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Clinical Study

Low-frequency repetitive transcranial magnetic stimulation for dyskinesia and motor performance in Parkinson's disease

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ABSTRACT

Dyskinesias are one of the most frequent and disabling complications of the long-term treatment of Parkinson's disease (PD). Although the cause is not completely understood, it appears that an imbalance between excitatory and inhibitory inputs from the basal ganglia to the motor cortex leads to overactivation of motor and premotor areas. Overactivation of the supplementary motor area (SMA) has been observed in neuroimaging studies in dyskinetic PD patients. We investigated the effects of low-frequency repetitive transcranial magnetic stimulation (rTMS) of the SMA on levodopa-induced dyskinesias (LID) and motor performance in PD. We tested whether longer duration (10 days) and higher number of total pulses (1800 pulses) would enhance the beneficial effect. Seventeen dyskinetic PD patients were randomly assigned to real rTMS or sham (placebo) rTMS, and 1 Hz rTMS or sham rTMS was applied over the SMA for 10 consecutive days. Patients were assessed at baseline and 1 day after the last rTMS with a levodopa challenge test, and video recordings were taken. Dyskinesias and motor performance were rated off-line by two blinded raters using video recordings. After 10 days of treatment with rTMS, we observed that 1 Hz rTMS delivered over the SMA had decreased LID lasting for 24 hours without a change in motor performance, whereas sham rTMS induced no significant change in dyskinesia scores. These results support a possible therapeutic effect of low-frequency rTMS in LID. However, in order to suggest rTMS as an effective treatment, long-term observations and further investigations with a larger patient population are essential.

1. Introduction

Levodopa (L-dopa) is still the most effective drug for the symptomatic treatment of Parkinson's disease (PD). However, severe motor complications usually occur in conjunction with its chronic use. One of the most frequent and disabling complications of long-term treatment of PD is levodopa-induced dyskinesias (LID) [1–4]. Although the exact neural mechanisms underlying LID remain unknown, it is considered to be the result of reduced inhibition of thalamocortical neurons and overactivation of cortical motor and premotor areas, caused by the imbalance between excitatory and inhibitory inputs from the basal ganglia to the motor cortex [5–8]. Functional neuroimaging studies have demonstrated overactivation of primary cortical motor areas and the supplementary motor area (SMA) in dyskinetic PD patients [9,10].

The effects of repetitive transcranial magnetic stimulation (rTMS) over these cortical areas have been tested in a series of studies in dyskinetic PD patients. In these studies, 1 Hz rTMS applied either over the SMA or the motor cortex improved LID. However, the beneficial effects were not permanent and not potentiated by repeated sessions of stimulation [8,11–13].

Based on recent literature, we aimed to investigate the effects of low-frequency rTMS over the SMA on LID and on motor performance in patients with PD. Furthermore, we tested whether or not a longer duration (10 days) and higher number of total pulses (1800 pulses) of 1 Hz rTMS applied over the SMA would alleviate LID and prolong the beneficial effect without causing undesired side effects.

2. Method

Seventeen advanced PD patients (10 women, seven men) who had disabling peak-dose dyskinesias under dopaminergic treatment were enrolled in the study. Patients were diagnosed by a

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neurologist (R.C.) who specialises in movement disorders. The diagnosis of PD was made according to the United Kingdom Brain Bank Criteria [14]. Exclusion criteria were previous PD surgery and contraindications for rTMS. Antiparkinsonian medications producing the best control of PD symptoms were fixed for at least 1 month before enrollment until the end of the study except on the days of the L-dopa challenge test. The local Ethics Committee approved the study protocol, and informed consent was obtained from each patient.

The mean age of the patients was 61.88 ± standard deviation (SD) 9.06 years, and the mean disease duration was 11.41 ± SD 4.6 years. The patients were randomly assigned to the real rTMS (Group 1) or sham (placebo) rTMS (Group 2) treatment. The average equivalent dose of L-dopa in Group 1 was 1258 ± SD 238 mg/day and 1189 ± SD 200 mg/day in Group 2. Patient characteristics are presented in Table 1.

The MagPRO X100 magnetic stimulator and Keypoint 8-channeled Evoked Potential and EMG Recording System (Medtronic Sofamor Danek, Memphis, TN, USA) were used. A MCF-B65 figure-of-eight coil with 5 cm outer diameter was used for the real rTMS application, and a MC-P-B70 placebo coil (both Medtronic Sofamor Danek) with 7 cm outer diameter for the sham rTMS application. The figure-of-eight coil was placed over the scalp, 3 cm anterior to the Cz electrode of the 10–20 electroencephalography system in the sagittal midline with the coil handle pointing posteriorly [8,11]. In this way, a posteroanterior-directed current was created, and the SMA of both hemispheres were stimulated simultaneously.

The rTMS at 1 Hz frequency with duration of 30 minutes (total 1800 pulses, 90% of resting motor excitability threshold) was applied over the SMA for 10 consecutive days, at the same time each day for each Group 1 patient. For the sham application the same procedure was performed using the placebo coil instead.

The patients were assessed before the first rTMS application and 1 day after the last rTMS session using the L-dopa challenge test. In this test, patients received 1.5 times the equivalent dose of their morning medication with a single oral dose of L-dopa and benserazide after 12 hours of overnight withdrawal from L-dopa. After the completion of 10 days of rTMS procedure, each patient was evaluated at the same time and at the same dosage of L-dopa as in the previous baseline test. Motor performance and dyskinesias were evaluated and videotaped three times: at the "off period" (t0), and at 90 (t90) and 120 (t120) minutes after L-dopa administration. Dyskinesias were assessed during the following activation tasks: (1) sitting in a chair with hands on knees and sitting with hands hanging unsupported; (2) opening the mouth, with the tongue at rest within the mouth; (3) protruding the tongue; (4) tapping the thumb with each finger for 10–15 seconds with the right hand and then with the left hand; (5) standing up; (6) extending both arms, outstretched in front with palms down; and (7) walking a few paces, turning and walking back to the chair. The videos before and after rTMS applications were recorded to compact discs for evaluation by blinded raters. Two blinded neurologists specialising in the field of movement disorders (G.G.Y., E.Y.) then scored dyskinesias and motor performances off-line with video recordings. The means of the raters' scores were used for the statistical analyses. The motor performances were scored according to the Unified Parkinson Disease Rating Scale (UPDRS) Motor Section (Part 3) [15], and the dyskinesias were rated using the Abnormal Involuntary Movement Scale (AIMS) [16]. According to the AIMS, visible dyskinesias in each of the seven body parts (face, neck, trunk and each limb) were scored from 0 (absence of dyskinesia) to 4 (severe dyskinesia). Scores were lowered by one point if dyskinesias were provoked by action.

Subjective evaluation of the treatment by each patient was done using a visual analogue scale (VAS) on each day during the entire rTMS procedure. Items 32 and 33 of UPDRS Part 4, which evaluate motor complications of dopaminergic treatment, were also obtained before rTMS treatment (baseline) and on the first and tenth day (after the last rTMS session).

2.1. Statistical analysis

The Mann-Whitney U test was used for comparison of scores of the two groups before and after the rTMS procedure, and Wilcoxon signed rank test was used for the comparison of scores before and after the rTMS procedure within the same group. The collected analysis of the VAS scores was evaluated by Friedman analysis of variance. For all statistical analyses, a p value under 0.05 was considered significant.

3. Results

Nine patients received real rTMS (Group 1) and eight patients received sham rTMS (Group 2). No adverse effects were reported during the study. At the beginning of the study, there were no statistically significant differences between the two groups regarding sex, age, Hoehn–Yahr stage, and disease duration ($p > 0.5$, Mann-Whitney U test, Table 1).

At the baseline assessment, there was no significant difference between the groups in mean "off period" UPDRS motor scores ($p = 0.2$). Before rTMS treatment, analysis of AIMS scores at t90 and t120 showed that the mean AIMS score of Group 1 was significantly higher than of Group 2 ($p = 0.005$ and $p = 0.012$, respectively). Considering that the effect of medication could differ among patients, with some responding earlier and some later, we calculated the mean AIMS scores of t90 and t120 (t-mean), and found that the t-mean was also higher in Group 1 ($p = 0.007$, Table 2, Fig. 1).

Table 1
Baseline clinical characteristics of Parkinson's disease patients

	Group 1 (n = 9)	Group 2 (n = 8)	p value
Sex (Female/Male)	7/2	3/5	0.09[a]
Age, years (range)	64.78 ± 9.82 (50–79)	58.63 ± 7.39 (46–70)	0.22[b]
Hoehn–Yahr stage (range)	2.94 ± 0.53 (2–4)	2.81 ± 0.259 (2.5–3)	0.46[b]
Disease duration, years (range)	10.78 ± 5.87 (5–21)	12.13 ± 2.85 (9–17)	0.24[b]
UPDRS Part 3	28.83 ± 12.83	35.47 ± 6.02	0.21[b]
Average LED, mg/day	1251 ± 238	1189 ± 200	0.36[b]

Data are presented as mean ± standard deviation unless otherwise stated.
LED, levodopa equivalent dose; UPDRS, Unified Parkinson Disease Rating Scale.
[a] Pearson chi-square test.
[b] Mann–Whitney U test.

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Table 2
Abnormal Involuntary Movement Scale scores before and after treatment

	Group 1			Group 2		
	Pre-rTMS	Post -rTMS	*p* value[a]	Pre-rTMS	Post-rTMS	*p* value[a]
Time						
t90	16.61 ± 6.23	13.72 ± 7.28	0.024	8.31 ± 3.52	9.56 ± 4.06	0.123
t120	17.28 ± 6.50	13.92 ± 8.28	0.192	8.94 ± 3.02	8.56 ± 4.66	0.735
t-mean	16.94 ± 6.24	13.80 ± 7.64	0.161	8.63 ± 3.05	9.06 ± 4.17	0.779

Data are presented as mean ± standard deviation.
rTMS = repetitive transcranial magnetic stimulation, t90 = 90 minutes after stimulation, t120 = 120 minutes after stimulation.
[a] Wilcoxon signed ranked test between pre-rTMS and post-rTMS within groups.

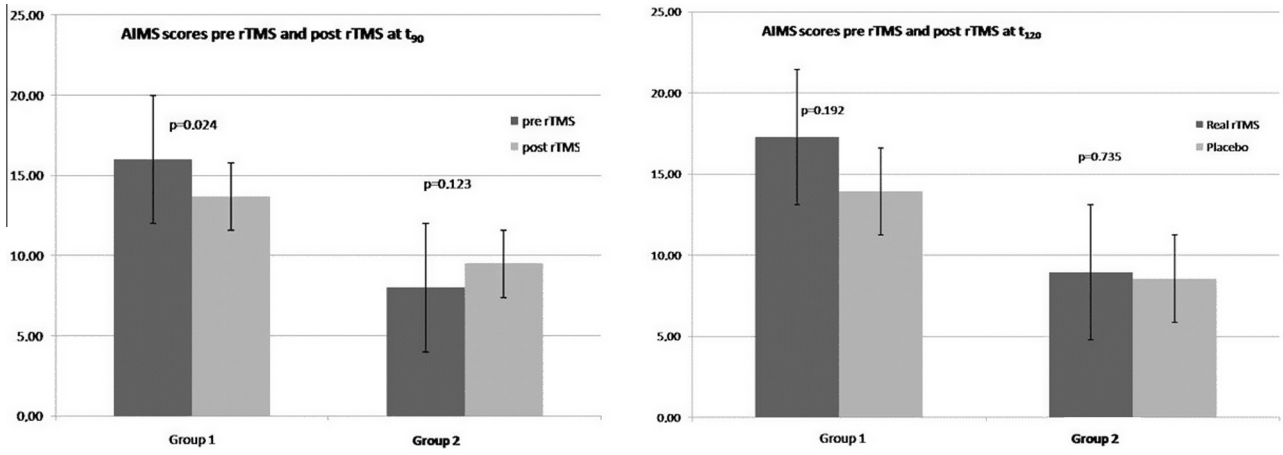

Fig. 1. Abnormal Involuntary Movement Scale scores evaluated before repetitive transcranial magnetic stimulation and at (left) 90 minutes and (right) 120 minutes after repetitive transcranial magnetic stimulation. AIMS = Abnormal Involuntary Movement Scale, rTMS = repetitive transcranial magnetic stimulation, t90 = 90 minutes after stimulation, t120 = 120 minutes after stimulation.

After 10 days of real rTMS treatment, no significant change was detected between the "off period" UPDRS motor scores pre-rTMS and post-rTMS ($p = 0.17$). However, when the same comparison was made for Group 2, UPDRS t0 scores were significantly lower after sham rTMS ($p = 0.03$).

A significant reduction in the AIMS score was observed only at t90 after rTMS treatment in Group 1 ($p = 0.024$). With respect to t120 and t-mean, although the post-rTMS AIMS score was still lower than the pre-rTMS AIMS score, the difference was not statistically significant ($p = 0.192$). Regarding the placebo group, there were no significant differences between AIMS scores as evaluated before and after rTMS application at any time point (t90, t120, and t-mean, Table 2, Fig. 1).

When the repeated scores of item 32 of UPDRS were evaluated by Friedman analysis of variance, no significant difference was detected between the two groups (Group 1 $p = 0.13$ and Group 2 $p = 0.36$). As for item 33 of UPDRS, when we compared the scores before and after rTMS application, no significant difference was detected in the placebo group, but a significant difference was present in the real rTMS group ($p = 0.02$). On the other hand, when binary analysis was performed using Wilcoxon signed rank test, after rTMS application a significant difference was detected in both evaluation scales with lower scores after application.

The Friedman test for analysis of the VAS scores, in which the patients evaluated their dyskinesia over 10 points, revealed no significant difference in the placebo group ($p = 0.44$) before and after the application. However, in the real rTMS group, VAS scores differed significantly before and after the application ($p = 0.001$). Also, when binary analysis was performed using the Wilcoxon signed rank test, VAS points on day 7 and day 10 were found to be significantly lower than those of day 0 in Group 1 ($p = 0.01$ and $p = 0.02$, respectively).

4. Discussion

We have shown that 1 Hz rTMS decreased LID without a change in motor performance, whereas sham rTMS induced no significant change in dyskinesia scores. These results support a possible therapeutic effect of low-frequency rTMS in LID.

Based on the evidence of insufficient thalamocortical inhibition and cortical motor and premotor overactivation, reported in neuroimaging and experimental studies [6,17,18], the effects of rTMS over these cortical areas have been investigated in a series of studies in dyskinetic PD patients.

First, Koch et al. found that a single session of rTMS at 1 Hz to the SMA markedly reduced LID for 30 minutes after the stimulation [11]. In a subsequent study testing the effects of a similar protocol in their group of PD patients, they showed that the beneficial effects lasted 15 minutes after the end of the stimulation but could not be prolonged by repeated sessions of the stimulation for 5 days [8].

Wagle-Shukla et al. tested longer sessions of stimulation such as 10 days of 1 Hz rTMS, to the primary motor cortex in six patients, with an expectation of a longer-lasting reduction of LID. Similar to the results of our study, the improvement was significant a day after the last session but not 2 weeks later [12].

In another study, Filipović et al. assessed the effects of 1 Hz rTMS applied over the motor cortex for 4 consecutive days. They found that direct comparison between sham rTMS and real rTMS effects showed no significant difference. However, comparison with the baseline values showed a small but significant reduction in dyskinesia after real rTMS [13].

Recently, a few studies have reported changes in cerebellothalamocortical networks in PD and, in some cases, in LID [19,20]. Koch et al. applied rTMS over the lateral cerebellum in a group of PD

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patients with dyskinesia and found that a single session of cerebellar continuous theta burst stimulation (cTBS) transiently reduced LID. In another experiment, they observed that a 2 week course of bilateral cerebellar cTBS reduced peak-dose LID for up to 4 weeks after the end of the daily stimulation period [21].

Our results are in agreement with the previous two studies [8,11] that reported transient improvement in LID after a low-frequency rTMS application over the SMA. In contrast to those studies, we show that the beneficial effects of rTMS lasted for 24 hours after the last session. Longer sessions of stimulation (10 consecutive days) and a higher number of stimuli (1800 pulses) may be the possible explanation for the difference. This result is also in agreement with the hypothesis that repeated sessions of stimulation are capable of inducing cumulative changes that may lead to modify the excitability of the stimulated and the interconnected areas [18,22].

Analogies exist between the inhibitory effect of low-frequency rTMS and the well-known phenomenon of synaptic depotentiation, in which stimulation at frequencies in the 1 Hz range is able to reverse a previously induced long-term potentiation [8,23]. Consistent with these premises, the reduction in LID may be explained by the transient depression of excitatory synaptic transmission and the promotion of depotentiation at corticostriatal inputs from the SMA to the putamen [8].

In the previous rTMS studies for the treatment of dyskinesia, a crossover design was used. In this study, we aimed to overcome the placebo effect by including a second group of patients receiving only placebo treatment. This difference in the study design might be regarded as superior to other studies, with more objective results.

In our study, we found that 1 Hz rTMS induced no significant change on the UPDRS motor scores. However, we detected a significant improvement in the motor performance after the sham stimulation. We suggest that this result is mainly due to the placebo effect. It is well known that prominent placebo effects are seen in PD [24–26]. It has been reported that the placebo effect in PD is mediated by the release of endogenous dopamine in both dorsal and ventral striatum, and the strength of belief in improvement can directly modulate dopamine release in PD patients [27,28].

During the blind off-line evaluation of the video recordings, differences had been detected between the baseline dyskinesia scores of the real and sham rTMS groups before the rTMS application. This might be due to the randomization method and the small sample size. The baseline AIMS scores were significantly higher in the real rTMS group and thus it is possible that the anti-dyskinetic effects were overestimated. However, in our opinion this difference did not affect the results, since no improvement was detected in the placebo rTMS group, whereas a significant reduction in AIMS scores was observed in the real rTMS group after rTMS application.

In conclusion, although the data of our study support the possible therapeutic effect of low-frequency rTMS in LID, it is difficult to suggest rTMS as an effective treatment because of the small sample size and transient beneficial effect. Therefore, further studies with longer rTMS application and follow-up periods with a larger patient population are essential.

Conflicts of Interest/Disclosures

The authors declare that they have no financial or other conflicts of interest in relation to this research and its publication.

References

[1] Marconi R, Lefebvre-Caparros D, Bonnet AM, et al. Levodopa-induced dyskinesias in Parkinson's disease phenomenology and pathophysiology. Mov Disord 1994;9:2–12.
[2] Fahn S. The spectrum of levodopa-induced dyskinesias. Ann Neurol 2000;47:S2–9.
[3] Rascol O, Brooks DJ, Korczyn AD, et al. A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa. 056 Study Group. N Engl J Med 2000;342:1484–91.
[4] Fabbrini G, Brotchie JM, Grandas F, et al. Levodopa-induced dyskinesias. Mov Disord 2007;22:1379–89.
[5] Obeso JA, Rodriguez-Oroz MC, Rodriguez M, et al. Pathophysiology of levodopa-induced dyskinesias in Parkinson's disease: problems with the current model. Ann Neurol 2000;47:S22–32.
[6] Bezard E, Brotchie JM, Gross CE. Pathophysiology of levodopa-induced dyskinesia: potential for new therapies. Nat Rev Neurosci 2001;8:577–88.
[7] Widnell K. Pathophysiology of motor fluctuations in Parkinson's disease. Mov Disord 2005;20:17–22.
[8] Brusa L, Versace V, Koch G, et al. Low frequency rTMS of the SMA transiently ameliorates peak-dose LID in Parkinson's disease. Clin Neurophysiol 2006;117:1917–21.
[9] Rascol O, Sabatini U, Brefel C, et al. Cortical motor overactivation in parkinsonian patients with l-DOPA-induced peak-dose dyskinesia. Brain 1998;121:527–33.
[10] Brooks DJ, Piccini P, Turjanski N, et al. Neuroimaging of dyskinesia. Ann Neurol 2000;47:S154–8.
[11] Koch G, Brusa L, Caltagirone C, et al. rTMS of supplementary motor area modulates therapy-induced dyskinesias in Parkinson disease. Neurology 2005;65:623–5.
[12] Wagle-Shukla A, Angel MJ, Zadikoff C, et al. Low-frequency repetitive transcranial magnetic stimulation for treatment of levodopa-induced dyskinesias. Neurology 2007;68:704–5.
[13] Filipović SR, Rothwell JC, van de Warrenburg BP, et al. Repetitive transcranial magnetic stimulation for levodopa-induced dyskinesias in Parkinson's disease. Mov Disord 2009;24:246–53.
[14] Hughes AJ, Daniel SE, Kilford L, et al. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992;55:181–4.
[15] Fahn S, Elton RL, UPDRS Development Committee. Unified Parkinson's disease rating scale. In: Fahn S, Marsden CD, Calne D, Golstein M, editors. Recent developments in Parkinson's disease, 2. Florham Park, NY: MacMillan Healthcare Information; 1986. p. 153–63 [293-304].
[16] May PR, Lee MA, Bacon RC. Quantitative assessment of neuroleptic-induced extrapyramidal symptoms: clinical and nonclinical approaches. Clin Neuropharmacol 1983;6:35–51.
[17] Centonze D, Bernardi G, Koch G. Mechanisms of disease: basic-research-driven investigations in humans—the case of hyperkinetic disorders. Nat Clin Pract Neurol 2007;3:572–80.
[18] Koch G. RTMS effects on levodopa induced dyskinesias in Parkinson's disease patients: searching for effective cortical targets. Restor Neurol Neurosci 2010;28:561–8.
[19] Yu H, Sternad D, Corcos DM, et al. Role of hyperactive cerebellum and motor cortex in Parkinson's disease. Neuroimage 2007;35:222–33.
[20] Lewis MM, Slagle CG, Smith AB, et al. Task specific influences of Parkinson's disease on the striato-thalamo-cortical and cerebello-thalamo-cortical motor circuitries. Neuroscience 2007;147:224–35.
[21] Koch G, Brusa L, Carrillo F, et al. Cerebellar magnetic stimulation decreases levodopa-induced dyskinesias in Parkinson disease. Neurology 2009;73:113–9.
[22] Bäumer T, Lange R, Liepert J, et al. Repeated premotor rTMS leads to cumulative plastic changes of motor cortex excitability in humans. Neuroimage 2003;20:550–60.
[23] Hoffman RE, Cavus I. Slow transcranial magnetic stimulation, long-term depotentiation, and brain hyperexcitability disorders. Am J Psychiatry 2002;159:1093–102.
[24] Goetz CG, Leurgans S, Raman R, et al. Objective changes in motor function during placebo treatment in PD. Neurology 2000;54:710–4.
[25] de la Fuente-Fernández R, Stoessl AJ. The placebo effect in Parkinson's disease. Trends Neurosci 2002;25:302–6.
[26] de la Fuente-Fernández R, Schulzer M, Stoessl AJ. Placebo mechanisms and reward circuitry: clues from Parkinson's disease. Biol Psychiatry 2004;56:67–71.
[27] de la Fuente-Fernández R, Lidstone S, Stoessl AJ. Placebo effect and dopamine release. J Neural Transm Suppl 2006;70:415–8.
[28] Lidstone SC, Schulzer M, Dinelle K, et al. Effects of expectation on placebo-induced dopamine release in Parkinson disease. Arch Gen Psychiatry 2010;67:857–65.

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