

Slow (1 Hz) repetitive transcranial magnetic stimulation (rTMS) induces a sustained change in cortical excitability in patients with Parkinson's disease

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ABSTRACT

Objective: Low-frequency (≤ 1 Hz) rTMS (LF-rTMS) can reduce excitability in the underlying cortex and/or promote inhibition. In patients with Parkinson's disease (PD) several TMS elicited features of motor corticospinal physiology suggest presence of impaired inhibitory mechanisms. These include shortened silent period (SP) and slightly steeper input–output (I–O) curve of motor evoked potential (MEP) size than in normal controls. However, studies of LF-rTMS effects on inhibitory mechanisms in PD are scarce.

Objective: In this companion paper to the clinical paper describing effects of four consecutive days of LF-rTMS on dyskinesia in PD (Filipović et al., 2009), we evaluate the delayed (24 h) effects of the LF-rTMS treatment on physiological measures of excitability of the motor cortex in the same patients. There are very few studies of physiological follow up of daily rTMS treatments.

Methods: Nine patients with PD in Hoehn and Yahr stages 2 or 3 and prominent medication-induced dyskinesia were studied. This was a placebo-controlled, crossover study, with two treatment arms, “real” rTMS and “sham” rTMS (placebo). In each of the treatment arms, rTMS (1800 pulses; 1 Hz rate; intensity of the real stimuli just-below the active motor threshold) was delivered over the motor cortex for four consecutive days. Motor cortex excitability was evaluated at the beginning of the study and the next day following each of the four-day rTMS series (real and sham) with patients first in the practically defined “off” state, following 12 h withdrawal of medication, and subsequently in a typical “on” state following usual morning medication dose.

Results: The SP was significantly longer following real rTMS in comparison to both baseline and sham rTMS. The effect was independent from the effects of dopaminergic treatment. There was no difference in MEP size, rest and active motor threshold. The I–O curve, recorded from the relaxed muscle, showed a trend towards diminished slope in comparison to baseline, but the difference was not significant. There was no consistent correlation between prolongation of SP and concomitant reduction in dyskinesia following real rTMS.

Conclusions: Low-frequency rTMS delivered over several consecutive days changes the excitability of motor cortex by increasing the excitability of inhibitory circuits. The effects persist for at least a day after rTMS.

Significance: The results confirm the existence of a residual after-effect of consecutive daily applications of rTMS that might be relevant to the clinical effect that was observed in this group of patients and could be further exploited for potential therapeutic uses.

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1. Introduction

A number of studies have shown that rTMS can modulate the excitability of the motor cortex beyond the period of stimulation.

Increased excitability usually occurs if higher frequencies (above 5 Hz) are used (Pascual-Leone et al., 1994), while decreases in excitability have been shown not only in the motor cortex, but also in the visual cortex, if low-frequency (≤ 1 Hz) trains are given for 5 min or more (Chen et al., 1997; Boroojerdi et al., 2000; Cantello et al., 1991; Maeda et al., 2000; Muellbacher et al., 2000). The mechanism involved is not known, but the stimulation rate is similar to that producing long-term depression in animal studies (reviewed in Post et al., 1999; and Ziemann, 2004). In addition, the

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effects of rTMS are not restricted only to the point of stimulation, but can be also detected at distant though connected sites within the same functional circuit both at cortical and subcortical levels (Fox et al., 1997; Gerschlagler et al., 2001; Siebner et al., 2003).

There are reports of a beneficial clinical effect of low-frequency rTMS (LF-rTMS) on diseases with increased cortical excitability such as focal hand dystonia (Siebner et al., 1999, 2003) and epilepsy (Tergau et al., 1999; Fregni et al., 2006). There is also evidence that the physiological effect in patients may even be stronger than that seen in healthy subjects (Siebner et al., 1999, 2003). In patients with Parkinson's disease (PD) several TMS elicited features of motor corticospinal physiology suggest that inhibitory mechanisms are impaired. These include shortened silent period (SP) and slightly steeper input–output (IO) curves of motor evoked potential (MEP) size than in normal controls – changes that are typically ameliorated by levodopa/dopaminergic medication in concert with relief of clinical symptoms (reviewed in Cantello et al., 2002; and Lefaucheur, 2005).

We have recently reported a beneficial clinical effect of LF-rTMS on medication-induced dyskinesia in PD (Filipović et al., 2009). As a part of that study we also recorded neurophysiological parameters of cortical excitability. This provided an opportunity to test whether in a group of patients with a condition characterized by reduced cortical inhibition, LF-rTMS applied over motor cortex for several consecutive days is able to induce a sustained and measurable change in the excitability of the motor cortex and in particular increase the excitability of inhibitory mechanisms.

2. Methods

2.1. Design of study

This was a placebo-controlled, single-blinded, crossover study, with each treatment arm lasting 1 week, and each period of treatment separated by a minimum of 2 weeks (Fig. 1). The two treatment arms consisted of four successive daily visits (from Monday to Thursday) each, when either “real” rTMS or “sham” rTMS (placebo) were delivered. The same type of rTMS was used throughout successive 4 days and the order of the treatments was randomly assigned. The time of day for treatment visits was kept constant for each patient.

The baseline evaluation session ($e0$) was during a week preceding the first treatment session. The treatment evaluation sessions ($e1$ and $e2$) were on the first Friday after the end of the each rTMS series (i.e. next day after the last rTMS session of each series),

respectively. At each evaluation session, a set of clinical and neurophysiological tests was carried out with patients in so called practically defined “off” state, following at least 12 h (overnight) refrain from anti-parkinsonian medication. Following this, a second set of tests was carried out once patients achieved a stable “on” state, after taking their usual morning medication dose. Since the study was designed to test the effect of rTMS on medication-induced dyskinesia in Parkinson's disease, each evaluation visit also included a clinical assessment. Patients were examined using Unified PD Rating Scale (UPDRS) Motor Section (Part 3). In addition, in the “on” state, dyskinesias were rated off-line from videotapes using the Clinical Dyskinesia Rating Scale (CDRS) developed by Hagell and Widner (1999). The most severe involuntary movements observed are scored from 0 (none) to 4 (extreme), in each of the seven body areas: face, neck, trunk, and four extremities, separately for hyperkinesias (i.e., choreic movements) and dystonia. The clinical results have been already published (Filipović et al., 2009). Sessions were always organised in the morning hours at the earliest convenience to the patient.

2.2. Patients

Nine right-handed, non-demented patients with idiopathic PD, satisfying United Kingdom Parkinson's Disease Society Brain Bank criteria (Gibb and Lees, 1988), manifesting obvious dyskinesias present most of the day were studied. They were recruited through the outpatient department of the Frenchay Hospital (Bristol, UK). All patients were on the fixed dose of their usual anti-parkinsonian medication for at least 1 month prior to starting the study until the end of the study. Informed consent was obtained from each patient according to the Declaration of Helsinki, and study protocol was approved by the Frenchay Local Research Ethics Committee. The details of patients' characteristic are presented on Table 1. They were essentially the same patients as in Filipović et al. (2009) paper, but without one patient whose neurophysiological data had to be discarded because inability to relax adequately due to excessive dyskinesias in the “on” phase.

2.3. Transcranial magnetic stimulation (TMS)

All transcranial magnetic stimulations, either single or repetitive, were performed with Magstim Rapid Transcranial Magnetic Stimulator (Magstim Company, Dyfed, UK). For “real” TMS a standard Magstim's 70 mm figure-of-eight coil was used. The “sham” rTMS was carried out with Placebo Coil (Magstim Company) that

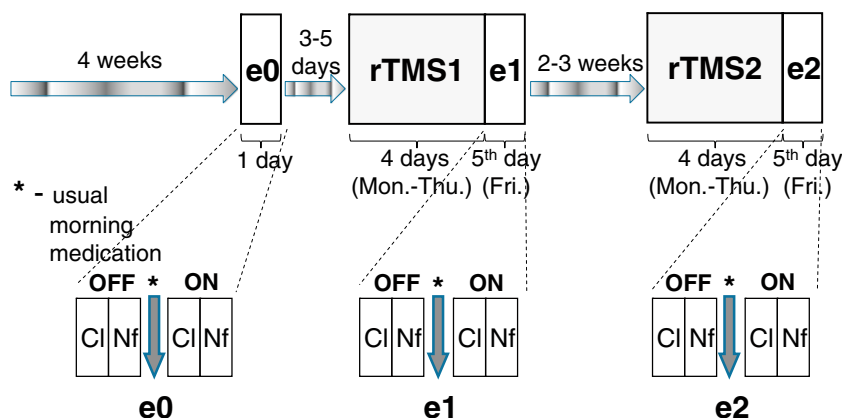


Fig. 1. Design of the study. The rTMS, either real or sham (placebo), was delivered in two four-day (from Monday to Thursday) long series (rTMS1 and rTMS2). Within a week before the first rTMS treatment series, the first/baseline evaluation session ($e0$) was scheduled. Subsequent evaluation sessions ($e1$ and $e2$) were on the next day after the last rTMS session (i.e. Friday) of the each rTMS series, respectively. At each evaluation session, two identical sets of clinical (Cl) and neurophysiological (Nf) tests were carried out, first with patients in practically defined “OFF” state, and then once patients achieved a stable “on” state, after taking their usual morning medication dose.

Table 1
Patients' characteristics.

Pt	Gender	Age (years)	PD duration (years)	Type	UPDRS III OFFMED ^a	UPDRS III ONMED ^a	CDRS score ^a	Worst side	Morning medication (mg; l-dopa equivalent) ^b	Total daily medication (mg; l-dopa equivalent) ^b
1	M	66	8	AR	31	16	15	L	350	1150
2	F	48	8	AR&T	32	11	9	R	350	650
3	F	71	22	T&AR	63	23	23	R	100	600
4	F	73	18	T&AR	50	33	33	L	100	700
5	M	48	16	T&AR	60	12	26	R	300	900
6	F	61	17	AR&T	49	22	20	L	100	600
7	M	64	16	AR	40	24	10	R	250	1400
8	M	71	11	AR	37	11	24	L	325	850
9	M	69	14	AR	42	19	28	L	200	950

M – male, F – female, AR – akinetic-rigid, T – tremor, UPDRS III – Unified Parkinson's Disease Rating Scale Part 3 (Motor Score); CDRS – Clinical Dyskinesia Rating Scale, OFFMED – off medication, ONMED – on medication, R – right, L – left.

^a At baseline evaluation.

^b Anti PD medication dosage is expressed as levodopa equivalent following published formulas: 1 mg pergolide = 1.05 mg pramipexole = 6 mg ropinirole = 1.5 mg cabergoline = 100 mg levodopa (Grosset et al., 2004).

looked the same and gave similar skin sensation and noise as a “real” coil but no effective magnetic field was generated. The hemisphere contralateral to the more severely affected side was target in all cases.

2.3.1. Neurophysiological assessment of cortical excitability

Cortical excitability was evaluated using single-pulse TMS. The target muscle was the first dorsal interosseous muscle (FDI). At the beginning of each experiment the optimal scalp site (“hot-spot”) and the resting motor threshold (rMT) for FDI were determined following a standard procedure (Rossini et al., 1994). The coil position was marked on the head and its coordinates on midsagittal (nasion–inion line) and biauricular (line connecting external auditory meati) axes in relationship to the vertex were recorded. In order to ensure consistent positioning of the coil throughout the experiment the same coordinates were used in further sessions. The hot-spot and MT finding procedures were replicated at each first treatment session (Mondays) and each evaluation session (Fridays) to check for consistency of coil positioning and MT changes following investigated procedures, respectively. No differences in hot-spot position were found at any of these occasions.

Neurophysiological testing was carried out first with FDI in complete rest. Ten stimuli were delivered at TMS intensities of 110%, 120%, 130%, and 150% rMT, each. Next, participants were asked to maintain voluntary contraction during TMS delivery. Series of ten stimuli of 120% rMT intensity were delivered during each of three different levels of background contraction – ‘mild’, ‘moderate’, and ‘maximal’. With the help of a custom made visual feedback device, participants were asked to maintain contraction of target FDI muscle either at 20–30% of the maximal voluntary contraction (MVC) strength (‘mild’ condition), 50–60% MCV (‘moderate’), or 90–100% MCV (‘maximal’). The MVC was determined beforehand and subjects trained to maintain required levels of contraction.

The peak-to-peak amplitude of each MEP was measured and the mean MEP amplitude was calculated separately for each condition. Also, in the conditions with voluntary contraction, the “silent-period” (SP) offset latency was measured from single traces and then averaged for each condition. The SP offset latency was determined as either the latency of the onset of a burst of EMG activity reaching at least 75% of the pre-stimulus background activity and lasting at least 20 ms, or the latency of the onset of continuous EMG activity.

2.3.2. Low-frequency rTMS

During LF-rTMS three series of 600 stimuli of 1 Hz rate, with one-minute breaks in between, were applied during each session

(1800 stimuli in total, duration 32 min). Stimulation variables were in accordance with published safety recommendations (Wassermann, 1998). The intensity was set individually to be just below active motor threshold (aMT). The aMT was determined with the target muscle maintaining 20% of the maximal voluntary contraction (MCV) strength and was defined as the minimum stimulator intensity capable to evoke a MEP of 200–300 μ V in amplitude at least in 50% of 10 consecutive trials (Rothwell et al., 1999). The aMT values were typically equal or below the 90% of resting motor threshold (rMT).

2.4. Data analysis

From recorded data several outcome measures were derived: rest and active motor thresholds (rMT and aMT), rest MEP (measured with 120% rMT TMS intensity), MEP input–output (I–O) curve (MEPs measured with TMS intensities of 110%, 120%, 130%, and 150% rMT, with FDI muscle at rest), MEP facilitation with voluntary contraction, and silent period (SP). For the later two, voluntary MEP facilitation and SP, the results were analysed in relationship to the level of the background muscle contraction (measured as mean of rectified EMG for 50 ms interval before TMS pulse) regardless of the exact instruction set during which the measurement was made. The levels of the background muscle contraction were grouped into three levels: mild (10–33% of the maximal voluntary contraction (MCV)), moderate (34–66% MCV) and strong (67–100% MCV).

Data were analysed two-fold in a pair-wise fashion. Results obtained after one of the rTMS interventions (i.e. either real or sham) were first compared with results at baseline, and then with each other. For statistical assessment two-way and three-way repeated-measures analyses of variance (ANOVA) were used with factors rTMS type (real vs. sham) and dopaminergic treatment status (off vs. on medication, OFFMED and ONMED, respectively), as well as TMS intensity or level of background contraction, where appropriate. Results were considered as significant if $P < 0.05$. Given that comparisons with baseline were planned hypothesis-driven, i.e. we wanted to check whether 1 Hz rTMS could promote inhibitory mechanism manifested by shortening of SP and/or diminution of MEP, one-tailed directional probability was used. In contrast, since there was a possibility for a placebo effect of sham stimulation mimicking the expected effect of real stimulation, no reliable hypothesis could be formed whether TMS variables would be in any way different following real and sham rTMS, and thus for real vs. sham comparisons two-tailed non-directional probability was used.

Due to the non-parametric nature of clinical measures used, correlations between clinical and neurophysiological data were

carried out using non-parametric Spearman's rank order correlation method with significance set at $P < 0.05$ level. Given that this was an exploratory study, no adjustments for multiple measurements were applied.

3. Results

Questioned at the end of their participation in the study, none of the patients were able to identify which type of rTMS (i.e. whether real or sham) was delivered in each of the treatment sessions.

3.1. Neurophysiology data

3.1.1. Motor thresholds

There was no difference in rMT across all conditions regardless whether recorded on or off medication and at baseline or after real or sham rTMS (Table 2). Equally, there was no difference in aMT across all conditions (Table 2).

3.1.2. MEP at rest and during voluntary activation

MEP at rest in OFFMED condition was slightly lower after real rTMS than it was at baseline and after sham rTMS, while in ONMED condition there was no obvious difference (Fig. 2, Table 2). The data were analysed by two-way repeated measures ANOVA with factors *rTMS type* (i.e. baseline vs. real or sham, and real vs. sham), and *medication status* (i.e. OFFMED vs. ONMED). No significant effect of any of the two factors and their interactions was found for any of the comparisons ($F(1,8) < 1.00$, $P > 0.1$, in all cases). Only for baseline vs. real rTMS comparison the effect of *rTMS type* ($F(1,8) = 2.63$) was slightly stronger ($P = 0.072$), while post-hoc least-square difference (LSD) pair-wise test showed as significant ($P = 0.03$) baseline vs. real rTMS difference in MEP in OFFMED phase.

MEP facilitation during various levels of voluntary contraction was analysed by three-way repeated measures ANOVA with fac-

tors *rTMS type*, *medication status*, and *contraction level* (i.e. rest vs. mild vs. moderate vs. strong). MEP recruitment curves showed no major differences regardless of the medication status and whether recorded at baseline or after either real or sham rTMS type (Fig. 2, Table 3). Only *contraction level* and interactions between all three factors had significant effect in all pair-wise comparisons due to significant differences between MEP size at rest and MEP sizes at all three levels of contraction and between MEP size at mild contraction and MEP sizes at moderate and strong contractions; there was no significant difference between MEP sizes at moderate and strong contractions.

3.1.3. I–O curve

In the OFFMED condition, the I–O curve following real rTMS was slightly less steep than at baseline or after sham rTMS (Fig. 3). We did not formally calculate the slope but the I–O curves were analysed by three-way repeated measures ANOVAs (Table 3) with factors *rTMS type*, *medication status*, and *test TMS intensity level* (i.e. 110% vs. 120% vs. 130% vs. 150% rMT). When baseline and real rTMS were compared, the *rTMS type* and interaction of all three factors showed an effect of borderline significance (for both, $P = 0.05$), and in particular MEP sizes at 120% rMT and 130% rMT intensities off medication, and at 150% rMT on medication were significantly smaller (Post-hoc LSD test, $P = 0.03$, 0.007, and 0.03, respectively). No other comparison showed significant effects.

3.1.4. Silent period

In one patient silent period (SP) could not be reliably determined due to excessive rest tremor in off condition. Therefore, analyses were carried out on data from eight patients (Fig. 4, Table 3). The SP was analysed by three-way repeated measures ANOVA with factors *rTMS type*, *medication status*, and *contraction level*. As expected, SP was longer in ONMED than in OFFMED condition. In addition, level of background contraction had significant effect as well; the SP was progressively shorter with higher levels of

Table 2

Motor thresholds at rest (rMT) and during activation (aMT), and MEP size at rest (values are presented as mean \pm SD), in OFFMED and ONMED state.

	Baseline		real rTMS		sham rTMS	
	OFFMED	ONMED	OFFMED	ONMED	OFFMED	ONMED
rMT ^a	48.7 \pm 9.8%	50.6 \pm 10.7%	49.0 \pm 8.7%	49.1 \pm 8.6%	49.2 \pm 8.5%	49.3 \pm 8.5%
aMT ^a	43.7 \pm 7.8%	43.6 \pm 7.7%	43.2 \pm 8.0%	43.0 \pm 7.9%	43.4 \pm 7.7%	43.6 \pm 7.7%
MEP ^b	422.3 \pm 307.0	349.7 \pm 244.9	283.2 \pm 111.2 ^c	300.5 \pm 155.0	410.6 \pm 244.7	377.9 \pm 245.6

^a Motor threshold values are percentages of the stimulator output.

^b MEP amplitudes are expressed in μ V.

^c Significant ($P < 0.05$) difference vs. baseline/OFFMED (post-hoc least-square difference (LSD) pair-wise test).

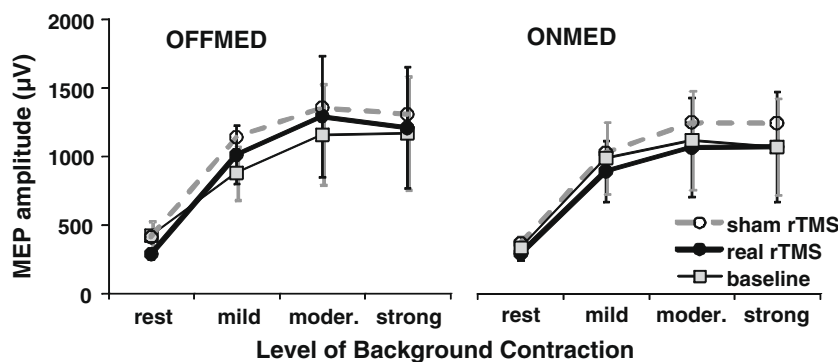
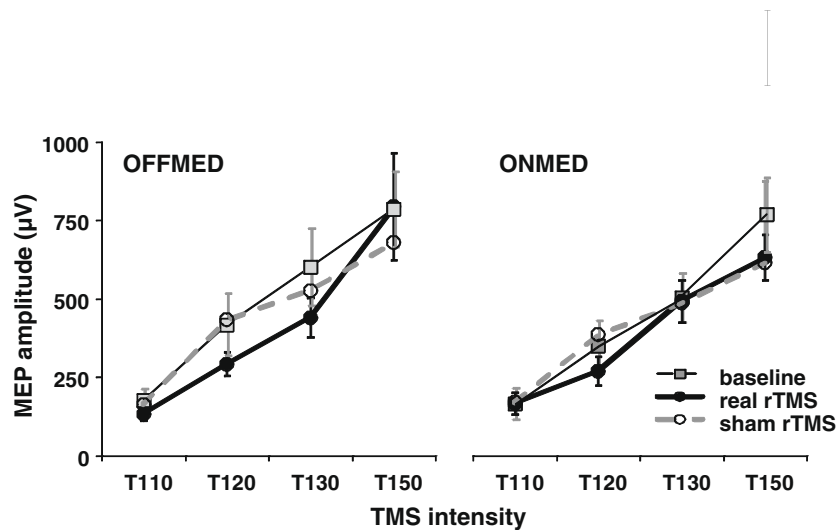


Fig. 2. MEP facilitation during various levels of voluntary contraction. Presented are group means with standard errors. Slightly lower MEP size can be seen at rest following real rTMS in ONMED condition. No major difference and large overlaps between responses at baseline and following both real and sham rTMS can be seen in MEP sizes recorded with different levels of background contraction.

Table 3

Results of ANOVAs on silent period (SP), MEP facilitation with voluntary muscle contraction, and input–output (IO) MEP curve.

	Factors			Interactions			
	rTMS type (1)	on/off state (2)	Muscle contraction (3)	1 × 2	1 × 3	2 × 3	1 × 2 × 3
<i>SP</i>							
Baseline vs. real rTMS	F = 3.728 P = 0.047	F = 9.631 P = 0.009	F = 26.248 P < 0.001	F = 0.339 P = 0.289	F = 4.624 P = 0.014	F = 1.281 P = 0.154	F = 2.922 P = 0.043
Baseline vs. sham rTMS	F = 1.448 P = 0.134	F = 19.162 P = 0.002	F = 21.802 P < 0.001	F = 0.381 P = 0.278	F = 0.210 P = 0.406	F = 4.662 P = 0.014	F = 1.477 P = 0.131
Real rTMS vs. sham rTMS	F = 7.318 P = 0.030	F = 10.286 P = 0.015	F = 32.246 P < 0.001	F = 0.010 P = 0.924	F = 1.102 P = 0.360	F = 4.271 P = 0.036	F = 1.850 P = 0.194
<i>MEP facilitation</i>							
Baseline vs. real rTMS	F = 0.004 P = 0.475	F = 0.735 P = 0.208	F = 4.598 P = 0.006	F = 2.298 P = 0.084	F = 0.784 P = 0.257	F = 1.007 P = 0.203	F = 4.678 P = 0.005
Baseline vs. sham rTMS	F = 2.167 P = 0.090	F = 0.186 P = 0.339	F = 4.073 P = 0.009	F = 0.745 P = 0.207	F = 1.183 P = 0.168	F = 0.609 P = 0.308	F = 2.371 P = 0.048
Real rTMS vs. sham rTMS	F = 1.364 P = 0.276	F = 3.800 P = 0.087	F = 4.185 P = 0.016	F = 0.704 P = 0.426	F = 0.047 P = 0.986	F = 1.764 P = 0.181	F = 1.251 P = 0.313
<i>IO MEP</i>							
			(TMS intensity [3])				
Baseline vs. real rTMS	F = 3.375 P = 0.052	F = 0.721 P = 0.210	F = 25.614 P < 0.001	F = 0.064 P = 0.403	F = 0.728 P = 0.273	F = 1.248 P = 0.157	F = 2.278 P = 0.053
Baseline vs. sham rTMS	F = 0.178 P = 0.342	F = 0.497 P = 0.250	F = 46.203 P < 0.001	F = 0.084 P = 0.389	F = 1.981 P = 0.072	F = 0.476 P = 0.351	F = 0.666 P = 0.290
Real rTMS vs. sham rTMS	F = 0.151 P = 0.707	F = 1.069 P = 0.331	F = 37.590 P < 0.001	F = 0.028 P = 0.871	F = 1.680 P = 0.198	F = 2.462 P = 0.087	F = 0.926 P = 0.443

Significant ($P < 0.05$) results are presented in bold.**Fig. 3.** Input–output (I–O) curves. Presented are group means with standard errors. Lower MEP sizes can be seen following real rTMS in responses recorded with single-pulse TMS intensities of 120% and 130% of rMT.

background contraction. The interaction between the two factors was also significant although not for baseline vs. real rTMS.

Following real rTMS the SP was significantly longer than both at baseline and following sham rTMS and the effect was independent of medication status while showing some interaction with contraction levels but only for baseline vs. real rTMS comparison (Table 3). Post-hoc pair-wise LSD test (with all three factors) showed as significant baseline vs. real rTMS difference at mild, moderate, and strong levels of contraction in OFFMED condition ($P = 0.00002$, 0.00005 , and 0.01 , respectively), and at mild and strong levels of contraction in ONMED condition ($P = 0.00005$ and 0.0015 , respectively). For real vs. sham rTMS comparison, the difference was significant at mild and moderate levels of contraction in OFFMED condition ($P = 0.004$ and 0.029 , respectively), and at mild and strong levels of contraction in ONMED condition ($P = 0.029$ and 0.034 , respectively). No significant effect of order of rTMS series

(i.e. whether real or sham was first) on SP prolongation following real rTMS in comparison to baseline was found. This was tested by the Mann–Whitney U test for each of the medication states and contraction levels separately.

3.1.5. Clinical variables – neurophysiology interaction

Patients reported no side effects following rTMS. As already reported (Filipović et al., 2009), rTMS did not have any adverse effects on patients' motor functions and other PD symptoms – total UPDRS score and Motor Section score (both in ON phase) did not differ after real and sham rTMS.

As it was reported (Filipović et al., 2009), following real rTMS, scores on dyskinesia scale (CDRS) changed significantly in comparison to the baseline while following sham rTMS the change was not significant. However, on direct comparison, difference in CDRS scores following real and sham rTMS although obvious was not sig-

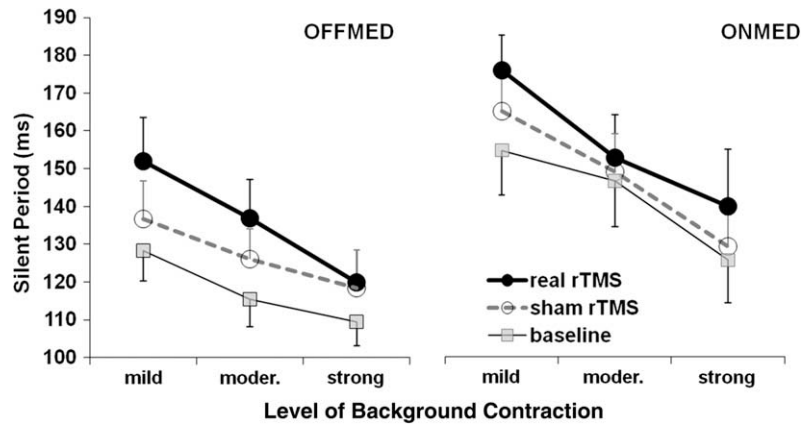


Fig. 4. Silent period during various levels of voluntary contraction. Presented are group means with standard errors. Longer SP duration can be seen following real rTMS in responses recorded with different levels of background contraction in both OFFMED and ONMED conditions.

nificant. Following real rTMS mean relative reduction in CDRS scores in comparison to baseline in the subpopulation of patients whose SP data were reported in this study ($N = 8$) was 8.0% (SD 7.9), which was in keeping with the reduction reported for the whole group ($N = 10$, 8.3%, SD 8.3; Filipović et al., 2009). In comparison to baseline, seven patients had reduced CDRS scores following real rTMS and in one the score was unchanged.

In order to check whether any clinical factors influenced SP measurements in this study, correlations were analysed between selected SP variables and relevant clinical variables. The SP variables were SP offset latencies at baseline and the SP offset latency change following real rTMS (calculated as a difference between measurements after real rTMS and at baseline), for all three levels of contraction. The clinical variables were age, duration of disease, UPDRS scores off and on medication at baseline, CDRS scores at baseline, and medication level (total daily levodopa equivalents). The only consistent correlation was between UPDRS scores on medication and SP offset latencies at baseline (Table 4). The higher the UPDRS scores, the later the SP offset. The correlations were significant for mild and moderate levels of background contraction for SP offset latencies measured both in off and on medication states. There were two further isolated correlations as well. Duration of the disease correlated with SP offset latency at baseline in off medication state when the background contraction was moderate. The SP offset latency change following real rTMS correlated negatively with the amount of total daily medication. Furthermore, correlations were analysed between mentioned SP variables, on one side, and CDRS scores following real rTMS and the change in CDRS

scores between baseline and post-real rTMS, on the other side (Table 4). Only one isolated correlation was found to be significant. The SP offset latency change following real rTMS, in on medication state when the background contraction was mild, correlated with the change in CDRS scores between baseline and post-real rTMS.

4. Discussion

The key finding of this study is that, in PD patients, low-frequency rTMS delivered for four consecutive days increases motor corticospinal inhibition as indexed by a significant prolongation of the SP and a trend towards a diminished slope of the MEP I–O recruitment curve, which are detectable 24 h after the last rTMS delivery. As far as we are aware, this is first demonstration of such an extended effect of rTMS on cortical excitability in PD.

Traditionally, cortical excitability is measured as either the resting motor threshold (rMT) or motor evoked potential (MEP) size (reviews in Pascual-Leone et al., 1998; and Fitzgerald et al., 2002a). The effect of 1 Hz rTMS on rMT level in healthy subjects was assessed in several studies (reviewed in Fitzgerald et al., 2006). Most of them reported no change which is in keeping with the results of this study.

Most of the studies investigating post-train effects of low-frequency stimulation found that it reduced MEP size (amplitude, area or recruitment curve) (reviewed in Fitzgerald et al., 2006). However, the effect appears to be intensity related; almost all studies providing stimulation at relatively low stimulation intensities (85–90% of rMT or 90% of active MT), comparable with intensities

Table 4

Results of Spearman Rank Order Correlation test for correlations between SP offset latency and clinical variables. The values of SP offset latencies recorded at baseline evaluation and the difference between values recorded following real rTMS and at baseline were analysed. The R coefficients are presented and significant results are marked in bold. Results are presented separately for medication conditions and levels of background contraction.

Medication status Background contraction	Baseline						Real rTMS – Baseline difference					
	OFFMED			ONMED			OFFMED			ONMED		
	Mild	Mod.	Max.	Mild	Mod.	Max.	Mild	Mod.	Max.	Mild	Mod.	Max.
Age	0.26	0.24	–0.04	0.52	0.61	0.31	0.29	0.48	0.53	0.17	0.24	0.65
UPDRS III off @ Baseline	0.38	0.59	0.59	0.40	0.52	0.59	–0.05	0.05	0.33	0.12	0.26	0.52
UPDRS III on @ Baseline	0.83	0.83	0.69	0.74	0.71	0.48	–0.24	–0.24	0.36	–0.48	–0.29	0.05
PD duration	0.55	0.75	0.67	0.52	0.65	0.65	–0.10	–0.07	0.48	0.05	0.19	0.47
Daily medication	0.43	0.26	0.26	0.19	0.00	0.07	–0.33	–0.43	0.05	–0.74	–0.50	–0.59
CDRS @ Baseline	0.19	0.19	0.05	0.33	0.31	0.14	0.38	0.59	0.48	–0.14	0.29	0.62
CDRS diff. Real – Base	–0.45	–0.27	–0.31	–0.34	–0.06	0.16	0.52	0.39	0.36	0.87	0.63	0.63

Mod. – Moderate; Max. – Maximal. UPDRS III – Unified Parkinson's Disease Rating Scale Part 3 (Motor Score); off – off medication; on – on medication; @ Baseline – Recorded at baseline evaluation session; CDRS – Clinical Dyskinesia Rating Scale; diff. Real – Base. – Difference between scores obtained at evaluation session following real rTMS and at baseline evaluation session.

used in this study, reported no effects (Gerschlager et al., 2001; Modugno et al., 2003; Brighina et al., 2005; Houdayer et al., 2008). However, they were all single-session studies; the results of this study suggest that by repeated application of low-frequency rTMS over several days it is possible to elicit a modest but sustainable effect on cortical excitability even when using sub-threshold TMS intensities.

There are no studies of the effect of LF-rTMS on MEP facilitation during voluntary contraction. In the present group of PD patients there were no significant changes following either real or sham rTMS suggesting a lack of LF-rTMS effects on facilitatory corticospinal mechanisms in PD. Relatively weak changes in MEP facilitation with various levels of voluntary contractions found in this study were in keeping with previously reported results in PD patients (Valls-Solé et al., 1994).

Previous studies of 1 Hz rTMS effects on the SP in healthy subjects provided conflicting results. Two studies reported a shortening (Fierro et al., 2001; Fitzgerald et al., 2004), three no change (Fitzgerald et al., 2002b; Gilio et al., 2003; Modugno et al., 2003), one a small increase (Daskalakis et al., 2006), and only one a clear increase (Stinear and Byblow, 2004) of SP duration following a single session of 1 Hz rTMS.

Data for PD are scarce. In a group of 12 PD patients off medication, about half-an-hour after single 20 min-long session of 0.5 Hz rTMS applied at 80% rMT intensity (600 stimuli in total) over the left primary motor cortical area, Lefaucheur et al. (2004) found significant prolongation of the SP and increased short-latency intracortical inhibition (SICI) in comparison to the pre-rTMS values; sham rTMS did not elicit such changes. These results would be very much complimentary with those from our study, suggesting that even a single LF-rTMS session can prolong the SP in PD patients.

Apparently contradictory are the results from the Wagle-Shukla et al. (2007) study. Using a comprehensive battery of TMS measures of cortical excitability, which included MEP at rest and MEP I–O curve as well as SP, in 6 PD patients, they did not find any significant change 24 h after 10 successive daily 15 min-long sessions of 1 Hz rTMS applied at 90% rMT (900 stimuli) in comparison to the pre-rTMS values. Interestingly, they found a significant reduction of dyskinesia following rTMS treatment which was in keeping with the clinical results of this study (Filipović et al., 2009).

The difference in results regarding SP between Wagle-Shukla et al. (2007) and this study may be due to slight differences in methodology. In our study twice as many stimuli were applied. Longer duration rTMS trains may be necessary for physiological effects to be detectable after 24 h even if clinical effects are clearly present. In addition, Lefaucheur et al. (2004), who also found SP prolongation following slow rTMS, tested their patients in the off phase. We tested our participants in a clearly defined off phase and subsequently in the on phase following their usual morning medication. Wagle-Shukla et al. (2007) carried out neurophysiology testing after the levodopa challenge test using 125% of patients' usual morning levodopa equivalent dose. Levodopa and dopaminergic drugs prolong SP in healthy subjects (Ziemann et al., 1997) and PD patients (Priori et al., 1994; Ridding et al., 1995; Diószeghy et al., 1999; Strafella et al., 2000; Pierantozzi et al., 2001). We also found a significant effect of levodopa and dopaminergic medication on SP prolongation which was independent from and statistically stronger than rTMS effect. It may be that the magnitude of physiological response to higher doses of levodopa used for levodopa challenge in Wagle-Shukla et al. (2007) study blurred the effect of rTMS.

Siebner et al. (2000) reported a significant prolongation of the SP following a single session of sub-threshold 5 Hz rTMS in non-medicated PD patients but not in healthy subjects. This may suggest an increased susceptibility towards inhibitory effects of rTMS in PD, which extends beyond the range of rTMS frequencies known

to promote inhibitory mechanisms in healthy subjects. Increased susceptibility to rTMS inhibitory effects has been already demonstrated in another basal ganglia disorder, focal hand dystonia (Siebner et al., 2003). This is an issue that requires further investigation.

Although CDRS scores diminished following real rTMS and SP offset latencies became longer in comparison to baseline, there was no correlation between the two. This was surprising, since both changes happened following the same intervention. The small sample size might have precluded detection of a statistically significant link. Alternatively, the finding may indicate that SP duration and dyskinesia are not causally related but rather are manifestations of close but not identical physiological processes.

In patients with PD several indices of motor cortex inhibition are impaired. Apart from the most consistently reproduced finding of shortened duration of the SP after TMS in patients when off medication or when taking low levodopa doses (Cantello et al., 1991; Priori et al., 1994; Nakashima et al., 1995; Valzania et al., 1997; Diószeghy et al., 1999), reduced short-latency intra-cortical inhibition (SICI) (Ridding et al., 1995; Hanajima et al., 1996; Strafella et al., 2000) and long-latency afferent inhibition (LAI) (Sailer et al., 2003; Tamburin et al., 2003) were also found. Low-frequency rTMS in PD most likely does not affect only mechanisms responsible for SP generation but a range of different inhibitory mechanisms, such as one responsible for SICI (Lefaucheur et al., 2004). It may well be that dyskinesias are mostly mediated through impairment in these other mechanisms thus explaining the lack of correlation between SP prolongation and improvement of clinical dyskinesia in this study. As a further proof for this, increased SICI has been reported after subthalamic nucleus (STN) deep-brain stimulation (DBS) (Cunic et al., 2002; Däuper et al., 2002; Pierantozzi et al., 2002) and similar findings were reported after internal globus pallidus DBS (Pierantozzi et al., 2002). In addition, increased LAI was reported after STN DBS (Sailer et al., 2007). Both DBS procedures are well known to be exceptionally effective in calming dyskinesias in PD (Benabid, 2003; Anderson et al., 2005).

In healthy subjects, dopaminergic stimulation was found to enhance LF-rTMS induced motor cortex inhibition, measured by changes in MEP amplitude (Lang et al., 2008). However, in this study, medication status had no effect on rTMS variables and in particular the rTMS induced SP prolongation was independent from the medication effect, which also prolonged the SP. Our findings were in keeping with previous findings of Morgante et al. (2006) who used another non-invasive method to modulate motor cortex excitability, paired-associated stimulation (PAS). While the PAS method they used caused significant SP prolongation in healthy subjects, it failed to do the same in PD patients; levodopa prolonged the SP, but did not improve the response to PAS. The lack of a modulatory effect of levodopa on the plasticity of inhibitory systems may relate directly to the pathophysiology of dyskinesia in PD.

It has been shown that SP duration is sensitive to GABA-B modulation (Werhahn et al., 1999). It is thought that dopaminergic medication influences SP duration by enhancing the post-synaptic sensitivity to GABA (Beauregard and Ferron, 1991). The mechanism through which LF-rTMS exercises its effect on cortical excitability is not yet certain (Fitzgerald et al., 2006). Most likely, it is similar to the mechanisms involved in the phenomenon of long-term depression (LTD) seen in animal experiments (Ziemann, 2004). The lack of statistical interactions between rTMS and medication effects in this study suggests that two interventions change SP duration through different mechanisms. This finding provides further proof for the feasibility of therapeutical use of LF-rTMS.

An interesting finding of this study was that the severity of PD motor symptoms affected SP duration. Higher UPDRS scores on medication were significantly associated with longer SP duration

both off and on medication. The physiological and clinical significance of this relationship is not clear. Nevertheless, severity of PD motor symptoms did not have any obvious effect on the principal finding of this study, the SP prolongation following real rTMS in comparison to baseline. Other significant correlations between SP duration and clinical variables were not consistent and most likely were detected by chance due to multitude of comparisons.

Another interesting finding of this study is that the duration of the SP in studied PD patients was significantly influenced by the degree of contraction. It is commonly considered that in healthy subjects, the degree of background contraction has little influence on SP duration (e.g. Chen et al., 2008). This is certainly true for higher intensities of stimulation, however, the available evidence seems to suggest that at low stimulus intensities, at or below 120% MT, and with the explicit instruction given to the participants to keep the contraction level constant, the SP gets progressively shorter with increased background contraction (Cantello et al., 1992; Wilson et al., 1993; Mathis et al., 1998; Filipović et al., 2008). Results of this study suggest that the relationship might be even more pronounced in PD or at least in a subset of PD patients displaying prominent dyskinesias as further manifestation of impaired inhibitory mechanisms. This is an issue that may be of interest for further studies.

Dopaminergic medication was shown to induce changes in cortical interactions and plasticity (Mir et al., 2005; Morgante et al., 2006). The rTMS in this study was delivered with patients on medication. It is yet unknown whether the effects may be different and even stronger if rTMS is delivered off medication. This issue requires to be evaluated further.

Before concluding, it should be noted that in this study the strength of rTMS pulses was relatively low. It was set for each patient separately to be just below active motor threshold (aMT) to avoid patients perceiving the difference between “active” and “sham” sessions. However, weaker rTMS pulses induce weaker physiological effects (Fitzgerald et al., 2002b) and it might well be that with the same experimental setting as in this study stronger rTMS would be able to induce more pronounced effects on cortical excitability in general and inhibitory mechanisms in particular. This is an issue that would require further studies.

The encouraging results of this study regarding both physiological and clinical effects, suggest a need for further studies that would systematically evaluate relevant methodological features able to establish more prominent and longer lasting effects. That is, clinical trials that would involve not only stronger TMS stimuli, but also more days of rTMS and bilateral stimulation.

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