rTMS of supplementary motor area modulates therapy-induced dyskinesias in Parkinson disease

Abstract—The neural mechanisms and circuitry involved in levodopa-induced dyskinesia are unclear. Using repetitive transcranial magnetic stimulation (rTMS) over the supplementary motor area (SMA) in a group of patients with advanced Parkinson disease, the authors investigated whether modulation of SMA excitability may result in a modification of a dyskinetic state induced by continuous apomorphine infusion. rTMS at 1 Hz was observed to markedly reduce drug-induced dyskinesias, whereas 5-Hz rTMS induced a slight but not significant increase.

NEUROLOGY 2005;65:623–625

G. Koch, MD; L. Brusa, MD; C. Caltagirone, MD; A. Peppe, MD; M. Oliveri, MD; P. Stanzione MD; and D. Centonze, MD

The neural mechanisms that underlie levodopa-induced dyskinesias (LIDs) in Parkinson disease (PD) are unclear.[1] Dyskinesia has been associated with a sequence of events that include pulsatile stimulation of dopamine receptors, downstream changes in proteins and genes, and abnormalities in nondopamine transmitter systems.[2,3] All these events combine to produce alterations in the firing patterns that signal between the basal ganglia and the cortex,[3,4] leading to excessive disinhibition of thalamocortical neurons and overactivation of cortical motor and premotor areas.[3]

Here we utilized repetitive transcranial magnetic stimulation (rTMS) to investigate whether modulation of excitability of the supplementary motor area (SMA) may result in modification of LID in patients with PD treated with continuous apomorphine infusion.

Based on the assumption that the SMA is overactive in dyskinetic patients with PD,[3] we hypothesized that inhibition of the SMA by low-frequency rTMS may reduce drug-induced dyskinesias, whereas an opposite effect would follow facilitation by high-frequency rTMS.[5]

Methods. Eight patients with advanced PD, who had disabling dyskinesias under L-dopa treatment and had been switched to subcutaneous continuous apomorphine infusion to obtain a stable condition, were enrolled (table 1). The study was approved by our local ethics committee. All participants provided informed consent. Diagnosis of idiopathic PD was made according with Brain Bank Criteria. During each experimental session, apomorphine infusion was adjusted at an optimal rate around the individual threshold for dyskinesia to obtain a stable dyskinetic state for basal evaluation. No L-dopa add-on was administered during the testing sessions. Videotape recordings were performed at baseline (T - 1) and repeated immediately after rTMS protocol (T0, post) and then 15 (T1, 15 minutes post) and 30 (T2, 30 minutes post) minutes later.

Videotapes were rated by two raters expert in the field of movement disorders using the Abnormal Involuntary Movement Scale (AIMS).[6] AIMS was scored for visible dyskinesias in six body parts (neck, trunk, and each limb), with a 5-point (0 = absence of dyskinesia to 4 = severe dyskinesia) scale. Raters were blinded to the type of rTMS paradigm adopted. The AIMS score for each patient in each condition was calculated as the mean between the scores attributed independently by the two raters. In a prestudy session, the clinical scoring of AIMS and Unified Parkinson's Disease Rating Scale (UPDRS) was performed at time 0 and 15 and 30 minutes later to establish baseline stable measurements.

TMS protocol. In eight patients, a MagStim Rapid magnetic stimulator (Magstim, Whitland, UK), connected with a figure-of-eight coil with a diameter of 70 mm, was used to deliver rTMS over the scalp site corresponding to the SMA, 3 cm anterior to C_z of the 10–20 EEG system in the sagittal midline, so that the coil was stimulating simultaneously the SMA of both hemispheres.[7] The coil was applied with the handle pointing posteriorly, so as to induce in the underlying brain tissue a current flowing with a posterior–anterior direction. Before applying rTMS, the individual resting motor excitability threshold (RMT) defined according to international standards was determined for both hemispheres. Three different rTMS protocols were adopted to modulate SMA excitability.

Low-frequency rTMS. rTMS trains at 1 Hz with a duration of 15 minutes (total pulses 900) were applied over the SMA. TMS intensity was set at 90% of RMT.

High-frequency rTMS. Eighteen rTMS trains of 50 stimuli at 5-Hz frequency (train duration 10 seconds) separated by 40 seconds of pause were delivered at 110% RMT for a total of 900 pulses (procedure duration 15 minutes) over the SMA.

Sham rTMS. rTMS trains at 1 Hz of 15-minute duration (total pulses 900) were applied over the SMA. TMS intensity was set at 90% RMT. During sham stimulation, the coil was held close to the target site but angled away so that no current was induced in the brain, tilting the coil at 90° off the scalp with one wing touching the scalp.

The order of presentation of the different rTMS conditions was pseudo-randomized across subjects.

In a control experiment, another PD group treated with subcutaneous apomorphine (n = 6; mean age 62.4 ± 3.6; mean disease duration 11.3 ± 3.4 years) was enrolled, in which 900 rTMS stimuli at 1 Hz were delivered over a parietal site corresponding to P_z.

Data analysis. Nonparametric Friedman analysis of variance (ANOVA) for repeated measures with time as the main effect was applied on mean AIMS and UPDRS section III scores for different experimental conditions (no stimulation, sham rTMS, 1-Hz rTMS, 5-Hz rTMS). Wilcoxon test was performed as a post-hoc comparison.

Results. The mean subject RMT was 58 ± 4.5%. We observed a significant stability of the clinical scores (AIMS and UPDRS) over the time of the session when stimulation was not performed. Sham rTMS did not modify AIMS or UPDRS scores. SMA rTMS induced different time-

From the Fondazione Santa Lucia IRCCS (Drs. Koch, Brusa, Caltagirone, Peppe, Oliveri, Stanzione, and Centonze), Rome, Clinica Neurologica (Drs. Koch, Brusa, Caltagirone, Stanzione, and Centonze), Dipartimento di Neuroscienze, Università di Tor Vergata, Rome, and Dipartimento di Psicologia (Dr. Oliveri), Università di Palermo, Italy.

Disclosure: The authors report no conflicts of interest.

Received February 9, 2005. Accepted in final form April 18, 2005.

Address correspondence and reprint requests to Dr. G. Koch, Fondazione Santa Lucia, IRCCS, Laboratorio di Neurologia Clinica e Comportamentale, Via Ardeatina 306, 00179 Roma, Italy; e-mail: Giakoch@libero.it

Table 1 *Clinical characteristic of patients with Parkinson disease submitted to repetitive transcranial magnetic stimulation*

Patient no.	1	2	3	4	5	6	7	8
Sex	F	F	M	F	M	F	M	M
Age, y	70	52	49	64	48	68	73	62
Education, y	13	13	8	17	8	13	18	8
Disease duration, y	11	22	13	26	21	16	14	9
Duration of L-dopa therapy, y	11	18	10	11	14	16	9	9
Standard subcutaneous apomorphine infusion, mg/h	4.5	5.0	4.0	4.2	3.7	4.2	5.2	4.8
Overoptimal subcutaneous apomorphine infusion,* mg/h	5.4	6.0	4.8	5.1	4.6	5.2	6.3	5.9

* During the experimental sessions.

dependent effects on dyskinesias depending on the stimulation protocol utilized. Friedman ANOVA showed an effect for the 1-Hz rTMS condition ($\chi^2 = 15.3$, $p < 0.001$). AIMS scores decreased comparing pre (T - 1) and post (T0) 1-Hz rTMS conditions (6.75 ± 2.03 vs 2.25 ± 1.83; $p < 0.01$). The effect was still observable at T1, after 15 minutes (6.75 ± 2.03 vs 4.00 ± 1.41; $p < 0.05$), but not at T2, after 30 minutes from stimulation (6.75 ± 2.03 vs 7.03 ± 1.51; $p < 0.6$) (table 2). No effect was induced by 5-Hz rTMS. In this case, in comparison with pre rTMS (T - 1), AIMS mean score slightly increased immediately after rTMS, although not reaching significance (Friedman ANOVA: $\chi^2 = 5.6$, $p = 0.12$). The pre-rTMS AIMS mean scores did not differ between the two rTMS conditions. Moreover, the comparison between post 5-Hz and 1-Hz rTMS conditions was significant at T0 (7.37 ± 2.77 vs 2.25 ± 1.83; $p < 0.01$) and T1 (7.12 ± 2.64 vs 4.00 ± 1.41; $p < 0.01$) (figure). In the PD control group submitted to 1-Hz rTMS over P_z, no effect due to stimulation was observed (see table 2). Motor abilities scored by the mean UPDRS section III were not modified by any rTMS condition as revealed by Friedman ANOVA (see table 2).

Table 2 *Mean (SD) AIMS and UPDRS section III scores in patients with Parkinson disease in different conditions of stimulation*

	T - 1	T0	T1	T2
AIMS				
Basal	6.25 (2.1)	6.10 (1.7)	6.55 (1.5)	6.88 (1.9)
Sham SMA rTMS	6.40 (2.3)	6.35 (1.9)	6.75 (2.3)	6.25 (2.2)
1-Hz SMA rTMS	6.75 (2.0)	2.25 (1.8)	4.00 (1.4)	7.10 (1.5)
5-Hz SMA rTMS	6.00 (1.7)	7.38 (2.7)	7.13 (2.7)	6.00 (2.0)
1-Hz Pz rTMS*	6.00 (1.8)	5.25 (1.5)	5.40 (2.2)	5.50 (2.0)
UPDRS				
Basal	14.2 (7.5)	13.7 (5.7)	14.4 (5.5)	14.9 (6.4)
Sham rTMS	15.3 (6.2)	14.2 (4.1)	14.8 (6.2)	15.6 (4.6)
1-Hz rTMS	14.8 (6.3)	14.3 (3.3)	13.1 (4.5)	13.5 (4.4)
5-Hz rTMS	13.7 (7.5)	12.1 (5.8)	12.2 (5.1)	13.2 (7.2)
1-Hz Pz rTMS*	11.7 (6.3)	11.0 (7.2)	12.4 (6.6)	10.5 (5.0)

* Experiment conducted in an independent Parkinson disease control group.

AIMS = Abnormal Involuntary Movement Scale; UPDRS = Unified Parkinson's Disease Rating Scale; SMA = supplementary motor area; rTMS = repetitive transcranial magnetic stimulation.

Discussion. The main finding of the current study is that SMA rTMS can modulate abnormal involuntary movements in patients with PD, depending on the protocol utilized. These results are consistent with the hypothesis that SMA plays a central role in the developing of dyskinesia induced by dopaminergic stimulation.

Using PET, Brooks et al.[8] found a relative overactivation of SMA, motor cortical areas, and basal ganglia in patients with dyskinetic PD, the degree of which correlated with the severity of dyskinesias. Indeed, a relative overactivity of motor and premotor areas of the cortex, including SMA, has been reported when comparing nondyskinetic and dyskinetic patients with an SPECT study.[9] Our findings seem to confirm the hypothesis that the overactivation of the SMA observed in neuroimaging studies reflects a state of altered cortical excitability in dyskinetic PD patients. In particular, we suggest that LID are associated with increased excitability of the SMA, as drug-induced dyskinesias were markedly reduced by 1-Hz rTMS, a procedure commonly believed to induce transient inhibition of this cortical area. Five-Hertz rTMS, conversely, was associated

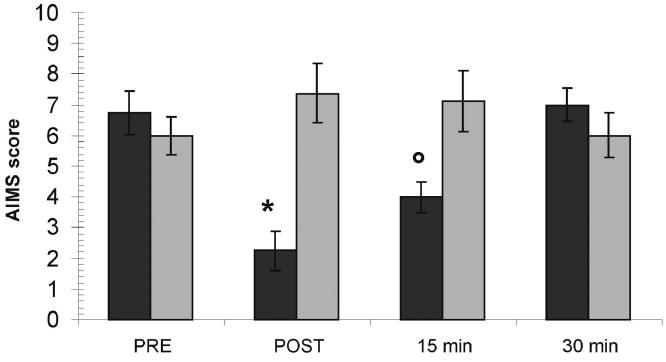

*Figure. Mean Abnormal Involuntary Movement Scale (AIMS) scores before and after repetitive transcranial magnetic stimulation (rTMS) trains. Black columns = 1-Hz rTMS; gray columns = 5-Hz rTMS. Error bars indicate 1 SEM. *p < 0.01; °p < 0.05.*

with only a slight, but not significant, increase of dyskinetic behavior in PD patients, a result compatible with the idea that SMA hyperfunctioning was not susceptible to further enhancement by excitatory rTMS. It is possible that the beneficial effects against dyskinesia of rTMS might rely on the transient depression of synaptic excitability at the cortical level or on the promotion of depotentiation at corticostriatal inputs from SMA to the putamen.[10] Further studies with repeated rTMS sessions could evaluate possible long-lasting beneficial effects of 1-Hz rTMS on drug-induced dyskinesias.

References

1. Rascol O, Brooks DJ, Korczyn AD, De Deyn, PP, Clarke CE, Lang AE. 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;342:1484–1491.
2. Piccini P, Weeks RA, Brooks DJ. Alterations in opioid receptor binding in Parkinson's disease patients with levodopa-induced dyskinesias. Ann Neurol 1997;42:720–726.
3. Bezard E, Brotchie JM, Gross CE. Pathophysiology of levodopa-induced dyskinesia: potential for new therapies. Nat Rev Neurosci 2001;2:577–588. Review.
4. Filion M, Tremblay L, Bedard PJ. Effects of dopamine agonists on the spontaneous activity of globus pallidus neurons in monkeys with MPTP-induced parkinsonism. Brain Res 1991;547:152–161.
5. Wassermann EM, Lisanby SH. Therapeutic application of repetitive transcranial magnetic stimulation: a review. Clin Neurophysiol 2001; 112:1367–1377.
6. May PR, Lee MA, Bacon RC. Quantitative assessment of neuroleptic-induced extrapyramidal symptoms: clinical and nonclinical approaches. Clin Neuropharmacol 1983;6:S35–S51.
7. Koch G, Oliveri M, Brusa L, Stanzione P, Torriero S, Caltagirone C. High-frequency rTMS improves time perception in Parkinson disease. Neurology 2004;63:2405–2406.
8. Brooks DJ, Piccini P, Turjanski N, Samuel M. Neuroimaging of dyskinesia. Ann Neurol 2000;47:S154–S158. Review.
9. Rascol O, Sabatini U, Brefel C, et al. Cortical motor overactivation in parkinsonian patients with L-dopa-induced peak-dose dyskinesia. Brain 1998;121:527–533.
10. Picconi B, Centonze D, Hakansson K, et al. Loss of bidirectional striatal synaptic plasticity in L-DOPA-induced dyskinesia. Nat Neurosci 2003;6: 501–506.