under the influence of traditional and proposed therapy was absent. In the group of traditional therapy there were no changes in the intellectual component of the FS scale, while in patients receiving TMS, there was some improvement: from 1.5 ± 0.8 points to 1.4 ± 0.8 points, although these changes were statistically insignificant ($p > 0.05$).

Table 2Indicators on FS and EDSS scales before and after TMS, $M \pm m$, (in points)

Indicator	Comparison group, $n = 30$		Intervention group, $n = 80$	
	before treatment	after treatment	before treatment	after treatment
Optic nerve damage	1.5 ± 0.9	1.5 ± 0.9	1.5 ± 0.9	1.5 ± 0.9
Disorders of the cranial nerves	1.9 ± 1.1	2.0 ± 1.0	1.5 ± 1.0	1.4 ± 1.0
Symptoms of pyramidal pathway damage	4.1 ± 1.1	3.5 ± 1.3	3.6 ± 1.4	$3.3 \pm 1.3^{**}$
Impaired coordination	3.8 ± 1.2	3.3 ± 1.2	3.1 ± 1.4	$2.8 \pm 1.3^*$
Sensitivity disorders	1.4 ± 1.2	1.4 ± 1.2	1.1 ± 1.1	$1.0 \pm 1.0^*$
Pelvic dysfunction	1.6 ± 0.9	1.6 ± 1.1	1.2 ± 1.0	1.2 ± 1.0
Disorders of intelligence	1.9 ± 0.8	1.9 ± 0.8	1.5 ± 0.8	1.4 ± 0.8
Indicator on the EDSS scale	5.5 ± 1.5	5.1 ± 1.9	5.0 ± 1.9	$4.5 \pm 2.0^{**}$

Note: * – discrepancies are statistically significant ($p < 0.05$); ** – differences are statistically significant ($p < 0.01$)

The overall EDSS score in the comparison group improved during treatment: from 5.5 ± 1.5 points to 5.1 ± 1.9 points, but this improvement was statistically insignificant ($p > 0.05$). In the group of patients receiving TMS, the improvement was statistically significant: from 5.0 ± 1.9 points to 4.5 ± 2.0 points ($p < 0.01$).

Certain positive changes under the influence of therapy have occurred in relation to the restoration of gait function (Table 3).

Thus, under the influence of traditional and proposed therapy, gait performance improved somewhat: the number of patients who were able to restore gait without restrictions increased and the number of patients with gait restrictions decreased. In the intervention group, a slightly greater improvement in gait recovery was achieved than in the comparison group, however, these differences were statistically insignificant ($p > 0.05$).

Important was the therapeutic effect of TMS on the manifestations of fatigue in MS. Given the complex nature of asthenic manifestations in MS, we studied the dynamics of the various components of fatigue using several valid and reliable techniques.

Analysis of the dynamics of indicators on the MFIS scale allowed to establish the presence of a certain positive dynamics of fatigue under the influence of traditional therapy. Thus, the indicator on the physical subscale decreased from 16.2 ± 11.2 points to 15.9 ± 11.1 points, on the cognitive subscale from 22.7 ± 11.1 points to 22.3 ± 10.9 points, on the psychosocial subscale from 4.0 ± 2.1 points to 3.9 ± 2.1 points (Table 4).

The overall score on the MFIS scale during treatment according to the traditional scheme decreased from 43.0 ± 23.9 points to 42.0 ± 23.4 points. At the same time, the decrease in indicators

on all subscales, as well as the integrated fatigue rate on the MFIS scale under the influence of traditional therapy was statistically insignificant ($p > 0.05$).

Table 3

The results of the study of gait function before and after TMS

Gait	Comparison group, $n = 30$				Intervention group, $n = 80$			
	before treatment		after treatment		before treatment		after treatment	
	abs.	$M \pm m$	abs.	$M \pm m$	abs.	$M \pm m$	abs.	$M \pm m$
Without limits	6	20.0 ± 7.3	8	26.7 ± 8.1	27	33.6 ± 5.3	30	37.2 ± 5.4
more than 500 m	1	3.3 ± 3.3	1	3.3 ± 3.3	5	6.3 ± 2.7	9	11.3 ± 3.5
300–500 m	3	10.0 ± 5.5	1	3.3 ± 3.3	7	8.8 ± 3.2	3	3.8 ± 2.1
200–300 m	2	6.7 ± 4.6	3	10.0 ± 5.5	6	7.5 ± 2.9	5	6.3 ± 2.7
100–200 m	9	30.0 ± 8.4	9	30.0 ± 8.4	12	15.0 ± 4.0	13	16.3 ± 4.1
20–100 m	5	16.7 ± 6.8	5	16.7 ± 6.8	13	16.3 ± 4.1	13	16.3 ± 4.1
A few steps	3	10.0 ± 5.5	2	6.7 ± 4.6	8	10.0 ± 3.4	5	6.3 ± 2.7
None	1	3.3 ± 3.3	1	3.3 ± 3.3	2	2.5 ± 1.7	2	2.5 ± 1.7
Total	30	100	30	100	80	100	80	100

Table 4

Indicators on the MFIS scale before and after treatment, $M \pm m$ (in points)

Indicator	Comparison group, $n = 30$		Intervention group, $n = 80$	
	before treatment	after treatment	before treatment	after treatment
Physical subscale	16.2 ± 11.2	15.9 ± 11.1	16.6 ± 11.3	$16.3 \pm 11.3^*$
Cognitive subscale	22.7 ± 11.1	22.3 ± 10.9	24.3 ± 9.8	$24.0 \pm 9.8^*$
Psychosocial subscale	4.0 ± 2.1	3.9 ± 2.1	4.0 ± 2.1	$3.8 \pm 2.1^*$
Overall indicator for MFIS	43.0 ± 23.9	42.0 ± 23.4	44.8 ± 22.7	$44.1 \pm 22.7^*$

Note: * – discrepancies are statistically significant ($p < 0.05$)

Instead, in the process of treatment with TMS it was possible to achieve a significant improvement in fatigue, and the therapeutic effect of TMS also extended to its cognitive and psychosocial components. Thus, the indicator on the physical scale under the influence of treatment according to the proposed scheme decreased from 16.6 ± 11.3 points to 16.3 ± 11.3 points ($p < 0.05$), on the cognitive subscale – from 24.3 ± 9.8 points to 24.0 ± 9.8 points ($p < 0.05$), on the psychosocial subscale – from 4.0 ± 2.1 points to 3.8 ± 2.1 points ($p < 0.05$). The overall indicator on the MFIS scale under the influence of the proposed scheme decreased significantly: from 44.8 ± 22.7 points to 44.1 ± 22.7 points ($p < 0.05$).

At the same time, it should be noted that the dynamics of fatigue during treatment was uneven and differed in different groups depending on the type of MS. Thus, in patients with primary progressive and secondary progressive types of MS, similar levels of fatigue were observed; the severity of asthenic manifestations in them was related to the duration of the disease and was

determined mainly by physical components. In contrast, in the remitting type of MS, the overall low rate of fatigue was due to the presence in this group of a significant number of patients with mild course and low severity of pathological manifestations, including in the cognitive and psychosocial spheres. At the same time, patients with very high cognitive and psychosocial fatigue subscales were found in this group; indicators in these patients exceeded those found in patients with primary progressive and secondary progressive types. The positive dynamics of asthenia in the group of patients with remitting type was largely due to the reduction of asthenic manifestations associated with cognitive and psychosocial dysfunction.

The obtained patterns are confirmed in the analysis of indicators on the ASS and FSS scales during treatment (**Table 5**).

Table 5

Indicators on the ASS and FSS scales before and after treatment, $M \pm m$ (in points)

Indicator	Comparison group, $n = 30$		Intervention group, $n = 80$	
	before treatment	after treatment	before treatment	after treatment
Indicator for ASS	76.6 ± 21.1	75.8 ± 20.5	76.0 ± 20.9	$75.5 \pm 20.5^*$
Overall FSS score	41.3 ± 14.0	40.9 ± 13.7	40.4 ± 13.7	$40.2 \pm 13.6^*$

Note: * – discrepancies are statistically significant ($p < 0.05$)

Thus, in the process of treatment according to the traditional scheme, the fatigue rate on the SCA scale decreased from 76.6 ± 21.1 points to 75.8 ± 20.5 points, however, this decrease was statistically insignificant ($p > 0.05$). Instead, the proposed scheme allowed to achieve a significant reduction in fatigue: from 76.0 ± 20.9 points to 75.5 ± 20.5 points ($p < 0.05$).

Similarly, the FSS scale in the comparison group decreased slightly: from 41.3 ± 14.0 points to 40.9 ± 13.7 points ($p > 0.05$), and in the intervention group significantly: from 40.4 ± 13.7 points to 40.2 ± 13.6 points.

Thus, the proposed scheme of intervention using TMS has significantly reduced the manifestations of asthenia in patients with MS, including through the impact on the cognitive and psychosocial components of fatigue.

Adverse events were observed in 68.75 % of patients during rTMS. They depended on the chosen protocol. In most cases (72.7 %) patients complained of discomfort at the site of stimulation, moderate local pain. Tics of facial muscles were observed in 5 % of cases. Also, 23.63 % of patients complained of dizziness, drowsiness and fatigue after the session. All of the above side effects were temporary and passed after the end of the rTMS session after some time.

4. Discussion

MS refers to diseases that steadily progress and lead to early disability. Early administration of disease-modifying therapy (DMT) drugs can inhibit the demyelinating process, but not cure [2, 3]. This disease mainly affects people of young, working age.

Therefore, rehabilitation at the very initial stages of MS development, along with taking DMT drugs, is a priority [4]. Recently, much attention has been paid by researchers to the study of various methods of non-invasive neuromodulation. The issue of differentiated application of these methods in the treatment of MS is debatable [19].

The non-invasive method of neuromodulation includes rTMS. Safety, non-invasiveness and a wide range of effects on MS symptoms have allowed us to suggest a possible positive effect of rTMS on the components of fatigue.

Fatigue makes a significant contribution to disability and significantly reduces the quality of life [16]. The peculiarities of fatigue manifestations in MS were studied in the work. Modern valid scales FSS, MFIS, asthenic state scale (ASS) were used. The data obtained during the study

allowed us to consider fatigue in MS as a separate clinical and socio-medical phenomenon, characterized by certain clinical and phenomenological features and the mutual influence of different clinical factors.

Thus, in the works of Vynychuk S. M. no direct correlations were obtained with the degree of disability [21]. However, according to our study, the overall severity of the EDSS scale was found to be directly correlated with the severity of fatigue on all scales used in the study. And the inverse correlation was obtained between the preservation of gait function (distance that the patient can walk) and indicators of the severity of fatigue.

However, none of the indicators of the severity of clinical symptoms of MS on the FS scale showed significant correlations with fatigue ($p > 0.05$). Indicators of fatigue correlate with the duration of the disease, but have no relationship with age ($p > 0.05$). Such tendencies coincide with the published results of Kopchak O. O. [18].

The results obtained during the study indicate the complex multifactorial nature of fatigue and its significant impact on the clinical manifestations of MS. The second stage was to study the effect of TMS on the leading symptoms of MS, primarily on the components of fatigue. Protocols with high-frequency stimulation of DLPFC and primary motor cortex zones, M1 (D, S) zones with a frequency of 10 Hz, amplitude of 90–100 %, duration of 10 sessions, from 1600 to 2000 stimuli per session were selected. The use of TMS reduced the severity of the main neurological symptoms of MS. This was confirmed in the works of Iodice R., 2017, Leocani L., 2019 [6, 13]. The improvement in the overall EDSS score in the group of patients receiving TMS was statistically significant: from 5.0 ± 1.9 points to 4.5 ± 2.0 points ($p < 0.01$), in the comparison group ($p > 0.05$). Under the influence of TMS, gait function improved, but these indicators were statistically insignificant ($p > 0.05$). The greatest effect of rTMS was obtained on the manifestations of fatigue and also extended to its cognitive and psychosocial components. The dynamics of fatigue indicators under the influence of rTMS was uneven and depended on the type of MS. Improvement from non-invasive neuromodulation was observed in all types of MS. The obtained patterns are confirmed in the analysis of indicators on the ASS and FS scales. Involvement in the treatment of patients with MS rTMS allowed to achieve a significant reduction in the manifestations of all components of fatigue: from 76.0 ± 20.9 points to 75.5 ± 20.5 points ($p < 0.05$).

The data obtained during the study confirm the effectiveness, safety and viability of non-invasive neuromodulation by rTMS in the treatment and rehabilitation of patients with MS.

Study limitations. This study combines the observation of MS patients during one course of rTMS (10 sessions, two weeks) on the background of the use of drug-modifying therapy.

Prospects for further research. Since the results obtained during the study indicate a positive effect of rTMS on the clinical manifestations of MS, primarily on the components of fatigue, we plan in the following studies to develop an algorithm for non-invasive neuromodulation in the treatment of MS depending on MS activity.

5. Conclusions

Fatigue is a very common (78 %) symptom in the structure of neurological disorders in patients with MS, which deepens disability and affects quality of life.

The symptom of fatigue in patients with MS, which contains both motor and cognitive components, differently affect the neurological manifestations at different types of course, at different stages of progression.

The level of motor fatigue correlates with the level of disability. There is a connection between the level of motor fatigue and the level of damage to the pyramidal pathways. Cognitive fatigue is not connected with age, sex ($p > 0.05$), but moderately correlates with level of disability and considerably correlates with duration of a disease ($p < 0.05$).

The use of rTMS has a positive effect on the manifestations of fatigue, both motor and cognitive, in patients with MS at all types of course and at different stages of progression (76.0 ± 20.9 points to 75.5 ± 20.5 points, at $p < 0.05$), primarily due to the cognitive component (16.6 ± 11.3 points to 16.3 ± 11.3 points, at $p < 0.05$), to a lesser extent due to the motor component.

Non-invasiveness, safety and ease of use, the possibility of differentiated use allow the use of TMS in the clinic of rehabilitation and become an important component of active drug and non-drug rehabilitation of patients.

Conflict of interests

The author declares there is no conflict of interests.

Financing

The study was performed without financial support.

Acknowledgments

Acknowledgments of the Department of Autoimmune and Degenerative Diseases of the Nervous System, the Center for Multiple Sclerosis of the «Institute of Neurology, Psychiatry and Narcology of the National Academy of Medical Sciences of Ukraine», where a set of material for this work was carried out and which was a fragment of the research «To study the clinical and pathogenetic, neurobiological and biochemical mechanisms of neuroplasticity as a basis for adaptation in demyelinating and degenerative pathology» NAMS. ND.8F.19.

References

- [1] Thompson, A. J., Baranzini, S. E., Geurts, J., Hemmer, B., Ciccarelli, O. (2018). Multiple sclerosis. *The Lancet*, 391 (10130), 1622–1636. doi: [http://doi.org/10.1016/s0140-6736\(18\)30481-1](http://doi.org/10.1016/s0140-6736(18)30481-1)
- [2] Muratova, T. M., Nehrych, T. I., Voloshyna, N. P., Mialovytska, O. A., Pashkovskiy, V. M., Khubetova, I. V. et. al. (2020). Rozsiiani skleroz v Ukraini: personalizovana stratehiia likuvannia. *Zdorovia Ukrainy*, 2, 14–16.
- [3] Hauser, S. L., Cree, B. A. C. (2020). Treatment of Multiple Sclerosis: A Review. *The American Journal of Medicine*, 133 (12), 1380–1390.e2. doi: <http://doi.org/10.1016/j.amjmed.2020.05.049>
- [4] Khan, F., Amatya, B. (2017). Rehabilitation in Multiple Sclerosis: A Systematic Review of Systematic Reviews. *Archives of Physical Medicine and Rehabilitation*, 98 (2), 353–367. doi: <http://doi.org/10.1016/j.apmr.2016.04.016>
- [5] Белова, А. Н. (2002). Нейрореабилитация. Moscow: Антидор, 736.
- [6] Leocani, L., Chieffo, R., Gentile, A., Centonze, D. (2019). Beyond rehabilitation in MS: Insights from non-invasive brain stimulation. *Multiple Sclerosis Journal*, 25 (10), 1363–1371. doi: <http://doi.org/10.1177/1352458519865734>
- [7] Chervyakov, A. V., Poydasheva, A. G., Korzhova, Yu. E. (2016). Ritmicheskaya transkraniálnaya magnitnaya stimulyatsiya v neyroreabilitatsii. *Vosstanovitel'naya nevrologiya. Innovatsionnye tekhnologii v neyroreabilitatsii*. Moscow: Izdatel'stvo «MIA Moskva», 247–282.
- [8] Rossi, S., Antal, A., Bestmann, S., Bikson, M., Brewer, C., Brockmüller, J. et. al. (2021). Safety and recommendations for TMS use in healthy subjects and patient populations, with updates on training, ethical and regulatory issues: Expert Guidelines. *Clinical Neurophysiology*, 132 (1), 269–306. doi: <http://doi.org/10.1016/j.clinph.2020.10.003>
- [9] Suponeva, N. A., Bakulin, I. S., Poydasheva, A. G., Piradov, M. A. (2017). Safety of transcranial magnetic stimulation: review of international guidelines and new findings. *Neuromuscular Diseases*, 7 (2), 21–36. doi: <http://doi.org/10.17650/2222-8721-2017-7-2-21-36>
- [10] Kuznetsov, V. V., Skachkova, N. A. (2016). *Neinvazivnaya stimulyatsiya golovnoho mozga*. Kyiv: «Izdatel'stvo «Feniks», 246.
- [11] Evtushenko, S. K., Kazaryan, N. E., Simonyan, V. A. (2007). Primenenie metoda transkraniálnoy magnitnoy stimulyatsii v klinicheskoy nevrologii. *Mezhdunarodniy nevrologicheskii zhurnal*, 5, 119–126.
- [12] Hallett, M. (2007). Transcranial Magnetic Stimulation: A Primer. *Neuron*, 55 (2), 187–199. doi: <http://doi.org/10.1016/j.neuron.2007.06.026>
- [13] Iodice, R., Manganelli, F., Dubbioso, R. (2017). The therapeutic use of non-invasive brain stimulation in multiple sclerosis – a review. *Restorative Neurology and Neuroscience*, 35 (5), 497–509. doi: <http://doi.org/10.3233/rnn-170735>
- [14] Akhmedova, G. M., Sabirov, Z. F., Yakupov, M. A., Khaybullin, T. I. (2018). Movement disorders in patients with multiple sclerosis. *Modern Problems of Science and Education*, 5. doi: <http://doi.org/10.17513/spno.28058>
- [15] Peresedova, A. V. et. al. (2002). Mekhanizmy labilnosti nevrologicheskikh simptomov pri rasseyannom skleroze. *Zhurnal nevrologii i psikiatrii im. S. S. Korsakova*, 1, 15–19.
- [16] Gekht, B. M., Kasatkina, L. F., Gilvanova, O. V. (2003). Sindrom khronicheskoy ustalosti. *Nevrologicheskii zhurnal*, 8 (1), 52–55.

- [17] Kasatkin, D. S. (2006). Sindrom astenii i sindrom patologicheskoy utomlaemosti pri remittiruyuschem rasseyannom skleroze. Moscow, 190.
- [18] Kopchak, O. O. (2005). Mekhanizmy vynykennia ta proiavy vtomy u khvorykh na rozsiiani skleroz, metody diahnos-tyky ta likuvannia. Kyiv, 21.
- [19] Palm, U., Ayache, S. S., Padberg, F., Lefaucheur, J.-P. (2014). Non-invasive Brain Stimulation Therapy in Multiple Sclerosis: A Review of tDCS, rTMS and ECT Results. Brain Stimulation, 7 (6), 849–854. doi: <http://doi.org/10.1016/j.brs.2014.09.014>
- [20] Oknin, V. Yu. (2004). Problema utomleniya, stressa i khronicheskoy ustalosti. Russkiy meditsinskiy zhurnal, 12 (5).
- [21] Vynychuk, S. M., Mialovytska, O. A., Koliendo, O. O. (2004). Vtoma u khvorykh na rozsiiani skleroz: do pytan-nia pro vzaïmozv'yazok iz ii nevrolohichnoi invalidyzatsiïu ta depresiïu i suchasni metody korektsii. Ukr. visn. Psykhonevrolohii, 12 (3 (40)), 17–20.

Received date 22.06.2021

Accepted date 27.07.2021

Published date 30.07.2021

© The Author(s) 2021

This is an open access article

under the Creative Commons CC BY license

How to cite: Gaponov, P. (2021). Rationale for the efficiency of transcranial magnetic stimulation in multiple sclerosis. EUREKA: Health Sciences, 4, 54–64. doi: <http://doi.org/10.21303/2504-5679.2021.001984>