Multitarget transcranial magnetic theta-burst stimulation in the correction of cognitive impairment in patients with progressive multiple sclerosis

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Cognitive impairment (CI) is a common symptom in multiple sclerosis (MS) that significantly impairs quality of life. Severe cognitive impairment with a multidomain phenotype is observed in progressive MS (PMS). Given the limitations of available therapeutic approaches to the treatment of CI in PMS, the investigation of transcranial magnetic stimulation (TMS) for its correction is relevant.
Objective: *To investigate the safety, tolerability and efficacy of multitarget navigated TMS in PMS with CI.*
Material and methods. *A protocol for multitarget intermittent theta-burst stimulation (iTBS) of the left dorsolateral prefrontal and posterior parietal cortex was developed. Fifteen patients with PMS and CI were enrolled in the study: 8 patients received sham stimulation followed by active iTBS, and 7 patients received only active iTBS. Safety and tolerability were assessed by questionnaires, efficacy by neuropsychological testing and questionnaires on subjective CI and fatigue.*
Results. *No serious adverse events (AEs) or discontinuation of TMS were observed. Mild AEs were recorded during 39.8% of sessions and within 24 hours after 23.3% of sessions, with no statistically significant differences between sham- and active iTBS. Verbal working and short-term memory (p=0.012 and p=0.049) as well as information processing speed (p=0.026), visuospatial perception (p=0.023), subjective CI (p=0.016) and fatigue (p=0.041) improved after the active protocol. Sham-iTBS had no significant effects. Significant differences between the effects of the sham and the active protocol were only observed for verbal working memory (p=0.043).*
Conclusion. *Thus, this pilot study confirmed good safety and tolerability of the TMS protocol in PMS with CI. It was shown that there is a potential efficacy for verbal working and short-term memory, information processing speed, visuospatial perception, subjective CI and fatigue. The efficacy needs to be confirmed in further large studies.*

Keywords: *progressive multiple sclerosis; cognitive impairment; transcranial magnetic stimulation; intermittent theta burst stimulation; multitarget stimulation; dorsolateral prefrontal cortex; posterior parietal cortex.*
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Cognitive impairment (CI) is the so-called "hidden" symptom of multiple sclerosis (MS), which is often underrecognized in clinical practice [1]. CI is registered in 25–45% of patients with relapsing-remitting MS (RRMS) and 45–80% of patients with secondary progressive MS (SPMS) [2, 3]. In SPMS CI is more severe and often multi-domain [4]. CI is associated with decreased quality of life [5] and also can be a marker of disease progression [6, 7].

One of the pathogenetic mechanisms of CI in MS is the impairment of brain network connectivity due to lesions in the hubs and connections of neural networks [8, 9]. As supposed, at early stages connectivity increases as a compensatory mechanism, but later collapse of connections and disintegration of networks occurs, which also affects the frontoparietal control network (FPCN) [10]. However, this hypothesis is currently under discussion [11].

The therapeutic approaches for CI in MS are limited: there is lack of data regarding pharmacotherapy [12, 13], and the only approach with confirmed efficacy is cognitive training [14, 15]. Therefore, searching for additional techniques of CI correction, including non-invasive neuromodulation, remains important.

Transcranial magnetic stimulation (TMS) is intensively investigated in CI of different etiology [16–18] and has an *evidence level C* according to guidelines of the International Federation of Clinical Neurophysiology in Alzheimer's disease (AD) [19]. This protocol includes stimulation of six areas (3 at each session): dorsolateral prefrontal cortex (DLPFC) and parietal network bilaterally, Broca and Wernicke areas – combined with a matching cognitive task, which is performed online [19, 20].

Currently, more and more attention is paid to theta-burst stimulation (TBS), in which stimuli are applied as bursts consisting of 3 stimuli with a frequency of 50 Hz, the frequency of bursts is 5 Hz [21]. The neuromodulating effects of TBS can be induced within a short stimulation time [22] that makes these

protocols convenient for clinical practice. Intermittent TBS (iTBS) has shown a positive effect in MS-related spasticity *(level of evidence B)* [19].

Currently available data regarding TMS effects on cognitive functions (CF) in patients with MS are limited. There are results of a study investigating the effects of a single fMRI-navigated high frequency (HF) repetitive TMS (rTMS) on the working memory [23]. Some studies assessing effects of TMS on CF in MS are being conducted [24, 25], but their results have not been published yet.

Taking into account the effectiveness of multifocal TMS in AD and the high rate of multi-domain CI in progressive MS (PMS) we have developed a protocol of multitarget iTBS. Hubs of FPCN – left DLPFC and posterior parietal cortex (PPC) are chosen as the stimulation targets.

The aim of this study is research of safety and tolerability of this protocol as well as assessment of its effectiveness in CI and fatigue.

Material and methods. The study was conducted in accordance with the principles of the Declaration of Helsinki and was accepted by the local ethical committee of the Research Center of Neurology (protocol №1-7/23 25.01.2023). All patients gave their written informed consent to participate in the study.

Inclusion criteria:

– age 18–70 y.o.;
– diagnosed PMS;
– no signs of relapse and ⩾1 months after relapse treatment;
– disease severity according to Expanded Disability Status Scale (EDSS) <7 points;
– CI: decrease of 1.5 standard deviations or more from the mean normative data according to Brief International Cognitive Assessment in Multiple Sclerosis (BICAMS) [26], performance should be assessed more than 1 month after relapse therapy;
– dominating right hand [27].

Non-inclusion criteria:

– diseases or conditions other than MS that can be the cause of CI (other diseases with CI; depression; prescribed drugs with confirmed negative effects on CF; abuse of alcohol or psychoactive substances);
– diseases or conditions, complicating test performance (uncorrected vision/hearing impairments; severe dysarthria, tremor or dominating hand paresis);
– severe concomitant somatic/neurologic disease;
– TMS and/or MRI contraindications;
– diagnosed epilepsy, history of epileptic seizures or epileptiform activity according to electroencephalography (EEG).

Exclusion criteria:

– rejection to participate in the study;
– confirmed diagnosis other than MS;
– decompensation or development of acute concomitant disease;
– TMS/MRI contraindications;
– necessity to treat the relapse or change disease-modifying drugs

At first, T1-MPR (multiplanar reconstruction) sequence was performed using Siemens Magnetom Prisma tomograph (Siemens Healthineers AG, Germany) with the following parameters: TR 2300 ms, TE 2.98 ms, slice thickness 1 mm, 176 slices. For iTBS the system MagPro X100+ MagOption (Tonica Elektronik A/S, Denmark) with robotised manipulator Axilum Robotics TMS-Cobot (Axilum Robotics, France) and figure-eight coil with liquid cooling were used.

The study included two stages. At the first stage five sessions of sham-iTBS following five sessions of active iTBS were applied. Each session included two stimulation blocks: of the left DLPFC and PPC, which were applied consecutively. Left DLPFC was determined as the area of superior or middle frontal gyrus located 5 cm from the hotspot for the first dorsal interosseus muscle and PPC – as the area of inferior parietal lobulus or angular gyrus (according to MRI). Stimuli were applied with the frequency of 50 Hz in bursts of three stimuli with the burst frequency of 5 Hz. The stimuli were applied in trains of 2 seconds with the interval of 8 seconds between them (20 trains, 600 stimuli in a block). The intensity was 75% of the individual resting motor threshold because it was for this intensity that the maximal effect was shown in healthy volunteers [28]. A special coil reproducing iTBS sounds and local sensation (imitated by peripheral electric stimulation), but not inducing magnetic fields, was used for sham iTBS.

TMS sessions were performed on consecutive weekdays. The patients filled out the questionnaires regarding adverse events (AEs) during rTMS and within 24 hours after TMS. Cognitive testing was conducted before the stimulation course, after sham and after active iTBS. The following tests were used:

- *Symbol Digit Modalities Test (SDMT)* for the assessment of information processing speed (the number of correct symbols pronounced within 90 seconds is assessed).
- *Californian Verbal Learning Test, version II (CVLT-II)* for the assessment of short-term verbal memory. Immediate recall is assessed as the sum of correctly reproduced words in 5 trials; delayed – as the number of words recalled 15 minutes after the presentation.
- *Brief Visuospatial Memory Test – Revised (BVMT-R)* for the assessment of short-term spatial memory. Immediate recall is assessed by the sum of correctly reproduced figures in three trials, delayed – within 25 minutes after presentation, interference – as the number of correct answers when congruent and non-congruent stimuli are presented.
- *Stroop test* for the assessment of executive functions. The test consists of reading color names printed in black, naming the colors of hexagons as well as naming the color of words, which are non-matching and matching color names; interference coefficient was calculated [29].
- *Controlled Word Association Test (COWAT)* for the assessment of verbal fluency. Literal fluency was assessed as the sum of numbers of words beginning with a consonant said within 1 minute (each test – 3 trials), categorial – as the number of animals named within a minute.

Computerized tests using Psychology Experiment Building Language (PEBL) [30] were also used for the cognitive assessment:

- *Letter Digit Test (LDT)* assessing information processing speed (reaction time was assessed);
- *n-back with verbal and spatial stimuli (n=1, 2)* to assess verbal and spatial working memory; the accuracy was assessed by calculation d' [31].

- *Pattern Comparison (PatComp)* test, assessing visuospatial perception (reaction time was assessed).

Patients also filled out Perceived Deficit Questionnaire (PDQ) to assess subjective CI and Modified Fatigue Impact Scale (MFIS) to assess fatigue [32].

At the second stage of the study we conducted five sessions of active iTBS without initial sham iTBS in order to minimize the effect of protocol order. Effects were assessed by the same test battery before and after the stimulation course.

IBM SPSS Statistics v.25 (IBM, USA) program package was used for the *statistical analysis*. The distributions of testing results were different from normal, therefore, methods of non-parametric statistics were applied (Mann–Whitney test for comparisons between the groups, Wilcoxon test and Friedman's ANOVA for comparisons within a group as well as Fisher's exact test for the comparison of frequencies). Bonferroni correction was applied to multiple comparisons.

Results. *Description of the patient group*. 26 patients were screened, 9 of them had non-inclusion criteria [conditions, complicating test performance (n=4), EDSS more than 7.0 (n=3), drugs negatively affecting CF (n=2)]. Two patients were excluded from the study: one – because of the necessity to treat a relapse with corticosteroids, another one – because of acute respiratory infection. The data of 15 patients were included in the analysis (13 patients with SPMS, 7 men, age – 53 [40; 65] y.o.; here and further the data are given in the form of median (Me) [2^{5th} and 75^{th} percentiles]). Eight patients had sham iTBS followed by the active protocol, 7 – active protocol only.

Protocol safety. No serious AEs or TMS discontinuation because of poor TMS tolerability were observed. Mild AEs were registered during 39.8% of all sessions (45.5% of sham and 37.1% of active stimulation sessions), and within 24 h – in 23.3% sessions (32.4% of sham and 17.9% of active stimulation sessions). No significant differences of main AE frequencies were observed between sham and active stimulation (exact Fisher's test, p=0.52). The most frequent AE during the stimulation was sleepiness (36.4 and 22.9% of sham and active stimulation sessions, respectively, p=0.16). Mild pain was reported only during sham iTBS (9.1% sessions), unpleasant non-painful sensations (tapping, face muscle contractions or burning) – only during active iTBS (21.4% sessions). Headache was the most prevalent AE, occurring within 24 hours after stimulation session (17.6% sham and 8.9% active stimulation sessions; p=0.32).

Cognitive effects of the stimulation. At the first stage a comparison of cognitive performance was conducted at three time points (T1 – before sham, T2 – after sham, T3 – after active iTBS) using Friedman's ANOVA (Table 1). Significant differences were found for COWAT (categorical fluency, p=0.028), verbal n-back with n=1 (p=0.041), PatComp (p=0.002) and PDQ questionnaire (p=0.04).

In post-hoc analysis significant differences were found for COWAT (categorical fluency) between T2 and T3 and for PatComp between T2 and T3, T1 and T3 (Table 2).

When the effects of sham and active iTBS (determined as the differences in cognitive performance between T2–T1 and T3–T2, respectively) were compared, significant differences were observed only for n-back with verbal stimuli and n=1 (p=0,043); active iTBS was more effective.

Table 1. *Evaluation of the effect of iTBS sham and active protocol*

Test	T1	T2	T3	p
SDMT	40,50 [37,00; 54,50]	46,50 [37,75; 54,25]	45,00 [37,25; 48,25]	0,381
CVLT-II				
Immediate recall	47,50 [40,00; 56,50]	48,5 [44,25; 61,25]	52,50 [45,50; 61,50]	0,079
Delayed recall	10,00 [8,25; 12,75]	11,00 [9,00; 13,50]	11,50 [8,25; 14,50]	0,891
BVMT-R				
Immediate recall	19,50 [15,00; 23,00]	20,00 [14,50; 26,75]	22,50 [18,75; 24,75]	0,417
Delayed recall	9,00 [5,50; 10,75]	9,00 [5,00; 10,75]	8,00 [6,25; 9,50]	0,786
Interference	12,00 [10,25; 12,00]	12,00 [10,25; 12,00]	12,00 [11,00; 12,00]	0,861
Stroop test	4,53 [-2,28; 16,55]	7,65 [3,63; 12,83]	6,35 [2,53; 12,26]	0,882
COWAT				
Literal fluency	41,50 [32,00; 45,75]	43,00 [38,25; 57,75]	50,00 [36,50; 55,00]	0,053
Categorical fluency	16,00 [14,00; 24,00]	19,00 [13,00; 25,00]	23,00 [17,00; 28,00]	**0,028**
LDT	3136,00 [2495,00; 3620,00]	3209,00 [2492,00; 3563,00]	3116,00 [2278,00; 3579,00]	0,368
n-back				
verbal, n=1	2,49 [2,47; 3,22]	2,80 [2,22; 3,22]	3,22 [2,80; 3,22]	**0,041**
spatial, n=1	3,22 [2,80; 3,22]	3,22 [2,88; 3,22]	3,22 [3,22; 3,22]	0,174
verbal, n=2	2,29 [1,96; 2,50]	2,29 [1,46; 3,25]	2,29 [1,86; 3,25]	0,595
spatial, n=2	2,53 [1,53; 2,92]	1,86 [1,44; 2,90]	2,29 [1,53; 3,22]	0,607
PatComp	2203,29 [1731,58; 2682,29]	1719,70 [1584,58; 2027,83]	1590,35 [1475,77; 1774,21]	**0,002**
PDQ	29,00 [21,00; 37,00]	21,00 [13,50; 28,75]	18,50 [11,75; 35,25]	**0,040**
MFIS	88,50 [76,75; 107,00]	82,00 [56,50; 97,00]	86,00 [57,50; 93,00]	0,368

Note. In tables 1–3 p<0.05 are marked as semi-bold

Because of possible effects of the protocol order, we have also compared the effects of sham iTBS with the active protocol in the second group receiving only five sessions of active iTBS without previous sham (Mann–Whitney test). No significant differences were found.

In order to clarify the effect of the protocol order, active iTBS effects were compared between the groups, where it was applied after sham iTBS or as the only protocol. Significant differences were found only for BVMT-R (immediate recall, Mann–Whitney test, p=0.04) and verbal n-back with n=2 (p=0.038).

Table 2. *Results of the post-HOC analysis of the pairwise comparisons*

Test	$p_{T1–T2}$*	$p_{T2–T3}$*	$p_{T1–T3}$*
COWAT, categorial fluency	1,000	**0,033**	0,184
n-back, verbal, n=1	1,000	0,098	0,425
PatComp	0,952	**0,001**	**0,037**
PDQ	1,000	0,081	0,119

Note. * – Bonferroni-corrected values

Table 3. *Efficacy of the active protocol*

Test	Before	After	p
SDMT	40,00 [33,00; 47,00]	41,00 [34,00; 46,00]	0,572
CVLT-II			
Immediate recall	45,00 [39,00; 51,00]	48,00 [40,00; 56,00]	**0,049**
Delayed recall	11,00 [8,50; 12,00]	48,00 [40,00; 56,00]	0,181
BVMT-R			
Immediate recall*	–	–	–
Delayed recall	9,50 [7,75; 11,00]	8,00 [6,75; 10,00]	0,363
Interference	12,00 [11,00; 12,00]	12,00 [10,75; 12,00]	0,317
Stroop test	4,00 [-4,26; 12,30]	2,90 [1,04; 8,10]	0,443
COWAT			
Literal fluency	38,50 [27,50; 45,00]	41,50 [30,25; 51,25]	0,248
Categorical fluency	18,00 [13,50; 23,00]	22,50 [17,25; 26,00]	0,182
LDT	3209,00 [2744,00; 3563,00]	3098,00 [2541,00; 3321,00]	**0,026**
n-back			
verbal, n=1	2,65 [1,93; 3,22]	3,22 [2,80; 3,22]	**0,012**
spatial, n=1	1,86 [1,27; 2,68]	3,22 [3,13; 3,22]	0,248
verbal, n=2	–	–	–
spatial, n=2	1,86 [1,27; 2,68]	2,13 [1,44; 2,85]	0,346
PatComp	1899,38 [1705,80; 2396,08]	1766,13 [1542,95; 2318,28]	**0,023**
PDQ	20,00 [9,00; 27,00]	15,50 [6,00; 21,00]	**0,016**
MFIS	73,00 [44,50; 89,00]	71,00 [44,00; 89,00]	**0,041**

Note. * – effects were not assessed because of the possible effects of the protocol order

Because no impact of the protocol order was found for the most part of applied tests, we have analyzed the iTBS effects in the combined group of all patients (Table 3). Significant improvement was shown for immediate recall in the test CVLT-II (Wilcoxon test; p=0.049), LDT (p=0.026), verbal n-back with n=1 (p=0.012), PatComp (p=0.023) as well as PDQ and MFIS (p=0.016 and 0.041, respectively).

Discussion. In this study safety and tolerability of multitarget iTBS protocol in patients with PRS and CI were confirmed. Significant positive effect was shown for verbal short-term and working memory, information processing speed, and visuospatial perception. No significant effects were shown for sham iTBS. Active iTBS also diminished subjective CI and fatigue. Significant differences between active and sham iTBS were shown only for verbal working memory performance.

The data regarding TMS effects on CF in patients with MS are currently limited by the study assessing the effects of a single session of fMRI-targeted HF rTMS of the right DLPFC on the spatial n-back task (n=2, 3) and brain activation as well as functional connectivity measured by task-fMRI [23]. However, a direct comparison of this study with our results is not possible because of the different design. Currently studies are being conducted that assess cognitive effects of iTBS of the left DLPFC with fMRI-based targeting (based on the maximal connectivity of DLPFC with caudate nucleus) [25] or the effects of HF rTMS of supplementary motor area; however, their results have not been published yet.

Considering the possible role of maladaptive changes of neural networks in CI pathogenesis, we have chosen a protocol including consecutive stimulation of the left DLPFC and PPC. Multifocal TMS has a proven efficacy in AD (TMS-CoG protocol) [20], but currently there is no available data regarding the effects of similar protocols in CI of different etiology or healthy volunteers.

Significant iTBS effects on verbal short-term and working memory are consistent with the literature data regarding the effects of protocols with one target. In particular, working memory improvement has been shown after TMS of the left DLPFC in healthy volunteers [33, 34] as well as in the patients with moderate CI of neurodegenerative [35] or vascular [17] origin. Positive effects on verbal short-term memory were observed in patients with AD after HF rTMS of the left parietal cortex [36].

We have also shown significant changes in MFIS score. Positive effects in MS-related fatigue were shown previously for deep TMS [37], iTBS [38] and HF rTMS of the motor cortex [39]. A study protocol was published for the investigation of effects of iTBS applied to the left DLPFC on fatigue in patients with RRMS [40].

Significant differences of cognitive effect between active and sham iTBS were shown only for verbal n-back (n=1) and no other tests that might be explained by low statistical power. It should be noted that no significant effects were observed for sham iTBS, which makes learning effect unlikely and indirectly confirms the efficacy of active protocol.

This pilot study has some *limitations*. Besides small sample size, there is lack of randomization and "blinding" of the investigator as well as lack of questionnaires regarding their suggestion about the protocol applied (active iTBS or sham). Another limitation could also be a relatively small number of sessions, however, the data regarding the impact of session number on TMS effects are inconsistent. We have not investigated long-term effects of our protocol either, which should be taken into consideration in future studies.

Our data can be a basis for further investigation of iTBS protocols in patients with MS and CI. Besides the investigation of the protocol effects in larger studies, assessment of its effects in other MS types as well as comparison to standard protocols can be performed. It is also advisable to investigate the effects of a larger number of sessions and "maintaining" sessions after the main TMS course.

Conclusion. Thus, our study has shown a good tolerability and safety profile of the multitarget navigated iTBS in patients with PMS and CI. Positive effects were observed for verbal short-term and working memory, information processing speed, visuospatial perception as well as subjective CI and fatigue. However, further investigation is needed for final conclusions.

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