Stimulation in Supplementary Motor Area Versus Motor Cortex for Freezing of Gait in Parkinson's Disease

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Background and Purpose Freezing of gait (FOG) is a frustrating problem in Parkinson's disease (PD) for which there is no effective treatment. Our aim was to find brain stimulation areas showing greater responses for reducing FOG.

Methods Twelve PD patients with FOG were selected for inclusion. We explored the therapeutic effect of repetitive transcranial magnetic stimulation (rTMS) in the supplementary motor area (SMA) and the motor cortex (MC). We measured the number of steps, completion time, and freezing episodes during the stand-walk-sit test before and after rTMS treatment. We also tested freezing episodes in two FOG-provoking tasks.

Results There was a trend for a greater reduction in freezing episodes with SMA stimulation than MC stimulation (p=0.071). FOG was significantly improved after SMA stimulation (p<0.05) but not after MC stimulation.

Conclusions Our study suggests that the SMA is a more-appropriate target for brain stimulation when treating PD patients with FOG. This study provides evidence that stimulating the SMA using rTMS is beneficial to FOG, which might be useful for future developments of therapeutic strategies.

Key Words freezing of gait, Parkinson's disease, repetitive transcranial magnetic stimulation, supplementary motor area, motor cortex.

INTRODUCTION

Freezing of gait (FOG) is a symptom of Parkinson's disease (PD) described as "brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk."[1] FOG interferes with mobility and causes frequent falls,[1] and appears in both early- and advanced-PD patients.[2,3] It was reported that 80% of advanced-PD patients had FOG, with this also being present in 10–30% of patients in the early stages of PD.[3-6]

Treating FOG is challenging. Levodopa is generally effective, but it does not completely eliminate FOG, with patients still finding that FOG interferes with walking.[7,8] Levodopa was found to reduce the severity and frequency of FOG, but not completely eliminate it in 80% of PD patients.[7] Deep brain stimulation (DBS) of the subthalamic nucleus reduced the number of FOG episodes in a small off-medication patient cohort with short-term follow-up.[9,10] However, it has also been reported that DBS can aggravated FOG.[10] Further, the effects of rehabilitation have been inconsistent, possibly due to the smallness of included samples and evaluations being performed during the on-medication state.[11] More-effective treatments are therefore needed for FOG in PD.

Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive brain stimulation technique used to modulate brain function. The mechanism underlying the efficacy of rTMS

is poorly understood. rTMS is thought to induce cortical excitability and synaptic plasticity. Its aftereffects are postulated to be associated with calcium dynamics for cellular processes, gene activation and regulation, protein expression, homeostatic plasticity, and changes in the glial network.[12,13] Two recent meta-analyses suggested that rTMS can improve motor function in PD, although FOG was not addressed.[14,15] The few studies that have investigated the effects of rTMS on FOG have produced inconsistent results, possibly due to the application of diverse stimulation methods and the unpredictability and episodicity of FOG.[1] The motor cortex (MC) was suggested as a suitable stimulation site for add-on treatment in medicated PD with FOG,[16] but this effect was not confirmed in another study.[17] Stimulation of the dorsolateral prefrontal and premotor cortices produced negative results.[17,18] The supplementary motor area (SMA) might be efficacious since it is a pivotal area in the basal ganglia-cortical motor loop, is impaired in PD,[19] and is activated less in PD with FOG than in PD without FOG.[20]

Our aim was to identify an effective stimulation area based on objective measurements in PD with FOG. We provoked FOG by applying specific methods that were also used in a previous study.[21]

METHODS

Patients
We enrolled 12 PD right-handed patients (age 68.5±7.1 years, mean±SD; 6 women) with FOG who visited our hospitals from September 2014 to April 2016. PD was diagnosed according to UK Brain Bank criteria.[22] FOG was identified in participating patients at an outpatient clinic by a movement disorder specialist (S.J.K.). All participants could walk without assistance. Exclusion criteria were neurological disorders other than PD, previous history of seizure, epilepsy, and intracranial or cardiac metallic implants.[23] All patients provided written informed consent. The study was approved by our Internal Review Board (approval number: 2013-011). The clinical trial identifier number is NCT01853150.

Study design
This study employed a pseudorandomized, double-blind, parallel design to compare between SMA and MC stimulation. Patients were evaluated based on the Hoehn and Yahr stage (HY stage), the Unified Parkinson's Disease Rating Scale (UPDRS), Korean version of the Mini Mental State Examination, Beck Depression Inventory (BDI), Festination of Gait Questionnaire (FSG-Q), Freezing of Gait Questionnaire (FOG-Q), and antiparkinsonian medication at the first visit.[24,25] The levodopa equivalent daily dose (LEDD) was calculated using the standard formula.[26] All experiments were conducted at the same time point in each patient's daily treatment cycle. The evaluations were performed in the on-medication state.[27]

rTMS interventions
Participants received focal rTMS over two consecutive days, with it being applied via a 70-mm double-air-film coil over the left MC or SMA. The location of rTMS was newly determined at each visit. rTMS was applied with the right first dorsal interosseous muscle at rest. The resting motor threshold (RMT) was measured as the lowest stimulus intensity required to produce motor-evoked potentials of at least 50 μV in at least 5 of 10 consecutive trials, and the rTMS stimulation intensity was then set at 100% of this RMT. In the MC stimulation group, the MC hand area was stimulated because it is more accessible than the leg area, and several previous studies have shown that several body parts can be simultaneously affected by stimulation to the distal hand area. Positive effects of rTMS have been reported on gait[28-30] and on shoulder bradykinesia with distal hand area stimulation.[31] In the SMA stimulation group, the coil was centered on the midline at 4 cm anterior to the vertex (Cz in the International 10−20 EEG system).[32] rTMS was delivered using a Magstim Super-Rapid[2] stimulator (Magstim, Wales, UK) in a series of four rTMS blocks separated by 10 minutes. Each block consisted of 15 to 25 pulse trains of 1-second duration at 25 Hz, with an intertrain interval of 10 seconds. The intertrain interval refers to the interval between the last pulse of a train to the first pulse of the next train (Fig. 1).[31] rTMS was applied in the on-medication state.[27]

Outcome measurements
Participants were asked to perform the tasks as described below before rTMS was applied on the 1st day and immediately after rTMS was applied on the 2nd day. All task performances were recorded on video and were assessed by a blinded rater.

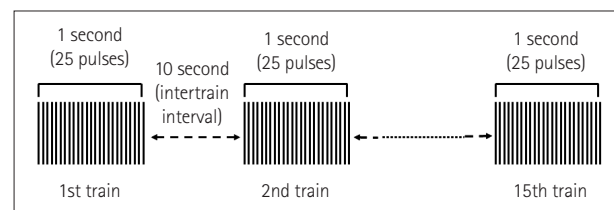Patients were asked to perform the stand-walk-sit (SWS)

Fig. 1. One block of the protocol for repetitive transcranial magnetic stimulation. The intertrain interval is the interval between the last pulse of a train to the first pulse of the next train. Four blocks were applied with a 10-minute interval during each visit.

test by standing up, walking 10 m, turning back, and sitting down as quickly as possible. To elicit FOG, patients performed 360° turns as rapidly as possible from a standstill within a restricted area with two leftward turns and two rightward turns in random order. Patients performed another task simultaneously (called the dual task, which involved subtracting 7 serially from 100) during the SWS test.[21] At the end of the experiment on the 2nd day, the Patient Global Impression and Clinical Global Impression rating scales were applied to assess the effect of rTMS.[33] The number of steps and the completion time of the SWS test were measured. Freezing episodes during the SWS test, rapid-full-turn test, and the dual task during SWS test were analyzed.

Statistical analyses

Demographics, clinical variables, and relative changes in the outcome measurements were compared between the two interventions by Mann-Whitney and Fisher's exact tests as appropriate. The relative change in each measurement between pre- and postintervention was calculated as [(value at postintervention-value at preintervention)/(value at postint-

ervention+value at preintervention)/2]×100. If both values were 0 at the pre- and postinterventions, 1.0 was added in order to prevent the denominator from being 0. The outcome measurements before and after interventions within each group were compared using Wilcoxon signed-rank tests. Probability values of $p < 0.05$ were considered statistically significant.

RESULTS

There was no difference in demographics, BDI score, HY stage, UPDRS score, total LEDD, FSG-Q total score, or FOG-Q total score between the two interventions (Table 1). There was also no difference in the relative change in gait or freezing variables after rTMS between the SMA and MC groups, but trends for relative changes in freezing episodes during the SWS test ($p = 0.097$) and the rapid-full-turn test ($p = 0.071$) were seen. There were fewer freezing episodes in the SMA group than in the MC group (Table 1). A significant improvement in gait and a reduction in the number of freezing episodes from baseline were seen in the SMA group ($p < 0.05$)

Table 1. Clinical features of patients and the relative changes in gait parameters after rTMS

	SMA (n=6)	MC (n=6)	p
Age (years)	69.5±6.2	67.5±8.3	0.935
Sex (women)	4	2	0.284
K-MMSE	26.2±2.4	26.5±3.8	0.686
Education (years)	8.3±3.5	7.8±4.2	0.870
BDI	22.5±14.8	19.8±11.0	0.748
HY stage	2.8±0.3	2.8±0.7	0.388
UPDRS total	55.7±11.9	55.5±17.4	0.873
UPDRS I	2.8±1.8	4.0±1.1	0.138
UPDRS II	16.2±5.0	16.8±7.1	0.936
UPDRS III	29.0±8.5	28.1±11.7	0.631
UPDRS IV	7.7±5.4	6.7±4.0	0.746
Total LEDD (mg)	958.5±226.0	813.5±313.5	0.262
FSG-Q score	4.3±2.3	3.5±2.1	0.327
FOG-Q score	18.0±3.6	15.0±4.0	0.145
RMT (%)	56.7±4.4	61.0±3.7	0.106
SWS test (%)			
Relative change in steps*	-20.1±13.7	-20.7±22.8	0.873
Relative change in time*	-16.1±12.5	-17.0±26.1	0.873
Relative change in freezing episodes*	-127.8±85.4	-44.8±78.0	0.097
SWS test with provocation (%)			
Relative change in freezing episodes during turning*	-114.9±81.0	1.7±141.5	0.071
Relative change in freezing episodes during a dual task*	-70.0±83.7	-3.7±9.1	0.153

Data are n or mean±SD values.
*Negative value indicates that the value of the gait parameter decreased after rTMS.
BDI: Beck Depression Inventory, FOG-Q: Freezing of Gait Questionnaire, FSG-Q: Festination of Gait Questionnaire, HY stage: Hoehn and Yahr stage, K-MMSE: Korean version of the Mini Mental State Examination, LEDD: levodopa equivalent daily dose, RMT: resting motor threshold, rTMS: repetitive transcranial magnetic stimulation, SWS test: stand-walk-sit test, UPDRS: Unified Parkinson's Disease Rating Scale.

(Fig. 2A-E), whereas there were no significant changes from baseline in the MC group (Fig. 2F-J).

DISCUSSION

Our results suggest that the SMA is a more-appropriate site for rTMS in PD patients with FOG. SMA stimulation improved FOG, with there being fewer steps, a shorter walk time, and fewer freezing events during the SWS test in the SMA group than in the MC group, although the differences were not statistically significant. Compared with prestimulation findings, the number of freezing episodes clearly decreased significantly after SMA stimulation but not after MC stimulation.

Previous imaging studies suggest that the SMA is closely associated with FOG. During gait motor imaging, brain activity was decreased in the SMA and increased in the mesen-
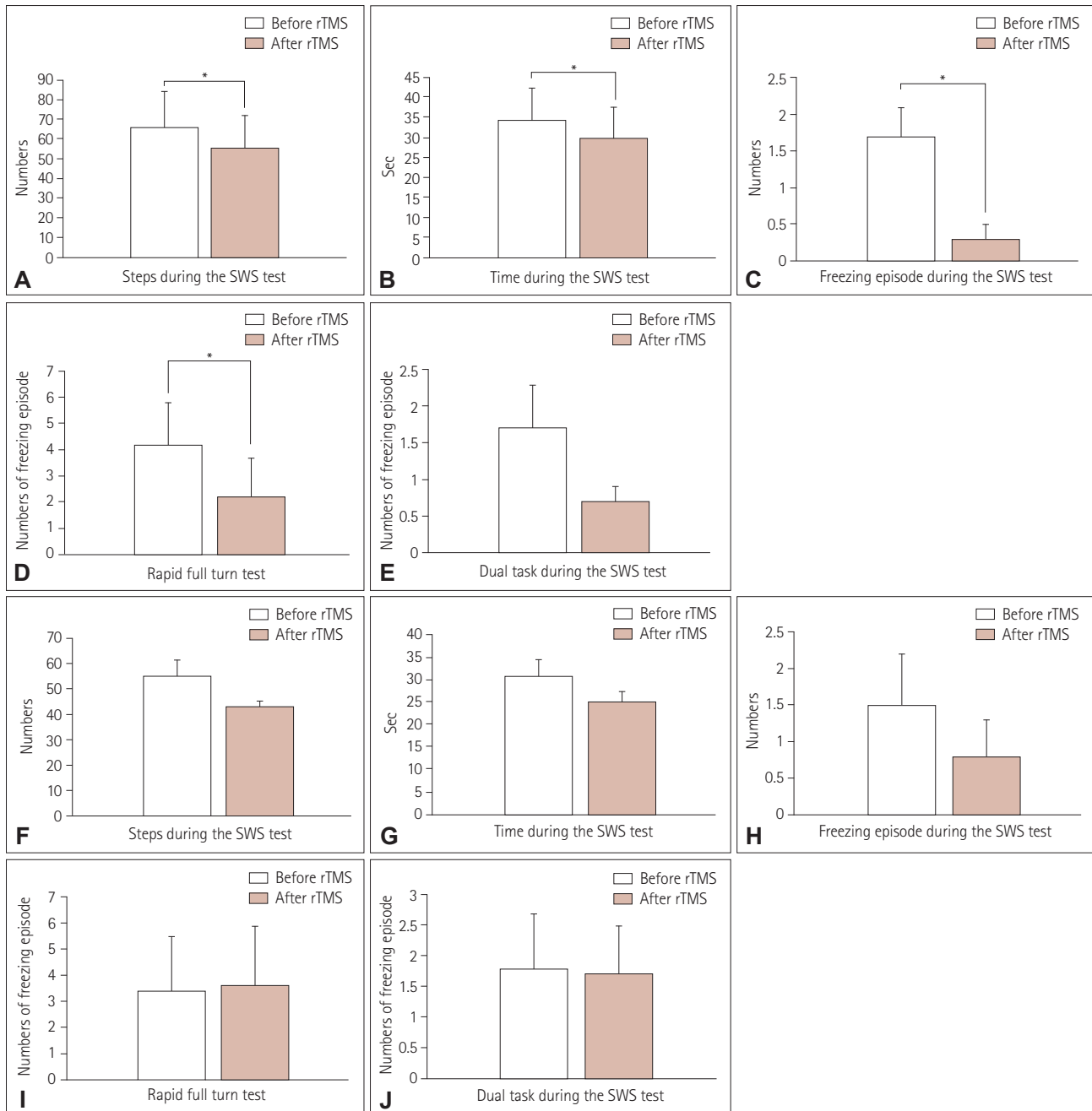

Fig. 2. Comparison of gait parameters before and after stimulation of the SMA (A-E) and after MC stimulation (F-J). Gait parameters were improved and freezing episodes were reduced from baseline in the SMA group, whereas there were no significant changes in gait and freezing episodes from baseline in the MC group. *$p<0.05$. MC: motor cortex, rTMS: repetitive transcranial magnetic stimulation, SMA: supplementary motor area, SWS: stand-walk-sit.

cephalic locomotor region in PD with FOG.[20] Those brain areas that were active during cognitive loading, which is associated with FOG, showed less recruitment in PD with FOG (bilateral anterior insula, ventral striatum, and pre-SMA).[34]

The SMA is located anterior to the MC leg area. Recent anatomical studies suggest that the SMA comprises two distinct parts: the pre-SMA (rostral part) that is linked to the prefrontal cortex, and the SMA proper (caudal part) that is joined directly to the MC, dorsal premotor cortex, and spinal cord.[35,36] The SMA is important in several types of motor processes and is activated before movement initiation.[19,36] It is active during voluntary and externally triggered actions, sequential movements, learning processes, and executive control.[19] During movements, the SMA participates in action preparation, the initiation and selection of actions, motor learning, inhibition, conditional action, action control, and monitoring of action outcomes;[36] however, its precise roles in these various processes remain uncertain. It was recently suggested that the SMA participates in cognitive processes underlying sensorimotor integration, and its role might be to combine individual actions into a sequential process.[35]

Because the SMA reportedly adjusts anticipatory postures by shifting the body weight during gait, it might coordinate postural adjustment and stepping. The SMA might be unable to regulate submovements in FOG, which would hinder the performing of sequential movements during automatic gait.[37]

Only one previous study has investigated rTMS therapeutic effects over three different regions (MC, SMA, and dorsolateral prefrontal cortex) in heterogeneous disease populations showing parkinsonism, including patients with PD, vascular parkinsonism, multiple-system atrophy, and Lewy-body disease.[38] Those authors reported that MC stimulation was effective for FOG and gait, whereas SMA stimulation was not. It is difficult to compare that study with ours due to differences in their designs in terms of stimulation frequencies, disease groups, and methods of FOG evaluation. FOG is generally difficult to measure because it occurs episodically in specific situations such as turning or passing through a narrow walkway. This means that the specific task used to provoke FOG is important. A previous study found that 360° turns were more effective than 180° turns,[21] and so the former were used in the present study. We also used another provocation task (the dual task) to substantiate our findings.

rTMS has recently been shown to exert therapeutic effects in several neurological and psychiatric disorders.[12] Despite the positive results obtained when applying rTMS, greater standardization may be needed in order to facilitate its implementation in clinical practice. Many different types of stimulation protocols have been used previously, with some taking a long time (due to the numbers of stimulations or the num-

ber of visits required for treatment) and also the stimulation sites used being inconsistent even in the same disease.[14-18] Because patients with neurological and psychiatric diseases may be fragile both physically and mentally, it is essential to apply rTMS in the most effective way possible and in as a short time as possible. Our study suggests that the SMA is a more-effective therapeutic target for FOG, and hence should be considered the primary target area for FOG treatments.

This study was subject to some limitations. First, the sample was small and we did not include a control group. We had difficulty registering patients for several reasons, including the poor mobility associated with FOG, the distance from home to our hospitals the requirement for several visits, and the application of rather strict exclusion criteria. Patients with dementia were initially excluded since cognition can affect gait, and patients with cognitive impairment might also be less cooperative due to their impaired understanding. However, this adversely affected the sample size since most PD patients with FOG are in an advanced state, and they often exhibit cognitive impairment. Second, we targeted the MC hand area due to ease of accessibility. The left-hemisphere MC was also stimulated, whereas SMA stimulation was presumed to affect both hemispheres simultaneously.[39] Bilateral MC stimulation should be addressed in future studies. We do not know whether stimulation of the dominant or bilateral hemisphere is more effective. The same number of rTMS pulses should have been applied to a specific area in the MC and SMA groups, but this is impossible in bilateral MC stimulation if the total number of pulses must be constant in each group. Also, we had to conduct our experiment as rapidly as possible, because participants with advanced PD are more likely to tire quickly. Bilateral MC stimulation lengthens the duration of its experiment, which would have resulted in bias. Third, we did not use a computerized navigation system to localize the SMA, instead targeting the area based on a previous study.[32] The closeness of the SMA to the MC for the leg may make it difficult to discern if the rTMS effects came from the SMA or the leg-area MC stimulation. This issue could be addressed by performing objective navigation to confirm the stimulation site or including a control group that receives leg MC rTMS. Fourth, we did not assess later time points after rTMS (e.g., 24 hours). Because some studies have shown greater improvement of motor function at later times,[16,40] including measurements at later time points would have been helpful for drawing definitive conclusions. All of these limitations mean that further studies are needed to confirm the present findings, including larger sham-controlled trials, the use of navigation systems for accurately identifying the location of stimulation targets, and more-extended exploration for determining possible candidates in-

cluding the dorsolateral prefrontal cortex, leg area MC, and bilateral MC stimulation.

Our study found that SMA stimulation improved the general gait pattern and FOG in PD, whereas MC stimulation did not. These results suggest that SMA stimulation is a more-appropriate target in PD patients with FOG. The results of our study provide evidence that stimulating the SMA using rTMS can exert beneficial effects on FOG, which might be useful for future developments of therapeutic strategies.

Conflicts of Interest

Acknowledgements

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