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High-frequency rTMS over the supplementary motor area improves bradykinesia in Parkinson's disease: Subanalysis of double-blind sham-controlled study

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ABSTRACT

A double-blind sham-controlled study demonstrated that high-frequency repetitive transcranial magnetic stimulation (rTMS) over the supplementary motor area (SMA) provided relief of motor symptoms in patients with Parkinson's disease (PD). However, it remains to be determined which parkinsonian symptoms were improved by this treatment. Subanalysis of Unified Parkinson Disease Rating Scale revealed that rTMS over SMA significantly improved bradykinesia in PD. Results support the hypothesis that neuronal activity of SMA was profoundly associated with hypokinetic symptoms in PD.

1. Introduction

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive method used for human brain stimulation, offering potential for Parkinson's disease (PD) treatment [1]. High-frequency rTMS induces facilitation of some cortical neuronal excitability [1]. The supplementary motor area (SMA) executes complex function in motor regulation [2]; PD patients have shown SMA impairment [3–7]. In a double-blind sham-controlled study, the effect of high-frequency rTMS over SMA was compared with that of a realistic sham stimulation [8]. The SMA-stimulation group exhibited modest but significant improvements in motor symptoms: mean improvements in motor scores were 4.5 points in the SMA-stimulation group (i.e. 20% reduction from baseline) and −0.1 points in the sham-stimulation group (i.e. 0% reduction from baseline). The results implied to us that SMA is an appropriate stimulation site for PD treatment, but which symptoms were improved by SMA stimulation remains unknown. We therefore analyzed the subscores of UPDRS to clarify the nature of improvements provided by SMA stimulation.

2. Patients and methods

2.1. Study design and patients

This study, performed at 15 centers throughout Japan, was a double-blind trial with a parallel design comparing SMA stimulation with sham stimulation. The study design — inclusion and exclusion criteria, clinical evaluations, evaluation time points, and procedures for interventions — has been described in detail [8].

In brief, all patients provided written informed consent before intervention. The protocol was approved by the ethics committee at each participating center. The inclusion criteria were idiopathic PD patients according to the British Parkinson's Disease Society Brain Bank criteria [9]. The exclusion criteria were dementia, major psychiatric illness, contraindications to TMS [10] and patients who had undergone TMS treatment prior to the study. Patients were assigned randomly to the SMA-stimulation group and sham-stimulation group at each center.

Clinical evaluations were conducted by another doctor who was completely blind to the type of intervention. All assessments were performed at the same time during the daily treatment cycle in each subject in all interventions to exclude some effects of time in daily life. The evaluation time points were selected when anti-parkinsonian drugs had some effect (neither the off state nor the best on state) to evaluate an add-on effect of rTMS to the usual treatment. Although a definite off and best on condition seem more appropriate for the treatment study, we were unable to set this level because our studied

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patients were all outpatients. This possible heterogeneity might limit the validity of this study's results.

The Unified Parkinson's Disease Rating Scale (UPDRS) [11] was assessed before intervention (week 1) and immediately before the stimulation sessions at weeks 2, 4, 6, and 8. They were also assessed at weeks 10 and 12. The primary outcome measure was score changes in UPDRS part 3 (UPDRS-III). It was analyzed according to the intention-to-treat (ITT) principle using the last observation carried forward (LOCF) analysis.

One session of intervention was performed once a week for the first 8 weeks. For SMA stimulation, focal rTMS was applied using a hand-held figure-of-eight coil (9 cm external diameter at each wing) connected to a magnetic stimulator, which gives a biphasic pulse; 1000 magnetic stimuli were given in one session. One train consisted of 50 pulses at 5 Hz with inter-train interval of 50 s. The stimulus intensity was fixed at the 110% active motor threshold (AMT) for the right TA muscle. The coil was centered at points 3 cm anterior to the leg motor area in the sagittal midline. For sham stimulation, we employed a realistic sham-stimulation method [8,12].

2.2. Data analysis

We performed a subanalysis of subscores of UPDRS-III on the SMA and sham-stimulation groups. The tremor score was the sum of items 20 and 21. The rigidity score was the sum of item 22 for the neck and upper/lower limbs. Other scores were speech (item 18), facial expression (item 19), rising from chair (item 27), posture (item 28), gait (item 29), postural stability (item 30), and body bradykinesia (item 31). The "bradykinesia" score was the sum of items 23–26. Item 31 was not included because it might not reflect bradykinesia directly: it was rated by the examiner's global impression after observing spontaneous gestures while sitting, and the nature of rising and walking. The above scores at baseline (week 1) and those at week 12 were compared using two-way repeated measures analysis of variance (ANOVA) (between-subject factor, INTERVENTION (SMA/sham); within-subject factor, TIME (week)). The Greenhouse–Geisser correction was used if necessary to correct for nonsphericity. Post hoc paired t tests (2 tailed) were used for additional analyses: p values less than 0.05 were considered significant. These statistical analyses were conducted on actual values of the scores.

To evaluate possible effects of our SMA stimulus on the primary leg motor area adjacent to the SMA, we analyzed the bradykinesia score in SMA group in the following ways. First, the patients in SMA group were divided into two groups based on gait improvements (item 29). The improvement group comprised patients who showed −1 point or greater improvement in the gait score. The non-improvement group comprised patients who showed 0 points or worsening of item 29. Subsequently, we compared changes in bradykinesia scores (items 23–26) in these groups using Wilcoxon's rank sum test. We also performed Fisher's exact test to determine whether item 29 and the bradykinesia score are independent. Second, the patients in the SMA group were divided into two groups based on improvements of the lower extremity function (item 26). Here again, the improvement group comprised patients who showed −1 point or greater improvement, whereas the non-improvement group comprised patients who showed 0 points or worsening for item 26. We then compared the changes in upper extremity functions (items 23–25) in these groups using Wilcoxon's rank sum test. We also performed Fisher's exact test to determine whether score changes of items 23–25 and item 26 were independent. Finally, for general interest, we performed additional correlation analyses to explore a possible relation between the baseline UPDRS-III score and the degree of bradykinesia score response to SMA stimulus. Statistical analyses were performed using software (SPSS Statistical Package, ver. 13.0; SPSS Inc.).

3. Results

We have already shown that background clinical features such as gender, Hoehn and Yahr stage, age, age of onset, duration of illness, and initial values of UPDRS-III were not different between the two intervention groups (Table 1) [8]. The means (SD) of the modified Hoehn and Yahr stage were 2.8 (0.6) for the SMA-stimulation group, and 2.9 (0.7) for the sham-stimulation group. Of the 99 patients, one was excluded from analysis because the medical treatment was changed during intervention.

Among the subscores of UPDRS-III, a significant interaction between INTERVENTION and TIME was found only in the bradykinesia score (Table 2) (two-way repeated measures ANOVA: effect of INTERVENTION, $F_{1,96}=4.207$, $p=0.043$; effect of TIME, $F_{1,96}=9.012$, $p=0.003$; TIME × INTERVENTION interaction, $F_{1,96}=5.976$, $p=0.016$). Post hoc analysis revealed a significant improvement in the bradykinesia score at week 12. No significant interaction was found in the other subscores (Table 2).

Comparison of the bradykinesia scores (items 23–26) between gait improvement and non-improvement groups based on item 29 shows that the median of score changes in the improvement group was −3 (range, −11 to 1); that in the non-improvement group was −2 (range, −6 to 6). We found no significant difference between the two groups ($p=0.075$). Table 3 presents a 2×2 cross table of changes in item 29 and bradykinesia scores. Fisher's exact test also revealed these factors as independent ($p=0.304$). We next compared changes in upper extremity functions (items 23–25) between the lower limb function improvement and non-improvement groups. We argue that if the current over the SMA spreads to the primary motor cortex for leg muscles and if it might contribute to bradykinesia score improvement, then it would present some dissociation between the changes in these scores. The median of score changes in the improvement group was −2 (range, −9 to 2); that in the non-improvement group was −1 (range, −4 to 5). We found a significant difference between the two groups ($p=0.024$), indicating that the changes in items 23–25 were associated with those in item 26. Table 4 shows a 2×2 cross table of changes in items 23–25 (upper extremity functions) and item 26 (lower extremity function). Fisher's exact test revealed that these factors are dependent ($p=0.039$). Finally, no significant correlation was found between baseline UPDRS-III scores and changes in the sum of items 23–26 (bradykinesia score) (correlation coefficient, −0.222, $p=0.103$).

Table 1
Baseline Characteristics of Patients.

	SMA group ($N=55$)	Sham group ($N=43$)
Age (year)		
Mean (SD)	65.3 (8.9)	67.4 (8.5)
Median (range)	66 (39–82)	69 (43–82)
Interquartile range	59.0–71.5	63.5–72.5
Male sex — no. (%)	29 (53)	25 (58)
Age of onset (year)		
Mean (SD)	57.2 (9.9)	59.5 (10.2)
Median (range)	58 (28–78)	61 (34–79)
Interquartile range	50.0–65.0	56.0–66.5
Duration of illness (year)		
Mean (SD)	8.1 (4.2)	7.8 (6.7)
Median (range)	8.0 (1–16)	5.0 (1–32)
Interquartile range	5.0–11.0	3.0–10.5
Hoehn–Yahr stage — no. (%)		
1	0 (0)	0 (0)
2	19 (34.5)	13 (30.2)
3	33 (60.0)	23 (53.5)
4	3 (5.5)	7 (16.3)
5	0 (0)	0 (0)

No significant difference was found between two groups for any parameter.
SMA, Supplementary motor area.

Table 2
ANOVA results.

Subscores of UPDRS-III	Item	SMA		Sham			*df*	*F*	*p*
		Baseline mean (SD)	Week 12 mean (SD)	Baseline mean (SD)	Week 12 mean (SD)				
Speech	18	0.87 (0.64)	0.92 (0.53)	1.05 (0.82)	1.16 (0.84)	TIME	1	2.907	0.091
						INTERVENTION	1	2.311	0.132
						TIME × INTERVENTION	1	0.380	0.539
Facial expression	19	1.12 (0.69)	1.10 (0.55)	1.40 (0.82)	1.35 (0.87)	TIME	1	0.470	0.495
						INTERVENTION	1	3.339	0.056
						TIME × INTERVENTION	1	0.007	0.933
Tremor	20,21	4.84 (3.65)	4.20 (3.01)	5.20 (4.10)	5.23 (4.38)	TIME	1	1.566	0.214
						INTERVENTION	1	2.099	0.151
						TIME × INTERVENTION	1	2.099	0.151
Rigidity	22	4.85 (3.18)	3.72 (2.77)	5.53 (3.63)	4.90 (3.72)	TIME	1	11.435	0.001
						INTERVENTION	1	2.239	0.138
						TIME × INTERVENTION	1	0.926	0.338
Bradykinesia	23–26	7.82 (3.68)	6.00 (4.07)	8.77 (4.90)	8.58 (5.59)	TIME	1	9.012	0.003
						INTERVENTION	1	4.207	0.043
						TIME × INTERVENTION	1	5.976	0.016
Arising from chair	27	0.60 (0.65)	0.53 (0.76)	0.86 (0.94)	0.98 (0.96)	TIME	1	0.104	0.747
						INTERVENTION	1	5.308	0.023
						TIME × INTERVENTION	1	1.965	0.164
Posture	28	1.20 (0.80)	0.98 (0.69)	1.51 (0.98)	1.44 (0.93)	TIME	1	6.818	0.010
						INTERVENTION	1	5.185	0.025
						TIME × INTERVENTION	1	1.811	0.182
Gait	29	1.15 (0.79)	1.04 (0.69)	1.30 (0.74)	1.30 (0.77)	TIME	1	0.996	0.321
						INTERVENTION	1	2.161	0.145
						TIME × INTERVENTION	1	0.996	0.321
Postural stability	30	1.12 (0.85)	0.93 (0.89)	1.21 (0.99)	1.21 (0.91)	TIME	1	1.816	0.181
						INTERVENTION	1	1.225	0.271
						TIME × INTERVENTION	1	1.816	0.181
Body bradykinesia	31	1.52 (0.79)	1.13 (0.77)	1.69 (0.99)	1.53 (0.93)	TIME	1	19.800	<0.001
						INTERVENTION	1	3.095	0.082
						TIME × INTERVENTION	1	3.517	0.064

4. Discussion

The present results showed that, in comparison to the sham stimulation, significant improvements in bradykinesia were induced by the SMA stimulation.

The pathophysiology of parkinsonian motor symptoms remains a matter of controversy [13]. Hypokinetic symptoms are apparently implicated in impaired activity of the SMA, presumably ascribed to decreased positive efferent feedback arising from the basal ganglia–thalamocortical motor loop [3–7]. The fact that only the bradykinesia scores were significantly decreased by the SMA stimulation concurs with the view that hypokinetic symptoms are associated with the SMA dysfunction in PD patients [2–7]. Furthermore, these improvements were observed two weeks after the end of the rTMS protocol. Although the mechanism of this delay remains to be determined, possible cumulative effects of rTMS and a long-lasting effect of rTMS, which lasted up to 8 days in the primate brain [14], might partly explain this delay.

We noted at least four limitations of this study. First, the SMA might not be stimulated or other parts might be affected, although the effects should be derived mainly from modulation of neuronal activity of SMA, according to several precedent reports [15]. Moreover, the evaluation of possible effects of our SMA stimulus on the primary leg motor area showed that our SMA stimulus produced substantial effects on motor functions of the upper extremities as well as on the lower extremities. Based on these observations, improvement in bradykinesia is ascribed to modulation of motor functions of upper and lower extremities. Second, more data related to UPDRS scores (in the off and best on) should be provided. Consequently, the improvement might well be attributable simply to the medication and not to rTMS of the SMA. However, it was impossible to assess an off state in our patients because all outpatients had difficulty in making hospital visits during off states. Furthermore, the baseline scores of assessments did not differ between SMA and sham groups. Importantly, we found no significant effect of the stage of the disease on the UPDRS score changes [8]. No significant correlation was found between the baseline state and the response of bradykinesia to our SMA stimulus. Third, the structure of the UPDRS motor part might be inappropriate to assess (possible) improvements of other motor symptoms (e.g. gait, postural stability,) which contain a single score item. The assessment might therefore lack sufficient sensitivity to detect small changes. Finally, recent studies of rTMS over SMA with small numbers of PD patients revealed worsening of complex movements [16]. That discrepancy might be ascribed to methodological differences such as the coil orientation (handle pointing laterally in this study versus no description in the previous study [16]), stimulus intensity (110% AMT for foot muscles in this study versus various stimulus intensities of 58–110% resting motor threshold for hand muscles in the earlier study [16]), stimulus frequency (5 Hz in

Table 3
2×2 cross table of changes in item 29 and bradykinesia score.

		Item 29 (gait)		Sum
		Improvement	Non-improvement	
Bradykinesia score (items 23–26)	Improvement	10	28	38
	Non-improvement	2	15	17
Sum		12	43	55

Table 4
2×2 cross table of changes in items 23–25 (upper extremity functions) and item 26 (lower extremity function).

		Item 26 (L/E)		Sum
		Improvement	Non-improvement	
Items 23–25 (U/E)	Improvement	24	5	29
	Non-improvement	14	12	26
Sum		38	17	55

this study versus 10 Hz [16]), session numbers (multiple sessions versus single session [16]), timing of evaluation (two weeks after rTMS versus immediately after rTMS session [16]), and the number of subjects (99 patients in this study, but only 10 subjects in the previous study [16]).

Although some shortcomings limit the scientific validity of this study, the SMA stimulation might exert modest improvement of hypokinetic symptoms in PD. These results support the hypothesis that neuronal activity of SMA is associated with hypokinetic symptoms in PD.

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Appendix A

The following doctors and institutions participated in the Group to Study Effectiveness of rTMS on Parkinson's Disease, Japan.

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