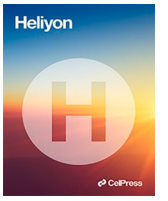
Heliyon 10 (2024) e32799

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

Differential symptom cluster responses and predictors to repetitive transcranial magnetic stimulation treatment in Parkinson's disease: A retrospective study

Jinmei Sun [a,c,d,1], Fengbo Xing [a,c,d,1], Jingjing Feng [a,c,d], Xin Chen [a,c,d], Lingling Lv [a,c,d], Xiaoqing Yao [a,c,d], Mengqi Wang [b,c,d], Ziye Zhao [a,c,d], Qian Zhou [a,c,d], Tingting Liu [a,c,d], Yuqian Zhan [a,c,d], J.I. Gong-Jun [a,b,c,d,e,f,**], Kai Wang [a,b,c,d,e,f,***], Panpan Hu [a,b,c,d,e,f,*]

[a] Department of Neurology, The First Affiliated Hospital of Anhui Medical University, Anhui Medical University, Hefei, 230000, China
[b] School of Mental Health and Psychological Sciences, Anhui Medical University, Hefei, 230000, China
[c] Anhui Province Key Laboratory of Cognition and Neuropsychiatric Disorders, Hefei, 230032, China
[d] Collaborative Innovation Centre of Neuropsychiatric Disorder and Mental Health, Hefei, 230000, China
[e] Institute of Artificial Intelligence, Hefei Comprehensive National Science Center, Hefei, 230088, China
[f] Anhui Institute of Translational Medicine, Hefei, 230000, China

ARTICLE INFO

Keywords:
Parkinson's disease
Repetitive transcranial magnetic stimulation
United Parkinson's disease rating scale part III
Motor symptom clusters
Baseline predictors
Individualized therapy

ABSTRACT

Background: Repetitive transcranial magnetic stimulation (rTMS) is an effective noninvasive neuromodulation technique for Parkinson's disease (PD). However, the efficacy of rTMS varies widely between individuals. This study aimed to investigate the factors related to the response to rTMS in PD patients.

Methods: We retrospectively analyzed the response of 70 idiopathic PD patients who underwent rTMS for 14 consecutive days targeting the supplementary motor area (SMA) in either an open-label trail (n = 31) or a randomized, double-blind, placebo-controlled trial (RCT) (n = 39). The motor symptoms of PD patients were assessed by the United Parkinson's Disease Rating Scale Part III (UPDRSIII). Based on previous studies, the UPDRSIII were divided into six symptom clusters: axial dysfunction, resting tremor, rigidity, bradykinesia affecting right and left extremities, and postural tremor. Subsequently, the efficacy of rTMS to different motor symptom clusters and clinical predictors were analyzed in these two trails.

Results: After 14 days of treatment, only the total UPDRSIII scores and rigidity scores improved in both the open-label trial and the RCT. The results of multiple linear regression analysis indicated that baseline rigidity scores ($\beta = 0.37$, $p = 0.047$) and RMT ($\beta = 0.30$, $P = 0.02$) positively predicted the improvement of UPDRSIII. The baseline rigidity score ($\beta = 0.55$, $P < 0.0001$) was identified as an independent factor to predict the improvement of rigidity.

* Corresponding author. Department of Neurology, The First Affiliated Hospital of Anhui Medical University, Hefei, 230000, China.
** Corresponding author. School of Mental Health and Psychological Sciences, Anhui Medical University, Hefei, 230000, China.
*** Corresponding author. Department of Neurology, The First Affiliated Hospital of Anhui Medical University, Hefei, 230000, China.
E-mail addresses: jigongjun@163.com (J.I. Gong-Jun), wangkai1964@126.com (K. Wang), hpppanda9@126.com (P. Hu).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.heliyon.2024.e32799
Received 25 November 2023; Received in revised form 8 June 2024; Accepted 10 June 2024
Available online 12 June 2024

Conclusion: This study demonstrated significant improvements in total UPDRSIII scores and rigidity after 14-day treatment, with baseline rigidity scores and RMT identified as predictors of treatment response, underscoring the need for individualized therapy.

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease, affecting more than six million individuals worldwide [1]. Motor dysfunctions, such as resting tremor, postural instability, bradykinesia, and postural instability are the most typical symptoms and the main burdens in PD patients [2]. In recent years, repetitive transcranial magnetic stimulation (rTMS) has emerged as a non-invasive neuromodulation technique that has been reported to be effective in alleviating the motor symptoms of PD. However, the efficacy of rTMS varies widely between individuals. Less than half PD patients responded as expected to the stimulation and some individuals even experienced worsening symptoms [3,4].

One possible reason for this variability is that PD is a disease characterized by high heterogeneity in clinical features and neural mechanisms [5,6]. For example, among the symptom clusters of PD, rigidity and bradykinesia often exhibit good early responses to dopamine therapy [7]. In contrast, the severity and progression of tremor is independent of other motor symptoms and its response to dopamine is relatively poor [8]. Neuroimaging studies indicated that bradykinesia and rigidity in PD may be related to cortico-striatal-thalamo-cortical circuit (CSTC) dysfunction. However, tremor may involve dysfunction in peripheral and other central neuronal systems, such as the cerebellothalamocortical (CTC) circuit dysfunction [9]. Therefore, the distinct symptom clusters of PD may originate from dysfunction in specific neural circuits, leading to different responses to rTMS treatment.

In addition, patient demographics, clinical characteristics, and cortical excitability also likely contribute to differences in the efficacy of rTMS. For instance, in a long-term follow-up DBS study, preoperative disease severity in PD patients has been demonstrated as a positive predictor of motor outcome [10], but whether it is also a predictor of rTMS efficacy remains to be validated. Cortical excitability is often considered as an important indicator reflecting the functional status of cortico-subcortical motor circuits [11,12]. Chung et al. found that a combination of treadmill training and rTMS achieved motor improvements associated with changes in the cortical excitability in PD patients [13]. Thus, the baseline cortical excitability of patients may also be related to the rTMS effect.

In this study, we aimed to identified factors related to the efficacy of rTMS in PD patients. To this end, we retrospectively analyzed the motor symptom responses of 70 idiopathic PD patients who have underwent rTMS for 14 consecutive days in the two independent clinical trails. We first examined the response of different symptom clusters separately in the two trails. To increase the sample size, we then combined the data from both trials to further explore the predictors of efficacy.

2. Participants and methods

2.1. Standard protocol approvals, registrations, and patient consents

The study protocol was approved by the institutional ethics committee of the Anhui Medical University (Approval Number: PJ2016-10-06). According to the Declaration of Helsinki, all participants provided written, informed consent before participating in the experiments. The study was registered at ClinicalTrials.gov with the identifier NCT02969941.

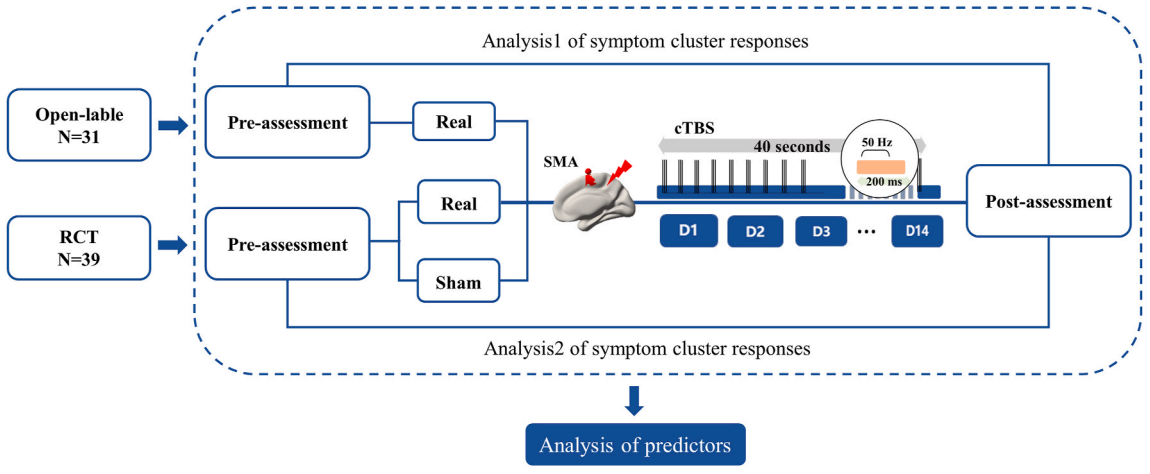


Fig. 1. Experimental design. Seventy PD patients received rTMS treatment in an open-label trial or a randomized, double-blind controlled trial (RCT). The therapeutic efficacy of various symptom clusters was firstly assessed independently in both trails. Subsequently, to increase the sample size, the data were pooled from the two trials to further investigate baseline predictors. SMA, supplementary motor area.

2.2. Study design

The study retrospectively included two independent rTMS clinical trials [4]. The first was an open-label trial. The second was a randomized, double-blind, placebo-controlled trial (RCT). During the RCT, patients received real or sham rTMS over the left supplementary motor area (SMA) for a consecutive period of 14 days (days 1–14). The randomization process in the RCT was carried out by an independent researcher with no involvement in any other aspect of the trial. Following the 14-day treatment, the efficacy of neuronavigational rTMS was assessed separately in each of the two independent clinical trials. Subsequently, the data from both trials were combined to further explore the baseline predictors. The study design is presented in Fig. 1.

To exclude the acute effects of medicine on symptom estimation and imaging features, all patients stopped the consumption of medication for at least 12 h (so called "off" state) before the assessment of symptoms.

2.3. Participants

Participants were prospectively enrolled at the First Affiliated Hospital of Anhui Medical University from November 2016 through December 2018. The inclusion criteria were as follows: (1) diagnosis of idiopathic PD according to the UK Brain Bank Criteria, and confirmed by a neurologist (author P. H.) with expertise in movement disorders; (2) ongoing treatment with a stable dose of any medication for 2 months; and (3) 40 years of age or older. The exclusion criteria were as follows: (1) a history of addiction or psychiatric disorders; (2) head lesions or neurological disorders other than PD; (3) substance abuse within the past 6 months; (4) non-removable metal objects in or around the head; (5) history of seizure or history of seizure in first-degree relatives; and (6) prior rTMS treatment.

2.4. Structural MRI data acquisition

High spatial resolution T1-weighted anatomic images were acquired in the sagittal orientation using a three-dimensional brain-volume sequence (repetition/echo time, 8.16/3.18 ms; flip angle, 12°; field of view, 256 × 256 mm ^{2}; 256 × 256 matrix; section thickness, 1 mm, without intersection gap; voxel size, 1 × 1 × 1 mm ^{3}; and 188 sections).

2.5. MRI-navigated rTMS

TMS was performed using a Magstim Rapid2 transcranial magnetic stimulator (Magstim Company, Whitland, UK) with a 70-mm aircooled figure-of-eight coil using continuous theta-burst stimulation (cTBS) [4]. The cTBS parameters were as follows: three pulses, 50 Hz bursts given every 200 ms (at 5 Hz) until a total of 600 pulses was reached, and an intensity of 80 % of the resting motor threshold (RMT). Patients received three cTBS sessions (1800 pulses) separated by 15-min intervals each day for 14 consecutive days. Patients in the sham rTMS group were treated using a placebo coil (Magstim Company) that produced a similar sound and sensation on the scalp as the real coil, but did not produce any electrical currents in the cortex. All the treatments were performed in the morning after normal drug intake.

All stimulations were guided by the participant's structural image (1 × 1 × 1 mm ^{3}) and a frameless neuronavigation system (Brainsight; Rogue Research, Montreal, QC, Canada). The stimulation was delivered on the left SMA proper using Montreal Neurological Institute (MNI) coordinates (−6, −6, 77) [14]. We used SPM 12 (www.fl.ion.ucl.ac.uk/spm) and an in-house TMStarget Software (http://www. brainhealthy.net) to transform the MNI coordinates into individual space.

The RMT was measured based on the stimulation intensity from the abductor pollicis brevis muscle using a handheld 70 mm figure-of-eight coil. RMT was defined as the lowest intensity required to evoked a small response (>50 mV) in more than five of 10 consecutive trials in the right abductor pollicis brevis muscle.

2.6. Symptom and neuropsychological assessments

Demographic information and neuropsychological scores were obtained before rTMS treatment. Cognitive function was assessed using the Montreal Cognitive Assessment (MoCA) scale. The motor symptoms were assessed using the Unified Parkinson's Disease Rating Scale Part III (UPDRSIII). The UPDRSIII measurements are detailed in the supplementary methods. Based on previously reported confirmatory factor analyses, we divided the 27 items of UPDRSIII into six symptom clusters [15,16], including axial dysfunction, resting tremor, rigidity, left bradykinesia, right bradykinesia, and postural tremor. In both clinical trials, all patients with clear records for these 27 items were included in the analysis.

2.7. Statistical analysis

In the open-label trial, the treatment outcomes were analyzed using paired *t*-tests or Mann-Whitney U tests according to the normality of the data distribution. In the RCT, the baseline demographic and neuropsychological scores were compared between the two groups using independent two-sample *t*-tests or Mann-Whitney U tests depending on the normality of the data distribution. The male/female ratio was assessed using the chi-squared test. Treatment outcomes in the open-label trial were analyzed using t-tests or Wilcoxon Signed-Rank Test. Treatment outcomes, including UPDRSIII and six symptom clusters were analyzed using two-way ANOVA or the Scheirer-Ray-Hare test with the group (real and sham rTMS) serving as the between-subjects factor and time as the within-

subjects factor. Post hoc analyses were performed using Sidak's multiple comparison test.

In the analysis of predictors, we first conducted the correlation analysis using sex, age, education, MoCA, duration, levodopa equivalent dose (LED), Hoehn and Yahr stage, UPDRSIII score and the score of six symptom clusters as the independent variables, while symptom improvement served as the dependent variables. Pearson's, Spearman's, or point biserial correlation analyses was used based on the data type. Then, the univariate and multivariate linear regression analyses were performed to identify the independent baseline factors associated with motor outcome. All statistical analyses were carried out using GraphPad Prism 8.3.0 or SPSS 21.

3. Results

3.1. Demographic and clinical features

3.1.1. Patients in the open-label trail

The open-label trial included 31 PD patients (22 [71 %] men) with a mean age of 64.84 ± 2.04 years and mean education of 9.26 ± 0.99 years and mean disease duration of 4.32 ± 0.50 years. The mean MoCA score was 21.5 ± 0.98 and the mean H–Y stage was 2.11 ± 0.16. Motor symptom measures are provided in Table 1.

3.1.2. Patients in the RCT

A total of 39 PD patients completed the RCT. Twenty-two patients were assigned to receive real stimulation and 17 were assigned to receive the sham stimulation. No significant difference in demographic and clinical characteristics were found between the real and sham groups (Table 2).

3.2. Symptom cluster response

3.2.1. Response in the open-label trial

After treatment of the six symptom clusters, the axial dysfunction, resting tremor, rigidity, left bradykinesia, and right bradykinesia scores were significantly reduced (Table 1). The total UPDRIII scores were also significantly reduced (Table 1).

3.2.2. Responses in the RCT

There was a significant interaction effect between time and group on rigidity ($F = 4.54$, $P = 0.04$) (Fig. 2C) and total UPDRIII scores ($F = 5.65$, $P = 0.02$) (Table 3). The post hoc analysis revealed that rigidity and total UPDRIII scores only decreased in the real group (rigidity, $t = 3.23$, $P = 0.005$; UPDRSIII, $t = 3.46$, $P = 0.003$) but not in the sham group (rigidity, $t < 0.001$, $P > 0.99$; UPDRSIII, $t = 0.12$, $P = 0.99$). No significant interaction effects were observed for the other five symptom clusters [Fig. 2A-B, D-F].

The average score improvement percentages of the six symptom clusters in RCT are shown in the supplementary results (Table S1). Given the low baseline average scores of each symptom cluster, this study continues to utilize the difference in scores, rather than percentages, as a variable for intergroup comparison.

3.3. Baseline predictors of rTMS response

To further explore the baseline predictors with good response of rTMS, we aggregated the data from the real stimulation group across two trials. A total of 53 PD patients were included in the analysis of baseline predictors. Given the significant reduction in rigidity and UPDRS-III scores observed in both the open-label trial and the RCT, we treated them as separate dependent variables separately in the correlation and regression analyses.

3.3.1. Predictors of the improvement of total UPDRSIII scores

A significant correlation was found between the baseline total UPDRSIII ($r = 0.54$, $P < 0.0001$), axial dysfunction ($r = 0.35$, $P = 0.01$), rigidity ($r = 0.52$, $P = 0.0001$), left bradykinesia ($r = 0.44$, $P = 0.002$) scores, RMT ($r = 0.28$, $P = 0.047$), and improvement of UPDRSIII (Table 4). Subsequently, a multivariate regression analysis was conducted using the five baseline clinical variables as

Table 1
Symptom measures in the open-label experiment.

	Pre-treatment	Post-treatment	Statistics	P
UPDRSIII	26.39(2.44)	21.94(1.72)	2.67	0.01[a]
Axial dysfunction	9.03(0.77)	8.07(0.70)	−2.79	0.005[b]
Resting tremor	1.94(0.36)	1.19(0.26)	−3.46	0.001[b]
Rigidity	5.81(0.60)	4.23(0.51)	4.78	<0.0001[a]
Left bradykinesia	4.42(0.68)	3.58(0.58)	−2.59	0.01[b]
Right bradykinesia	5.45(0.60)	4.19(0.48)	4.00	0.0004[a]
Postural tremor	1.00(0.19)	0.77(0.14)	1.75	0.09[a]

Data are expressed as the mean (SEM). UPDRS-III, Unified Parkinson's Disease Rating Scale Part III.

[a] Paired *t*-test.

[b] Wilcoxon Signed-Rank Test.

Table 2
Baseline demographic and clinical measures in the RCT.

	Real group	Sham group	Statistics	P
Age (years)	61.91(1.73)	59.41(8.91)	0.91	0.37[a]
Sample size (m/f)	13/9	12/5	0.16	0.69[b]
Education (years)	10.50(0.90)	8.82(4.69)	1.17	0.25[a]
Duration (years)	4.25(0.61)	5.47(3.97)	0.91	0.38[c]
H–Y	1.55(0.11)	1.68(0.50)	0.96	0.36[c]
LED (mg)	445(58.55)	460.90(334)	0.16	0.87[a]
MoCA	23.68(0.85)	24.82(3.25)	0.96	0.34[a]
UPDRSIII	26.775(2.24)	30.47(11.74)	1.04	0.31[a]
Axial dysfunction	6.91(0.62)	6.94(3.83)	0.03	0.97[a]
Resting tremor	0.89(0.27)	2.24(2.56)	−1.31	0.23[c]
Rigidity	6.91(0.83)	8.12(0.82)	1.02	0.32[a]
Left bradykinesia	5.18(0.75)	6.12 (1.03)	0.75	0.46[a]
Right bradykinesia	5.32(0.77)	6.71(0.93)	1.15	0.26[a]
Postural tremor	0.73(0.15)	0.41(0.15)	−1.48	0.19[c]

Data are expressed as the mean (SEM). H–Y, Hoehn and Yahr stage; LED, levodopa equivalent dose; MoCA, Montreal cognitive assessment; UPDRS-III, Unified Parkinson's Disease Rating Scale Part III.

[a] Two-sample *t*-test.

[b] Chi-square test.

[c] Mann-Whitney test.

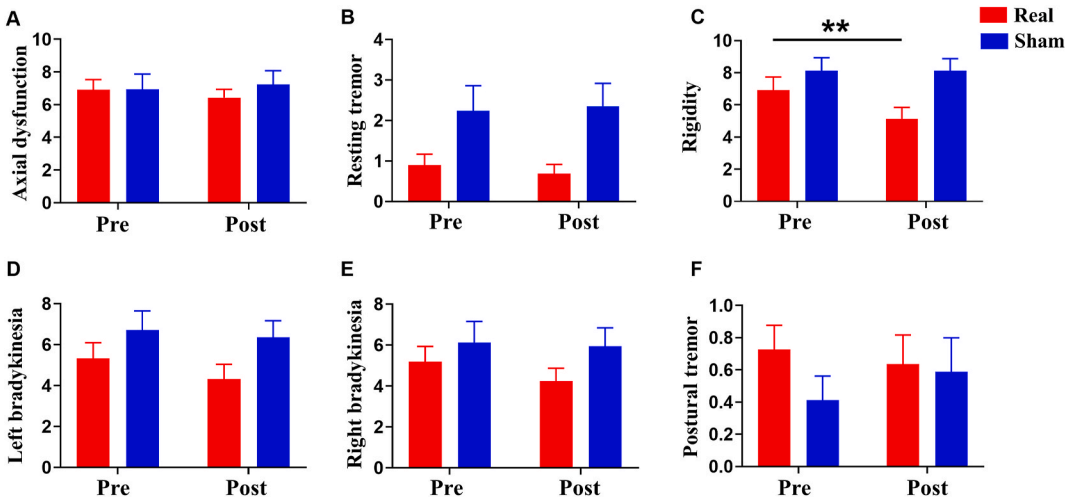


Fig. 2. Responses of the six symptom clusters in the RCT. Among the six symptom clusters, a significant interaction was observed between the real and sham group specifically for rigidity scores (C), whereas no significant interactions were detected among the remaining five other symptom clusters (A-B, D-F). Error bars indicate the SEM. **P < 0.01.

Table 3
Symptom measures after the 14-day treatment in the RCT.

	Real group	Sham group	Statistics	P
UPDRSIII	22.45(2.36)	30.65(2.65)	5.65	0.02[a]
Axial dysfunction	6.43(0.51)	7.24(0.85)	1.70	0.20[a]
Resting tremor	0.68(0.23)	2.35(0.56)	0.39	0.53[b]
Rigidity	5.14(0.71)	8.12(0.76)	4.54	0.04[a]
Left bradykinesia	4.23(0.64)	5.94(0.89)	1.10	0.30[a]
Right bradykinesia	4.32(0.72)	6.35(0.81)	0.86	0.36[a]
Postural tremor	0.64(0.18)	0.59(0.21)	0.72	0.40[b]

Data are expressed as the mean (SEM). UPDRSIII, Unified Parkinson's Disease Rating Scale Part III.

[a] Two-way ANOVA.

[b] Scheirer-Ray-Hare.

independent variables. The results indicated that baseline RMT (β = 0.30, P = 0.02) and rigidity scores (β = 0.37, P = 0.047) were significant positive predictors of the improvement of the overall UPDRSIII scores (Table 5).

3.3.2. Predictors of the improvement in rigidity scores

Only a significant correlation was observed between the baseline rigidity scores (r = 0.55, P < 0.0001) and improvements in rigidity (Table 6). Furthermore, baseline rigidity scores (β = 0.55, P < 0.0001) were identified as independent predictors of the improvements in rigidity.

4. Discussion

This study investigated the responses of different symptom clusters and the baseline predictors of rTMS efficacy in PD. This retrospective analysis incorporated data from two independent clinical trials. Our findings indicated that rTMS targeted at the left SMA led to significant improvements in motor symptoms, particularly rigidity, in PD patients. The regression analysis revealed that baseline rigidity scores and RMT were positive predictors for improvements for motor symptoms improvements in PD patients.

4.1. Global symptom responses to rTMS in PD

Overall, the findings of this study demonstrated a positive effect of rTMS intervention on motor improvement in PD, which were consistent with the previous studies. However, most meta-analyses have indicated that excitatory TMS intervention targeting the M1 appears to be the optimal parameters for motor improvement [17–19], rather than inhibitory TMS intervention targeting the SMA as conducted in this study [20]. This difference may be attributed to variations in the stimulation sequence. Both low-frequency stimulation (≤1 Hz) and cTBS can decrease motor cortex excitability [21]. Although our previous research [4] suggested cTBS-induced improvement appears to be higher than that induced by 1-Hz stimulation of the SMA [22], there was limited inclusion of cTBS studies in the current meta-analysis. Therefore, future studies should further investigate the effects of cTBS intervention in PD.

Recent years, there has been growing attention towards the non-motor symptoms of PD. Among them, depression is the most common and could be effectively treated as a nonmotor symptom [23]. Nevertheless, it remains unclear whether rTMS intervention in PD had antidepressant effects superior to that of oral medication [20,24]. The newly developed high-dose, MRI–guided rTMS may further optimize the treatment of PD depression [25]. In addition to mood, other non-motor symptoms of PD, such as cognitive impairment, pain, sleep disturbance, and autonomic disorders have also received increasing attention [26–28], but the effectiveness of TMS in treating them still needs to be tested. The Nonmotor Symptoms Scale, which include multiple non-motor symptoms, can be evaluated in PD in the future rTMS intervention studies and can be divided into multiple symptom clusters for analysis, similar to this study [29].

4.2. Motor symptom cluster responses to rTMS

Rigidity is a typical and common motor symptom of PD. The depletion of dopamine in the basal ganglia play an important in rigidity. Consistent with previous dopamine [30] and intervention research [31], in the present study, we also found rigidity responded well to the cTBS. This indicated that dysfunction of CSTC circuit is the pathological mechanism of rigidity in PD and motor cortex is an

Table 4
Correlation analysis with total UPDRSIII scores.

Baseline Variable	r	P
Sex	0.01	0.94[a]
Age	0.06	0.66 [b]
Duration	−0.06	0.70[c]
Education	−0.09	0.55[b]
RMT	0.28	**0.047**[b]
LED	−0.02	0.87[b]
H–Y	0.08	0.61[c]
MoCA	−0.04	0.82[c]
UPDRSIII	0.54	**<0.0001**
Axial dysfunction	0.35	**0.01**[c]
Resting tremor	0.01	0.95[c]
Rigidity	0.52	**0.0001**[b]
Left bradykinesia	0.44	**0.002**[c]
Right bradykinesia	0.15	0.32[b]
Postural tremor	−0.004	0.98[b]

RMT, Resting motor threshold; LED, levodopa equivalent dose; H–Y, Hoehn and Yahr stage; MoCA, Montreal cognitive assessment; UPDRSIII, Unified Parkinson's Disease Rating Scale Part III.

[a] Point biserial correlation analysis.

[b] Pearson's correlation analysis.

[c] Spearman's correlation analysis.

Table 5
Multiple linear regression analysis on the improvement of total UPDRSIII scores.

Baseline Variables	VIF	β	t	P
RMT	1.05	0.30	2.44	0.02
Axial dysfunction	3.63	−0.03	−0.11	0.91
Rigidity	2.29	0.37	2.05	0.047
Left bradykinesia	2.07	0.10	0.55	0.58
UPDRSIII	7.60	0.16	0.47	0.64

RMT, Resting motor threshold; UPDRSIII, Unified Parkinson's Disease Rating Scale Part III; VIF, variance inflation factor; β, Standardized coefficient.

Table 6
Correlation analysis with rigidity scores.

Baseline Variables	r	P
Sex	−0.07	0.64[a]
Age	0.03	0.83 [b]
Duration	0.002	0.99[c]
Education	0.06	0.67 [b]
RMT	0.11	0.45[b]
LED	0.08	0.56[b]
H–Y	0.10	0.49[c]
MoCA	0.12	0.38[c]
UPDRSIII	0.25	0.07[c]
Axial dysfunction	0.11	0.42[c]
Resting tremor	0.08	0.57[c]
Rigidity	0.55	**<0.0001**[b]
Left bradykinesia	0.07	0.61[c]
Right bradykinesia	−0.03	0.82 [b]
Postural tremor	−0.06	0.66 [b]

RMT, Resting motor threshold; LED, levodopa equivalent dose; H–Y, Hoehn and Yahr stage; MoCA, Montreal cognitive assessment; UPDRSIII, Unified Parkinson's Disease Rating Scale Part III.
[a] Point biserial correlation analysis.
[b] Pearson's correlation analysis.
[c] Spearman's correlation analysis.

effective stimulation target. In contrast to the rigidity, there was no significant improvement in postural tremor in either experiment. Several lines of evidence have suggested PD tremor may have different underlying pathophysiology processes from other motor symptoms [32–34]. A task-based functional MRI found tremor predominant patients exhibited significantly increased activation in the CTC circuit compared to akinetic-rigidity predominant PD patients [9]. Zhen et al. further suggested resting and postural tremors in PD may be mediated by different neuronal pathways as resting tremor in PD was only suppressed by M1 stimulation but postural tremor can be suppressed by both M1 and cerebellar stimulation [35]. These evidences suggest that cerebellum may be a potential target for treating postural tremor in PD. Moreover, we found significant improvement of other four symptom clusters in the open-lable study, but not in the RCT, indicating that efficacy of the protocol in this study was not clear for these symptoms. Future studies can further expand the sample size or explore TMS intervention with different targets and parameters to develop of more effective therapeutics for PD.

4.3. Baseline predictors

In PD patients, Tomoo et al. have shown that RMT in the more affected cortex is significantly lower than in the less affected cortex [36]. In this study, we found higher baseline RMT can predict a better motor outcome of 2 weeks of TMS intervention. These findings indicated patients with a higher RMT may have less cortical damage and may exhibit better cortical plasticity and efficacy of TMS. Furthermore, consistent with the DBS study [10], we showed more severe baseline symptom can predict motor improvement in the off-medication state. However, most studies are typically assessed symptom of PD using the sum score change of the motor scale [4,10,13,37,38]. It is not clear whether scores for single symptom cluster have a predictive effect to TMS efficacy. In the present work, we found that baseline rigidity predicted both the overall motor performance and rigidity improvement for TMS treatment, suggesting rigidity may be a more sensitive predictive index compared to the baseline overall motor performance. Furthermore, recent studies have shown that some mathematical and neuroimaging models are excellent tools for characterizing dynamic diseases [39–43]. Hence, it is advisable for future studies to further investigate the predictive effects of symptom clusters in PD by utilizing these models.

4.4. Limitations

Several limitations in this study are worth mentioning. Firstly, the sample size was relatively small, and the patients enrolled had a

short duration of the disease and were of mild severity. Second, the first study was an open-label trial. Hence, it should be further validated in another RCT study. Third, this was a single-center study, and therefore, the findings must be confirmed in a large-scale, multicenter clinical trial.

5. Conclusion

In summary, this study showed significant improvements in total UPDRSIII scores and rigidity after 14-day treatment, with baseline rigidity scores and RMT identified as positive predictors of treatment response, underscoring the need for individualized therapy.

Ethics statement

This study was reviewed and approved by institutional ethics committee of the Anhui Medical University with the approval number: PJ2016-10-06, dated: October 27, 2016. All participants provided written informed consent before participating in this study.

Data availability statement

Data will be made available on request.

CRediT authorship contribution statement

Jinmei Sun: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Fengbo Xing:** Formal analysis. **Jingjing Feng:** Investigation. **Xin Chen:** Investigation. **Lingling Lv:** Investigation, Data curation. **Xiaoqing Yao:** Investigation, Data curation. **Mengqi Wang:** Investigation, Data curation. **Ziye Zhao:** Investigation, Data curation. **Qian Zhou:** Investigation, Data curation. **Tingting Liu:** Investigation, Formal analysis, Data curation. **Yuqian Zhan:** Investigation, Data curation. **J.I. Gong-Jun:** Writing – review & editing, Validation, Supervision, Funding acquisition, Formal analysis. **Kai Wang:** Supervision, Conceptualization. **Panpan Hu:** Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors thank the participants of this study. This work was supported by the National Natural Science Foundation of China, Grant/Award Numbers: 82171917, 81971689, 31970979, 82090034; the Collaborative Innovation Center of Neuropsychiatric Disorders and Mental Health of Anhui Province, Grant/Award Numbers: 2020xkjT05; and the Postgraduate Innovation Research and Practice Program of Anhui Medical University, Grant/Award Numbers: YJS20230200, YJS20230199.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e32799.

References

[1] Global regional, National burden of neurological disorders during 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015, Lancet Neurol. 16 (11) (2017) 877–897, https://doi.org/10.1016/s1474-4422(17)30299-5.
[2] B. Thomas, M.F. Beal, Parkinson's disease, Hum. Mol. Genet. 16 (2) (2007) R183–R194, https://doi.org/10.1093/hmg/ddm159.
[3] J.Y. Kim, E.J. Chung, W.Y. Lee, H.Y. Shin, G.H. Lee, Y.S. Choe, Y. Choi, B.J. Kim, Therapeutic effect of repetitive transcranial magnetic stimulation in Parkinson's disease: analysis of [11C] raclopride PET study, Mov. Disord. 23 (2) (2008) 207–211, https://doi.org/10.1002/mds.21787.
[4] G.J. Ji, T. Liu, Y. Li, P. Liu, J. Sun, X. Chen, Y. Tian, X. Chen, L. Dahmani, H. Liu, K. Wang, P. Hu, Structural correlates underlying accelerated magnetic stimulation in Parkinson's disease, Hum. Brain Mapp. 42 (6) (2021) 1670–1681, https://doi.org/10.1002/hbm.25319.
[5] B.R. Bloem, M.S. Okun, C. Klein, Parkinson's disease, Lancet 397 (10291) (2021) 2284–2303, https://doi.org/10.1016/s0140-6736(21)00218-x.
[6] C. Marras, K.R. Chaudhuri, N. Titova, T.A. Mestre, Therapy of Parkinson's disease subtypes, Neurotherapeutics 17 (4) (2020) 1366–1377, https://doi.org/10.1007/s13311-020-00894-7.
[7] G.A. Kang, J.M. Bronstein, D.L. Masterman, M. Redelings, J.A. Crum, B. Ritz, Clinical characteristics in early Parkinson's disease in a central California population-based study, Mov. Disord. 20 (9) (2005) 1133–1142, https://doi.org/10.1002/mds.20513.
[8] J. Stochl, A. Boomsma, E. Ruzicka, H. Brozova, P. Blahus, On the structure of motor symptoms of Parkinson's disease, Mov. Disord. 23 (9) (2008) 1307–1312, https://doi.org/10.1002/mds.22029.
[9] M.M. Lewis, G. Du, S. Sen, A. Kawaguchi, Y. Truong, S. Lee, R.B. Mailman, X. Huang, Differential involvement of striato- and cerebello-thalamo-cortical pathways in tremor- and akinetic/rigid-predominant Parkinson's disease, Neuroscience 177 (2011) 230–239, https://doi.org/10.1016/j.neuroscience.2010.12.060.

[10] F. Cavallieri, V. Fraix, F. Bove, D. Mulas, M. Tondelli, A. Castrioto, P. Krack, S. Meoni, E. Schmitt, E. Lhommée, A. Bichon, P. Pélissier, E. Chevrier, A. Kistner, E. Seigneuret, S. Chabardès, E. Moro, Predictors of long-term outcome of subthalamic stimulation in Parkinson disease, Ann. Neurol. 89 (3) (2021) 587–597, https://doi.org/10.1002/ana.25994.

[11] S. Casarotto, F. Turco, A. Comanducci, A. Perretti, G. Marotta, G. Pezzoli, M. Rosanova, I.U. Isaias, Excitability of the supplementary motor area in Parkinson's disease depends on subcortical damage, Brain Stimul. 12 (1) (2019) 152–160, https://doi.org/10.1016/j.brs.2018.10.011.

[12] J.P. Lefaucheur, Motor cortex dysfunction revealed by cortical excitability studies in Parkinson's disease: influence of antiparkinsonian treatment and cortical stimulation, Clin. Neurophysiol. 116 (2) (2005) 244–253, https://doi.org/10.1016/j.clinph.2004.11.017.

[13] C.L. Chung, M.K. Mak, M. Hallett, Transcranial magnetic stimulation promotes gait training in Parkinson disease, Ann. Neurol. 88 (5) (2020) 933–945, https://doi.org/10.1002/ana.25881.

[14] G.J. Ji, F. Yu, W. Liao, K. Wang, Dynamic aftereffects in supplementary motor network following inhibitory transcranial magnetic stimulation protocols, Neuroimage 149 (2017) 285–294, https://doi.org/10.1016/j.neuroimage.2017.01.035.

[15] G.T. Stebbins, C.G. Goetz, A.E. Lang, E. Cubo, Factor analysis of the motor section of the unified Parkinson's disease rating scale during the off-state, Mov. Disord. 14 (4) (1999) 585–589, https://doi.org/10.1002/1531-8257(199907)14:4<585::aid-mds1006>3.0.co;2-3.

[16] G.T. Stebbins, C.G. Goetz, Factor structure of the unified Parkinson's disease rating scale: motor examination section, Mov. Disord. 13 (4) (1998) 633–636, https://doi.org/10.1002/mds.870130404.

[17] R. Li, Y. He, W. Qin, Z. Zhang, J. Su, Q. Guan, Y. Chen, L. Jin, Effects of repetitive transcranial magnetic stimulation on motor symptoms in Parkinson's disease: a meta-analysis, Neurorehabilitation Neural Repair 36 (7) (2022) 395–404, https://doi.org/10.1177/15459683221095034.

[18] W. Zhang, B. Deng, F. Xie, H. Zhou, J.F. Guo, H. Jiang, A. Sim, B. Tang, Q. Wang, Efficacy of repetitive transcranial magnetic stimulation in Parkinson's disease: a systematic review and meta-analysis of randomised controlled trials, EClinicalMedicine 52 (2022) 101589, https://doi.org/10.1016/j.eclinm.2022.101589.

[19] C. Yang, Z. Guo, H. Peng, G. Xing, H. Chen, M.A. McClure, B. He, L. He, F. Du, L. Xiong, Q. Mu, Repetitive transcranial magnetic stimulation therapy for motor recovery in Parkinson's disease: a Meta-analysis, Brain Behav 8 (11) (2018) e01132, https://doi.org/10.1002/brb3.1132.

[20] S. Li, R. Jiao, X. Zhou, S. Chen, Motor recovery and antidepressant effects of repetitive transcranial magnetic stimulation on Parkinson disease: a PRISMA-compliant meta-analysis, Medicine (Baltim.) 99 (18) (2020) e19642, https://doi.org/10.1097/md.0000000000019642.

[21] V. Di Lazzaro, M. Dileone, F. Pilato, F. Capone, G. Musumeci, F. Ranieri, V. Ricci, P. Bria, R. Di Iorio, C. de Waure, P. Pasqualetti, P. Profice, Modulation of motor cortex neuronal networks by rTMS: comparison of local and remote effects of six different protocols of stimulation, J. Neurophysiol. 105 (5) (2011) 2150–2156, https://doi.org/10.1152/jn.00781.2010.

[22] Y. Shirota, H. Ohtsu, M. Hamada, H. Enomoto, Y. Ugawa, Supplementary motor area stimulation for Parkinson disease: a randomized controlled study, Neurology 80 (15) (2013) 1400–1405, https://doi.org/10.1212/WNL.0b013e31828c2f66.

[23] D. Weintraub, E. Mamikonyan, The neuropsychiatry of Parkinson disease: a perfect storm, Am. J. Geriatr. Psychiatr. 27 (9) (2019) 998–1018, https://doi.org/10.1016/j.jagp.2019.03.002.

[24] C.L. Xie, J. Chen, X.D. Wang, J.L. Pan, Y. Zhou, S.Y. Lin, X.D. Xue, W.W. Wang, Repetitive transcranial magnetic stimulation (rTMS) for the treatment of depression in Parkinson disease: a meta-analysis of randomized controlled clinical trials, Neurol. Sci. 36 (10) (2015) 1751–1761, https://doi.org/10.1007/s10072-015-2345-4.

[25] E.J. Cole, A.L. Phillips, B.S. Bentzley, K.H. Stimpson, R. Nejad, F. Barmak, C. Veerapal, N. Khan, K. Cherian, E. Felber, R. Brown, E. Choi, S. King, H. Pankow, J. H. Bishop, A. Azeez, J. Coetzee, R. Rapier, N. Odenwald, D. Carreon, J. Hawkins, M. Chang, J. Keller, K. Raj, C. DeBattista, B. Jo, F.M. Espil, A.F. Schatzberg, K. D. Sudheimer, N.R. Williams, Stanford neuromodulation therapy (snt): a double-blind randomized controlled trial, Am. J. Psychiatr. 179 (2) (2022) 132–141, https://doi.org/10.1176/appi.ajp.2021.20101429.

[26] D. Aarsland, K. Brønnick, J.P. Larsen, O.B. Tysnes, G. Alves, Cognitive impairment in incident, untreated Parkinson disease: the Norwegian ParkWest study, Neurology 72 (13) (2009) 1121–1126, https://doi.org/10.1212/01.wnl.0000338632.00552.cb.

[27] J. Lei, L.L. Tang, H.J. You, Pathological pain: non-motor manifestations in Parkinson disease and its treatment, Neurosci. Biobehav. Rev. 161 (2024) 105646, https://doi.org/10.1016/j.neubiorev.2024.105646.

[28] A.B.R. Leite Silva, R.W. Gonçalves de Oliveira, G.P. Diógenes, M.F. de Castro Aguiar, C.C. Sallem, M.P.P. Lima, L.B. de Albuquerque Filho, S.D. Peixoto de Medeiros, L.L. Penido de Mendonça, P.C. de Santiago Filho, D.P. Nones, P.M.M. da Silva Cardoso, M.Z. Ribas, S.L. Galvão, G.F. Gomes, A.R. Bezerra de Menezes, N.L. Dos Santos, V.M. Mororó, F.S. Duarte, J.C.C. Dos Santos, Premotor, nonmotor and motor symptoms of Parkinson's Disease: a new clinical state of the art, Ageing Res. Rev. 84 (2023) 101834, https://doi.org/10.1016/j.arr.2022.101834.

[29] H.M. Lee, S.S. Lee, M. Kim, S.H. Kang, W.K. Seo, J.H. Kim, S.B. Koh, Clinical phenotype of drug-naïve Parkinson's disease based on nonmotor symptoms, Arch. Gerontol. Geriatr. 61 (3) (2015) 517–522, https://doi.org/10.1016/j.archger.2015.07.001.

[30] L. Schneider, V. Seeger, L. Timmermann, E. Florin, Electrophysiological resting state networks of predominantly akinetic-rigid Parkinson patients: effects of dopamine therapy, Neuroimage Clin 25 (2020) 102147, https://doi.org/10.1016/j.nicl.2019.102147.

[31] J.P. Lefaucheur, X. Drouot, F. Von Raison, I. Ménard-Lefaucheur, P. Cesaro, J.P. Nguyen, Improvement of motor performance and modulation of cortical excitability by repetitive transcranial magnetic stimulation of the motor cortex in Parkinson's disease, Clin. Neurophysiol. 115 (11) (2004) 2530–2541, https://doi.org/10.1016/j.clinph.2004.05.025.

[32] A. Zaidel, D. Arkadir, Z. Israel, H. Bergman, Akineto-rigid vs. tremor syndromes in Parkinsonism, Curr. Opin. Neurol. 22 (4) (2009) 387–393, https://doi.org/10.1097/WCO.0b013e32832d9d67.

[33] T.H. Haapaniemi, A. Ahonen, P. Torniainen, K.A. Sotaniemi, V.V. Myllylä, [123I]beta-CIT SPECT demonstrates decreased brain dopamine and serotonin transporter levels in untreated parkinsonian patients, Mov. Disord. 16 (1) (2001) 124–130, https://doi.org/10.1002/1531-8257(200101)16:1<124::aid-mds1007>3.0.co;2-r.

[34] J. Pasquini, R. Ceravolo, Z. Qamhawi, J.Y. Lee, G. Deuschl, D.J. Brooks, U. Bonuccelli, N. Pavese, Progression of tremor in early stages of Parkinson's disease: a clinical and neuroimaging study, Brain 141 (3) (2018) 811–821, https://doi.org/10.1093/brain/awx376.

[35] Z. Ni, A.D. Pinto, A.E. Lang, R. Chen, Involvement of the cerebellothalamocortical pathway in Parkinson disease, Ann. Neurol. 68 (6) (2010) 816–824, https://doi.org/10.1002/ana.22221.

[36] T. Mano, K. Kinugawa, S. Fujimura, K. Sugie, The lateralization of resting motor threshold to predict medication-mediated improvement in Parkinson's disease, Brain Sci. 12 (7) (2022), https://doi.org/10.3390/brainsci12070842.

[37] J. Sun, X. Gao, Q. Hua, R. Du, P. Liu, T. Liu, J. Yang, B. Qiu, G.J. Ji, P. Hu, K. Wang, Brain functional specialization and cooperation in Parkinson's disease, Brain Imaging Behav (2021), https://doi.org/10.1007/s11682-021-00526-4.

[38] G.-J. Ji, C. Ren, Y. Li, J. Sun, T. Liu, Y. Gao, D. Xue, L. Shen, W. Cheng, C. Zhu, Y. Tian, P. Hu, X. Chen, K. Wang, Regional and network properties of white matter function in Parkinson's disease, Hum. Brain Mapp. 40 (4) (2019) 1253–1263, https://doi.org/10.1002/hbm.24444.

[39] B. Maayah, O. Abu Arqub, S. Alnabulsi, H. Alsulami, Numerical solutions and geometric attractors of a fractional model of the cancer-immune based on the Atangana-Baleanu-Caputo derivative and the reproducing kernel scheme, Chin. J. Phys. 80 (2022) 463–483, https://doi.org/10.1016/j.cjph.2022.10.002.

[40] B. Maayah, A. Moussaoui, S. Bushnaq, O. Abu Arqub, The multistep Laplace optimized decomposition method for solving fractional-order coronavirus disease model (COVID-19) via the Caputo fractional approach, Demonstr. Math. 55 (1) (2022) 963–977, https://doi.org/10.1515/dema-2022-0183.

[41] G.J. Ji, W. Liao, F.F. Chen, L. Zhang, K. Wang, Low-frequency blood oxygen level-dependent fluctuations in the brain white matter: more than just noise, Sci. Bull. 62 (9) (2017) 656–657, https://doi.org/10.1016/j.scib.2017.03.021.

[42] G.J. Ji, C. Ren, Y. Li, J. Sun, T. Liu, Y. Gao, D. Xue, L. Shen, W. Cheng, C. Zhu, Y. Tian, P. Hu, X. Chen, K. Wang, Regional and network properties of white matter function in Parkinson's disease, Hum. Brain Mapp. 40 (4) (2019) 1253–1263, https://doi.org/10.1002/hbm.24444.

[43] G.-J. Ji, J. Sun, Q. Hua, L. Zhang, T. Zhang, T. Bai, L. Wei, X. Wang, B. Qiu, A. Wang, H. Sun, W. Liao, F. Yu, C. Zhu, Y. Tian, K. He, K. Wang, White matter dysfunction in psychiatric disorders is associated with neurotransmitter and genetic profiles, Nature Mental Health 1 (9) (2023) 655–666, https://doi.org/10.1038/s44220-023-00111-2.