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Short Communication

Excitatory Deep Repetitive Transcranial Magnetic Stimulation With H-coil as Add-on Treatment of Motor Symptoms in Parkinson's Disease: An Open Label, Pilot Study

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ABSTRACT

Background: Repetitive transcranial magnetic stimulation (rTMS) has been proposed as a potential treatment for Parkinson's disease (PD). H-coils, inducing deeper and wider magnetic fields compared to traditional coils, may be potentially useful in PD, characterized by widespread, bilateral involvement of cortico-subcortical circuits.
Objective: To evaluate the safety of repetitive deep TMS (rDTMS) with H-coil as add-on treatment of motor symptoms in PD.
Methods: Twenty-seven PD patients (aged 60.1 ± 6.8 y; PD-duration: 6.3 ± 2.8 y; motor-UPDRS: 39.6 ± 10.1) underwent 12 rDTMS sessions over 4 weeks at excitatory (10 Hz) frequency over primary motor (M1) and bilateral prefrontal (PF) regions. Motor UPDRS off therapy was assessed before and after the last rDTMS session, together with safety records at each treatment session.
Results: No drop-outs or adverse events were recorded. Motor UPDRS significantly improved after rDTMS (10.8 points average reduction; $P < 0.0001$).
Conclusions: High-frequency rDTMS might be a safe treatment for PD motor symptoms. Further placebo-controlled, randomized studies are warranted.

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The possibility to offer a non-surgical neuromodulation approach in Parkinson's disease (PD) is appealing [1] and has been reinforced after the observation of changes in cortical excitability following rTMS [2,3]. PD motor improvement especially after high frequency rTMS over primary and nonprimary (i.e. prefrontal-PF) motor areas has been reported [2,4–10]. The main limit of a wider application of standard coils TMS for therapeutic purposes may be overcome by the H-coil, capable to reach wider and deeper brain structures and thereby affect more extended cortical and subcortical brain regions [11]. A detailed configuration and electric field distribution of the H-coil has been described elsewhere [11]. Thanks to the summation of separate small magnetic fields and minimization of non-tangential elements in the coil [11–13], H-coils are able to stimulate deeper brain regions directly, due to a much slower decay of electric field as a function of distance. The ability of H-coil to directly influence the functioning of deep brain sites offers new perspective to non-invasive neuromodulatory approaches in various neuropsychiatric conditions, such as major depression [14,15], schizophrenia [16], primary progressive aphasia [17,18], diabetic neuropathy [19], or blepharospasm [20].

Our aim was to evaluate safety of high frequency rDTMS over M1 and PF cortex in PD. This is an open-label pilot study designed to test the rationale for subsequent larger, double blind, placebo-controlled studies.

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Methods

Patients

Twenty-seven PD-patients without contraindications for TMS were enrolled. Demographic and clinical data of patients are shown in Table 1. The study was approved by the institutional ethics committee and subjects signed an informed consent prior to participation.

rDTMS

Within 3–6 months from baseline assessment (OFF drug), patients underwent 3 weekly sessions of repetitive DTMS for 4 weeks, over M1 and prefrontal areas, in sequence. All rDTMS sessions were performed ON drug [10], except for the last one when patients were asked not to take their usual antiparkinsonian medications and underwent clinical assessment after rDTMS.

The coil contains two symmetric components [11], ideally designed to stimulate both hemispheres simultaneously. However, since the individual distance between the two 'hot spots' for hand muscles cannot fit exactly the distance between the two components of the coil, we choose to apply M1 stimulation focusing on the more affected hemisphere, with stimulus intensity at 90% of resting motor threshold (RMT) for abductor pollicis brevis-APB muscle. Therefore, the less affected hemisphere received stimulation from the other component of the coil, although not reaching the same intensity over the corresponding 'hot spot'.

For prefrontal cortex stimulation, the coil was moved in a symmetrical position and 6 cm anteriorly [18], and stimulation intensity was raised to 100% RMT. For each target, a total of 840 stimuli at 10 Hz were delivered (42 trains of 2 s duration, wait time 22 s).

Safety

Vital signs (body temperature, blood pressure, cardiac frequency) were monitored before and after each sessions and patients were interviewed for adverse events, particularly on the most frequently reported rTMS-side effects such as headache, dizziness [21].

Clinical measures

Motor evaluation was obtained at baseline and after the last rDTMS session using the Unified Parkinson's Disease Rating Scale III (UPDRS III) [22]. Both evaluations were performed OFF drug.

Statistical analysis was performed using SPSS software v.13 (SPSS Inc., Chicago, USA). UPDRS changes were tested using ANOVA for repeated measures, testing factor TIME (2 levels) and SIDE (2 levels) as within-subjects factors. Post-hoc comparisons were performed using paired *t*-tests. Correlation between pre-post rDTMS change in UPDRS III and clinical-demographic parameters was calculated using the Pearson's test for parametric measures (age, disease duration, baseline UPDRS III) and Spearman's test (Hoehn & Yahr scale).

Table 1
Demographic and clinical characteristics of PD-patients enrolled to the study (mean ± standard deviation).

Gender ($n = 27$)	7F, 20M
Age (y)	61.1 ± 6.8
PD-duration (y)	6.3 ± 2.8
Worse side	14L, 13R
Motor UPDRS[a]	39.6 ± 10.1
H&Y[b]	2.2 ± 0.3

[a] Unified Parkinson's Disease Rating Scale.
[b] Hoehn & Yahr scale.

Results

Safety

All the patients completed the study and no serious adverse events were reported during the protocol. Slight and transitory hypotension in one patient (blood pressure moving from 110/80 mm Hg to 90/60 mm Hg, with a rapid recovery after lying down) and headache in another case occurred; however both patients decided to carry on with the protocol. No significant modifications in vital signs were appreciated after rTMS.

Four advanced patients, suffering from levodopa-induced dyskinesia (LID) before the rDTMS treatment, experienced temporary mild dyskinesia after the last rDTMS session while they were OFF drug. Despite not initially considered as an aim of our study, mild dyskinesia appeared to be a frequent side-effect after rDTMS (15% in our PD-patients), affecting only patients already experiencing LID due to chronic levodopa intake. Dyskinesia were not distressing and self-limiting, lasting about 30 min since the end of rDTMS and with the same body distribution of patients' usual involuntary movements.

UPDRS III improved after treatment, with a significant effect of time (10.8 ± 6.6 points reduction after rDTMS; $F(2,25) = 78.33$; $P < 0.0001$, corresponding to a decrease of 27% ± 16%), and no significant effect of SIDE or interaction between the two factors (Fig. 1). All patients but five (one with post-rTMS dyskinesia) reached the threshold of five points considered as clinically relevant change in UPDRS III [23].

Correlations

A significant correlation was found between the UPDRS III score at baseline and its absolute improvement after rTMS (Pearson's $r = 0.41$, $P = 0.035$), but not with percent improvement. No significant correlation emerged between other clinical-demographic features and rDTMS motor effect.

Discussion

In the present study, non-invasive high frequency rDTMS applied over the motor and prefrontal cortices with H-coil was shown to be safe in PD. The choice of M1 followed by PF stimulation was based on previous studies [8,10,24]. In particular, high

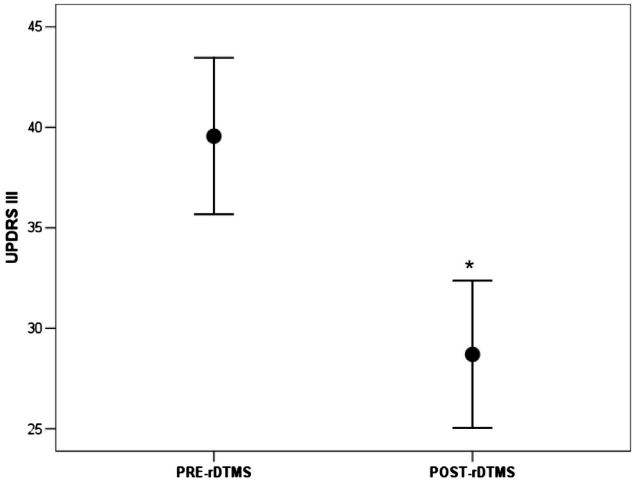

Figure 1. Motor UPDRS improvement after rDTMS. Data are shown as mean ± standard error (*$P < 0.001$; paired *t*-test).

frequency rTMS of M1 and PF resulted in long-lasting improvement in gait and bradykinesia in the real group, but not in the sham group [10]. rTMS in PD has been reported as more effective when applied during levodopa therapy, when the plasticity mechanisms may be more functional [25–27]. In our study, some slight dyskinesia were observed OFF drug after rDTMS, probably masked by those induced by levodopa during the previous stimulation sessions. To our knowledge, this is the first report of a possible acute dyskinetic effect of excitatory rTMS OFF drug. The explanation for such a phenomenon in our study is speculative, and may depend on the wide and deep field of action of H-coil, possibly acting as a more powerful dopamine enhancer than traditional coils. Consistently, worsening of dyskinesia has been reported after 5 Hz rTMS [28] together with a potential anti-dyskinetic effect of rTMS, especially when applied with low frequencies [28–30].

Alternatively, it could be indirectly mediated through a possible effect on striatal medium spiny neurons through ionotropic N-methyl-D-aspartic acid (NMDA) modulation of glutamatergic corticostriatal fibers [31]. Animal studies indicate that prefrontal stimulation modulate dopamine release in the striatum, possibly through the substantia nigra [32–35]. Using (11C)-Raclopride PET, bilateral dopamine striatal release has been found after unilateral M1 targeting with a focal coil using high frequency rTMS [36]. Even sham rTMS has been found capable of increasing dopamine concentration in the striatum [37], suggesting a possible contribution of the placebo effect. This is a well known phenomenon in therapeutic trials for PD [38], probably related to the role of dopamine itself in mediating expectations [39,40]. Complicated medical devices may also enhance the placebo effect [41], and as a consequence the dopaminergic release, with amelioration of motor features. Then we may expect a relevant placebo effect associated with our procedure that makes any conclusion about rDTMS efficacy unattainable. Further randomized, placebo-controlled studies should be performed.

However, our findings represent a strong argument to further investigate the value of rDTMS as a novel add-on treatment for PD. We reserved for future studies the investigation of mechanisms explaining such effects, the relative contribution of targeting separately different brain regions, as well as the advantage of the H-coil with respect to standard coil stimulation.

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