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High-frequency rTMS over the supplementary motor area improves freezing of gait in Parkinson's disease: a randomized controlled trial

Tao-Mian Mi[a,b,c], Saurabh Garg[c], Fang Ba[d], Ai-Ping Liu[e,**], Tao Wu[b], Lin-Lin Gao[b], Xiao-Juan Dan[b], Piu Chan[a,b,f,g,*], Martin J. McKeown[c,h]

[a] National Clinical Research Center for Geriatric Disorders, Beijing, China
[b] Department of Neurology, Neurobiology and Geriatrics, Xuanwu Hospital of Capital Medical University, Beijing Institute for Brain Disorders, Beijing, China
[c] Pacific Parkinson's Research Centre, University of British Columbia, Vancouver, Canada
[d] Division of Neurology, Department of Medicine, University of Alberta, Edmonton, Canada
[e] University of Science and Technology of China, Hefei, Anhui, China
[f] Clinical Center for Parkinson's Disease, Capital Medical University, Beijing, China
[g] Key Laboratory for Neurodegenerative Disease of the Ministry of Education, Beijing Key Laboratory for Parkinson's Disease, Beijing, China
[h] Department of Medicine (Neurology), University of British Columbia, Vancouver, Canada

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ABSTRACT

Introduction: Freezing of gait (FOG) contributes to falls in Parkinson's disease (PD), but robust, effective treatments remain elusive. There is evidence indicating that the supplementary motor area (SMA) plays an important role in the pathogenesis of FOG and may therefore be a potential neuromodulation target. The present study explored the clinical efficacy of high-frequency repetitive transcranial magnetic stimulation (rTMS) over the SMA on FOG in PD patients.

Methods: A group of 30 PD patients with FOG were enrolled in a randomized, double-blind, sham-controlled trial. Patients were randomly allocated 2:1 to receive ten sessions of either *real* (N = 20) or *sham* (N = 10) 10 Hz rTMS over SMA. The patients were assessed at baseline (T_0), after the 5th (T_1) and 10th (T_2) sessions, and then 2 weeks (T_3) and 4 weeks (T_4) after the last session. The primary clinical outcome was the Freezing of Gait Questionnaire score (FOGQ), with the Movement Disorder Society-Unified Parkinson's Disease Rating Scale motor scores (MDS-UPDRS III) and Timed Up and Go test as secondary clinical outcomes. All the assessments were carried out at the "ON" state.

Results: With a four week's follow-up, there were significant interaction effects in the FOGQ (effect of group*-time, $p = 0.04$), MDS-UPDRS III ($p = 0.02$) and several gait variables (total duration, $p < 0.01$; cadence, $p = 0.04$; turn duration, $p = 0.01$; and turn to sit duration, $p = 0.02$). *Post-hoc* analyses revealed a significantly decreased FOGQ score at T_2 and T_4, and significant improvements of MDS-UPDRS III and gait variables at T_1, T_2, T_3 and T_4 in the rTMS group. No significant improvements were found in the *sham* group.

Conclusion: High-frequency rTMS over SMA may ultimately serve as an add-on therapy for alleviating FOG in PD patients.

1. Introduction

Freezing of gait (FOG), a common and debilitating symptom in Parkinson's disease (PD), is characterized by sudden and brief episodes of inability to produce effective forward stepping [1]. FOG is a major risk factor for falls and contributes greatly to reduced mobility and quality of life, with 21%–27% of PD patients report experiencing FOG even in the early stages [2], and increasing up to 80% in later stages [3]. Treatment of FOG can be very challenging, as evidence for pharmacological treatment, deep brain stimulation, and rehabilitation strategies, is inconclusive, with no widely accepted treatment protocols available [4]. Development of new effective therapeutic strategies is sorely needed. Repetitive transcranial magnetic stimulation (rTMS), a noninvasive neural modulation technique, has been applied as a treatment for various neurologic and psychiatric disorders [5]. Several meta-analysis studies have demonstrated that rTMS can improve motor

* Corresponding author. 45 Changchun Street, Xicheng District, Beijing, 100053, China.
** Corresponding author. 443 Huangshan Road, Hefei, Anhui, 230027, China.
E-mail addresses: aipingl@ustc.edu.cn (A.-P. Liu), pbchan@hotmail.com (P. Chan).

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symptoms for PD patients [5–7]. However, very few rTMS studies have so far focused on FOG in PD patients [8–13], and most prior rTMS studies have thus far targeted the dorsolateral prefrontal [8–10] or primary motor cortices [11,12] as stimulation sites. One recent study compared rTMS effects when applied to the SMA versus motor cortex on FOG, but only two sessions of rTMS were performed and only a small number of subjects were investigated (6 patients in each group). However, even in this small sample, significant improvements in FOG were observed after SMA, but not after motor cortex stimulation [13].

There is increasing evidence indicating that the supplementary motor area (SMA) plays an important role in the pathogenesis of FOG in PD [14–17], and may therefore be a potential stimulation target. Anticipatory postural adjustments mediated by SMA are crucial for gait initiation prior to voluntary movement [14], and progressively altered brain activity in the SMA [15] and dysfunction of circuits connected with the SMA [16] have also previously been implicated in the pathogenesis of FOG in PD. Similarly, the "decoupling model of FOG" suggests that breakdown in coupling between posture preparation by the SMA and step initiation by the motor cortex may be responsible for the "start hesitation" seen in FOG [17]. In light of the evidence showing impaired activity of the SMA in FOG, we propose that the SMA might be a suitable therapeutic site for rTMS treatment for FOG in PD. In the present study, we aimed to investigate the clinical efficiency of high-frequency rTMS over SMA on FOG in PD patients.

2. Material and methods

2.1. Participants

Thirty PD patients with FOG (PD-FOG) were recruited from the Movement Disorders Clinic of the Xuanwu Hospital of Capital Medical University between May 2016 and December 2018. Idiopathic PD was diagnosed according to the UK Brain Bank Clinical Criteria. FOG subjects were identified by three criteria as suggested previously [18]: (i) convincing subjective reports of FOG, based on consistent behavioral characteristics of the phenomenon (including a typical feeling of the feet being "glued" to the floor); (ii) patients' recognition of a typical phenotype by showing them a short video (70s) demonstrating typical freezing episodes; and (iii) response to a standardized gait task that contained specific elements known to provoke FOG, including gait initiation, a narrow passage, dual tasking, and rapid 360° axial turns in both directions. Patients presenting with one or more of these three criteria were classified as PD-FOG subjects. Exclusion criteria were: (i) presence of contraindications for rTMS; (ii) history of deep brain stimulation surgery; (iii) marked rest tremor; and (iv) history of receiving any kinds of rTMS.

The experiments were performed according to the Declaration of Helsinki and were approved by the Institutional Review Board of Xuanwu Hospital of Capital Medical University. Written informed consent was obtained from all participants prior to the study. The present study was registered at the Clinical Trial Registration (http://www.clinicaltrials.gov, NCT03219892).

2.2. Study design

This study was a randomized, double-blind, *sham*-controlled experiment with a parallel design consisting of two arms: 10-Hz rTMS over SMA and *sham* stimulation. The 30 PD-FOG patients were randomly assigned (with a 2:1 ratio) with sealed envelopes into two groups, to receive either a rTMS (N = 20) or *sham* (N = 10) protocol. An unbalanced allocation was chosen in the present study to maximize the likelihood of achieving recruitment targets. The randomization sequence was revealed only to the unmasked clinician responsible for the rTMS protocols. Patients were blinded to randomization group. Medication was kept constant throughout the trial, and intervention was performed at approximately the same time of day for each patient.

2.3. The rTMS and sham protocol

We performed the *rTMS* or *sham* protocol in ten sessions over two successive weeks, one session per day for five consecutive days per week. For the rTMS, a 7-cm, handheld, figure-of-8 coil was connected to a biphasic magnetic stimulator (Magstim Rapid; TheMagstim Co. Ltd., UK). As the SMA is located on the medial aspect of the brain, focal rTMS resulted in bilateral SMAs stimulation. As suggested previously [19], the SMA stimulation site was determined as 3 cm anterior to the optimal position for activation of the right abductor hallucis muscle by moving the coil along the sagittal midline around Cz with the handle pointing to the right, which equated to a position of 1–4 cm (2–3 cm in most subjects) anterior to Cz [20]. For those whose abductor hallucis muscle MEPs (3 subjects in the rTMS group and 1 in the *sham* group) were not able to be elicited, the SMA site was determined as 3 cm anterior to Cz. A prior TMS-neuronavigation combination study has suggested that the SMA is robustly stimulated by TMS with this position [21]. While we cannot totally rule out the possibility that other regions other than SMA were stimulated in a subset of subjects, prior work suggests that the effects are mainly from the neuromodulation of SMA [19]. The coil was held so that the induced current was perpendicular to the midline. The stimulus intensity was set to 90% of the resting motor threshold for the first dorsal interosseous muscle when the primary motor hand area was stimulated. The resting motor thresholds in the rTMS and *sham* group were 50.7% ± 7.4% and 55.1% ± 7.6% respectively, with a stimulus intensity of 45.6% ± 6.7% and 46.0% ± 6.8% respectively. In each session, a 5-s burst of 10-Hz rTMS was repeated every minute for 20 times (in total, 1000 pulses, 20 min' duration). For the *sham* rTMS, the same stimulation parameters were used, but the coil was placed in 90° angulation over the SMA so that no relevant current flow was induced in the cortical tissue. All the rTMS protocols were given at rest in a seated position, with the coil handle pointing to the right.

2.4. Clinical assessments

For the baseline clinical assessments (T_0), the patients were evaluated during their "ON" medication state, including the Movement Disorder Society-Unified Parkinson's Disease Rating Scale motor scores (MDS-UPDRS III), Hoehn and Yahr (H–Y) stage, Freezing of Gait Questionnaire (FOGQ), Mini-Mental State Examination (MMSE), and Montreal Cognitive Assessment (MoCA). The demographic and clinical characteristics of the participants are shown in Table 1.

The follow-up evaluations were performed four times for each

Table 1
Demographic and clinical features of participants.

Variables	rTMS group (N = 20)	*sham* group (N = 10)	P
Gender (female/male)	11/9	5/5	0.80
Age (years)	62.65 ± 10.56	65.60 ± 8.68	0.42
Disease duration (years)	9.15 ± 5.82	7.40 ± 4.83	0.39
Onset side (B/R/L)	3/12/5	2/7/1	0.62
H–Y stage	2.60 ± 0.85	2.35 ± 0.91	0.48
MDS-UPDRS III (ON)	34.15 ± 13.60	35.30 ± 16.71	0.85
LEDD (mg/d)	759.5 ± 458.4	637.2 ± 434.3	0.48
FOG subtype (OFF/OFF-ON freezer)	15/5	7/3	0.77
FOGQ	15.85 ± 4.87	14.70 ± 4.03	0.50
MMSE	28.30 ± 2.61	29.10 ± 1.60	0.31
MoCA	25.10 ± 4.61	25.50 ± 4.35	0.82

Means and SD are shown for continuous variables. FOG: freezing of gait; Onset Side (B/R/L): Bilateral/Right/Left onset; H–Y stage: Hoehn and Yahr stage; MDS-UPDRS III: Movement Disorder Society-Unified Parkinson's Disease Rating Scale motor score; FOGQ: freezing of gait questionnaire; LEDD: levodopa equivalent daily dose; MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment. *: $p < 0.01$.

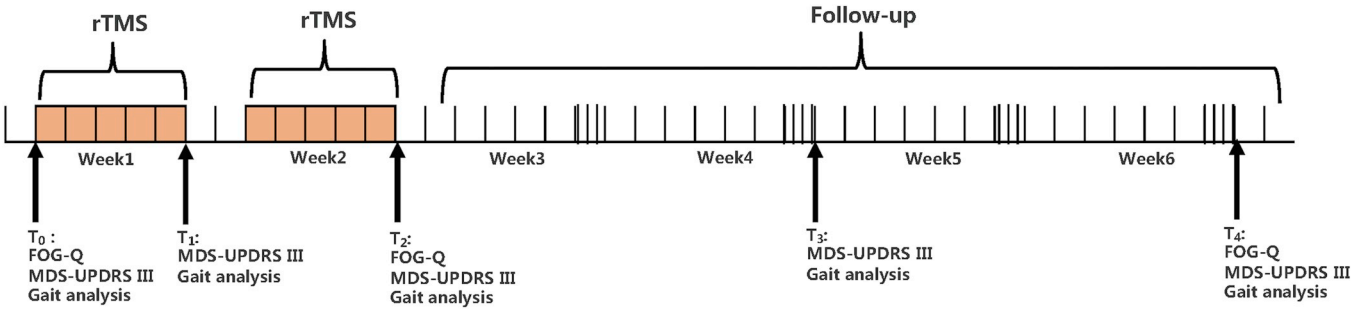

Fig. 1. Flow chart of the experimental design.

participant, that is, after the 5th and 10th sessions, and then 2 weeks and 4 weeks after the last session, defined as T_1, T_2, T_3 and T_4 respectively (Fig. 1). Because FOG episodes are highly variable and commonly transient [1], we adopted the FOGQ score (a self-assessment scale for evaluating FOG severity) as the primary clinical outcome [8–11]. The MDS-UPDRS III scores were included as a secondary clinical outcome. Additionally, as FOGQ is a subjective measure, we also adopted an additional objective evaluation tool, a Timed Up-and-Go (TUG) test, as another secondary outcome. The TUG test involved standing up from a chair, walking 7 m, turning around to walk back to the chair, and sitting back down. Quantitative assessments of gait were acquired using Opal inertial sensors and the clinical user interface and automated algorithms of MobilityLab (APDM Inc. http://apdm.com). Gait variables, including the duration from sit to stand, stride length, stride velocity, cadence, double support time percentage, turn duration and turn to sit duration, were determined by MobilityLab [22]. The TUG task was repeated twice in each turn direction and the average was used for further analysis. The FOGQ scores were assessed at T_0, T_2, and T_4, while the MDS-UPDRS III scores and gait analyses were assessed at T_0, T_1, T_2, T_3 and T_4. As the patients may need a long period to notice the effect on their routine activities and to change self-perceptions on the FOG phenomenon [8], the FOGQ scores were only assessed at T_0, T_2 and T_4 in the present study, rather than at all five time points. All assessments were carried out in the "ON" state at approximately the same time of the day.

2.5. Statistics analysis

The sample size was calculated using the pooled estimate of within-group SDs of FOGQ (the primary clinical outcome) obtained from a previous study [11]. The sample size was determined *a priori* using G*Power, assuming a moderate effect size of 0.48, $\alpha = 0.05$, power = 0.8, number of groups = 2, number of measurements (for the primary outcome/FOGQ) = 3 for a two-way repeated measures analysis of variance. The total sample size needed was 26. Our final sample size of 20 patients in the rTMS group and 10 patients in the *sham* group provided a power of 87.9% with a two-tailed $\alpha < 0.05$.

Demographic data were presented as mean ± SD for continuous variables. Independent two samples *t*-test was performed for the comparison of continuous variables, and the χ^2 test was used to compare categorical variables. A mixed effect model repeated measures (MMRM) model, widely used in many previous studies for repeated measured data [23,24], was applied to estimate the effects of rTMS on the clinical outcomes. For each variable, we applied a separate model where the independent variables were the group (rTMS, *sham*) and the time (T_0, T_1, T_2, T_3, and T_4), and the group*time condition interaction term. The fixed factors in these models were group and time, while the random factor was the subject. The threshold for the level of significance was set at $\alpha = 0.05$. All statistical analyses were performed using JMP Pro 12.0 software (SAS Institute Inc., NC).

3. Results

3.1. Participants

The demographic and clinical characteristics of the participants are shown in Table 1. All of the PD-FOG subjects enrolled in the present study were either OFF freezers (freezing occurs predominantly or even exclusively in the OFF-state) or OFF/ON freezers (dopamine-resistant and no difference between ON and OFF-state). Patients in the rTMS and *sham* group had similar baseline characteristics, including gender, age, disease duration, H–Y stage, FOG subtype, MDS-UPDRS III scores, levodopa equivalent daily dose (LEDD), FOG subtype, FOGQ score, MMSE and MoCA.

3.2. Clinical efficacy-FOGQ score

As shown in Table 2, in the comparison of FOGQ score changes between the rTMS and *sham* group, there was a significant interaction between group and time (effect of group*time, p = 0.04). A *post-hoc* analysis demonstrated a significantly decreased FOGQ score at T_2 and T_4 in the rTMS group. Score changes from baseline at T_2 and T_4 were −1.60 (95% CI -2.37 to −0.83) and −2.13 points (95% CI -2.97 to −1.29), respectively. No significant changes were found in the *sham* group. These results indicated that the rTMS has an improved effect on FOGQ score over time (Fig. 2a).

3.3. Clinical efficacy-MDS-UPDRS scores

Similarly, MMRM analysis of the MDS-UPDRS III scores revealed a significant group*time interaction (effect of group*time, p = 0.02), indicating that the rTMS could significantly improve the MDS-UPDRS III scores over time, while they were unaffected by *sham* stimulation (Fig. 2b). *Post hoc* analyses also revealed that when compared to T_0, there were significant improvements in the rTMS group at T_1, T_2, T_3, and T_4, whereas no changes were found in the *sham* group. MDS-UPDRS III changed by −3.00 (95% CI -4.92 to −1.08), −5.20 (95% CI -7.12 to −3.28), −6.69 (95% CI -8.73 to −4.66) and −5.79 points (95% CI -7.86 to −3.71), from baseline (T_0) to T_1, T_2, T_3, and T_4 respectively. In addition, we further analyzed the change of FOG subscore of MDS-UPDRS (Item-11) among the two groups, and no significant group*time interaction was found (effect of group*time, p = 0.71).

3.4. Clinical efficacy-Gait variables

Among the MMRM analyses for gait variables, significant interactions between group and time were found in total duration (effect of group*time, $p < 0.01$), cadence (p = 0.04), turn duration (p = 0.01), and duration of turn to sit (p = 0.02) (Fig. 2c–f). The rTMS reduced the total duration, turn duration, and turn to sit duration from T_1 to T_4, whereas no improvements were found in the *sham* group. Changes of the total duration from baseline at T_1 to T_4 were −3.04 (95% CI -4.34 to −1.75), −2.54 (95% CI -3.86 to −1.22), −1.91 (95% CI -3.35 to

Table 2
Clinical efficiency of the rTMS and *sham* protocol.

	rTMS group	*Sham* group		DF	F	P
FOGQ						
T_0	16.04 ± 0.82	16.00 ± 1.84	group	1	0.34	0.56
T_2	14.44 ± 0.82	15.40 ± 1.83	time	2	3.04	0.06
T_4	13.91 ± 0.84	16.40 ± 1.84	group*time	2	3.57	0.04*
MDS-UPDRS III						
T_0	34.75 ± 3.08	35.40 ± 4.36	group	1	0.62	0.44
T_1	31.75 ± 3.08	35.10 ± 4.36	time	4	7.12	< .01*
T_2	29.55 ± 3.08	34.60 ± 4.36	group*time	4	3.15	0.02*
T_3	28.06 ± 3.10	33.41 ± 4.37				
T_4	28.96 ± 3.11	35.16 ± 4.39				
Gait performance						
Total Duration (s)						
T_0	26.15 ± 2.16	27.34 ± 3.06	group	1	1.44	0.24
T_1	23.11 ± 2.16	28.45 ± 3.07	time	4	1.41	0.23
T_2	23.61 ± 2.17	28.13 ± 3.06	group*time	4	4.97	< .01*
T_3	24.24 ± 2.19	29.46 ± 3.08				
T_4	23.70 ± 2.19	29.50 ± 3.10				
Stride Length (m)						
T_0	1.09 ± 0.05	1.02 ± 0.07	group	1	0.33	0.57
T_1	1.09 ± 0.05	1.03 ± 0.07	time	4	1.17	0.33
T_2	1.07 ± 0.05	1.04 ± 0.07	group*time	4	0.69	0.60
T_3	1.06 ± 0.05	1.03 ± 0.07				
T_4	1.10 ± 0.05	1.07 ± 0.07				
Stride Velocity (m/s)						
T_0	1.04 ± 0.04	0.98 ± 0.07	group	1	0.19	0.66
T_1	1.05 ± 0.05	1.01 ± 0.07	time	4	1.26	0.29
T_2	1.03 ± 0.05	1.02 ± 0.07	group*time	4	0.56	0.70
T_3	1.04 ± 0.05	1.00 ± 0.07				
T_4	1.06 ± 0.05	1.03 ± 0.07				
Cadence (steps/min)						
T_0	113.73 ± 2.07	122.89 ± 2.92	group	1	0.92	0.34
T_1	115.98 ± 2.07	118.24 ± 3.00	time	4	0.72	0.58
T_2	115.63 ± 2.09	118.33 ± 2.92	group*time	4	2.68	0.04*
T_3	117.16 ± 2.23	119.07 ± 3.09				
T_4	116.40 ± 2.23	114.89 ± 3.20				
Gait: Double Support (%)						
T_0	21.62 ± 1.25	23.91 ± 1.77	group	1	1.35	0.25
T_1	21.90 ± 1.25	24.87 ± 1.80	time	4	0.34	0.85
T_2	21.98 ± 1.26	24.57 ± 1.77	group*time	4	0.20	0.94
T_3	22.83 ± 1.32	24.48 ± 1.84				
T_4	22.62 ± 1.32	24.39 ± 1.89				
Turn: Duration (s)						
T_0	4.01 ± 0.47	4.10 ± 0.66	group	1	1.12	0.30
T_1	3.53 ± 0.47	4.61 ± 0.67	time	4	0.36	0.83
T_2	3.39 ± 0.47	4.46 ± 0.67	group*time	4	3.30	0.01*
T_3	3.59 ± 0.48	4.36 ± 0.67				
T_4	3.54 ± 0.48	4.69 ± 0.68				
Sit to Stand (s)						
T_0	2.46 ± 0.12	2.43 ± 0.18	group	1	0.12	0.73
T_1	2.16 ± 0.12	2.54 ± 0.18	time	4	0.65	0.63
T_2	2.51 ± 0.12	2.18 ± 0.18	group*time	4	2.33	0.06
T_3	2.40 ± 0.14	2.42 ± 0.19				
T_4	2.41 ± 0.14	2.65 ± 0.20				
Turn to Sit (s)						
T_0	5.73 ± 0.51	5.64 ± 0.72	group	1	0.96	0.34
T_1	4.91 ± 0.51	5.98 ± 0.72	time	4	0.71	0.59
T_2	4.83 ± 0.51	5.93 ± 0.72	group*time	4	3.05	0.02*
T_3	4.99 ± 0.52	6.07 ± 0.73				
T_4	5.15 ± 0.52	6.12 ± 0.74				

−0.48) and −2.46 s (95% CI -3.89 to −1.02), respectively; for turn duration, changes were −0.48 (95% CI -0.86 to −0.10), −0.62 (95% CI -1.03 to −0.22), −0.43 (95% CI -0.85 to −0.01), and −0.47 s (95% CI -0.89 to −0.05), respectively; for turn to sit duration, changes were −0.82 (95% CI -1.29 to −0.35), −0.89 (95% CI -1.37 to −0.42), −0.74 (95% CI -1.26 to −0.21), and −0.58 s (95% CI -1.09 to −0.06), respectively. Additionally, cadence in the *sham* group was found to be significantly reduced at T_4 (−7.99 steps/min, 95% CI -13.68 to −2.30), but remained the same in the rTMS group from T_0 to T_4. No significant interactions were found in the stride length, stride velocity, double support time percent, and the duration of sit to stand.

4. Discussion

The present study investigated the efficiency of high-frequency rTMS over SMA for the treatment of FOG in PD. Our results revealed beneficial clinical effects of the rTMS on FOG (including FOGQ score, MDS-UPDRS III scores and several gait variables), whereas *sham* stimulation did not, indicating that high-frequency rTMS over SMA could alleviate FOG in PD.

There have been relatively few studies investigating the effects of rTMS on FOG in PD [8–12]. Kim et al. [11] reported a significantly reduced FOGQ score after the application of 10 Hz rTMS over the lower leg primary motor cortex, while no significant improvement of FOGQ score was found after the *sham* stimulation. Dagan et al. [8] proposed that 10 Hz rTMS over the medial prefrontal cortex could improve scores on FOG-provoking test and gait variability, although a *sham* stimulation arm was not included. A recent study investigated the rTMS effect over SMA versus motor cortex on FOG, where Kim et al. [13] reported significant improvements after two sessions of high-frequency SMA stimulation, but not after motor cortex stimulation, though only a small number of patients (6 patients in each group) were enrolled. Three other studies failed to find improvements after rTMS over left premotor cortex [9], left dorsal lateral prefrontal cortex [10], left dorsal lateral prefrontal cortex and/or the motor cortex [12]. In accordance with Kim's study, but using a rTMS protocol with more treatment sessions, longer follow-up terms, and a bigger sample size, we also found that the rTMS significantly decreased FOGQ score by an average of 1.8 and 2.1 points at T_2 and T_4, respectively. This effect was not found in the *sham* group. These results suggested that 10 Hz rTMS over the SMA could effectively alleviate FOG in PD.

In the current study, we utilized the SMA as a stimulation site for rTMS to improve FOG. Previous studies [19,25] have demonstrated the efficacy of rTMS over the SMA for motor symptoms generally in PD. Hamada et al. [19] reported an average of 4.5 points improvement of the MDS-UPDRS III scores after eight weekly sessions of high-frequency rTMS over SMA with the benefit lasting for four weeks. Similarly, we found that ten sessions of 10 Hz rTMS over SMA improved the MDS-UPDRS III scores by 5.3 points, and its effect lasted for at least four weeks following the completion of the therapy. The long-term improvement of motor symptoms we observed is similar with the therapeutic effect of high-frequency rTMS over the motor cortex [26]. We found significantly lower MDS-UPDRS III scores assessed at T_2 compared to those of T_1 (31.78 ± 2.78 vs 29.91 ± 2.78, $p < 0.05$) suggesting a cumulative effect of the rTMS treatment. Interestingly, Shirota et al. [25] conducted a comparison of effects between high-frequency (10 Hz) and low-frequency (1 Hz) rTMS targeted at SMA on motor symptoms in PD. Their results demonstrated a long-lasting beneficial effect of the low-frequency rTMS, but only a transient beneficial effect of the high-frequency rTMS. An explanation for this discrepancy might be due to the fact that we only enrolled a subgroup of PD-FOG subjects in our study. Also, it has been suggested that rTMS effects are a function of the state of brain activity at the time of stimulation [6]. Although increased levels of activity in the SMA has been reported in PD patients in a PET study [27], BOLD responses are decreased in a subgroup of PD-FOG in resting state fMRI studies [15]. Therefore, high-frequency rTMS over SMA is assumed to increase the excitability of an underactive SMA [28] in PD-FOG, which may also impart a beneficial effect on motor symptoms.

We found that rTMS had complex effects on gait parameters. Many gait variables, including stride length, stride velocity, double support time percentage and sit to stand duration, were unaffected by any of rTMS protocols; while other variables, such as total duration, turn duration and turn to sit duration were improved in the rTMS group, and cadence was significantly reduced in the *sham* group, but not the rTMS group. Gait is a difficult motor task involving the ability to balance and

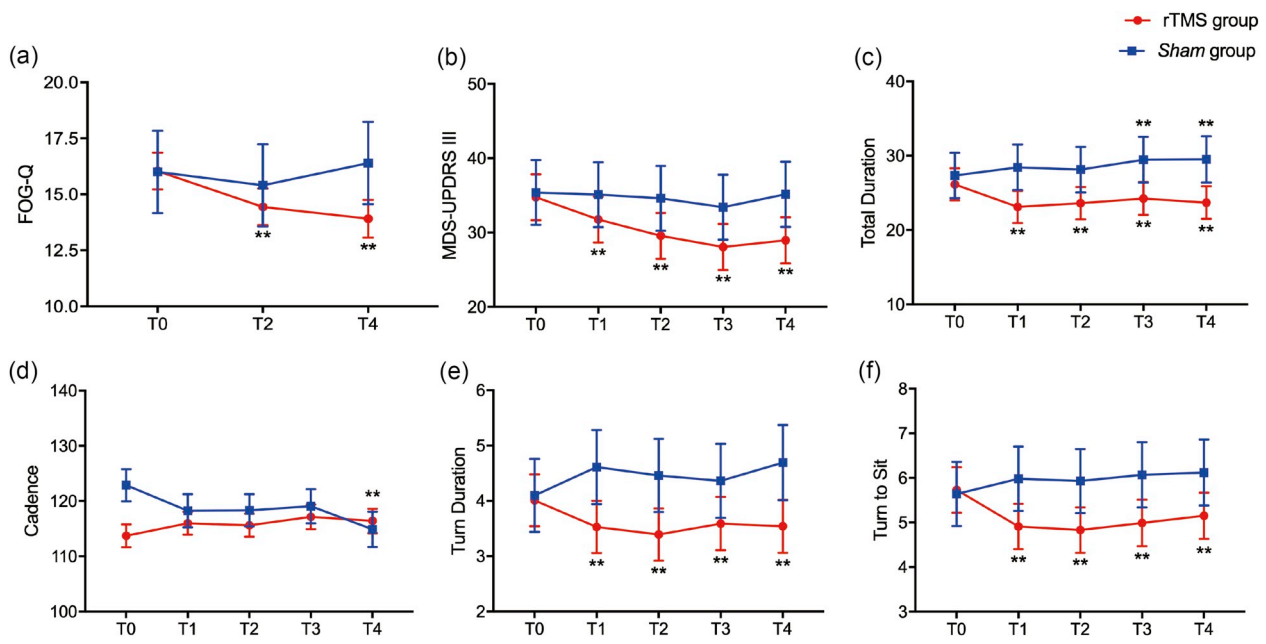

Fig. 2. Clinical score changes after the rTMS, including FOGQ score, MDS-UPDRS III scores and several gait variables (TUG total duration, cadence, turn duration, and turn to sit duration). Red: rTMS group; blue: *sham* group. Error bars represent Std Error; ***Post-hoc* analysis shows significant differences from the baseline (T_0) within group. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

execute a complex motor program simultaneously, requiring joint cognitive function and motor performance. Gait has several components, consisting of straight walking, initiation of gait and turning, each of which requires varying degrees of cognitive control [29]. Straight walking is typically the least cognitively demanding, while turning requires the most cognitive control to modify the gait pattern [29]. Our findings of improved turning parameters (turn duration and turn to sit duration), as well as the lack of improvement in straight walking parameters (stride length, stride velocity, double support time percent), imply that high-frequency rTMS over SMA improves gait variables that require more cognitive control, an aspect of gait especially impaired in PD-FOG [30]. Additionally, previous studies have suggested that PD patients are capable of modulating cadence to compensate for small step length [31]. Our findings showing significantly reduced cadence in the *sham* group but not in the rTMS group may therefore indicate that high-frequency rTMS over SMA augments some compensatory processes in PD-FOG patients.

Our study has a number of limitations. First, the study was carried out on an outpatient basis, and participants couldn't easily visit every day in their “OFF” state. Therefore, as all clinical measurements and treatments were performed in the “ON” state, our results can only reveal the beneficial effect of rTMS as a potential add-on therapy (which we note would be the most realistic situation). Second, as 73% (22/30) PD-FOG subjects in the rTMS study were OFF freezers, there was not enough FOG seen during the “ON” state. Moreover, it has been well-documented that capturing FOG in a laboratory setting is generally quite difficult [1]. Therefore, we only obtained the gait variables which are indirect reflections of FOG, and didn't measure direct objective measures (for instance, the number of freezing episodes and the percentage of time spent on freezing during the TUG trials). Additionally, we proposed this also could explain why we didn't find significant improvements of the FOG subscore of MDS-UPDRS in the present study. Third, the sham stimulation was conducted with the coil placed at 90° in the present study, as has been previously suggested [9–11], but this may still result in different scalp sensations for *rTMS* and *sham* stimulations. However, we note that all subjects were rTMS-naïve, mitigating this concern.

In conclusion, our findings suggest that high-frequency rTMS over SMA may ultimately serve as an add-on therapy for alleviating FOG in PD patients.

Authorship

Chan P, McKeown J. M and Liu AP designed the study; Mi TM, Gao LL, and Dan XJ carried out data collection; McKeown J. M, Garg S, Liu AP and Wu T analyzed the data; Mi TM and Garg S drafted the manuscript; McKeown J. M, Chan P and Ba F revised the manuscript. All authors read and approved the final version for publication.

Declaration of competing interest

The authors declare that they have no competing interests.

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