Intermittent theta-burst transcranial magnetic stimulation for treatment of Parkinson disease

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ABSTRACT

Objective: To investigate the safety and efficacy of intermittent theta-burst stimulation (iTBS) in the treatment of motor symptoms in Parkinson 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. Repetitive transcranial magnetic stimulation (rTMS) has shown promising results in improving gait, a major cause of disability, and may provide a therapeutic alternative. iTBS is a novel type of rTMS that may be more efficacious than conventional rTMS.

Methods: In this randomized, double-blind, sham-controlled study, we investigated safety and efficacy of iTBS of the motor and dorsolateral prefrontal cortices in 8 sessions over 2 weeks (evidence Class I). Assessment of safety and clinical efficacy over a 1-month period included timed tests of gait and bradykinesia, Unified Parkinson's Disease Rating Scale (UPDRS), and additional clinical, neuropsychological, and neurophysiologic measures.

Results: We investigated 26 patients with mild to moderate PD: 13 received iTBS and 13 sham stimulation. We found beneficial effects of iTBS on mood, but no improvement of gait, bradykinesia, UPDRS, and other measures. EEG/EMG monitoring recorded no pathologic increase of cortical excitability or epileptic activity. Few reported discomfort or pain and one experienced tinnitus during real stimulation.

Conclusion: iTBS of the motor and prefrontal cortices appears safe and improves mood, but failed to improve motor performance and functional status in PD.

Classification of evidence: This study provides Class I evidence that iTBS was not effective for gait, upper extremity bradykinesia, or other motor symptoms in PD. *Neurology*® 2011;76:601–609

GLOSSARY

ADL = activities of daily living; **AMT** = active motor threshold; **ANCOVA** = analysis of covariance; **ANOVA** = analysis of variance; **APB** = abductor pollicis brevis; **BB** = biceps brachii; **BDI** = Beck Depression Inventory; **BDNF** = brain-derived neurotrophic factor; **CSP** = cortical silent period; **cTBS** = continuous TBS; **DEL** = deltoid; **DLPFC** = dorsolateral prefrontal cortex; **ECR** = extensor carpi radialis; **FAB** = Frontal Assessment Battery; **FOG** = freezing of gait; **iTBS** = intermittent theta-burst stimulation; **LED** = levodopa equivalent dose; **MEP** = motor evoked potential; **PD** = Parkinson disease; **RMT** = resting motor threshold; **RT** = reaction time; **rTMS** = repetitive transcranial magnetic stimulation; **SRTT** = Serial Reaction Time Task; **UPDRS** = Unified Parkinson's Disease Rating Scale.

Parkinson disease (PD) is defined by a lack of dopamine and substitution remains primary therapy, but the degeneration of nondopaminergic neurons progresses and leads to the emergence of symptoms refractory to conventional therapy. Among them, difficulties with gait and recurrent falls are common and cause disability in advanced PD.

Trials of noninvasive 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 rTMS studies demonstrated gait improvement, suggesting more powerful stimulation protocols could enhance efficacy.[3-5]

Supplemental data at www.neurology.org

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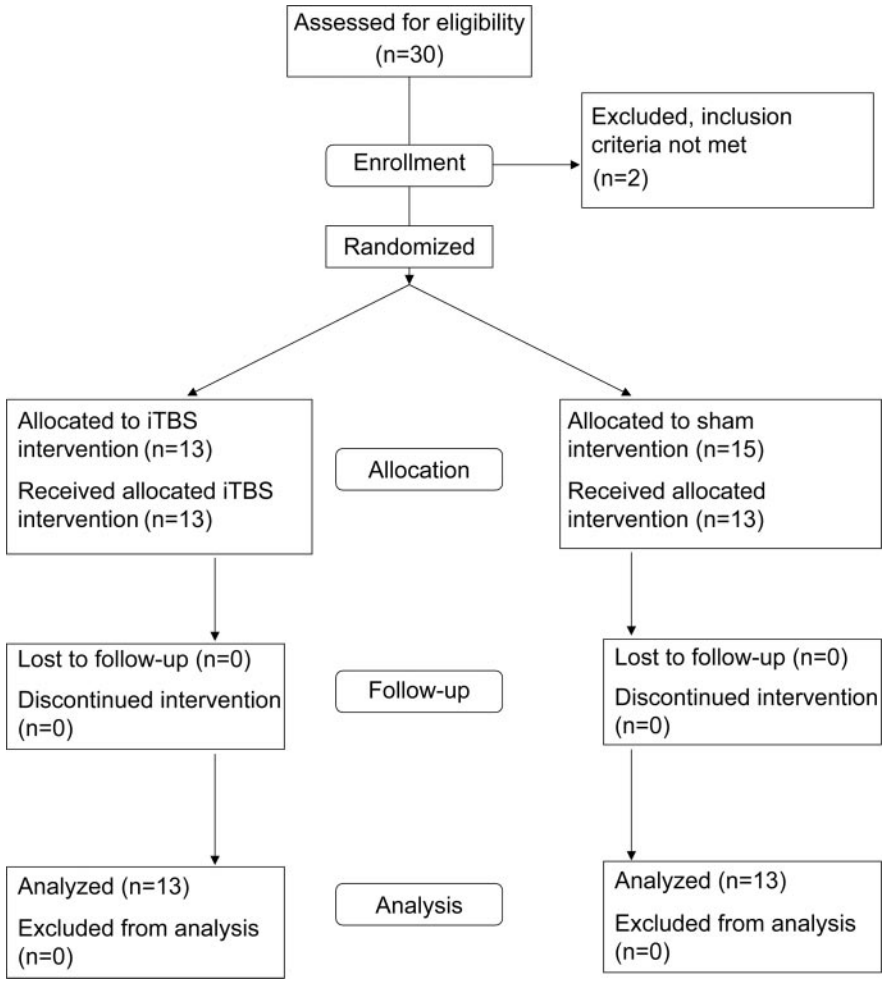
Figure 1 Patient enrollment



iTBS = intermittent theta-burst stimulation.

Intermittent theta-burst stimulation (iTBS), a novel form of excitatory rTMS, may induce larger and longer-lasting changes than standard rTMS,[6] but its therapeutic potential in PD has not been investigated.

In this double-blind, randomized, sham-controlled study, we investigated efficacy and safety of iTBS for the treatment of gait difficulties and bradykinesia in PD.

METHODS

Study population. The study population is illustrated in figure 1. Patients aged 40–80 years with PD according to UK PD Brain Bank criteria, Hoehn-Yahr stages 2–4 ("off" medication), who had slowing of gait defined as taking ≥6 seconds to walk 10 meters, were included. Severe freezing, inability to walk 10 meters, or daily falls were exclusionary. Optimal medication with a levodopa equivalent dose (LED) of ≥300 mg was required to remain unchanged during the study period. Exclusion criteria were significant medical or psychiatric illnesses, history of epilepsy or seizures, pregnancy, or metal devices in the head. Screening included EEGs reviewed by epileptologists for pathologic 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 2-sided $\alpha = 0.05$ to detect a similar gait improvement with iTBS as with 25-Hz rTMS.[3]

We prospectively enrolled 30 patients to investigate the target population of 26: 2 were excluded because of subclinical epileptiform discharges before and 2 withdrawn after enrollment. Randomization was based on a computer-generated block allocation schedule. The study lasted from October 2008 to July 2009.

Standard protocol approval, registration, and patient consent. The study was approved by NIH Institutional Review Board and registered (ClinicalTrial.gov:NCT00753519). All participants gave written informed consent.

iTBS intervention. We performed real or sham iTBS in 8 sessions over 2 successive weeks, a session/day for 4 consecutive days/week. iTBS consists of bursts of 3 pulses (stimulation intensity at 80% active motor threshold) at 50 Hz repeated at 200-msec intervals (5 Hz) for 2 seconds (10 bursts). These 2-s trains were repeated 20 times every 10 seconds. We applied iTBS using the same circular 90-mm coil to the primary motor (M1) and dorsolateral prefrontal cortex (DLPFC) bilaterally as with 25-Hz rTMS that improved gait and bradykinesia.[3] For M1 stimula-

tion, the coil (parasagittal orientation, handle back,) was placed at the optimal position for motor evoked potentials (MEPs) in abductor pollicis brevis (APB), and, for DLPFC stimulation, 5 cm rostral to this M1 position.[7] This setting provides a widespread motor and prefrontal cortex stimulation. The coil was connected to a Magstim Rapid magnetic stimulator (Whitland, UK) inducing an anterior-posterior/posterior-anterior biphasic current. The sham coil made a similar sound without a magnetic pulse. Patients received interventions while on medication. The stimulating apparatus was set up out of sight of blinded investigators. Patients were all naïve to rTMS.

Safety testing. We tested safety during the first intervention in both groups as a control and to maintain blinding as described.[8] We monitored patients for clinical and neurophysiologic 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 afterdischarges or seizure. We performed EEG after the first and last intervention. Clinical assessment included Verbal Fluency (letters FAS or CJM; each for 1 minute) and Frontal Assessment Battery (FAB) was repeated after the last iTBS.

Clinical assessment. Baseline and follow-up evaluations were performed before and 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 hours 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 10 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.[9] Before baseline assessment, patients practiced until performance appeared not to get faster and, then, abstained from further practice to minimize learning effects. 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 (≥12 hours) 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 before and after each intervention session for acute effects.

Secondary outcome measures included Beck Depression Inventory (BDI) and the short form of a health survey (SF-12v2™) addressing the subjective perception of health and well-being.

We tested visuomotor speed and procedural learning in the Serial Reaction Time Task (SRTT) as described except for a shorter sequence of 8 instead of 12 items.[8]

Neurophysiologic assessment. Resting motor threshold (RMT) and active motor threshold (AMT) were determined to the nearest 1% of the maximum stimulator output required to elicit an MEP of the APB ≥50 μV/≥100 μV 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, and 140%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 after the first and 24 hours after the eighth intervention, and, for safety testing,[8] MEP (left APB) at 120% RMT (30 stimuli every 6 seconds) before and after the first intervention. All measurements were performed in the "on" and "off" state except for those after the first intervention performed only in the "on" state.

Statistical analysis. Full factorial repeated-measures analyses of variance (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 (preintervention vs postintervention) when applicable. Since groups differed at baseline on several measures, we ran multiple analyses to verify the ANOVA results. First, we performed analysis of covariance (ANCOVA) to factor out baseline group differences. The original statistical model remained intact with the exception of the baseline as a covariate. All available data were used in the ANCOVAs. For treatment effects, we report results from these ANCOVA models. In addition, we reran the ANOVA of gait during "off" state without 3 extreme outliers. Regarding changes unrelated to treatment, we report results from the initial ANOVA models. Omnibus main effects and interactions were examined post hoc using Bonferroni-adjusted simple effects tests within the context of the ANOVA and ANCOVA. A priori comparisons were made as specified. Levene test was used to verify the homogeneity of variance assumption and Shapiro-Wilks 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.

Significance was evaluated at $p < 0.05$, 2-tailed. Adjustments for multiple comparisons were made separately for primary and secondary measures using Bonferroni procedure.

Cohen 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 17.0.1.

RESULTS Twenty-six patients completed the study. Two patients were withdrawn who received sham stimulation precluding causality with iTBS: a 74-year-old patient with heart disease had a myocardial infarction. In the other, we could not immediately rule out epileptogenic activity in the post 1 interventional EEG, but EEG 24 hours later strongly suggested wicket spikes, a normal variant. Nine patients receiving iTBS reported occasional local pain or discomfort during stimulation, predominantly of DLPFC, and one patient reported an isolated, nonpulsatile, left-sided tinnitus for a few minutes. Despite randomization, iTBS group had higher LED and greater prevalence of freezing of gait, fluctuations, and dyskinesias (table 1).

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

Table 1 Demographic and clinical findings in the patients with Parkinson disease receiving iTBS or sham[a]

	Sham (n = 13)	iTBS (n = 13)	p
Age, y	65.6 ± 9.0	62.1 ± 6.9	0.21[b]
Female	2 (15.4)	6 (46.2)	0.20[c]
Age at onset, y	59.2 ± 9.3	51.2 ± 11.8	0.06[d]
Duration of disease, y	6.5 ± 3.4	10.8 ± 7.1	0.06[d]
Hoehn-Yahr "on"	2.5 ± 0.1	2.6 ± 0.2	0.09[b]
Hoehn-Yahr "off"	2.9 ± 0.2	3.0 ± 0.4	0.48[b]
Total LED, mg	732.3 ± 344.8	1,180.9 ± 662.4	0.04[d]
Tremor	9 (69.2)	10 (76.9)	1.00[c]
Gait freezing	3 (23.1)	10 (76.9)	0.017[c]
Fluctuations	4 (30.8)	11 (84.6)	0.015[c]
Dyskinesias	2 (15.4)	9 (69.2)	0.015[c]
Falls	0 (0)	1 (7.7)	1.00[c]

Abbreviations: iTBS = intermittent theta-burst stimulation; LED = levodopa equivalent dose.
[a] Values are mean ± SD or n (%).
[b] Mann-Whitney test.
[c] Fisher exact test.
[d] Student *t* Test.

We found no worsening after the first intervention (table e-1 on the *Neurology*® Web site at www.neurology.org) in gait (treatment, $p = 0.19$), sequential hand and arm movements (treatment, $p = 0.9$), and UPDRS motor score (treatment, $p = 0.86$). Verbal fluency decreased (time, $p = 0.016$), significantly less with iTBS (treatment, $p = 0.002$), and reaction time lengthened slightly (time, $p = 0.011$), possibly reflecting fatigue after lengthy testing. But groups did not differ in reaction time (treatment, $p = 0.49$), sequence-specific learning (treatment, $p = 0.50$), or learning rate (treatment, $p = 0.77$) in the SRTT. FAB performance improved along the study (time, $p = 0.034$), which probably reflects learning without difference between groups (treatment, $p = 0.36$; treatment–time, $p = 0.23$).

Gait. Walking time decreased in "on" state (figure 2A, table 2; time, $p = 0.005$, "off" state: $p = 0.09$), but iTBS had no effects on gait in "on" or "off" state (treatment, $p = 0.85$, and $p = 0.67$; treatment–time, $p = 0.61$ and $p = 0.43$). Three participants receiving iTBS experienced severe gait freezing in the "off" state exclusively at baseline, but not in postinterventional assessments. These extreme outliers potentially biased our results in favor of iTBS, but reanalysis without outliers re-excluded effects of iTBS (treatment, $p = 0.62$; treatment–time, $p = 0.92$). A therapeutic effect of iTBS on freezing was also not supported by participants' reports (UPDRS II gait freezing item in "on" and "off" state (treatment, $p = 0.23$ and $p = 0.89$; treatment–time, $p = 0.71$ and $p = 0.11$).

Walking became faster after each session (table e-2, session, $p = 0.007$), but there was no gradual improvement with sessions (time–session, $p = 0.13$) and no discernible effect of iTBS (treatment–session, $p = 0.49$; treatment–session–time, $p = 0.57$).

Bradykinesia. Sequential hand and arm movements became faster (time, $p < 0.001$ "on" and "off"), but no effect of iTBS could be discerned in "on" or "off" state (treatment, $p = 0.26$ and $p = 0.45$; treatment–time, $p = 0.71$ and $p = 0.16$). Movement time decreased after every intervention session (table e-2, session, $p = 0.001$) to a similar extent (time–session, $p = 0.40$) without difference between groups (treatment–session, $p = 0.12$; treatment–session–time, $p = 0.73$).

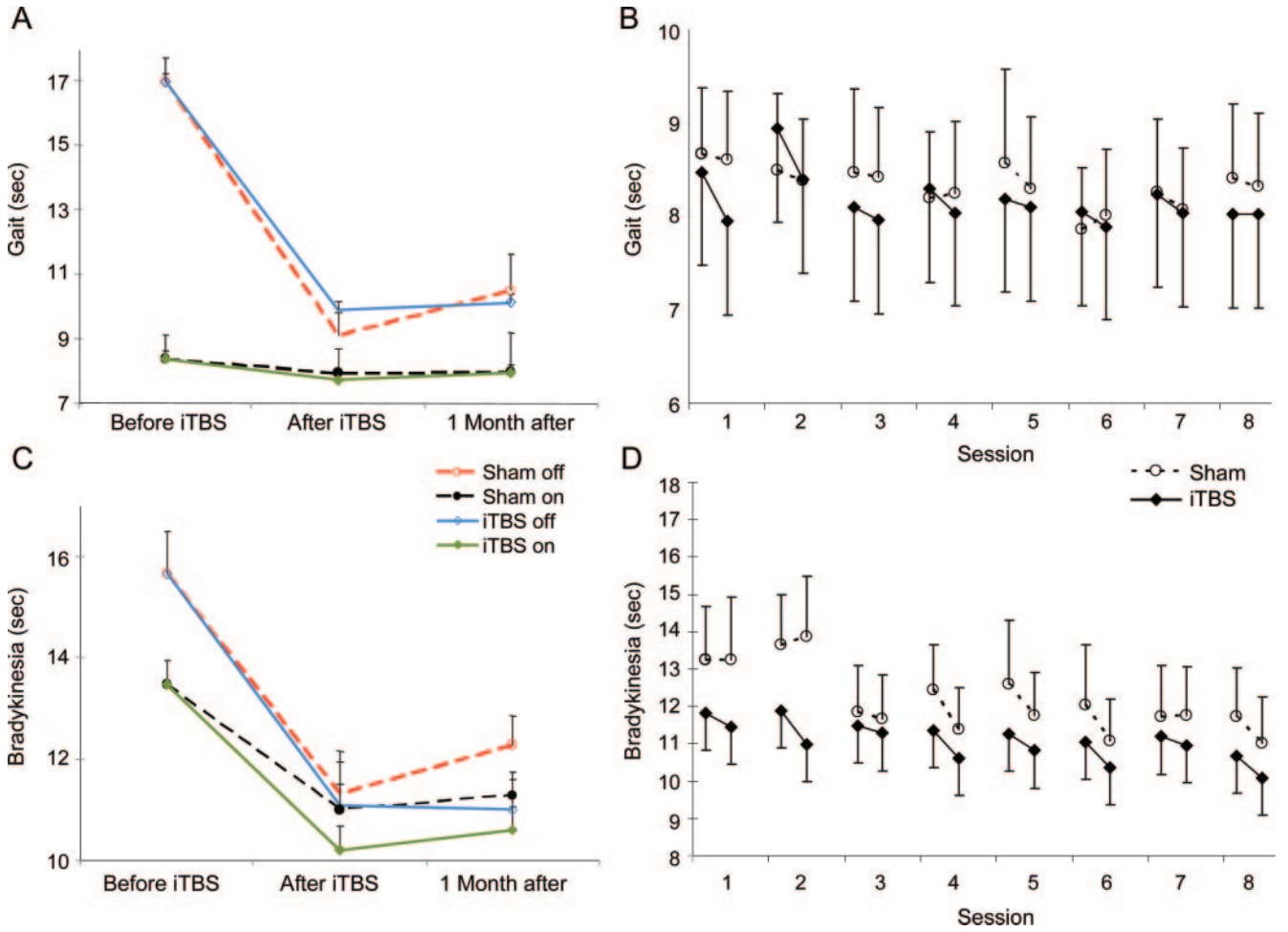
UPDRS. The iTBS had no effects on UPDRS scores in "on" and "off" state including motor examination (Table 3, part III; treatment, $p = 0.94$ and $p = 0.28$; treatment–time, $p = 0.30$ and $p = 0.18$), ADL (part II) (treatment, $p = 0.37$ and $p = 0.43$; treatment–time, $p = 0.41$ and $p = 0.27$), and total score (treatment, $p = 0.23$ and $p = 0.22$). But treatment–time interaction in total UPDRS score in the "off" state was significant ($p = 0.041$; "on" medication, $p = 0.22$). Post hoc tests revealed higher scores in the control group 1 month after the intervention ($p = 0.03$), which had increased compared to the first postintervention assessment ($p = 0.04$). This 1-month worsening in the control remains inconclusive, but disease progression seems improbable. There was a reduction in "on" and "off" state in total (time, both $p < 0.001$), motor (time, $p = 0.005$ and 0.001), and ADL-UPDRS scores (time, $p = 0.052$ and 0.012).

In the SRTT, reaction time (RT) shortened (time, $p = 0.002$) without differences between groups (treatment, $p = 0.92$ and treatment–time, $p = 0.33$). iTBS did not improve sequence-specific learning or learning rate (treatment, $p = 0.09$ and $p = 0.67$; treatment–time, $p = 0.18$ and $p = 0.22$).

iTBS lowered depression scores (treatment–time, $p = 0.013$), but this effect disappeared at 1 month (treatment, $p = 0.24$). iTBS had no effects on mental (treatment, $p = 0.43$; treatment–time, $p = 0.18$) and physical well-being (treatment, $p = 0.15$; treatment–time, $p = 0.21$).

Neurophysiology. At baseline, groups had similar RMT and AMT (%, 60 ± 9.7 vs 64.7 ± 9.3 and 48.8 ± 7.7 vs 49.3 ± 6.5) and MEP amplitudes ($p = 0.43$). Rest and active MEP recruitment curves and CSP were similar ($p = 0.93$, 0.89, and 0.23) in "on" and "off" state ($p = 0.91$, 0.21, and 0.31).

Figure 2 Gait and sequential hand and arm movement time



(A) Gait time before, 1 day and 1 month after the last intervention (least squares means ± standard errors following adjustment for the covariate). 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 intermittent theta-burst stimulation (iTBS) (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 iTBS (n = 13) and the dashed lines and open circles the sham group (n = 13). (C) Sequential hand and arm movement test before, 1 day and 1 month after the last intervention (least squares means ± standard errors following adjustment for the covariate). 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 iTBS (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) 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 iTBS (n = 13) and the dashed lines and open circles the sham group (n = 13).

iTBS increased MEP amplitudes after the first intervention (treatment, $p = 0.01$), but had no effects on rest and active MEP recruitment curves or on CSP after first (treatment, $p = 0.93$, 0.87, and 0.73) and 24 hours after eighth intervention (treatment, $p = 0.54$, 0.89, and 0.94). In both recruitment curves, MEP amplitudes increased with stimulation intensity in all conditions ($p < 0.001$).

DISCUSSION This double-blind, randomized, sham-controlled study investigated iTBS for the treatment of gait and bradykinesia in PD. Principal findings are that repeated iTBS of motor and prefrontal cortices appeared safe and improved mood, but had no effects on motor symptoms or functional status. In particular, iTBS did not improve gait, which was the primary objective. Participants shortened their walking time, but this probably resulted from familiarization with the test setting. This contrasts to gait improvement by 25 Hz rTMS with the same coil and targets[3] that provided the rationale for the current study. The question arose whether stimulation of the leg area might be superior. Yet clinical efficacy of 25 Hz rTMS in 2 RCTs was comparable,

Table 2 Gait and sequential hand and arm movement time (mean ± SD [least squares]) at baseline, 1 day, and 1 month after the last iTBS and sham intervention

Timed tests	$tDCS_{sham}$	Baseline	1 day after last intervention	1 month after last intervention	Treatment[a]	Treatment × time[a]	Time[b]	Effect size (Cohen *d*)
Gait	"On"	8.35 ± 1.98	7.68 ± 2.02	7.91 ± 2.03	0.85	0.61	0.005	0.33
		8.41 ± 1.98	7.96 ± 2.02	8.01 ± 2.03				
	"Off"	25.84 ± 26.1	10.88 ± 3.81	12.32 ± 7.65	0.67	0.43	0.09	0.26
		8.80 ± 25.0	8.20 ± 3.66	8.46 ± 7.35				
Bradykinesia	"On"	13.69 ± 5.33	10.32 ± 3.48	10.74 ± 3.76	0.26	0.71	<0.001	0.50
		13.25 ± 5.33	10.88 ± 3.48	11.13 ± 3.76				
	"Off"	17.23 ± 8.10	11.64 ± 4.19	11.72 ± 4.21	0.45	0.16	<0.001	0.09
		14.20 ± 7.78	10.80 ± 4.03	11.62 ± 4.05				

Abbreviation: iTBS = intermittent theta-burst stimulation; tDCS = transcranial direct current stimulation
[a] Analysis of covariance.
[b] Analysis of variance.

suggesting wider spread stimulation of the circular coil[3] may offset focal stimulation of leg and hand area,[5] and an investigation of 10-Hz rTMS targeting left DLPFC and/or M1 leg area for treatment of freezing of gait (FOG) was prematurely terminated because of inefficacy.[10] An interesting observation was that severe FOG in the "off" state was no longer seen in the postinterventional assessments. Since FOG is often refractory, any potential therapy raises interest. But the self-reported UPDRS freezing score could not substantiate a particular effect. Since we had focused on speed and the unpredictable nature of freezing complicates evaluation, we may have missed this and other qualitative changes in gait. Gait disturbances in PD arise from various pathogeneses that might respond differently to rTMS.

iTBS had no effects on bradykinesia, either, but movements became faster. This most plausibly results from motor learning through repeated testing, providing another rationale for controlled studies. In contrast to transcranial direct current stimulation, iTBS did not enhance motor learning.[11]

iTBS improved mood, but this effect appeared short-lived and selective since mental and physical well-being remained unchanged. In PD, repeated high-frequency rTMS of the left DLPFC has been found comparable to antidepressants.[12] Thus, iTBS of DLPFC, probably less of M1, improved mood in line with rTMS trials, indicating efficacy against major depression that led to Food and Drug Administration approval.

The lack of cumulative effects on walking and bradykinesia with repeated interventions contrasts with RCT of high-frequency rTMS.[3-5] Methodologic differences limit comparability, but changes in UPDRS motor score in various trials yielded a larger effect size of conventional rTMS[2] than iTBS. This raises questions about different stimulation protocols. Differences in coil geometry and shape of TMS pulse which determine waveform and current orientation appear not to influence effects on cortical excitability of iTBS.[13] A single controlled study in PD compared clinical efficacy of different rTMS frequencies finding superiority of 25-Hz over 10Hz-rTMS.[5] Thus, higher frequencies delivering more energy might increase efficacy. We powered this study assuming efficacy of iTBS in improving gait to be comparable to 25-Hz rTMS.[3] Yet even when investigating twice the number of patients required, we found no additional effect in the best "on" state this add-on intervention targeted.

The mechanisms of action of rTMS remain largely unknown. The discrepancy in effects suggests stimulation patterns might vary in their action. TBS has a biological rationale by imitating normal firing patterns in the hippocampus which is bolstered by the observation in animals that TBS induces long-term potentiation and depression which constitute mechanisms of plasticity.[6] iTBS transiently increased MEPs as in stroke,[14,15] but recruitment and cortical silent period remained unchanged. Silent period correlates with dopamine deficiency[16] and response to medication.[17] Since DBS[18] and rTMS[19-21] modulate silent period, they may act on dopaminergic circuits, but iTBS did not. Yet whether these neurophysiologic changes in M1 cause or result from clinical improvement remains unknown.

High-frequency rTMS of prefrontal and motor cortices causes striatal dopamine release,[22,23] also in PD,[24] and sham rTMS, indicating a possible placebo mechanism.[25] A similar mechanism in iTBS might underlie immediate postinterventional improvement, but could not be differentiated from the placebo response.

The failure of iTBS to produce persistent effects implies no changes in synaptic strength, basic mech-

Table 3 Secondary outcome measures (mean ± SD [least squares]) at baseline, 1 day, and at 1 month after the last iTBS and sham intervention

	$tDCS_{sham}$	Baseline	1 day after last intervention	1 month after last intervention	Treatment[a]	Treatment × time[a]	Time[b]	Effect size (Cohen *d*)
UPDRS total	"On"	55.54 ± 15.81	51.08 ± 16.37	53.15 ± 14.53	0.23	0.26	<0.001	0.67
		57.15 ± 15.81	47.62 ± 16.37	54.15 ± 14.53				
	"Off"	77.85 ± 17.05	70.85 ± 16.26	68.62 ± 16.78	0.22	0.04	<0.001	0.13
		65.92 ± 17.05	59.54 ± 16.26	64.69 ± 16.78				
UPDRS (III)	"On"	32.00 ± 12.86	29.08 ± 12.13	29.77 ± 11.47	0.94	0.30	0.005	0.31
		37.54 ± 12.86	32.31 ± 12.13	35.38 ± 11.47				
	"Off"	49.00 ± 12.88	43.92 ± 12.59	43.25 ± 10.74	0.28	0.18	0.001	0.04
		45.69 ± 12.38	41.31 ± 12.10	44.69 ± 10.32				
UPDRS (II)	"On"	13.92 ± 5.35	13.08 ± 5.20	13.69 ± 5.15	0.43	0.41	0.052	0.45
		13.92 ± 5.35	11.54 ± 5.20	13.31 ± 5.15				
	"Off"	24.92 ± 6.24	22.69 ± 6.15	22.46 ± 6.48	0.37	0.27	0.012	0.02
		16.77 ± 6.24	15.69 ± 6.15	16.46 ± 6.48				
UPDRS freezing	"On"	1.00 ± 0.88	1.08 ± 0.91	1.15 ± 0.93	0.23	0.71	0.94	0.39
		0.69 ± 0.88	0.62 ± 0.91	0.62 ± 0.93				
	"Off"	2.00 ± 1.06	1.92 ± 1.12	1.69 ± 1.15	0.89	0.11	0.23	0.54
		0.92 ± 1.06	0.62 ± 1.12	0.92 ± 1.15				
FAB		16.62 ± 1.56	17.15 ± 1.29	17.46 ± 0.87	0.36	0.23	0.034	0.08
		16.46 ± 1.56	17.00 ± 1.29	16.92 ± 0.87				
BDI		11.00 ± 6.75	6.67 ± 5.20	8.92 ± 5.69	0.24	0.013	0.279	0.94
		6.46 ± 6.48	7.92 ± 4.99	7.00 ± 5.46				
Mental health		47.46 ± 10.11	52.92 ± 8.70	50.35 ± 8.80	0.43	0.18	0.27	0.65
		52.27 ± 9.71	51.75 ± 8.36	52.88 ± 8.45				
Physical health		37.51 ± 9.95	36.28 ± 8.93	36.04 ± 9.39	0.15	0.21	0.58	0.38
		40.92 ± 9.56	40.42 ± 8.58	42.48 ± 9.02				
SRTT		705.84 ± 96.59	669.0 ± 93.94	677.27 ± 109.6	0.92	0.33	0.002	0.24
		736.58 ± 101.3	685.9 ± 98.53	718.90 ± 114.9				

Abbreviations: BDI = Beck Depression Inventory; FAB = Frontal Assessment Battery; iTBS = intermittent theta-burst stimulation; SRTT = Serial Reaction Time Task; tDCS = transcranial direct current stimulation; UPDRS = Unified Parkinson's Disease Rating Scale (part II, activities of daily living; part III, motor examination; freezing, UPDRS II, item 14, freezing when walking).

[a] Analysis of covariance.

[b] Analysis of variance.

anism of plasticity, were induced. Cortical physiology is altered in PD, but 1-Hz rTMS,[26] 5-Hz rTMS,[27] and paired associative stimulation[28] demonstrated preserved plasticity. Brain-derived neurotrophic factor (BDNF) polymorphism may influence synaptic plasticity in iTBS and continuous TBS (cTBS).[29] BDNF might contribute to the development of dyskinesias[30] due to its role in plasticity, postulated to be maladaptive in dyskinesias.[28] Nevertheless, cTBS of the cerebellum persistently reduced dyskinesias, indicating preserved plasticity,[31] but effects of cortical and cerebellar stimulation might differ. There were no differences in motor learning following repeated testing or in (absent) iTBS effects that would suggest an altered plasticity in dyskinesias or that preponderance of dyskinesias in the treatment group might have compromised our results.

Safety concerns limit clinical applicability of rTMS, and safety of iTBS was not yet investigated. Applying the same methodology reliably determining safety of 50-Hz rTMS,[8] iTBS appeared safe.

Participants' reports and robust placebo response suggested blinding was maintained, facilitated by TMS naïvety 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 has limitations. Time commitment might have biased patient selection, but only few contacted declined, mostly for professional reasons. No patient was lost, and outcome would probably

not have changed since those 2 excluded were in the sham group. Random assignment had not prevented some heterogeneity between groups. Since we assessed patients during best response and withdrawal state, confounding effects of fluctuations and medication may be minimal. The statistical model also corrected for baseline differences.

This study fails to provide evidence for a therapeutic potential of iTBS in PD, but these findings cannot be extrapolated to other brain disorders and rTMS protocols since pathophysiology and mechanisms of action remain incompletely understood.

AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by David A. Luckenbaugh and Dr. David H. Benninger.

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