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The Effect of Different Techniques of Repetitive Transcranial Magnetic Stimulation on Parkinsonian Tremor

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Abstract

Background. Tremor in Parkinson's disease (PD) is usually a disabling symptom that doesn't adequately respond to medications. Recently, the European clinical guidelines recommended repetitive transcranial magnetic stimulation (rTMS) as a Grade-B recommendation for improving motor function in PD. **Objectives.** To study the effect of different rTMS protocols on PD tremor. **Methods.** 60 PD patients were divided randomly into three groups equally according to rTMS protocols received; they were divided into Group I (5 Hz), Group II (1 Hz), and Group III (sham). Sessions were applied daily for 2 weeks. All patients were subjected to clinical assessment using different assessment tools; tremor Unified Parkinson's Disease Rating Scale (UPDRS) as well as total UPDRS, tremor amplitude and frequency by EMG before sessions, after last session, and 1 month later. **Results.** Group I showed the most significant reduction in mean UPDRS (tremor and total) after the last session and 1 month later ($p < .001$). Group I had the highest reduction in mean tremor amplitude and frequency by EMG after the last session and 1 month later ($p < .001$; $p < .05$, respectively). **Conclusion.** 5 Hz rTMS protocol was the most effective in improving PD tremor.

Keywords: Parkinson's disease; tremor; rTMS; UPDRS; EMG

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Introduction

Parkinson's disease (PD) is the second most common age-related neurodegenerative disorder after Alzheimer's disease. It is characterized clinically by resting tremor, rigidity, bradykinesia, and postural instability (Emamzadeh & Surguchov, 2018).

Tremor occurs in approximately 75% of PD patients. The pathophysiology of tremor has been linked to the combined actions of both the basal ganglia and the cerebello-thalamo-cortical circuit (Helmich, 2018). Tremor can be the predominant and most troublesome motor symptom, and poor response to dopaminergic agents is common (Abusrair et al., 2022).

It is well known from animal experiments that repetitive stimulation at the synaptic level can enhance or reduce synaptic transmission, a phenomenon known as long-term potentiation (LTP) or long-term depression (LTD). Transcranial magnetic stimulation (TMS) indirectly activates synapses so repeated pulses of TMS (i.e., rTMS) can theoretically activate the same set of synaptic connections multiple times and therefore replicate the situation seen in animal experiments (Di Lazzaro et al., 2018).

In 2020, the latest European clinical guidelines recommended rTMS over the primary motor cortex (M1) as a Grade-B recommendation for improving motor function in PD (Lefaucheur et al., 2020; Zhang et al., 2022).

High- and low-frequency rTMS have been shown to have different effects: enhance motor cortex excitability or briefly depress cortical excitability (Li et al., 2022).

In this study, we aimed to assess the effect of different rTMS techniques (5 Hz, 1 Hz, sham) on Parkinson's disease tremor.

Methods

A single-blind interventional controlled study was conducted on 60 patients with idiopathic PD, tremor dominant type which characterized by prominent tremor of one or more limbs with a relative lack of significant rigidity and bradykinesia. They were recruited from Kasr Al Ainy movement disorders clinic from October 2022 to November 2023. The diagnosis was made according to the UK PD Society Brain Bank Criteria (Hughes et al., 1992). Their ages ranged from 50 to 75 years. They were divided into three groups using simple random sampling method. This study was approved by the Research of Ethics Committee (REC) faculty of medicine Cairo University code: MD-357-2022. Written consent was obtained from all participants prior sharing in the study and was documented.

Group 1 (GI) received high-frequency (5 Hz) rTMS. Group 2 (GII) received low-frequency (1 Hz) rTMS. Group 3 (GIII) received sham rTMS, which is the control group. All groups received rTMS daily for 2 weeks using figure-of-eight coil applied to the primary motor area (M1). A repetitive transcranial magnetic stimulator (MagStim Rapid magnetic stimulator 2, Magstim company, White Land, Wales and UK), model S/N 2534, connected with a figure-of-eight coil with a diameter of 70 mm, was used in our sessions.

Group I (5 Hz)

Patients received rTMS to the primary motor area (M1; of 5 Hz frequency, 80% of resting motor threshold [RMT], 24 trains of 50 stimuli [train duration: 10 s separated by a 10-s pause]) delivered for a total of 1,200 pulses, daily for 2 weeks (six sessions; Lefaucheur et al., 2020).

Group II (1 Hz)

Patients received rTMS to the primary motor area (M1; of 1 Hz frequency, 80% of RMT for a total of 600 pulses, daily for 2 weeks (six sessions; Lefaucheur et al., 2020).

Group III (Sham)

Patients received sham rTMS stimulation to the primary motor area M1 daily for 2 weeks (six sessions; Lefaucheur et al., 2020).

Hot Spot Determination (Best Site)

Slightly changing the placement of the coil over the motor cortex (M1, which has been contralateral to the more affected upper limb). The position of figure-of-eight coil was adjusted at the beginning of each session to find the best scalp position (motor hot spot). M1 in general was 0–2 cm lateral to the vertex, tangentially to the subject's head surface, with the handle pointing posteriorly and positioned at 45° with respect to midsagittal axis to find the optimal scalp position to elicit motor responses in the contralateral thumb (motor hot spot; González-García et al., 2011).

Calculation of the Resting Motor Threshold (RMT)

RMT is defined as the lowest stimulus intensity that produced a minimal motor-evoked response and a visible abduction of the thumb contralateral to the stimulated hemisphere through contraction of the abductor pollicis brevis muscle (APB), about 50 µV in at least 5 of 10 trials at rest (González-García et al., 2011).

Sham Group

The control group got sham stimulation by turning the coil 90° from the scalp over the same area (M1) and the same intensity and protocol as real rTMS. This technique produced sound like active stimulation and some somatic sensations with negligible direct cortical sequalae (Benninger et al., 2012; Klirova et al., 2013).

Patients were kept on the same dopaminergic medications for a month prior to commencement rTMS sessions, during sessions, and for a month after the end of sessions. Exclusionary criteria were medications nonadherence, severe cognitive impairment (MMSE < 18), seizure disorders, presence of metallic head and/or neck implants, previous-skull surgeries and traumas, and recent forearm fracture (within 3 months).

All patients were subjected to history taking, medical and neurological examination, MMSE test (Folstein et al., 1975), PD assessment by Unified Parkinson's Disease Rating Scale (UPDRS; Goetz et al., 2008) and Modified Hoehn-Yahr staging (H&Y staging; Goetz et al., 2004).

Clinical assessment for tremor was done by tremor examination score of UPDRS Part III, from point 3.15a to 3.18 with total maximum score of 40. That included examination for postural tremor, kinetic tremor, resting tremor, presence of jaw or lip tremor, and constancy of tremor.

Further objective tool for tremor assessment was carried out using surface electromyography (EMG) to detect the amplitude and frequency of the tremor by Neuropack MEB9200 4-channels apparatus. The frequency and amplitude of a patient's tremor were recorded when the hand was in the sitting position at rest (put relaxed hand on thighs). The recording lasted for 30 s (Milanov, 2000).

Tremor frequency, or the number of oscillations per second, is measured in cycles per second (Hz). If the number of sampled points (N) is over a period in seconds (T), then the sampling rate is N/T (Hess et al., 2012). Tremor amplitude was measured peak to peak for each oscillation, and the mean value was considered (Hess et al., 2012). EMG measurements were done at three intervals: before sessions, after the last session, and 1 month from the last session (Rogasch et al., 2013).

All these measurements were done during off state (after overnight withdrawal of dopaminergic drugs) to avoid masking of tremor by medications effect (Dileone et al., 2017).

All patients were asked to report any side effects during sessions as seizures, dizziness, headache, etc.

Statistical Analysis

Data was coded and entered using the statistical package for the Social Sciences (SPSS) version 28 (IBM Corp., Armonk, NY, USA). Data was summarized using mean, standard deviation, median, minimum and maximum for quantitative variables, and frequencies (number of cases) and relative frequencies (percentages) for categorical variables. Comparisons between groups were done using analysis of variance (ANOVA) with multiple comparisons post hoc test in normally distributed quantitative variables while nonparametric Kruskal-Wallis test and Mann-Whitney test were used for non-normally distributed quantitative variables (Chan, 2003a; Chan, 2003b; Chan, 2004).

Results

Clinical Characteristics of the Studied Groups

The general clinical characteristics of the three groups of the current cohort are shown in Table 1.

Mean Reduction in Different Clinical and Investigational Parameters Between Studied Groups

GI received rTMS with frequency of 5 Hz showed the best reduction in total and tremor UPDRS scores reflecting improvement in the disease generally.

Table 1

General Clinical Characteristics of the Studied Groups

Variables		**GI (5 Hz)** *n* = 20	**GII (1 Hz)** *n* = 20	**GIII (Sham)** *n* = 20
Age		59.80 ± 5.77	59.90 ± 6.34	63.10 ± 7.52
Gender	Male	14 (70%)	14 (70%)	16 (80%)
	Female	6 (30%)	6 (30%)	4 (20%)
Disease duration (years)		4.20 ± 3.44	5.90 ± 4.55	4.45 ± 5.53
Smoking		6 (30%)	6 (30%)	4 (20%)
Positive family history of Parkinson's disease		2 (10%)	4 (20%)	3 (15%)
Modified H&Y Scale before sessions		2.25 ± 0.6	1.98 ± 0.5	1.95 ± 0.79
Total UPDRS score before sessions		85.6 ± 31.51	59.35 ± 27.07	64.15 ± 37.32
Tremors UPDRS score before sessions		24 ± 6.95	22.75 ± 7.77	20.60 ± 8.40

They also showed the best reduction regarding tremor frequency and amplitude assessed by EMG.

GII submitted to rTMS with frequency of 1 Hz; it showed only improvement in tremor UPDRS scores after 1 month from last session with no effect on total UPDRS scores and tremor UPDRS after last session, as well as on tremor amplitude and frequency Tables 2, 3, and 4.

Table 2
Comparison of Mean Reduction in Different Clinical and Investigational Parameters Between Studied Groups

Variables	**Assessment after**	**GI (5 Hz)** Mean reduction ± *SD*	**GII (1 Hz)** Mean reduction ± *SD*	**GIII (sham)** Mean reduction ± *SD*	***p-value***
Total UPDRS scores	**Last rTMS session**	34.90 ± 15.99	10.55 ± 8.85	9.80 ± 7.24	**< .001**
	1 month later	27.80 ± 18.73	5.60 ± 4.98	1.65 ± 9.13	**< .001**
Tremors UPDRS	**Last rTMS session**	9.25 ± 3.77	5.35 ± 2.37	3.90 ± 2.14	**< .001**
	1 month later	6.20 ± 3.50	4.40 ± 1.07	−0.50 ± 2.20	**< .001**
Tremors amplitude by EMG (µv)	**Last rTMS session**	188.75 ± 179.96	24.45 ± 26.23	20.45 ± 25.63	**> .001**
	1 month later	169.55 ± 159.39	18.20 ± 34.48	−12.75 ± 74.93	**> .001**
Tremors frequency by EMG (/sec)	**Last rTMS session**	1.25 ± 2.38	0.30 ± 0.57	0.05 ± 1.88	**.036**
	1 month later	0.65 ± 2.32	0.05 ± 0.60	−0.55 ± 2.42	**.028**

p*-value < .05 is considered significant. ** *p*-value < .01 is considered highly significant. * *p*-value < .001 is considered very highly significant.

Table 3
Post Hoc Pairwise Comparison of Reduction in Different Clinical and Investigational Parameters Between Studied Groups

Variables	**Assessment after**	**GI (5 Hz) vs. GII (1 Hz)** *p*-value	**GI (5 Hz) vs. GIII (sham)** *p*-value	**GII (1 Hz) vs. GIII (sham)** *p*-value
Total UPDRS scores	**Last rTMS session**	**< .001**	**< .001**	.720
	1 month later	**< .001**	**< .001**	.544
Tremors UPDRS	**Last rTMS session**	**< .001**	**< .001**	.602
	1 month later	**< .001**	**< .001**	**.003**
Tremors amplitude by EMG (µv)	**Last rTMS session**	**< .001**	**< .001**	1.000
	1 month later	**.002**	**< .001**	.790
Tremors frequency by EMG (/sec)	**Last rTMS session**	**.036**	**.035**	1.000
	1 month later	.870	**.028**	.373

p*-value < .05 is considered significant. ** *p*-value < .01 is considered highly significant. * *p*-value < .001 is considered very highly significant.

Table 4
Comparison of Side Effects of rTMS Between the Groups

Variables		Group I (5 Hz)		Group II (1 Hz)		Group III (sham)		*p*-value
		Count	%	Count	%	Count	%	
Side effects of rTMS	None	16	80.0%	15	75.0%	18	90.0%	.722
	Headache	3	15.0%	3	15.0%	1	5.0%	
	Dizziness	1	5.0%	1	5.0%	0	0.0%	
	Numbness	0	0.0%	1	5.0%	0	0.0%	
	Neck pain	0	0.0%	0	0.0%	1	5.0%	

*p-value < .05 is considered significant. ** p-value < .01 is considered highly significant. *** p-value < .001 is considered very highly significant. ****Transient insignificant side effects mainly in the form of headache and dizziness (not leading to drop out) were reported among those receiving rTMS regarding the frequency (5 Hz, 1 Hz).

Discussion

PD is associated with tremor in 75% of cases that are disabling and resistant to therapy (Abusrair et al., 2022). To our knowledge, few studies investigated the role of rTMS in the management of PD tremor here in Egypt.

This study showed marvelous improvement in PD patients on rTMS as an add-on therapy regarding all Parkinsonian symptoms, especially motor ones. However, this improvement is transient, lasting for 1 month after the last session, meaning that these sessions need to be repeated. This improvement was noted across different evaluation metrics.

On total UPDRS score, only a significant reduction was seen after last session and 1 month later in Group I, meaning that both Group II and III have a placebo effect, which agrees with many studies done, like that of Goetz et al. (2000) and Okabe et al. (2003).

Regarding tremor score of UPDRS, which is a more specific scale for assessment of PD tremor, the effect of rTMS in Group II appeared 1 month after the last session, which was less in comparison to Group I that appeared significantly from last session as well as later. In this study, we proved that low-frequency rTMS has an effect superior to sham, which disagrees with previous studies, like that of Goetz et al. (2000) and Okabe et al. (2003) who showed that both have similar placebo effect.

The meta-analytic study done by Kim et al. (2019) showed that both high- and low-frequency rTMS on M1 have the potential to enhance PD patient’s motor function, albeit with high frequency rTMS being more efficacious in mitigating motor symptoms and demonstrating a longer-term positive impact through long-term potentiation (LTP), often induced by high-frequency repetitive stimulations.

Several studies (Lefaucheur et al., 2020; Yang et al., 2018) have shown that the main causes of motor symptoms in Parkinson's disease are reduced neural reserve and automaticity due to malfunctioning basal ganglia. By directly enhancing cortical excitability, high-frequency rTMS augments the activity of the striatum and modulates inhibitory impulses within the globus pallidus interna. These mechanisms rectify basal ganglia dysfunction through the cortico-basal ganglia-thalamo-cortical circuit, resulting in improved motor function.

Another hypothetical explanation could be that high-frequency rTMS might directly activate dopaminergic neurons in the striatum, supplying endogenous dopamine as proven by a prior study conducted by Khedr et al. (2006, 2019) who reported that serum dopamine levels were significantly elevated after six daily sessions of high-frequency rTMS. Also, Strafella et al. (2003) found that high-frequency rTMS on motor cortex (M1) increases endogenous dopamine release in the ipsilateral dorsal striatum by using positron emission tomography (PET).

Regarding the same issue, in a large meta-analysis by Li et al. (2022) rTMS has been proven to be an effective treatment for motor symptoms of PD, and multisession high-frequency stimulation on bilateral M1 could be an optimal stimulation protocol. They found that high-frequency rTMS on M1 and supplementary motor cortex (SMA) has beneficial effects on limb function, tremor, and akinesia symptoms in PD patients, and low-frequency rTMS on SMA could relieve levodopa-induced dyskinesias symptoms (LID) by its inhibitory effect.

Moreover, in this study the significant reduction of total UPDRS in Group I over Group II and sham group, denoted that high-frequency protocol also could improve nonmotor symptoms of PD, even over M1 stimulation.

This finding is in agreement with Makkos et al. (2016), who found that the active treated group had significant improvement in nonmotor symptoms and health-related quality of life.

These results were explained by Lefaucheur (2019), as the repeated magnetic pulses can not only alter excitability at the site of stimulation but also influence brain regions anatomically connected to the stimulation site, which provide profound influence on the characteristics of brain circuitry. Indeed, recent meta-analysis studies recommended high-frequency rTMS over dorsolateral prefrontal cortex (DLPFC) as the best protocol for improving nonmotor PD symptoms (Lefaucheur et al., 2020; Zhang et al., 2022).

About the effects of rTMS on PD tremor that weren't sufficiently studied yet, the current study showed significant reduction in resting tremor amplitude and frequency with high frequency after last rTMS session and 1 month later.

The following results agree with Spagnolo et al. (2021) who evaluated the safety and efficacy of high-frequency rTMS with H-coil in PD management. They found that tremor scores revealed a mean decrease in the high-frequency group, while approximately no effect was detected in the sham group at the end of treatment measurement.

A study conducted by Siebner et al. (2000) found a slight decrease in tremor amplitude after a single session of 5 Hz rTMS over M1 in comparison to sham group in which assessment was done after 1 hr from rTMS session.

Indeed, a recent study by Qi et al. (2023) studied the effect of 1 Hz rTMS in comparison to sham and revealed no statistically significant difference in tremor frequency and amplitude by EMG after sessions among patients who received low-frequency rTMS and sham patients.

Conversely, a meta-analysis conducted by Zhu et al. (2015) determined that low-frequency rTMS demonstrated greater efficacy compared to sham stimulation for motor symptoms in PD tremor. Furthermore, they suggested that both high-frequency and low-frequency rTMS had beneficial effects on motor functions in PD patients. Additionally, they found that low-frequency rTMS exhibited higher safety in clinical practice compared to high-frequency rTMS.

The study assessed the adverse effects among three groups and found no significant differences. The transient and clinically insignificant side effects did not lead to dropouts. Headache was the most common side effect across all groups.

These findings agree with Kaur et al. (2019) and Vabalaite et al. (2021) who found that headache is the most common adverse effect of rTMS; however, they found it more in patients who received higher frequency rTMS. Lerner et al. (2019) explained headache from rTMS as it could be the direct stimulation of superficial nerves and muscles which depend on coil position or the increased cerebral blood flow as a response to stimulation, or both.

Conclusion

In view of the outcome of the current study, it could be concluded that 5 Hz rTMS protocol over M1 was more effective than 1 Hz rTMS protocol and sham rTMS, regarding the improvement in tremors UPDRS as well as total UPDRS scores and also improvement resting tremors frequency and amplitude in Parkinson's disease.

Limitation and Implication for Future Research

The current study highlighted the vital role of high-frequency rTMS as an add-on therapy in the management of all PD symptoms (motor, nonmotor) including tremor. This interventional study was conducted on an adequate number of patients which give reliability to the obtained results. However, more multicenter studies are needed and further studies with more prolonged time investigating nonmotor symptoms in detail after using rTMS to improve quality of life of PD patients.

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involved in ethical publication and affirm that this work is consistent with those guidelines.

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