Safety and preliminary efficacy of deep transcranial magnetic stimulation in MS-related fatigue

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ABSTRACT

Objective: To conduct a randomized, sham-controlled phase I/IIa study to evaluate the safety and preliminary efficacy of deep brain H-coil repetitive transcranial magnetic stimulation (rTMS) over the prefrontal cortex (PFC) and the primary motor cortex (MC) in patients with MS with fatigue or depression (NCT01106365).

Methods: Thirty-three patients with MS were recruited to undergo 18 consecutive rTMS sessions over 6 weeks, followed by follow-up (FU) assessments over 6 weeks. Patients were randomized to receive high-frequency stimulation of the left PFC, MC, or sham stimulation. Primary end point was the safety of stimulation. Preliminary efficacy was assessed based on changes in Fatigue Severity Scale (FSS) and Beck Depression Inventory scores. Randomization allowed only analysis of preliminary efficacy for fatigue.

Results: No serious adverse events were observed. Five patients terminated participation during treatment due to mild side effects. Treatment resulted in a significant median FSS decrease of 1.0 point (95%CI [0.45,1.65]), which was sustained during FU.

Conclusions: H-coil rTMS is safe and well tolerated in patients with MS. The observed sustained reduction in fatigue after subthreshold MC stimulation warrants further investigation.

ClinicalTrials.gov identifier: NCT01106365.

Classification of evidence: This study provides Class III evidence that rTMS of the prefrontal or primary MC is not associated with serious adverse effects, although this study is underpowered to state this with any precision. *Neurol Neuroimmunol Neuroinflamm* 2018;5:e423; doi: 10.1212/NXI.0000000000000423

GLOSSARY

ANOVA = analysis of variance; **BDI-IA** = Beck Depression Inventory IA; **BL** = baseline; **EDSS** = Expanded Disability Status Scale; **FSMC** = Fatigue Scale for Motor and Cognitive Functions; **FSS** = Fatigue Severity Scale; **9-HPT** = 9 Hole Peg Test; **IQR** = interquartile range; **MC** = motor cortex; **MDD** = major depressive disorder; **MFIS** = Modified Fatigue Impact Scale; **MSFC** = multiple sclerosis functional composite; **PASAT** = Paced Auditory Serial Addition Test; **PFC** = prefrontal cortex; **RMT** = resting motor threshold; **rTMS** = repetitive transcranial magnetic stimulation; **SAE** = serious adverse event; **T25FW** = timed 25-ft walk.

MS is the most common autoimmune inflammatory and neurodegenerative disease of the CNS.[1] Fatigue is one of the most frequent symptoms experienced in MS, affecting up to 90% of patients.[2] Although MS fatigue contributes to poor health-related quality of life[3] and is a major factor in disease-related unemployment,[4] its etiology has not yet been fully elucidated, and efficacious treatment options are scarce. Neuroimaging studies suggest that structural and functional connectivity alterations, particularly to interconnections between the basal ganglia

and the prefrontal cortex (PFC), the posterior cingulate cortex and cortical motor areas, may contribute to fatigue in MS.[5–9]

A potential treatment of functional connectivity impairment is noninvasive neuromodulation by means of repetitive transcranial magnetic stimulation (rTMS). High-frequency rTMS of the left PFC has been demonstrated as safe and efficacious in major depressive disorder (MDD).[10] Moreover, 5-Hz rTMS applied to the primary motor cortex (MC) improved lower limb spasticity[11] and bladder dysfunction[12] in patients with MS.

rTMS using H-coils, a technology developed several years later, allows brain stimulation 3 times deeper than that of standard figure-of-eight coils at the expense of focality.[13,14] It has also been widely proven as safe and well tolerated, including in a study of healthy volunteers[15] and, in the form of high-frequency stimulation of the left PFC, as effective and safe treatment of MDD.[16–18] PFC and MC stimulation directly targets circuits for which alterations in fatigue were reported,[5–9] and PFC stimulation is supported by the high overlap between fatigue and depressive symptoms.[19] MC stimulation, on the other hand, may also lead to an additional improvement of fatigue via reduction of spasticity.[11]

Against this background, we conducted a randomized, sham-controlled phase I/IIa pilot study to evaluate the safety, tolerability, and preliminary efficacy of deep brain H-coil rTMS over the left PFC and MC as treatment of fatigue and depression in MS.

METHODS **Study design and participants.** The study was designed as a prospective, randomized, semi-blinded, sham-controlled phase I/IIa pilot study involving 2 MS centers (NeuroCure Clinical Research Center, Charité–Universitätsmedizin Berlin, Germany, and the Institute of Neuroimmunology and Multiple Sclerosis research at the University Hospital Hamburg Eppendorf, Hamburg, Germany). Primary end point in this study was safety of rTMS stimulation in patients with MS. The study design and workflow are presented in figure 1. Patients underwent an initial screening/baseline (BL) visit 4 weeks before intervention, from which all BL characteristics were derived and a second scheduling visit to confirm study inclusion or exclusion and to schedule an appointment for commencement of the intervention 2 weeks later. Patients were then randomized into 3 groups on the day of treatment initiation, followed by 6 weeks of intervention. After the treatment phase, patients were followed up every 2 weeks over 6 weeks (follow-ups: FU1, 2, and 3). Recruitment period was from May 2010 to March 2011. This pilot trial was performed without sample size calculation; randomization of 33 patients was planned. Recruitment was stopped regularly after randomizing 33 patients. The study provides Class III evidence.

Inclusion criteria were diagnosis of MS according to the 2005 revised McDonald criteria,[20] either a score of ≥4 on the Fatigue Severity Scale (FSS)[21] or a score of ≥12 on the Beck Depression Inventory IA (BDI-IA),[22] age (18–65 years), relapse-free for at least 3 months, and free of steroid treatment within 30 days prior to inclusion, Expanded Disability Status Scale (EDSS) between 0.0 and 6.0, stable immunotherapy or antidepressant therapy for at least 3 months if applicable, and highly effective methods of contraception for females. Exclusion criteria were history of seizures (personal or family), history of stroke, head injury, metal fragments in the head, implanted devices such as cardiac pacemakers, cochlear implants, medical pumps, alcohol or drug abuse, pregnancy, comedication with neuroleptics or tricyclic antidepressants, increased intracranial pressure, bipolar affective disorder, significant neurologic, psychiatric, cardiovascular, hepatic, renal, gastrointestinal, metabolic, or other systemic comorbidities.
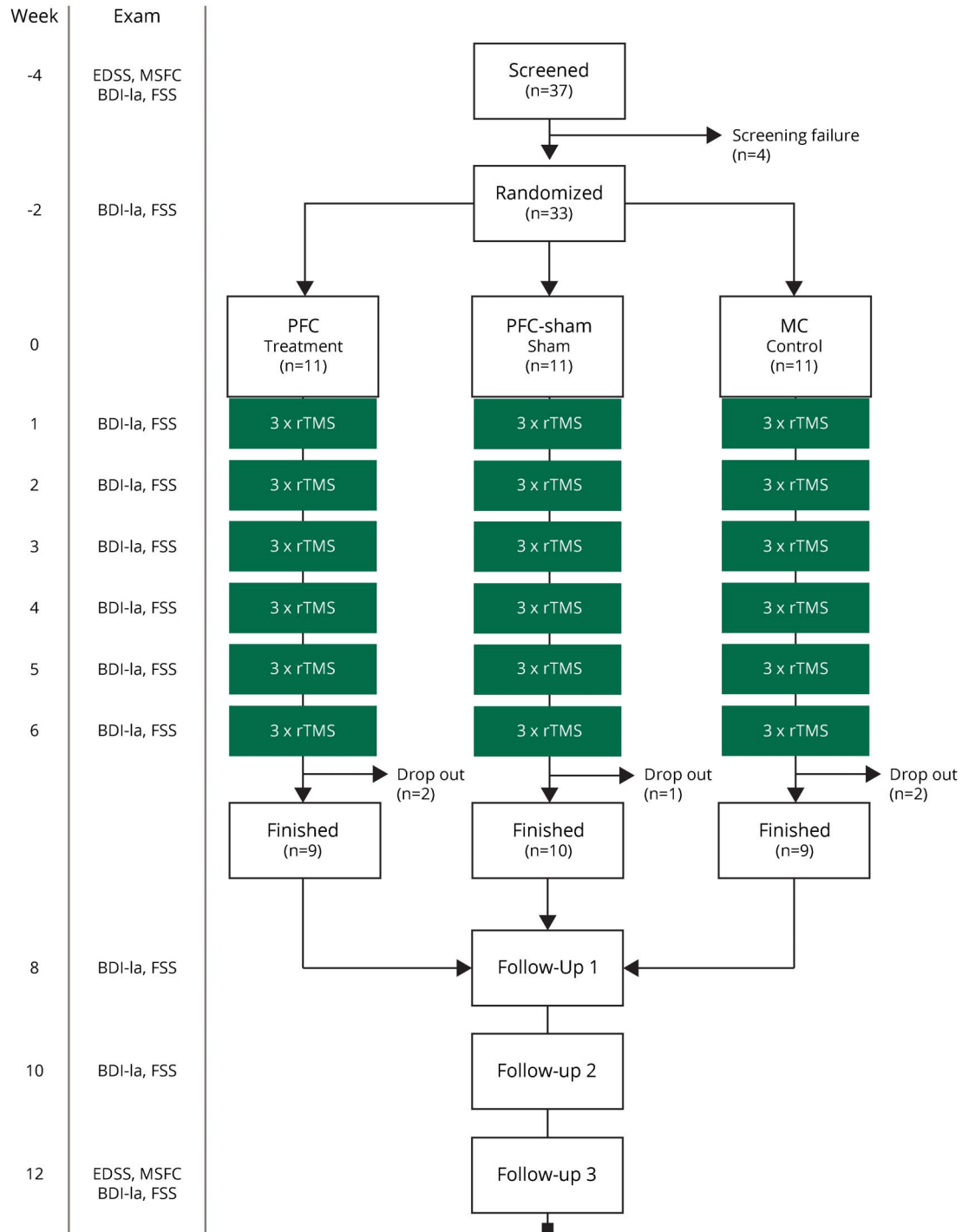
Abortion criteria were personal wish of the participant, any relapse, exacerbation of depressive symptoms including suicidality and suicide attempt, comedication with tricyclic antidepressant, pregnancy, safety concerns, noncompliance, loss to FU, and missing more than 3 treatment sessions.

Standard protocol approvals, registrations, and patient consents. The study was registered at clinicaltrials.gov as NCT01106365 and was approved by the local ethics committees of the Charité–Universitätsmedizin Berlin and by the Hamburg Board of Physicians. It was conducted in accordance with the Declaration of Helsinki and the guidelines of the International Conference on Harmonisation of Good Clinical Practice. All participants provided written informed consent.

Randomization and masking. Patients were randomized in a 1:1:1 ratio to receive H6 coil rTMS over the left prefrontal cortex ("PFC" group), sham rTMS over the same area ("PFC sham" group), or H10 coil rTMS over the primary motor cortex bilaterally ("MC" group). For randomization, Brainsway Ltd. created individual treatment cards, which guaranteed blinding.[18] Patients were enrolled in each center and assigned to groups using the treatment cards by independent operators. The PFC sham condition induced superficial magnetic sensations comparable to the 2 therapeutic stimulation conditions, preventing patients from distinguishing sham treatment by sensation or hearing. For PFC and PFC sham conditions, both patients and operators were blinded (double-blinded condition). For the MC stimulation, a different coil without extra sham function was used, thus operator blinding was not possible. Thus, TMS operators were aware of the MC stimulation condition, whereas the patients as well as interviewing and examining neurologists were not (single blinded).

Diagnostic procedures. During treatment and follow-up, a trained neurologist, who was masked to treatment allocation, conducted a weekly and biweekly clinical interview and physical examination, respectively, of each patient to assess safety and tolerability. Moreover, patients were advised to contact the study centers by phone or present to emergency services in case of severe adverse events. We a priori defined any seizure or MS relapse as serious adverse events (SAEs). Second, reports of the previous week's symptoms were assessed to calculate the FSS[21] and the BDI-IA[22] questionnaire as indicator of preliminary clinical efficacy. Patients with an FSS score of ≥4 were classified as fatigued.[21,23] Patients with a BDI score of ≥12 were classified as depressed.[22]

Figure 1 Patient flow diagram

Week	Exam	

Screened (n=37) → Screening failure (n=4)

Week -4: EDSS, MSFC BDI-la, FSS

Randomized (n=33)

Week -2: BDI-la, FSS

| PFC Treatment (n=11) | PFC-sham Sham (n=11) | MC Control (n=11) |

Week 0

Weeks 1–6: BDI-la, FSS — 3 x rTMS (each group, each week)

Drop out (n=2) / Drop out (n=1) / Drop out (n=2)

| Finished (n=9) | Finished (n=10) | Finished (n=9) |

Follow-Up 1 — Week 8: BDI-la, FSS

Follow-up 2 — Week 10: BDI-la, FSS

Follow-up 3 — Week 12: EDSS, MSFC BDI-la, FSS

Patient flow in this interventional study. The column on the left side lists the week relative to the first day of intervention. The second column lists the diagnostic parameters assessed at the visits. The column on the right side depicts the patient flow including randomization in the 3 treatment groups. BDI-IA = Beck Depression Inventory IA; EDSS = Expanded Disability Status Scale; FSS = Fatigue Severity Scale; MC = motor cortex; MSFC = Multiple Sclerosis Functional Composite; PFC = prefrontal cortex; rTMS = repetitive transcranial magnetic stimulation.

In addition, the EDSS[24] and the multiple sclerosis functional composite (MSFC), including the timed 25-ft walk (T25FW) test, the 9-Hole Peg Test (9-HPT), and the Paced Auditory Serial Addition Test (PASAT), were assessed at screening and in the final FU visit.[25] MSFC Z-scores were calculated from T25FW, 9-HPT, and PASAT results with reference to the screening examination including all patients.[25]

Transcranial magnetic stimulation. rTMS was performed by 3 operators using H-coils (Brainsway Ltd., Jerusalem, Israel) connected to a Magstim Rapid[2] stimulator (Magstim, Spring Gardens, United Kingdom). Each participant received 3 rTMS sessions per week over a period of 6 weeks (total of 18 treatments) followed by a 6-week FU period comprising biweekly clinical assessments and questionnaires.

Bilateral MC stimulation in the "MC" group was performed with the H10 coil, designed for the activation of hand or leg MC. We applied 40 trains of bihemispherical stimulation of the MC, with bursts of 20 stimuli with an intertrain interval of 20 seconds at a frequency of 5 Hz (intensity of 90% resting motor threshold [RMT]) with a total number of 800 stimuli and a total duration of 16 minutes, positioning the center of the coil mid-sagittally over the primary MC.

Real left PFC stimulation in the "PFC" group was performed with the left H6 coil, designed for the activation of superficial and deep left PFC structures. To determine the individual RMT, the coil center was positioned over the motor hand area, and contralateral motor responses of the first dorsal interosseous muscle were recorded. Individual RMT was defined as the minimum intensity that evoked a potential of 50 μV in 5 of 10 consecutive stimuli according to current international recommendations.[26] The coil was positioned 5 cm anteriorly to the left motor hot spot, parallel to the sagittal suture of the skull in order to provide stimulation of the left PFC region. We applied a total of 50 trains (intensity of 120% of RMT) in each session, with a duration of 2 seconds at a frequency of 18 Hz repeating at 20-second intervals (total number of stimuli per session: 1,800; duration: 18 minutes).

The H6 coil but not the H10 coil included a sham function. Superficial skin stimulation with a sham function, which led to a comparable sound and sensation like real TMS, was ensured, but not stimulation of the brain. For sham stimulation, the coil was placed identically to the real PFC stimulation condition. Fifty trains of superficial stimulation of the skin were applied at the same frequency (18 Hz) and duration (2 seconds) at 20-second intervals, as in the PFC stimulation paradigm (total number of stimuli per session: 1,800; duration: 18 minutes).

Statistical analysis. Results are reported as frequencies and percentages, median, and interquartile range (IQR), depending on the scale of the data. Baseline differences between PFC, PFC sham, and MC groups including all patients completing the trial were analyzed with nonparametric Kruskal-Wallis tests for ordinal and continuous data and with Fisher-Freeman-Halton exact tests for categorical data (table 1).

Clinical outcomes were FSS, BDI-IA, EDSS, and MSFC data assessed at BL, FU1, and FU3 visits (for FSS and BDI-IA) or FU3 (for EDSS and MSFC). FU1 FSS scores were not collected for 3 PFC, 1 MC-, and 1 PFC sham–stimulated patients, and BDI data for 2 PFC, 1 MC-, and 1 PFC sham–stimulated patients. Here, data from the next FU visit were used. For 1 PFC- and 1 MC-stimulated patient, the third FU score had to be used. Patients whose FU1 data were replaced with FU3 data were excluded in the preliminary sustainability analysis, comparing the first and last FU data. We analyzed preliminary clinical efficacy and sustainability in an exploratory analysis using nonparametric (rank based) analysis of variance (ANOVA)-like computation of longitudinal data in factorial settings (R-package "nparLD"). The Wilcoxon signed-rank test was used for pairwise post hoc analysis of changes over time within each treatment group. The analysis of potential effects on fatigue included only those patients who were classified as fatigued (FSS ≥4.0) at BL. Distribution of patients classified as depressed (BDI-IA >12.0) was uneven between the groups (table 1). We, therefore, abstained from further analyzing effects on depressive symptoms. To account for potential differences in fatigue and depression at BL between groups as potential confounders, we additionally performed a nonparametric (rank-based) ANOVA-like analysis for FSS score at FU1 visit, with adjustment for FSS and BDI values at BL.

Table 1	Cohort overview at baseline				
		PFC	PFC Sham	MC	p Value[a]
Condition		Treatment	Sham	Treatment	
Patients	n	9	10	9	
Disease course	RRMS/SPMS	8/1	9/1	9/0	1.000
Sex	M/F	3/7	2/7	1/8	0.845
Age, y	Median (IQR)	47 (32 to 51)	41 (39 to 45)	46 (42 to 48)	0.323
Time since diagnosis, mo	Median (IQR)	46 (37 to 110)	67 (38 to 224)	187 (91 to 258)	**0.048**
EDSS	Median (IQR)	2.5 (2.0 to 3.0)	3.0 (2.5 to 3.0)	2.5 (2.5 to 3.5)	0.719
T25FW, s	Median (IQR)	7.2 (6.1 to 9.5)	9.6 (6.5 to 11.7)	8.1 (6.3 to 8.7)	0.365
9-HPT dom., s	Median (IQR)	20.0 (18.7 to 21.0)	19.4 (17.5 to 23.6)	18.9 (18.5 to 21.1)	0.916
9-HPT ndom., s	Median (IQR)	20.0 (19.5 to 22.7)	20.3 (18.5 to 22.8)	20.9 (19.3 to 21.9)	0.864
PASAT, /60	Median (IQR)	56 (53 to 59)	45 (40 to 48)	51 (44 to 53)	0.102
MSFC-Z	Median (IQR)	0.5 (0.2 to 1.0)	−0.1 (−0.6 to 0.0)	0.0 (−0.1 to 0.4)	0.131
BDI-IA	Median (IQR)	22.0 (19.0 to 26.0)	14.0 (13.0 to 21.0)	12.0 (9.0 to 13.0)	**0.002**
BDI-IA >12	Yes/no	9/0	8/2	4/5	**0.023**
Antidepressant Tx	Yes/no	5/4	5/5	1/8	0.119
FSS	Median (IQR)	6.2 (5.3 to 6.3)	6.0 (4.6 to 6.1)	6.0 (5.6 to 6.4)	0.501
FSS ≥4.0	Yes/no	9/0	9/1	9/0	1.000

Abbreviations: 9-HPT = 9-hole peg test of the dominant hand; 9-HPT ndom. = 9-Hole Peg Test of the nondominant hand; BDI-IA = Beck Depression Inventory IA; EDSS = Expanded Disability Status Scale; FSS = Fatigue Severity Scale; IQR = interquartile range (25th and 75th percentiles); MC = motor cortex MSFC = multiple sclerosis functional composite; PASAT = paced auditory serial additions test; PFC = prefrontal cortex; RRMS = relapsing-remitting MS; rTMS = repetitive transcranial magnetic stimulation; SPMS = secondary progressive MS; T25FW = Timed 25-ft walk.
[a] For categorical data derived from Fisher exact tests with Freeman-Halton extension, all other data from Kruskal-Wallis tests. Significant p values are printed in bold.

Statistical analyses were performed using IBM SPSS Statistics software version 23 (IBM Corp., Armonk, NY), SAS 9.4 software (SAS Institute Software GmbH, Vienna, Austria), and R software version 3.2.4.[27] All tests were 2 sided, and statistical significance was determined at an α level of 0.05. Exploratory analyses had no previous sample size calculation, and no adjustment for multiple comparisons was applied.

RESULTS **Patients.** Thirty-seven patients with MS were assessed for eligibility. Four patients did not meet the inclusion criteria (figure 1). Of the remaining 33 patients, 5 dropped out before completion. Twenty-eight patients completed the treatment and FU phases. Detailed BL demographic and clinical data are presented in table 1. Eleven patients were on stable antidepressant therapy (5 citalopram, 2 fluoxetine, 2 venlafaxine, 1 sertraline, and 1 St. John wort [*Hypericum perforatum*]). Two patients in the MC group received symptomatic treatment with modafinil. Baseline data were similar across groups for disease course, age, sex, EDSS, and MSFC (table 1).

Safety and tolerability. No SAE were observed in any group; however, known trigeminal neuralgia intensified in 1 PFC sham patient. Twenty-five of 28 patients reported at least 1 adverse event during the entire treatment period, while 1 sham patient and 2 patients with MC did not (table 2). The adverse event frequency of each group was too low to allow for comparative analysis (table 2), and all patients fully recovered from AEs within a few days.

All 5 premature dropouts occurred during the treatment phase: 1 due to intensification of known trigeminal neuralgia, 3 (1 from each treatment group) due to scalp discomfort or headache during treatment (and, in 1 case, due to time constraints after the initial four treatments), and, last, 1 patient because of claustrophobia experienced under the stimulation device.

Exploratory clinical efficacy. Twenty-seven of 28 patients (96.4%) were classified as fatigued at BL with an FSS score of 4.0 or more (9 patients per group, table 1), of which 7 (7/27 = 25.9%) were nonfatigued at the final FU (3 sham-, 1 PFC-, and 3 MC-stimulated patients). The single nonfatigued patient at BL (FSS = 2.8) was subsequently assessed as fatigued (FSS = 5.7) after PFC sham stimulation (see also figure e-1, http://links.lww.com/NXI/A2 for individual data curves). There was no significant FSS difference at BL between the treatment groups (table 1).

All patients with fatigue at BL showed significant improvement after treatment (FU1, figure 2). Calculated at the group level, the median FSS score decreased by 1.0 points (BL vs FU1, 95% CI 0.45–1.65; time effect: df = 1.0, *p* < 0.001). This improvement was most evident in the MC group (1.74 points, 95% CI 0.41–2.95) compared with the PFC sham group (0.77 points, 95% CI 0.10–2.30) and the PFC group (0.35, 95% CI −0.35 to 1.70). However, FSS scores did not differ between treatment groups at BL or FU (FU1) (median FSS scores at FU1 [IQR] 6.3 [4.7–6.7] PFC group; 5.2 [3.9–5.6] PFC sham group; 4.4 [3.8–4.7] MC stimulation; nonparametric ANOVA-like analysis of BL vs FU1 group effect: df = 1.8, *p* = 0.279). In addition, FSS scores were still significantly lower 4 weeks later, at FU3 compared with BL (median decrease of the FSS score of 1.1 points, 95% CI 0.55–1.68; time effect: df = 1.0, *p* < 0.001, group effect: df = 1.9, *p* = 0.260), with the MC group (1.78 points, 95% CI 0.85–2.75) continuing to show more improvement compared with the PFC group (0.75, 95% CI −0.20 to 1.94) and PFC sham (0.41 points, 95% CI −0.35 to 1.8) group (interaction group × time df = 2.0, *p* = 0.037). Indeed, the fatigue score did not change significantly between FU1 and FU3 over all groups (median difference <0.01 points, 95% CI −0.40 to 0.35), and there were no significant differences in the changes over time between groups (group × time, df = 1.9, *p* = 0.073; figure 2). EDSS and MSFC showed no significant change over time or between groups (data not shown). We obtained a significant impact of treatment group on FSS scores at FU1 (*p* = 0.001) and also a significant

Table 2	Adverse events								
		Total		**PFC**		**PFC Sham**		**MC**	
Reported events		n	%	n	%	n	%	n	%
Increased headache during treatment		3	11	2	22	1	10	0	0
Headache on the day of treatment									
Mild		2	7	1	11	0	0	1	11
Middle		10	36	4	44	5	50	1	11
Intense		1	4	1	11	0	0	0	0
Headache on following days									
Mild		3	11	2	22	1	10	0	0
Middle		1	4	1	11	0	0	0	0
Intense		1	4	1	11	0	0	0	0
Paresthesia or pain of lower limb		10	36	4	44	3	30	3	33
Paresthesia of upper limb		6	21	1	11	3	30	2	22
Increased bladder spasticity		1	4	1	11	0	0	0	0
Unspecific facial pain		4	14	0	0	3	30	1	11
Restless legs/spasticity over night		3	11	2	22	0	0	1	11
Gait disturbance		2	7	0	0	1	10	1	11
Dizziness		1	4	0	0	1	10	0	0
Tiredness on the day following treatment		2	7	0	0	0	0	2	22
Dorsal pain		1	4	0	0	1	10	0	0
Unspecific feeling of discomfort		2	7	1	11	1	10	0	0

Abbreviations: MC = motor cortex; PFC = prefrontal cortex.

Figure 2   Changes in fatigue under treatment

Fatigue scores
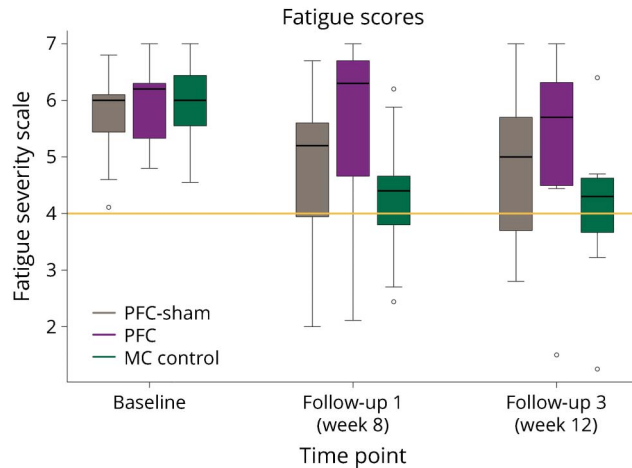
FSS changes during the study using standard boxplots. Treatment group "PFC" is shown in purple, treatment group "MC" in green, and sham group "PFC sham" in gray. Post-treatment visits are termed "follow-up" (plus follow-up visit number). The yellow line indicates FSS cutoff between fatigued (FSS ≥ 4) and nonfatigued values. FSS = Fatigue Severity Scale; MC = motor cortex; PFC = prefrontal cortex.

impact of FSS at BL ($p = 0.015$), but not of BDI at BL ($p = 0.848$) in nonparametric (rank-based) ANOVA-like analysis, confirming our findings without these covariates.

DISCUSSION This randomized, sham-controlled phase I/IIa study applied stimulation of deeper brain regions by means of interventional H-coil rTMS to patients with MS. We found that rTMS is safe in MS, and preliminary efficacy data further support investigating rTMS for symptomatic treatment of fatigue in MS. Approximately one-third of patients suffered from mild-to-moderate headache, which was the most frequently experienced adverse event, all of which were fully resolved within several days. The adverse events were distributed equally across treatment groups. In line with other clinical studies using rTMS, transient headache and scalp discomfort were the most frequently reported side effects.[28] Fifteen percent of patients discontinued before completion of the study, with the majority (3 of 5 patients) reporting scalp discomfort and headache as reasons. These data are instructive for the design of future trials, particularly for the calculation of sample size and obtaining the consent of study participants.

Our exploratory analysis showed that rTMS significantly reduced fatigue in our cohort of 27 patients. This effect was most pronounced in the MC stimulation group, with a median decrease of 1.74 points in the FSS score directly after treatment compared with BL, which should be considered clinically meaningful.[29] While the results are promising, they have to be interpreted with caution, given the small sample size and the exploratory nature of the study and of the efficacy analysis.

H-coil enables nonfocal stimulation of deeper neuronal structures as compared to standard figure-of-eight coils.[13,14] This may be an advantage when the therapeutic approach aims at targeting larger brain regions that are presumably involved in the pathophysiology of MDD (e.g., the lateral PFC, including the broader dorsolateral and ventrolateral PFC areas and their projections into subcortical networks[18]). Recent concepts propose that fatigue in MS is a network disorder associated with impaired functional connectivity. These connectivity alterations are thought to result from focal or diffuse tissue damage, with altered microstructural integrity of white matter tracts and gray matter.[8,30,31] Disease-related disruption of interconnections between critical anatomical regions, such as the basal ganglia with the PFC, the posterior cingulate cortex, or cortical motor areas, may result in profoundly altered striato-cortical connectivity. This, in turn, may impair motor (e.g., planning and execution of movements) and non-motor (e.g., motivation and reward processing) functions, thus contributing to the pathophysiology of fatigue in MS.[8,31] The network theory of MS fatigue is supported by numerous structural and functional neuroimaging studies and electrophysiologic investigations.[8,32,33] As these regions are within the reach of the H-coil, it is conceivable that deep TMS may at least in part and temporarily normalize the impaired functional connectivity and thus improve fatigue—similar to mechanisms thought to be involved in the reduction of depressive symptoms in MDD following rTMS.[18]

Although we found improvement in fatigue in both verum stimulation conditions, the decrease in fatigue severity was more pronounced following bilateral MC stimulation. Given the broad coverage of the H-coil, the MC stimulation paradigm may possibly have influenced the activity of additional brain regions beyond motor areas. However, by generating a facilitatory input on primary motor and supplementary MC areas, as has been previously demonstrated for rTMS at 5 Hz,[11] our stimulation paradigm may have ameliorated impaired recruitment patterns of supplementary motor areas, which are associated with fatigue.[9]

In contrast to previous studies, acute rTMS treatment in our study was not followed by a maintenance protocol.[18] Despite this, FSS did not return to BL levels during the entire 6-week FU phase, which is in line with reported sustained long-term effects for approximately 5 months in patients with MDD in an open label study.[34] The sustained effect without the maintenance protocol suggests that clinical rTMS protocols for MS fatigue could involve fewer stimulation sessions[18] following an initial induction phase, thereby reducing patients' burden of frequent visits to the clinic.

This study prioritized the assessment of safety and tolerability as a primary end point at the expense of investigating preliminary efficacy. Thus, all data on the effects of rTMS on MS-associated fatigue are preliminary and should be interpreted with caution. Placebo effects of rTMS may also lead to a relevant reduction of symptoms as observed in previous rTMS studies.[35] Furthermore, as our sham condition used the stimulation parameters of active PFC rTMS, but not MC, potential sensory side effects of sham (for example, alertness caused by auditory stimuli such as the frequency of the clicking sound) were controlled for PFC, but not for MC. To confirm our data, further studies should use stimulation parameters adapted to sham control for MC stimulation.

Fatigue can affect cognitive and motor aspects differently, which lead to the conceptualization of cognitive fatigue and motor fatigue as potentially independent constructs. Thus, some instruments, e.g., the Modified Fatigue Impact Scale (MFIS) differentiates motor, cognitive, and psychosocial fatigue in its subscales.[36] The FSS scale used in our study does not differentiate between cognitive and motor aspects, but treats fatigue as its own entity, which can affect both motor and cognitive tasks.[21] Although cognitive aspects are explicitly covered only in 1 question in the FSS, the total FSS score appropriately correlates with both cognitive and motor fatigue subscales of the MFIS, which is why the results of our study should be applicable for both motor and cognitive aspects of fatigue.[37] Nonetheless, it will be very interesting to apply an instrument like the Fatigue Scale for Motor and Cognitive functions, which is more appropriate to dissect cognitive and motor fatigue, in a future Phase IIb or III study.[38]

Finally, the study design included depression as assessed by the BDI-IA as further exploratory end point. However, after enrollment completion, the distribution of patients classified as depressed was uneven between the groups, which is why we abstained from further analyzing effects on depressive symptoms in this study.

In light of the safety and tolerability of rTMS treatment in MS-associated fatigue, our study strongly suggests further investigating its potential therapeutic efficacy and the underlying mechanisms.

AUTHOR CONTRIBUTIONS

Mr. Gaede: acquisition of data, interpretation of data, study supervision, and critical revision of the manuscript for intellectual content. Ms. Tiede and Ms. Lorenz: acquisition of data and interpretation of data. Dr. Brandt: analysis and interpretation of data and critical revision of the manuscript for intellectual content. Mr. Pfueller, Dr. Dörr, and Dr. Bellmann-Strobl: acquisition of data, interpretation of data, and study supervision. Dr. Piper: analysis and interpretation of data. Dr. Roth and Prof. Zangen: critical revision of the manuscript for intellectual content. Dr. Schippling and Prof. Paul: study concept and design and critical revision of the manuscript for intellectual content.

DISCLOSURE

G. Gaede, M. Tiede, and I. Lorenz report no disclosures. A.U. Brandt served on the scientific advisory board of Biogen; received travel funding and/or speaker honoraria from Novartis, Biogen, and Teva; has patents pending for perceptive visual computing based postural control analysis, multiple sclerosis biomarker, perceptive sleep motion analysis, and fovea morphometry; consulted for Novartis and Biogen; received research support from BMWi, BMBF, and Guthy Jackson Charitable Foundation; and holds stock or stock options in Motognosis. C. Pfueller reports no disclosures. J. Dörr served on the scientific advisory board of Bayer, Novartis, Teva, and Sanofi-Genzyme; received travel funding and/or speaker honoraria from Novartis, Sanofi-Genzyme, Biogen, Bayer, Teva, and Allergan; and received research support from Novartis and Bayer. J. Bellmann-Strobl received speaker honoraria and travel funding from Bayer, Sanofi-Aventis/Genzyme, Merck, and Teva. S.K. Piper is a statistical reviewer for the *Journal of Cerebral Blood Flow and Metabolism*. Y. Roth is employed by Brainsway Ltd. A. Zangen served on the scientific advisory board of Brainsway, a company that produces the H-coils for deep TMS (including the ones used in the current study); served as an editorial advisory board member for the journal *Brain Stimulation*; holds a patent for first inventor for H-coils for deep transcranial magnetic stimulation; consulted for Brainsway, Brainsway might gain profit if the current published article will end up being a basis for clinical practice in the treatment of multiple sclerosis in the future; received research support from the NIH, the Israel Science Foundation, the Binational Science Foundation, and the Bright-Focus Foundation; holds stocks in Brainsway; receives royalties from the NIH and the Weizmann Institute of Science; and participated in legal proceedings in Brainway. S. Schippling served on the scientific advisory board of Bayer, Biogen, Merck Serono, Novartis, Sanofi-Genzyme, and Teva; received travel funding and/or speaker honoraria from Bayer, Biogen, Merck Serono, Novarits, Sanofi-Genzyme, and Teva; served as an associate editor for *Frontiers in Neurology*; holds a patent in therapeutic vaccine in PML using VP1 and Il7; and received research support from Sanofi-Genzyme, Novartis, the University of Zurich, the Betty and David Koetser Foundation for Brain Research, and the Swiss Multiple Sclerosis Society. F. Paul served on the scientific advisory board of Novartis; received speaker honoraria and travel funding from Bayer, Novartis, Biogen, Teva, Sanofi-Aventis/Genzyme, Merck Serono, Alexion, Chugai, MedImmune, and Shire; served as an academic editor for *PLoS One*; is an associate editor for *Neurology® Neuroimmunology & Neuroinflammation*; consulted for Sanofi-Genzyme, Biogen, MedImmune, Shire, and Alexion; received research support from Bayer, Novartis, Biogen, Teva, Sanofi-Aventis/Genzyme, Alexion, Merck Serono, German Research Council, Werth Stiftung of the City of Cologne, German Ministry of Education and Research, Arthur Arnstein Stiftung Berlin, Arthur Arnstein Foundation Berlin, Guthy Jackson Charitable Foundation, and National Multiple Sclerosis Society of the United States. Go to Neurology.org/nn for full disclosure forms.

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