Evaluation of High-Frequency Repetitive Transcranial Magnetic Stimulation Role in improving Motor and Non-motor Manifestations of Parkinson's Disease in Minia University Hospital

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Abstract

Background: The second most common kind of neurodegenerative disease is Parkinson's disease (PD)., and there are still significant challenges with its pharmaceutical treatment. Due to its potential therapeutic benefits on motor functions in Parkinson's disease (PD), high-frequency repetitive transcranial magnetic stimulation (HF-rTMS) of the motor cortex is an exciting non-invasive brain stimulation (NIBS) for treating both motor and non-motor symptoms of PD.
Objectives: The purpose of this prospective sham-controlled double-blinded study was to quantify the treatable effects of high-frequency rTMS on PD-related motor and non-motor symptoms.
Patients and Methods: Between August 2022 and May 2023, 35 participants of both sexes were included in this research after being diagnosed with PD. All patients were attending Minia University Hospital Neurology outpatient clinic. Patients were randomly assigned as 1:1 to either the Real-rTMS group (high-frequency, 5 HZ) or SHAM-rTMS group. Ten consecutive sessions of TMS were performed. The Unified Parkinson's Disease Rating Scale (UPDRS) was used to evaluate all patients both before the first session and again after the tenth session was completed.
Results: After 10 consecutive sessions, only the real-rTMS group demonstrated statistically significant improvements in motor section of UPDRS score (UPDRS 3) and overall UPDRS scores. In contrast, the SHAM-group showed no statistically significant changes.
Conclusion: These findings suggest that high-frequency rTMS might play a significant role in treating motor manifestations of PD.

Keywords: High-frequency rTMS; Parkinson's Disease; Motor manifestations.

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Introduction

The second most prevalent neurodegenerative illness, Parkinson's disease (PD) typically affects middle-aged persons and is characterised by resting tremors, bradykinesia, stiffness, gait problem, and postural instability. Dopaminergic neurons, most of which are found in the substantia nigra pars compacta, die out progressively and selectively, leading to PD **(Randver, 2018).**

Psychological and cognitive symptoms of PD include depression, apathy, vision problems, and even cardiovascular autonomic dysfunction (PD) **(Nemade et al., 2021)**. Levodopa therapy is only one of several pharmaceutical options for treating Parkinson's disease symptoms **(Nemade et al., 2021, Connolly and Lang, 2014).** However, when administered long-term, these drugs might cause motor problems such as levodopa-induced dyskinesias (LIDs) and fail to provide the intended results **(Fahn, 2008 and Turcano et al., 2018)**.

As a result, non-invasive brain stimulation (NIBS) and other potential alternative therapies for PD must be investigated **(Nemade et al., 2021)**. One kind of NIBS, repetitive transcranial magnetic stimulation (rTMS), may alter neural activity **(Brunoni et al., 2017)**. To modulate cortical excitability in response to frequency variations, a wire coil is utilised to generate a magnetic field that may penetrate the scalp and skull. When applied at high frequencies (>5 Hz), repetitive transcranial magnetic stimulation (rTMS) increases cortical excitability, but when applied at low frequencies (1 Hz), it decreases cortical excitability. When a stimulus is administered for a longer period of time, its impact will last longer **(Brunoni et al., 2017 and Milev et al., 2016).**

Repetitive TMS stimulation may be applied to the cerebellum, supplementary motor area (SMA), dorsolateral prefrontal cortex (DLPFC), and even the major motor cortex (M1) for the treatment of motor disorders. **(Jankovic, 2008 and Shin et al., 2019).** The aim of our current study was to assess whether HF-rTMS has significant treatable effect on motor and non-motor manifestations in PD patients, and if this effect could add to the other treatment modalities available to these patients.

Patients and methods

Forty (40) people with a confirmed diagnosis of Parkinson's disease are shown here. All individuals met the idiopathic Parkinson's disease criteria established by the UK Brain Bank **(Hughes et al., 1992).** From August 2022 to May 2023, patients were culled from the Neurology clinics at Minia University Hospital. Participants were simply randomized to study groups as 1:1 (20 for real 5HZ rTMS and 20 for SHAM-rTMS). Only 35 participants finished the research; 19 received real-rTMS and 16 received SHAM-rTMS, as five patients dropped out during the sessions but not due to any complications or side effects from the procedure used.

All patients were instructed that they would have been treated by TMS but were blinded to the individual group assignment. Before beginning the trial, all patients had a thorough neurological and general history taken without any changes to their antiparkinsonian drugs for 3 weeks before initiating the study. No patients with any contraindication to TMS as metal implants, personal or family history of seizures or brain tumors were involved in this study.

Repetitive transcranial magnetic stimulation

Patients attended TMS sessions while reclined in a recliner; rTMS was given using a figure-eight coil attached to a Neurosoft TMS device. One TMS pulse was used to find out the motor evoked potential (MEP) threshold in the resting abductor digiti

minimi (ADM) muscle. We caught electromyogram (EMG) from ADM in the primary motor area situated by moving the coil until we obtained maximal amplitude motor evoked potentials. Once the best position was obtained, we have detected the motor threshold. Motor threshold of the hand was ascertained by providing single TMS pulse over the optimal location and by minimizing the stimulus intensity in steps of 1% stimulator output. The lowest TMS stimulus strength used to induce small motor evoked potential (usually 50 μV) while the recorded muscle was at rest, is the resting motor threshold. Real-rTMs were distributed to 19 test subjects (120 percent of RMT stimulation intensity; 5 Hz frequency; 10 sec on and 1 sec off with 2000 pulses per session; the total duration was 15 min per session). In order to give the other 16 participants the feeling of receiving rTMS without really stimulating the brain, the coil was lifted and slanted away from the head. The total number of sessions was 10, each occurring once a day for 10 successive days **(Khedr et al., 2003).** All subjects were evaluated objectively Without knowing which kind of rTMS was used.

All participants were submitted to be assessed by UPDRS (Unified Parkinson's Disease Rating Scale). This scale was created to combine features of many scales into one comprehensive, efficient, and adaptable tool for tracking disability and impairment caused by PD. This scale's four subscales are derived, in large part, from existing measures that have been analysed and modified by a panel of specialists in the area of movement disorders (Part I, Mentation, Behavior and Mood; Part II, Activities of Daily Living; Part III, Motor; Part IV, Complications). There are 14 different motor tasks on the scale, each of which may be scored from 0 (normal), 1 (mildly impaired), 2 (moderately impaired), 3 (severely impaired) to 4 (can hardly execute the task). Speech, facial expression, resting tremor, action tremor, stiffness, finger taps, hand motions, hand pronation/supination, limb dexterity, rising from a chair, stance, walking, postural stability, and bradykinesia are all examples. Both before the first rTMS session and after the tenth session, all individuals were assessed.

Ethical Approval

The Institutional Review Board of the School of Medicine at Minia University gave the present research its stamp of approval (108:10/2021). All participants provided signed informed permission after having the benefits, risks, and potential consequences explained to them. All procedures used in this research followed the guidelines laid forth in the Helsinki Declaration by the World Medical Association.

Statitical Analysis

We ran our analyses in SPSS 20 for Windows (Statistical Package for the Social Sciences; SPSS Inc., Chicago, IL, USA). Frequencies and percentages were calculated for categorical data, whereas means and standard deviations were calculated for continuous variables. Quantitative characteristics were compared using independent samples T-tests between the two group and paired samples T test between the two times within each group, while qualitative characteristics were evaluated using Chi-square tests. The critical P value was determined to be < 0.05.

Results

In this study, thirty-five (35) patients of both sexes completed the sessions, 19 of the real rTMS group and 16 of the SHAM-TMS group, as five patients dropped out during delivering the sessions. In the rTMS group, the age was 58.74 ± 10.115, 13 (68.4%) were male, and 6 (31.6%) were female, while in the SHAM group, the age was 59.38 ± 13.058, 11 (68.6%) was male and 5

(31.2%) were female with no statistically significant difference between the two groups regarding the age, sex or residency in urban or rural areas (**Table.1**).

Table 1. Demographic data of the sample between Sham and TMS groups

Variables	SHAM rTMS (N=16)	Real rTMS (N=19)	P vlaue
Age mean ± SD	59.38 ± 13.058	58.74 ± 10.115	0.872
Gender Number (%) **Male** **Female**	 11 (68.8%) 5 (31.2%)	 13 (68.4%) 6 (31.6%)	 0.636
Residence Number(%) **Urban** **Rural**	 6 (37.5%) 10 (62.5%)	 11(57.9%) 8 (42.1%)	 0.194

Also, there was no statistically significant difference between the two groups regarding medical comorbidities (e.g., family history, DM, hypertension or other comorbidities) (**Table. 2**).

Table 2. Medical comorbidities among the sample

Variables	SHAM rTMS (N=16)	Real rTMS (N=19)	P value
Family history Number (%) **No** **Have**	 13 (81.3%) 3 (18.7%)	 18 (94.7%) 1 (5.3%)	 0.238
DM Number (%) **No** **Have**	 14 (87.5%) 2 (12.5%)	 17 (89.5%) 2 (10.5%)	 0.630
Hypertension Number (%) **No** **Have**	 9 (56.2%) 7 (43.8%)	 11 (57.9%) 8 (42.1%)	 0.596
Other comorbidities Number (%) **No** **Have**	 14 (87.5%) 2 (12.5%)	 14 (73.7%) 5 (26.3%)	 0.280

In the real rTMS group, the mean duration of illness was 4.97 ± 4.63, while in the SHAM group, it was 7.53 ± 5.13, with no statistically significant difference between the two groups. Also, there was no statistically significant difference between the two groups as regard the starting limb or the predominant clinical feature (**Table. 3**).

Table 3. Clinical features of the sample

Variables	SHAM rTMS (N=16)	Real rTMS (N=19)	P value
Duration mean ± SD	7.53 ± 5.13	4.97 ± 4.63	0.131
Starting limb Number (%)			
Right upper limb	5 (31.25%)	8 (42.11%)	0.840
Left upper limb	7 (43.75%)	8 (42.11%)	
Right lower limb	2 (12.5%)	1 (5.26%)	
Left lower limb	2 (12.5%)	2 (10.53%)	
Predominant feature Number (%)			
	8 (50%)	10 (52.6%)	0.573
Rigidity	8 (50%)	9 (47.4%)	
Tremors			

Before delivering the sessions, no statistically significant difference was found between the groups either in UPDRS 1, UPDRS 2, UPDRS 3 or total UPDRS score (**Table 4**).

Table 4. Assessment at baseline

*Variables	SHAM rTMS Mean ± SD	Real rTMS Mean ± SD	P value
UPDRS 1	15.13±5.644	18.32±9.522	0.248
UPDRS 2	22.5±8.937	24.47±10.335	0.554
UPDRS 3	47.5±17.478	43.47±13.64	0.449
Total UPDRS	85.13±27.873	86.26±26.901	0.903

*UPDRS 1: Unified Parkinson's disease rating scale 1; UPDRS 2: Unified Parkinson's disease rating scale 2; UPDRS 3: Unified Parkinson's disease rating scale 3; Total UPDRS: Total score of Unified Parkinson's disease rating scale

Meanwhile, after the end of 10 successive sessions, When comparing the two groups, the real rTMS group showed significant improvement in motor UPDRS score (UPDRS 3) and overall UPDRS scores, whereas the SHAM group showed no significant change in any section of UPDRS score or in the total UPDRS scores (**Table .5**).

Table 5. Assessment after 10 sessions

Variables	SHAM rTMS Mean ± SD	Real rTMS Mean ± SD	P value
UPDRS 1	10.44±4.69	9.84±5.776	0.743
UPDRS 2	15.88±7.535	13.84±6.517	0.398
UPDRS 3	40.0±14.971	25.26±8.818	0.001**
Total UPDRS	66.31±22.458	48.95±17.002	0.014*

Results of comparison of each group (SHAM rTMS and real rTMS) pre- and post-sessions showed statistical significant change in each group as regard UPDRS 1, UPDRS 2, UPDRS 3, and Total UPDRS scores but with more significant change in favor of the Real rTMS group and particularly in UPDRS 3 and Total UPDRS score (**Table. 6**).

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Table 6. Comparison of each group pre- and post-TMS sessions

Variables		SHAM rTMS	Real rTMS	P value
UPDRS 1	At baseline Mean ± SD	15.13±5.644	18.32±9.522	0.248
	After 10 sessions Mean ± SD	10.44±4.69	9.84±5.776	0.743
	P value	**<0.001***	**<0.001***	
UPDRS 2	At baseline Mean ± SD	22.5±8.937	24.47±10.335	0.554
	After 10 sessions Mean ± SD	15.88±7.535	13.84±6.517	0.398
	P value	**<0.001***	**<0.001***	
UPDRS 3	At baseline Mean ± SD	47.5±17.478	43.47±13.64	0.449
	After 10 sessions Mean ± SD	40.0±14.971	25.26±8.818	**0.001****
	P value	**<0.001***	**<0.001***	
Total UPDRS	At baseline Mean ± SD	85.13±27.873	86.26±26.901	0.903
	After 10 sessions Mean ± SD	66.31±22.458	48.95±17.002	**0.014***
	P value	**<0.001***	**<0.001***	

Discussion

Our study's overarching goal was to demonstrate that high-frequency rTMS had a positive impact on motor and non-motor symptoms of idiopathic PD. High frequency (5 HZ) rTMS was applied for 10 successive days with an intensity of 120% of the RMT; 10 sec on and 1 sec off, 2000 pulses per session and the total duration was 15 min per session. These values agree with a previous study by **Khedr et al., 2003,** who used this protocol to evaluate the therapeutic effect of high-frequency rTMS on motor manifestations of PD. Still, they aimed mainly to test the long-lasting effect on motor performance as they continued to assess patients 1 month after receiving the last session.

The significant change in motor manifestations after stimulation of the primary motor area could be interpreted by the motor cortical- subcortical loop theory, as the standard basal ganglia circuit model involves damaged basal ganglia-thalamo-cortical drive as a major reason for the motor symptoms in PD patients, and therefore, the primary motor cortex is considered accepted location for neuromodulation of the cortex to stimulate the reduced thalamo-cortical drive. **(Grafton, 2004)**

The significant improvement in UPDRS 3, which includes mainly the motor functions, after receiving 10 sessions of 5 HZ rTMS could be explained mainly by dopamine release. This was in agreement

with an experimental study done in **1997** by **Ben-Shachar et al**. which could prove that rTMS could induce dopamine release in the striatum and frontal cortex. Furthermore, **Khedr et al., 2007** showed by the use of an enzyme immunoassay, that serum dopamine levels were remarkably raised after six daily sessions of high-frequency rTMS over the right and left hand and leg motor cortex.

This was corroborated also by the findings of **Strafella et al. (2001),** who used positron emission tomography (PET) in healthy human volunteers to demonstrate that rTMS of the prefrontal cortex induces the release of endogenous dopamine in the ipsilateral caudate nucleus. Direct stimulation of the corticostriatal axons may underlie the rTMS-induced dopamine release in the caudate nucleus **(Rothwell, 1997).**

As regard the different frequency of rTMS stimulation, there is considerable disparity between researchers in excitability after stimulation with 1 Hz, 5 Hz or theta burst stimulation, but the therapeutic effect in PD is a much significant sequel following the stimulation for 7 days **(Hamada et al., 2013).** Additionally, as was stated by **Khedr et al., 2006**, that 25 Hz rTMS exhibited a superior treatable effect than 10 Hz rTMS. Nevertheless, this does not certainly reflect that 25 Hz is the choicest frequency. So, to obtain the best results, a combination of more than one frequency/intensity might be the best selected way. Other previous studies showed also that different parameters of rTMS may be fitter for improvement of different symptoms **(Lefaucheur et al., 2004).**

Zhang et al. (2022) conducted a meta-analysis of all randomized-controlled trials (RCT) published from January 1, 1988, to January 1, 2022, and their findings agree with our study that employed rTMS stimulation to treat motor or non-motor PD symptoms. The purpose of this meta-analysis was to assess the effects of rTMS on motor function in a total of 381 individuals over 12 trials. Active rTMS considerably outperformed sham-rTMS on the motor scale, with an effect size of 0.51 (Z = 4.88, P 0.0001) to achieve statistical significance. The real-rTMS group saw a modest clinically significant difference in their motor scale score (4.61) compared to the control group (13.3) after treatment.

Lefaucheur et al. (2020) and Chou et al. (2015) have shown that It has been suggested that high-frequency rTMS (HF-rTMS) of the M1 in PD patients may alleviate motor symptoms of the disease. **Chou et al. (2015)** found that The motor symptoms of PD might be alleviated by rTMS directed at the major motor region (M1). Also this is in agreement with **Khedr et al., 2006**, that suggested that, motor areas of cortex are probably to be a principal site that all parkinsonian motor symptoms could be affected.

According to **Siebner et al. (2000)**, a rise in the period of the TMS-evoked silent-period (SP) in PD after 15 trains of 5-Hz rTMS over the hand area was gained. This reflects the efficiency of 5-Hz rTMS to influence short-term exchange in the excitability of intracortical inhibitory circuitry in PD patients. As dopamenergic medications lead to an indistinguishable change of the SP, the facilitatory effect of 5-Hz rTMS on intracortical inhibition might be a suitable procedure that explain the favourable sequel of 5-Hz rTMS of primary motor area in PD.

According to **Lang et al. (2008)**, to some extent, rTMS-induced cortical inhibition may be affected by anti-PD medication, which may include dopamine agonists. Participants in our research were required to have been using the same anti-parkinsonian medication for at least 3 weeks prior to enrollment.

Furthermore, results of our current study were supported by other studies that demonstrated the effect of rTMS on mood symptoms especially depressive symptoms associated with PD. This was proved by **McClintock et al. (2018)** who provided that rTMS had antidepressant like-effect but if delivered with different protocols as high frequency over left DLPFC and low frequency rTMS over right DLPFC not if delivered on M1 as was applied in our study and this was also consistent with prior study performed by **Lefaucheur et al. (2020).**

Studies examining the effect of rTMS treatments on cognitive function in PD patients corroborated our results. including those by **Buard et al. (2018), Makkos et al. (2016) and Pal et al. (2010)**, all of which focused on non-motor symptoms. Research methods and cognitive measures varied among these research. Multiple studies and meta-analyses suggest that rTMS intervention may have moderate but positive effects on executive function.**(Jiang et al., 2020)** or working memory **(Begemann et al., 2020).** However, **Lawrence et al. (2017)** concluded that the findings were inadequate to determine the efficacy of the rTMS intervention. Therefore, high-quality RCTs with relevant cognition tests are required to further evaluate the potential efficacy of rTMS intervention on cognitive function.

Our study has several limitations, First, This study has a small sample size and a limited number of patients. To confirm these results and the efficacy of this protocol, we need another study with a larger sample size in the future. Second, our current study did not evaluate the long-lasting effect of rTMS after the end of sessions due to difficulties for continuing follow-up of our participants after the sessions were ceased. Third, this study did not involve measurements of cortical excitability or other tools as fMRI to study and understand the mechanism of rTMS due to financial issues. Lastly, UPDRS-III scores fine outcomes sometimes could not be interperted as better life quality for PD patients as measured by the Parkinson's Disease Questionnaire (PDQ-39), as reported by some studies, in consequence possibly ensuing the debating end results. Therefore, these points should be taken into consideration and investigated thoroughly in the near future.

Conclusion

Overall, the findings of the present investigation provide support to the idea that real-rTMS, as opposed to sham-rTMS, may have a significant therapeutic role, particularly in motor symptoms of PD.

List of abbreviations

DLPFC: Dorso-lateral pre-frontal cortex.; HF-rTMS: High-frequency repetitive trans-cranial magnetic stimulation; LIDs: Levodopa-induced dyskinesia; M1: Primary Motor area; NIBS: Non-invasive brain stimulation; PD: Parkinson's Disease; PET: Positron Emission Tomography.

RCTs: Randomized controlled-trials; RMT: Resting motor threshold; r-TMS: repetitive trans-cranial magnetic stimulation; SP: Silent-period; UPDRS: Unified Parkinson's Disease Rating Scale.

Consent for publication

Not applicable.

Availability of data and material

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

Authors declare no competing interests.

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Author's contribution

M.M.A: revised the results and wrote the manuscript; W.T.S: revised the results and statistics; M.M.I: revised the clinical data obtained; B.H.S.S: recruited patients and

collected the needed data; A.E: revised the results.

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