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Controlled Study of 50 Hz Repetitive Transcranial Magnetic Stimulation for the Treatment of Parkinson's Disease

David H. Benninger[1,3], **Kazumi Iseki**[1], **Sarah Kranick**[1], **David A. Luckenbaugh**[2], **Elise Houdayer**[1], and **Mark Hallett**[1]

Kazumi Iseki: isekik@ninds.nih.gov; Sarah Kranick: sarah.kranick@nih.gov; David A. Luckenbaugh: luckenbd@mail.nih.gov; Elise Houdayer: houdayere@ninds.nih.gov; Mark Hallett: hallettm@ninds.nih.gov

[1]Medical Neurology Branch, National Institutes of Health (NIH), Bethesda, MD USA [2]National Institute of Neurological Disorders and Stroke (NINDS), National Institute of Mental Health (NIMH), National Institutes of Health (NIH), Bethesda, MD USA [3]Department of Neurology, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland

Abstract

Objective—To investigate the safety and efficacy of 50Hz repetitive Transcranial Magnetic Stimulation(rTMS) in the treatment of motor symptoms in Parkinson's disease(PD).

Background—Progression of PD is characterized by the emergence of motor deficits, which eventually respond less to dopaminergic therapy and pose a therapeutic challenge. RTMS has shown promising results in improving gait, a major cause of disability, and may provide a therapeutic alternative. Controlled studies suggest increasing stimulation frequency might enhance therapeutic efficacy.

Methods—In this randomized, double blind, sham-controlled study, we investigated safety and efficacy of 50Hz-rTMS of the motor cortices in 8sessions over 2weeks. Assessment of safety and clinical efficacy over a 1-month period included timed tests of gait and bradykinesia, UPDRS and additional clinical, neurophysiological and neuropsychological parameters. In addition, safety of 50Hz-rTMS was tested with EMG-EEG-monitoring during and after stimulation.

Correspondence: David H. Benninger, MD, Department of Neurology, Centre Hospitalier Universitaire Vaudois (CHUV), Rue du Bugnon 46, 1011 Lausanne, Switzerland, Tel +41 79 556 38 93 and +41 21 314 95 83, Fax +41 21 314 12 56, David.Benninger@chuv.ch.

Statistical analysis: David A. Luckenbaugh and David H. Benninger

Authors Contributions
David H. Benninger: Design and conceptualization of the study, analysis and interpretation of the data, drafting and revising the manuscript for intellectual content.
Kazumi Iseki: Conceptualization of the study, analysis and interpretation of the data, and revising the manuscript for intellectual content.
Sarah Kranick: Conceptualization of the study, analysis of the data and revising the manuscript for intellectual content.
David A. Luckenbaugh: Analysis and interpretation of the data and revising the manuscript for intellectual content.
Elise Houdayer: Conceptualization of the study and revising the manuscript for intellectual content.
Mark Hallett: Design and conceptualization of the study, analysis and interpretation of the data, and revising the manuscript for intellectual content.

Disclosures
D. H. Benninger, K. Iseki, S. Kranick, D. A. Luckenbaugh and E. Houdayer have no disclosures

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Results—We investigated 26 patients with mild to moderate PD: 13 received 50Hz-rTMS and 13 sham-stimulation. 50Hz-rTMS did not improve gait, bradykinesia, global and motor UPDRS, but there appeared a short-lived “on”-state improvement in activities of daily living (UPDRS II). 50Hz-rTMS lengthened the cortical silent period, but other neurophysiology and neuropsychological measures remained unchanged. EMG/EEG recorded no pathological increase of cortical excitability or epileptic activity. There were no adverse effects.

Conclusion—50Hz-rTMS of the motor cortices appears safe, but fails to improve motor performance and functional status in PD. Prolonged stimulation or other techniques with rTMS might be more efficacious, but need to be established in future research.

Keywords

repetitive transcranial magnetic stimulation (rTMS); 50 Hz rTMS; non-invasive brain stimulation; therapeutic study; Parkinson’s disease

Introduction

Gait difficulties in advanced Parkinson’s disease (PD) represent a primary cause of disability and a therapeutic challenge because of refractoriness to conventional therapy. Trials of non-invasive brain stimulation are promising. Meta-analyses concluded modest efficacy of high-frequency repetitive transcranial magnetic stimulation (rTMS) on motor performance in PD[1, 2]. Controlled 25 Hz rTMS-studies reported gait improvement[3, 4], which may be potentiated by increasing stimulation frequency[4].

In this double-blind, randomized, sham-controlled study (RCT), we investigated efficacy and safety of prolonged 50 Hz rTMS, that borders limits of safe use in humans[5] and technical possibilities of conventional rTMS, for the treatment of gait difficulties and bradykinesia in PD.

Methods

Study population

Patients aged 40–80 years with PD according to UK-PD-Brain-Bank-criteria, Hoehn-Yahr-stages 2–4 (“off”-medication) were included who had to have slowing of gait defined as taking ≥6 seconds to walk 10meters. Severe freezing, inability to walk 10 meters or daily falls were exclusionary. Optimal medication we considered to correspond to a levodopa-equivalent-dose (LED) of ≥300mg/day in HY stages 2–4 was required to remain unchanged during the study period. Exclusion criteria were dementia (MMSE ≤ 24/30), significant medical or psychiatric illnesses, history of epilepsy or seizures, pregnancy or metal devices in the head. Screening included EEGs reviewed by epileptologists for pathological activity.

A power analysis yielded a sample size of 6 and 13 participants per arm for on- and off-condition providing 80%-power with a two-sided alpha=0.05 to detect a similar gait improvement (primary outcome measure) as we reported previously with 25 Hz-rTMS[3].

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We prospectively enrolled the target population of 26 patients. Randomization was based on a computer-generated block allocation schedule. Study lasted 9/2009-4/2010.

Standard Protocol Approval, Registration, and Patient Consent

The study was approved by NIH Institutional Review Board and registered (ClinicalTrial.gov:NCT00977184). All participants gave written informed consent.

50Hz rTMS-intervention

We performed real or sham 50Hz rTMS in eight sessions over 2 successive weeks, a session/day for 4 consecutive days/week. We applied 50Hz rTMS to both primary motor cortices (M1) in each session in an alternating order at a stimulation intensity of 80% active motor threshold (AMT) for 6 seconds amounting to the same number of stimuli as with 25Hz rTMS that improved gait and bradykinesia[3]. We used the same circular 90mm-coil (parasagittal orientation, handle back) placed at the optimal position for motor-evoked potentials (MEPs) in abductor pollicis brevis (APB) on each side. This setting provides wide-spread motor cortex stimulation. The coil was connected to a Magstim-Rapid magnetic stimulator (Whitland,UK) inducing an anterior-posterior/posterior-anterior (AP-PA) biphasic current. In the sham condition, we placed an inactive coil similarly to the active coil and the active coil itself was oriented perpendicularly on top of the inactive coil, causing similar acoustic and vibratory sensations without exposing the patient to the magnetic field.

Patients received interventions while on medication. The stimulating apparatus was set up out-of-sight of blinded investigators.

Safety testing

We tested safety during the first intervention in both groups as a control and to maintain blinding as described[5]. We monitored patients for clinical and neurophysiological signs of a seizure. EMG activity was recorded from APB, extensor carpi radialis (ECR), biceps brachii (BB) and deltoid (DEL) muscles of either arm. We monitored EMG for spread of excitation to more proximal muscles (ECR, BB and DEL) which might indicate an increase of cortical excitability preceding epileptic activity, and for activity outlasting stimulation which might indicate after-discharges or seizure. We performed EEGs immediately after the first and last intervention. Clinical assessment included Verbal Fluency (letters FAS or CJM; each for 1 min) and Frontal Assessment Battery (FAB) was repeated after the last intervention.

Clinical assessment

Baseline and follow-up evaluations were performed before, 1 day and 1 month after the last intervention. Primary outcome measures were the change in the timed test of gait in the on- and off-state 24 hrs after the intervention period compared to baseline (Evidence class I). We assessed gait by measuring the time to walk 10 meters. Two trials were averaged. Patients were instructed to walk fast without taking the risk of falling wearing the same shoes and consistently using assistive devices if needed. We assessed bradykinesia by the time to perform the following sequence ten times: 1)hand-closing and -opening, 2)elbow-flexion, 3)hand-closing and –opening and 4)elbow–extension. This is similar to a sequential task shown to correlate with bradykinesia[6]. Before baseline assessment, patients practiced

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until performance appeared not to get faster and, then, abstained from further practice to minimize learning effects, which were controlled by the study design. We chose timed tests because they are more sensitive for detecting changes than scores and are independent from subjective assessment. These motor tests and UPDRS were assessed in the “best on-” and “practically-defined off-state” by the same blinded raters. Since “practically-defined off-state” required overnight (≥12hr) withdrawal of dopaminergic medication, assessment in the “best on-state” followed, considered by the patients and blinded rater the best response to their usual medication. Gait and bradykinesia were also timed immediately before and after each intervention sessions for acute effects.

Secondary outcome measures included Falls-and-Gait-Questionnaire (FGQ) containing the Freezing-of-Gait-Questionnaire (FOGQ)[7], Beck Depression Inventory (BDI) and a Health Survey(SF-12v2), addressing the subjective perception of health and well-being. We tested visuo-motor speed and procedural learning in the Serial Reaction Time Task (SRTT) as described except for a shorter sequence of 8 instead of 12 items[5].

Neurophysiological assessment

Resting (RMT) and active motor thresholds (AMT) were determined to the nearest 1% of the maximum stimulator output required to elicit an MEP of the APB ≥50μV/≥100μV in ≥5/10 trials during rest and weak voluntary contraction of 10% maximum quantitative EMG. We measured MEP recruitment curve at rest and during weak contraction at stimulus intensities of 90,100,110,120,130,140 and 150%RMT and AMT (8 pulses each every 6 seconds). We determined cortical silent period (CSP) during weak voluntary contraction with a TMS-pulse at 100%AMT and measured from MEP-onset until return of voluntary EMG-activity. Recruitment and CSP (right APB) were determined before and immediately after the 1st and 24h after the 8thintervention. All measurements were performed in the on- and off-state except for those after the 1stintervention performed only in the “on-state”.

Statistical Analysis

Full factorial repeated measures ANOVAs were used to examine all outcome measures. Each model included a between subjects factor for treatment and a within subjects factor for time and session (pre- versus post-intervention) when applicable. Omnibus main effects and interactions were examined post-hoc using Bonferroni adjusted simple effects tests within the context of the ANOVA. A priori comparisons were made as specified. Levene’s test was used to verify the homogeneity of variance assumption and Shapiro-Wilk’s test and standardized residuals were examined to verify the normality assumption. Linear mixed effect models were applied for the analysis of the recruitment curve at rest and weak voluntary contraction, and for the CSP.

Since the assessment after the first intervention (time 2) was done in the on-condition alone, we ran 2 models: 1) a model with the Factor Medication (on-condition vs. off-condition [plus Factor Med]) without time 2, and 2) a model with the on-condition alone at all time-points. Given concern about treatment effects being due to baseline differences in CSP, we ran an additional mixed model introducing baseline as covariate, which we also re-ran without 90% intensity due to limited variance in the model at that intensity.

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Significance was evaluated at p<.05, two-tailed. Adjustments for multiple comparisons were made separately for primary and secondary measures using Bonferroni's procedure. Cohen's d effect sizes are reported to show the size of group differences, where differences are measures at end point. Statistical analysis was done with SPSS Version 19.0.

Results

Twenty-six patients completed the study, but one patient withdrew from the 1-month follow-up assessment (secondary endpoint). Demographics and clinical findings did not differ between groups (Table 1), and neither did the outcome measures at baseline (all p>0.19). No patient reported discomfort or any other symptom. We observed no adverse events. No changes in dopaminergic or other medications were reported in this 6-week study period.

Safety testing

We observed no clinical or neurophysiological signs of impending or actual epileptic activity during or after the first and no EEG changes after the last intervention.

We found no worsening after the first intervention (Supplementary Table 1) in gait (Treatment, p=0.56) and sequential hand and arm movements (Treatment, p=0.26), but all improved despite practice before enrollment (Time, p=0.021 and <0.001). UPDRS motor score (Treatment, p=0.86), verbal fluency (Treatment, p=0.45) and FAB performance (Treatment, p=0.33) remained unchanged. In the SRTT, reaction time shortened slightly (Time, p=0.004) similarly in both groups (Treatment, p=0.44).

Gait

None depended on assistive devices. Walking time decreased in on- and off-state (Figure 2A; Table 2; Time, p<0.001 and p=0.002), but 50 Hz rTMS had no effects on gait in either state (Treatment, p=0.40 and p=0.29;Treatment-Time, p=0.85 and p=0.98). We found no changes in the Falls-and-Gait-Questionnaire (FGQ) and in the Freezing-of-Gait-Questionnaire (Table 3;FOGQ;Treatment, p=0.5 and p=0.57;Treatment-Time, p=0.12 and p=0.073, Time, p=0.76 and p=0.83), either.

Walking became faster after each session (Figure 2B; Supplementary Table 2, Session, p<0.001), but there was no discernible effect of 50 Hz rTMS (Treatment, p=0.66; Treatment-Session, p=0.64;Treatment-Session-Time, p=0.5).

Bradykinesia

Sequential hand and arm movements became faster (Figure 2C; Time, p<0.001 on and off), but no effect of 50 Hz rTMS could be discerned in on- or off-state (Treatment, p=0.39 and p=0.36; Treatment-Time, p=0.19 and p=0.69). Movement time decreased after every intervention session (Figure 2D; Supplementary Table 2, Session, p<0.001) without difference between groups (Treatment, p=0.51;Treatment-Session, p=0.63; Treatment-Session-Time, p=0.33).

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UPDRS

The 50 Hz rTMS had no effects on UPDRS scores in on- and off-state including motor examination (Table 3; part III; Treatment, p=0.77 and p=0.82; Treatment-Time, p=0.42 and p=0.71) and total score (Treatment, p=0.71 and p=0.56; Treatment-Time, p=0.13 and p=0.27). A day after the intervention period, an improvement in activities of daily living was reported (ADL [part II], Time, p=0.001 and p=0.027, resulting in reduction in the total UPDRS score: Time, p==0.04 and p=0.066) significantly more in 50 Hz rTMS-group on medication (Treatment-Time, p=0.012, post-hoc, p=0.038; in off-state, p=0.05), but these effects had disappeared at 1 month (Treatment, p=0.21 and p=0.15).

In the SRTT, reaction time (RT) shortened (Time, p<0.001) without differences between groups (Treatment, p=0.37 and Treatment-Time, p=0.48). 50 Hz rTMS did not improve sequence-specific learning or learning rate (Treatment, p>0.42 and p=0.30; Treatment-Time, p>0.44 and p=0.61).

50 Hz rTMS had no effects on depression scores (Treatment, p=0.93; Treatment-Time, p=0.42), mental (Treatment, p=0.66; Treatment-Time, p=0.63) and physical well-being (Treatment, p=0.59; Treatment-Time, p=0.94).

Neurophysiology

Rest and active MEP recruitment curves and CSP were similar in on- and off-state (p=0.68, 0.98 and 0.70). In both recruitment curves, MEP-amplitudes increased as did CSP duration with stimulation intensity in all conditions (all p<0.001). 50 HZ rTMS had no effects on rest and active MEP recruitment curves (Treatment, p=0.37 and 0.58 [plus Factor Med] and p=0.40 and 0.31 [no Factor Med]), but prolonged CSP (Treatment, p=0.003 and 0.04: real > sham stimulation). This effect remained near significant when correcting for baseline (Treatment, p=0.078) and fully significant without 90% intensity (Treatment, p=0.049) prior to correction for multiplicity (see supplementary file).

Discussion

In this double-blind, randomized, sham-controlled study, repeated 50 Hz rTMS of the motor cortex (M1) did not improve gait, upper extremity bradykinesia or global motor performance in PD. There appeared a short-lived “on”-state improvement in activities of daily living (ADL; UPDRS II), but without changes in functional status or self-reported well-being. Conversely, the intervention appears safe extending current safety limits of sub-threshold 50 Hz rTMS[5] to a duration of 6 seconds.

The absence of effects on motor function matches findings in our therapeutic trial of intermittent Theta-Burst stimulation (iTBS)[8]. Consequently, there is currently no evidence for therapeutic efficacy of 50 Hz rTMS, neither continuous nor patterned as in iTBS which consists of bursts of 50 Hz rTMS. In contrast to iTBS[8], we found no beneficial effects on mood with 50 Hz rTMS. A reason could be that we did not stimulate the dorsolateral prefrontal cortex (DLPFC) which had been found comparable to antidepressants in PD with depression[9]. We had refrained from its stimulation for concerns over safety of 50 Hz rTMS which we had solely established for M1[5]. On the other hand, stimulation of DLPFC may not

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contribute to the improvement of motor function. Twenty-five Hz rTMS of M1 and DLPFC[3] appeared not superior to stimulation of M1 alone[4], but these were not directly compared, and an investigation of 10Hz rTMS targeting left DLPFC and/or M1 for treatment of freezing of gait (FOG) was prematurely terminated because of inefficacy[10]. We focused on speed, but also assessed gait disturbances with a questionnaire focusing on freezing which is inherently difficult to ascertain in laboratory conditions. An observation of reduced freezing in the iTBS-study suggested potential responsiveness to high-frequency rTMS, which remained unsubstantiated in both 50 Hz rTMS and iTBS-trials[8].

Irrespective of type of intervention, we found comparable improvement in rTMS- and sham-treated patients. We presume these to result from motor learning, most manifest in the sequential hand and arm movements, familiarization with the test-setting, or to reflect a substantial Placebo-effect. Acute improvement after rTMS- and sham-intervention could result from striatal dopamine release caused by high-frequency rTMS[11] and can even arise from expectation alone since sham-rTMS had the same effect[12]. Latter could mediate the Placebo-response. These effects corroborate with findings in the tDCS-[13] and iTBS-trials[8], and underline the importance of a controlled study design. Conversely, both 50Hz-rTMS and iTBS[8] did not enhance motor learning in contrast to tDCS[13].

This absence of cumulative effects on gait and bradykinesia with repeated interventions contrasts with efficacy of 25Hz rTMS[3, 4]. Methodological reasons limit comparability between different stimulation patterns, but standardizing changes in UPDRS motor score in various trials yielded a larger effect size of conventional rTMS[2] than 50 Hz rTMS and iTBS[8]. The discrepancy between significant improvement with 25Hz rTMS and absence of effects with patterned and continuous 50 Hz rTMS raises questions as to whether and how stimulation patterns might vary in their mechanism of action. One controlled 25 Hz rTMS trial that provided the rationale for the current studies had applied the same coil and targets[3]. But, even though we had twice the statistical power to detect a therapeutic efficacy of 50Hz comparable to 25Hz rTMS[3], we found no effects in the best on-state that would constitute the reason for an add-on intervention.

We found no effects on recruitment curves either, but cannot exclude a potential effect on the cortical silent period (CSP; Figure 3) which needs to be further studied. The CSP is thought to reflect excitability of the motor cortex and to involve inhibitory circuits, which may be mediated by dopamine[14]. DBS[15] and conventional rTMS[16–18] modulate CSP suggesting 50 Hz rTMS may activate the same mechanism, which differs from iTBS[8]. The functional significance of CSP remains unknown, and CSP may not correlate with the motor function[19, 20]. The lack of clinical efficacy precludes conclusions on the role of physiology in mediating effects of non-invasive brain stimulation. In this and our previous study[8], CSP did not differ in the on and off condition, which is probably due to the lower stimulation intensities we tested[21, 22]. Few therapeutic trials have looked at changes in physiology and their correlation with clinical outcome. Increase of MEP-amplitudes correlated with clinical improvement with repeated 25 Hz rTMS[3], but not with iTBS[8], questioning a causal effect. These findings suggest persistent effects implying changes were induced in synaptic strength underlying plasticity that remains preserved in PD[23–25].

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Beyond the postulated potentiation of efficacy by increasing stimulation frequency and, thereby, delivering more power, i.e. rate of energy transfer[4], there might be a rationale specific for 50 Hz rTMS. This arises from the hypothesized role of oscillatory activity in the motor cortex and basal ganglia in motor control and in the pathogenesis of motor disorders, and also the possibility to modulate this activity. In PD in the medication off-condition, pathological oscillatory activity in the beta-frequency range (10–30 Hz) predominates[26]. This beta-activity decreases in response to dopamine[27] and high-frequency (130 Hz) DBS[28], while gamma activity (>30Hz) emerges along with clinical improvement[29]. Further evidence comes from beta-frequency (20 Hz) stimulation of the subthalamic nucleus which enhances bradykinesia[30] indicating a potential contribution of beta-activity to bradykinesia and rigidity in PD[26]. This shift in power of beta- to gamma-activity might underlie the effects of dopamine and DBS[31]. RTMS may entrain oscillatory activity[32] and 50Hz rTMS might, thereby, induce the hypothesized “pro-kinetic” gamma-frequency while suppressing the “akinetic” beta-frequency[26]. Safety concerns limit clinical applicability of high-frequency rTMS, and safety of 50 Hz rTMS for longer than 2 seconds[5] needed first to be established. Longer stimulation might be efficient considering that efficacy of DBS depends on chronic stimulation. This “entrainment” differs from the presumed mechanism in iTBS which is intended to imitate normal firing patterns in the hippocampus by coupling gamma-frequency bursts (50Hz) with theta-rhythm (5Hz). This is supported by the induction of long-term potentiation and depression which constitute mechanisms of plasticity in an animal model[33].

This study has limitations. Time-demand and safety concerns may have biased patient selection, although few declined, while hardly any disqualified indicating that this intervention may potentially be applied to most patients. One sham-treated patient withdrew from the 1-month follow-up, but this was a secondary endpoint. Participants’ reports and robust placebo-response suggested blinding was maintained, facilitated by sub-threshold rTMS and similar acoustic sensation during sham-stimulation. Different methods of sham-stimulation appear not to influence outcome of rTMS studies and placebo-response[2].

This study provides no evidence for a therapeutic potential of 50Hz rTMS at the current stimulation parameters, but safety concerns and technical limitations precluded prolonging stimulation which might be efficient. Future protocols need to further explore pathophysiology of PD and mechanism of rTMS to establish more powerful stimulation patterns.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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advisory board member, an editor, a writer, or a speaker. Dr. Hallett has received license fee payments from the National Institutes of Health for the H-coil, a type of coil for magnetic stimulation.

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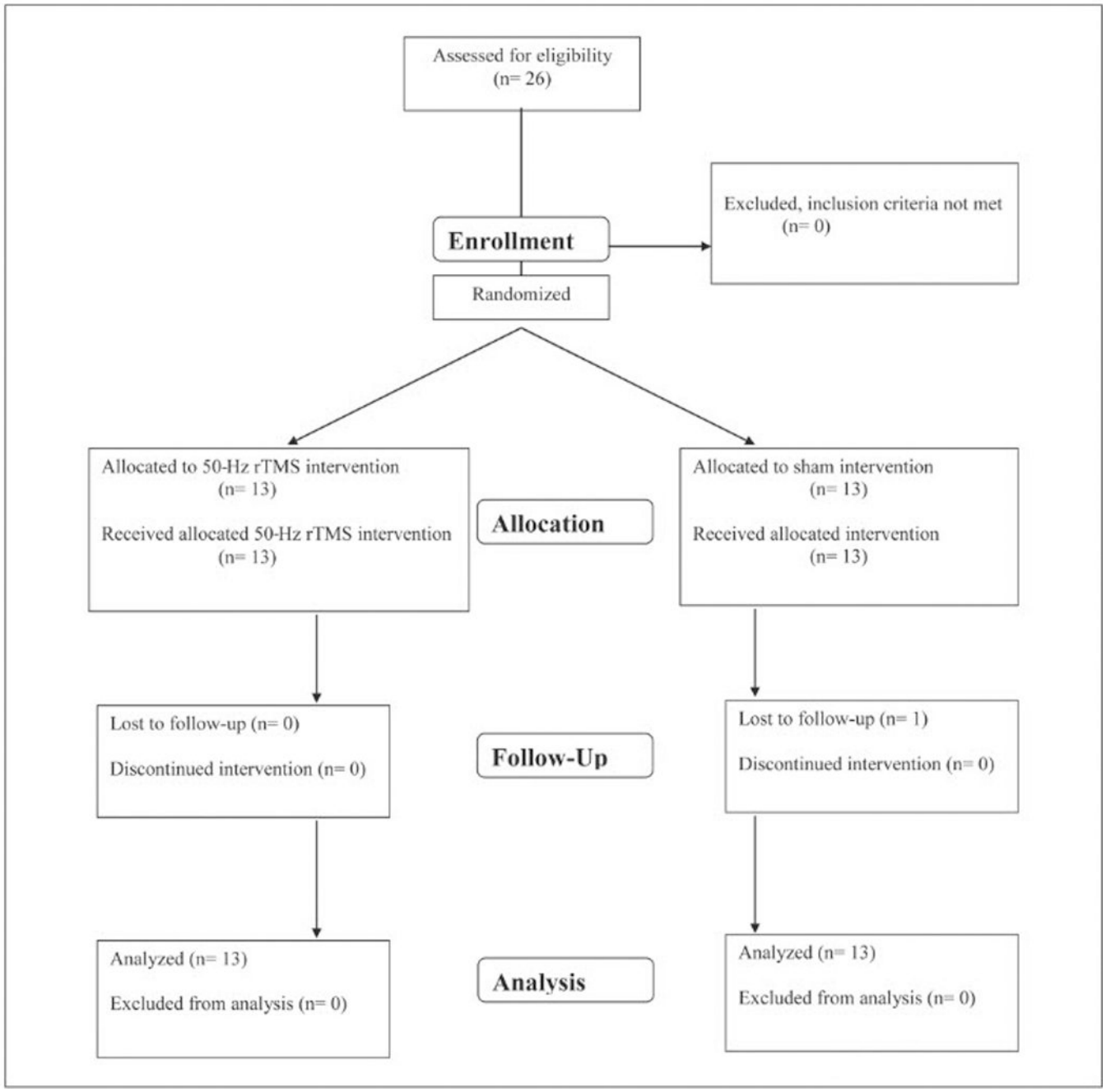


Figure 1.
Flow diagram of patients with Parkinson's disease (PD) enrolled in this therapeutic study.

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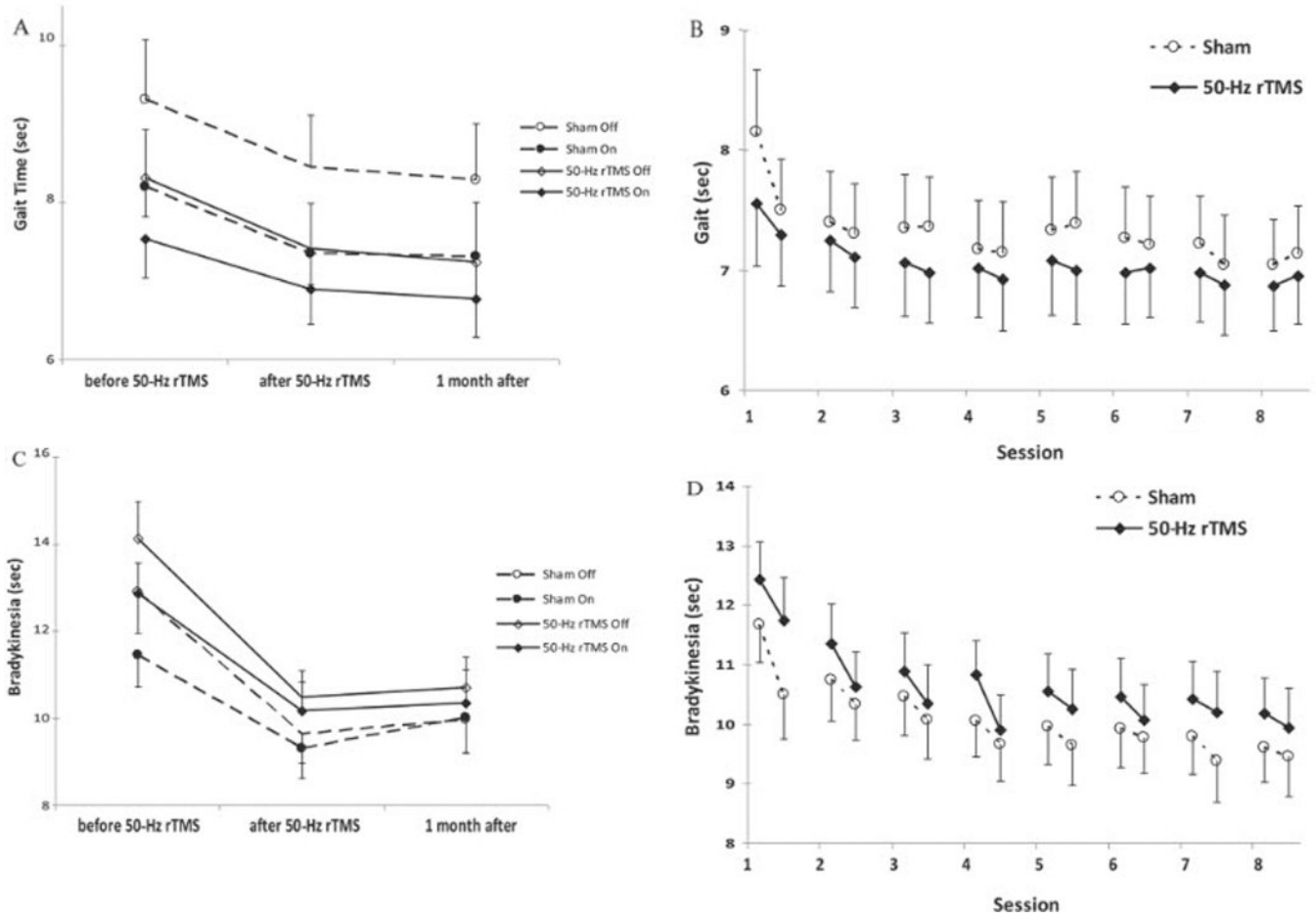


Figure 2.

A–D Gait and Sequential Hand and Arm Movement Time

(A) Gait time before, 1 day and 1 month after the last intervention (mean ± standard error). The figure shows the time needed to walk 10 meters in the “on” and “off” state. Abscissa indicates the time of measurement. Ordinate indicates the gait time. The solid lines and diamonds indicate the 50 Hz rTMS (n=13) and the dashed lines and circles the sham group (n=13). Open symbols indicate the “off” (medication) condition and filled symbols indicate the “on” condition measurements. (B) Gait time before and after each intervention (mean ± standard error). The figure shows the time needed to walk 10 meters. Abscissa indicates the time of measurement; ordinate indicates the walking time. The solid lines and filled diamonds indicate the 50 Hz rTMS (n=13) and the dashed lines and open circles the sham group (n=13). At baseline, gait time did not differ between groups.

(C) Sequential hand and arm movement test before, 1 day and 1 month after the last intervention (mean ± standard error). The figure shows the time needed to execute the sequential hand and arm movement test in the “on” and “off” state. Measurements for the left and right hands were pooled. Abscissa indicates the time of measurement. Ordinate indicates the execution time. The solid lines and diamonds indicate the 50 Hz rTMS (n=13) and the dashed lines and circles the sham group (n=13). Open symbols indicate the “off” (medication) condition and filled symbols indicate the “on” condition measurements. (D)

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Sequential hand and arm movement test before and after each intervention (mean ± standard error). The figure shows the time needed to execute the sequential hand and arm movement test. Measurements for the left and right hands were pooled. Abscissa indicates the time of measurement; ordinate indicates the execution time. The solid lines and filled diamonds indicate the 50 Hz rTMS (n=13) and the dashed lines and open circles the sham group (n=13). At baseline, sequential hand and arm movement time did not differ between groups.

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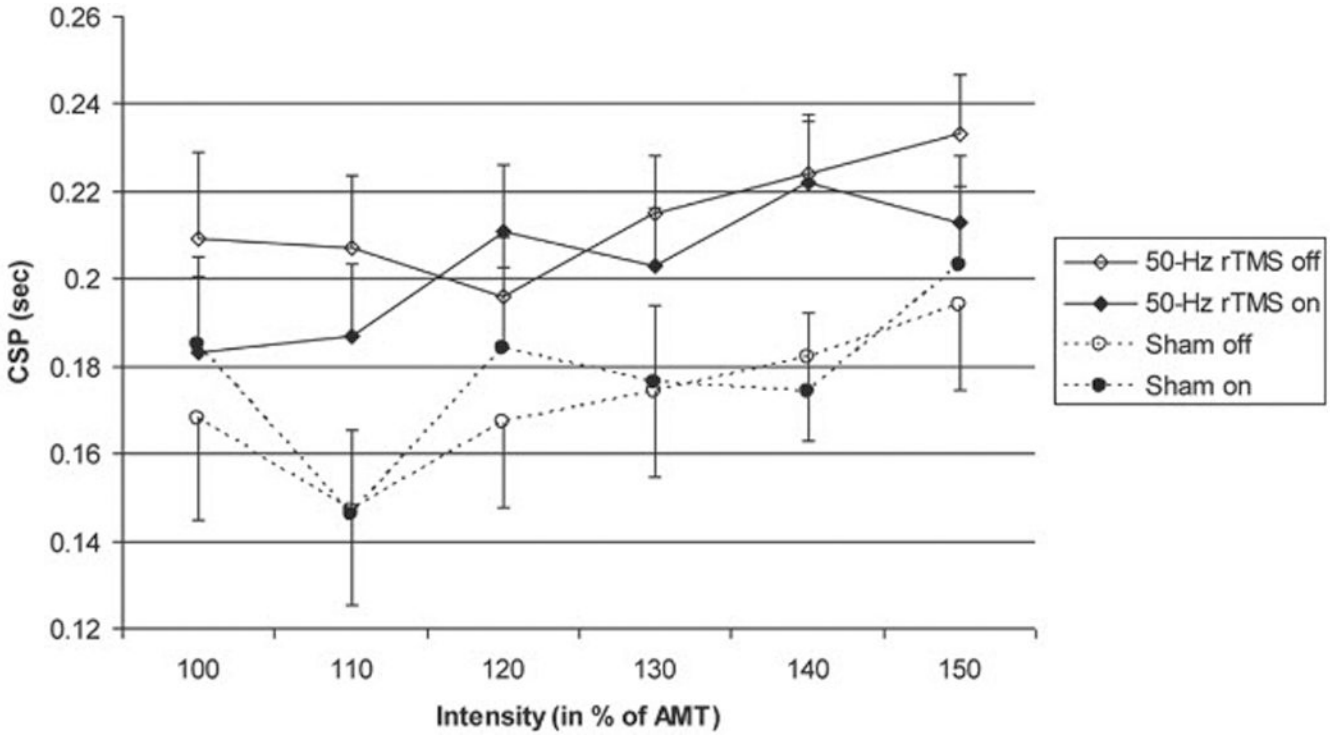


Figure 3.

Cortical Silent Period after 8 interventions

Cortical Silent Period (CSP) 1 day after the last intervention (mean ± standard error). The figure shows the duration of CSP in seconds (abscissa) at the different stimulation intensities (in percentage of active motor threshold [ordinate]). The solid lines and diamonds indicate the 50 Hz rTMS (n=13) and the dashed lines and circles the sham group (n=13). Open symbols indicate the “off” (medication) condition and filled symbols indicate the “on” condition measurements. In this mixed model analysis, in which baseline was introduced as covariate and 90% intensity not included due to limited variance (therefore, not shown in the figure), the effect of 50 Hz rTMS on CSP (Treatment, p=0.049) is significant prior to correction for multiplicity.

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Table 1

Demographic and clinical findings in the patients with Parkinson's disease receiving 50 Hz rTMS (n=13) or sham (n=13).

	Sham (n=13)	50 Hz rTMS (n=13)	p
Age (y)	63.7 ± 8.3	64.5± 9.1	0.81#
Women	4 (30%)	2 (15.4%)	0.65*
Age at onset (y)	54.3 ± 12.5	55.8 ± 9.1	0.74#
Duration of disease (y)	9.3 ± 6.8	8.6 ± 4.1	0.76#
Hoehn-Yahr ("on")	2.5 ± 0.3	2.4 ± 0.2	0.15#
Hoehn-Yahr ("off")	2.9 ± 0.6	2.7 ± 0.3	0.15#
Total LED (mg)	949 ± 677	861 ± 436	0.70#
Tremor (present)	10 (76.9%)	12 (92.3%)	0.59*
Gait freezing (present)	9 (69.2%)	7 (53.8%)	0.69*
Fluctuations (present)	8 (61.5%)	7 (53.8%)	1.0*
Dyskinesias (present)	5 (38.5%)	4 (30.8%)	1.0*
Falls (present)	0 (0%)	1 (7.7%)	1.0*

Mean values ± standard deviation.

Student T-Test,

* Fisher's exact test;

LED = Levodopa equivalent dose

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Table 2

Gait and sequential hand and arm movement time (mean ± standard error) at baseline, 1 day and at 1 month after the last 50 Hz rTMS and sham intervention

Timed tests	50Hz sham	Baseline	1 day after last intervention	1 month after last intervention	Treatment	Treatment × Time	Time	Effect size (Cohen's d)
Gait	On	7.54 ± 0.50	6.89 ± 0.45	6.76 ± 0.48	0.40	0.85	<0.01	0.34
		8.20 ± 0.50	7.35 ± 0.45	7.31 ± 0.48				
	Off	8.31 ± 0.73	7.41 ± 0.64	7.24 ± 0.69	0.29	0.98	0.002	0.45
		9.32 ± 0.76	8.45 ± 0.67	8.29 ± 0.72				
Bradykinesia	On	12.86 ± 0.71	10.17 ± 0.65	10.34 ± 0.78	0.39	0.19	<0.01	0.12
		11.46 ± 0.74	9.30 ± 0.68	10.01 ± 0.82				
	Off	14.12 ± 0.86	10.48 ± 0.62	10.70 ± 0.71	0.36	0.69	<0.01	0.29
		12.90 ± 0.93	9.65 ± 0.67	9.98 ± 0.77				

At baseline, primary and secondary outcome measures did not differ between groups.

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Table 3

Secondary outcome measures (mean ± standard error) at baseline, 1 day and at 1 month after the last 50 Hz rTMS and sham intervention

	50Hz sham	Baseline	1 day after last intervention	1 month after last intervention	Treatment	Treatment × Time	Time	Effect size (Cohen's d)
UPDRS	On	49.31 ± 4.1	45.00 ± 4.2	44.92 ± 3.5	0.71	0.13	0.04	0.33
total		48.92 ± 4.3	47.67 ± 4.4	48.92 ± 3.7				
	Off	57.77 ± 4.2	53.46 ± 4.0	53.54 ± 3.6	0.56	0.27	0.07	0.35
		58.75 ± 4.2	57.75 ± 4.2	58.00 ± 3.8				
UPDRS III	On	32.08 ± 2.5	29.85 ± 2.7	30.00 ± 2.2	0.77	0.42	0.09	0.09
(motor)		30.00 ± 2.6	29.58 ± 2.8	29.25 ± 2.5				
	Off	38.46 ± 2.2	36.46 ± 2.3	36.39 ± 2.1	0.82	0.71	0.053	0.13
		37.25 ± 2.3	36.50 ± 2.4	35.42 ± 2.2				
UPDRS II	On	11.15 ± 1.3	9.39 ± 1.4	9.00 ± 1.2	0.21	0.012	0.001	0.92
(ADL)		12.58 ± 1.4	11.33 ± 1.5	12.75 ± 1.2				
	Off	13.23 ± 1.5	11.23 ± 1.6	11.23 ± 1.5	0.15	0.050	0.027	0.85
		15.17 ± 1.6	14.50 ± 1.7	15.58 ± 1.5				
FGQ		12.17 ± 3.0	10.50 ± 3.0	10.08 ± 3.1	0.50	0.12	0.76	0.38
		13.08 ± 3.0	14.2 ± 3.0	14.08 ± 3.1				
FOGQ		6.17 ± 1.4	5.50 ± 1.3	5.17 ± 1.5	0.57	0.073	0.83	0.44
		6.25 ± 1.4	6.5 ± 1.3	7.33 ± 1.5				
FAB		16.15 ± 0.5	16.39 ± 0.5	16.77 ± 0.4	0.33	0.55	0.55	0.22
		17.10 ± 0.6	17.10 ± 0.5	17.10 ± 0.5				
BDI		9.50 ± 1.8	9.25 ± 1.5	8.58 ± 1.8	0.93	0.42	0.59	0.21
		9.33 ± 1.7	7.67 ± 1.5	9.83 ± 1.8				
Mental health		49.93 ± 2.6	50.02 ± 2.0	49.65 ± 2.5	0.66	0.63	0.49	0.03
		52.43 ± 2.7	51.84 ± 2.1	49.37 ± 2.6				
Physical health		37.39 ± 2.6	37.91 ± 2.4	36.40 ± 2.8	0.59	0.94	0.48	0.17
		39.40 ± 2.7	40.23 ± 2.45	38.62 ± 2.9				
SRTT		790.1 ± 45.6	707.8 ± 45.6	729.2 ± 46.3	0.37	<0.001	.34	0.34
		719.4 ± 45.6	667.9 ± 45.9	668.4 ± 47.3				

At baseline, secondary outcome measures did not differ between groups.

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BDI Beck Depression Inventory, FGQ Falls and Gait Questionnaire containing FOGQ Freezing of Gait Questionnaire[7], FAB Frontal Assessment Battery, Health survey (SF-12v2): mental and physical health, SRTT Serial Reaction Time Task, UPDRS Unified Parkinson's Disease Rating Scale, part II Activities of Daily Living (ADL), part III Motor Examination.