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RESEARCH

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Exploring the effect of transcranial magnetic stimulation on quality of sleep in Parkinson's disease

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Abstract

Background Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive therapeutic approach that targets particular brain regions that had been used and displayed significant impact in various neurological disorders. This study aimed to explore if high-frequency (HF) rTMS over the parietal cortex could influence sleep quality in Parkinson's disease (PD).

Methods This was a prospective sham-controlled study conducted on 40 individuals with PD. The enrolled patients were examined with Unified Parkinson's Disease Rating Scale (UPDRS-III) and Modified Hoehn and Yahr Staging Scale (H&Y staging) for motor disability evaluation and staging. Pittsburgh Sleep Quality Index (PSQI) was used for sleep quality and Epworth Sleepiness Scale (ESS) for excessive daytime sleepiness and Beck Depression Inventory-II (BDI-II) for depression. Patients were classified into 2 groups: patients who underwent real-rTMS positioned over their bilateral parietal cortex. 100% of the motor threshold. Patients had a total of 12 sessions, one every other day. Another group received sham rTMS.

Results The patients receiving active rTMS showed significant improvement in UPDRS-III, PSQI, ESS, and BDI-II immediately after the sessions and 1 month later. The follow-up PSQI had a significant positive correlation with the baseline BDI-II ($r=0.88$, $P=0.001$), H&Y staging ($r=0.78$, $P=0.001$), and UPDRS-III ($r=0.78$, $p=0.001$). Multivariate linear regression analysis exhibited that the age of the patients was a significant predictor of sleep quality.

Conclusion HF rTMS over the parietal cortex had shown a significant impact on sleep quality by the modulation of affected brain areas and by improving concomitant motor and mood manifestations.

Keywords Parkinson's disease, Sleep quality, Repetitive transcranial magnetic stimulation

Introduction

Parkinson's disease (PD) is an alpha-synucleinopathy manifested by tremors, bradykinesia, rigidity, and postural instability. Cognitive, autonomic, and sleep abnormalities were also reported as nonmotor manifestations. In patients with PD, both daytime and nocturnal signs of sleep disturbances are evident [1].

Many years before PD is clinically diagnosed, sleep problems can develop. However, it seems that patients' sleep problems are not appropriately recognized since up to 30% of PD patients prefer not to share sleep issues with their doctors, even though 80% of them report sleep problems [2]. It was assumed that nighttime motor and nonmotor symptoms including tremors, severe dystonia, psychiatric symptoms, or dopaminergic drugs may be the cause of these problems [3].

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Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive modality treatment that uses repetitive magnetic field pulses to target specific brain locations. Primary motor cortex stimulation has been exhibited to significantly relieve motor symptoms in PD for a period averaging 6 weeks [4]. When stimulation was used across the prefrontal cortex, PD-related psychiatric and cognitive dysfunctions showed improved results [5, 6].

The therapeutic role of rTMS is principally concerned to alter neuronal activity distinctively according to the stimulation parameters such as frequency, coil configuration, pulse waveform, or route of the current [7]. It has been found that high-frequency (HF) rTMS across the parietal cortex, enhanced deep sleep and efficiency, as well as lowered the mean duration of awakenings at nighttime [8]. The objective of this research was to explore if HF rTMS over the parietal cortex could influence sleep quality in Parkinson's disease.

Patient and methods

This was prospective randomized sham-controlled research with 40 patients with Parkinson's disease. From January 2022 to October 2022, eligible patients were assembled from the Department of Neurology. The PD patients were clinically evaluated at baseline and then again after the end of the rTMS sessions and after 1 month.

The enrolled patients were identified as PD using the UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria [9] with age > 50 years. Patients with altered levels of consciousness or other illnesses such as chronic obstructive pulmonary disease, ischemic heart disease, or stroke that could negatively impact sleep or they had experienced any sleep problems during their early life before parkinsonian features were excluded from the study. Patients known to have epilepsy, those having metal implants in the upper body that may interfere with TMS, those with Mini-Mental State Examination (MMSE) < 24 or diagnosed with Parkinson plus or secondary parkinsonism, and those using antidepressants or psychiatric medications that might impact sleep were also excluded from this study. The enrolled PD patients were all already on antiparkinsonian medications including L-dopa, dopamine agonist, and amantadine, and were informed not to modify their medication at any point during the research "ON state".

The PD patients were clinically evaluated at baseline, directly after the rTMS sessions, and one month later using the following battery of evaluation including motor disability assessment using the Unified Parkinson's Disease Rating Scale (UPDRS-III) [10], to measure motor disability in PD. Moreover, disability staging was done using the Modified Hoehn and Yahr Staging Scale (H&Y staging) [11] with the mild stage (1–2.5), moderate (3), and severe stage (4–5).

Furthermore, the PD patients' sleep quality was evaluated using the Pittsburgh Sleep Quality Index (PSQI) [12], with a total score ranging from 0 to 21, with a total score of 5–21 representing inadequate sleep. The Epworth Sleepiness Scale (ESS) [13] was applied to determine excessive daytime sleepiness, and a score of > 10 has been proposed to indicate excessive daily sleepiness. Beck Depression Inventory-II (BDI-II) [14] with Arabic edition [15] was used to assess the severity of the depression. All participants who were involved in this research provided written, fully informed consent, and the regional medical ethical committee approved it.

The rTMS stimulation was carried out using a noninvasive safe MagVenture device (MagVenture device Pro 30, Ltd Company, Denmark) comprised a figure-eight coil (each wing is 9 cm in its outer diameter and its maximum field strength is 1.5 Tesla) directed over the motor cortex to produce a magnetic field adjusted through the device's stimulator to enhance cortical excitability and device associated with an EMG amplifier. The patients underwent stimulation while lying comfortably semi-recumbent and wearing earplugs to block out the noise of the cooling equipment. The motor threshold of the resting abductor digiti minimi (ADM) muscle was determined using a single TMS pulse. An electromyogram was generated from ADM in the primary motor region by rotating the coil until motor-evoked potential maximal amplitude (typically around 50 μV) was elicited. To locate the parietal regions, we first identified the motor hotspot and determined the threshold. Then, we moved the TMS coil 10 mm posteriorly and administered single pulses at 110% of the motor threshold until no twitches were observed, and the participant stopped reporting any sensation in their hand. Typically, this site is situated 2–5 cm posterior to the motor hotspot [16].

The patients were randomly arranged into either group (1) those who underwent real-rTMS had the coil's center positioned over their bilateral parietal cortex. 100% of the motor threshold was used as the TMS intensity. Patients had a total of 12 sessions, one every other day. In each session, patients received 1000 pulses at a frequency of 10 Hz, divided into 20 trains, each lasting for 10 s with a 50-s intertrain interval, or group (2) who received sham rTMS, which was applied under the same circumstances with the coil tilted 45–90 degrees off the scalp and one or two of the coil's wings touching the scalp to mimic the similar perception of rTMS but prevent the induction of current in the brain. Follow-up clinical assessments of the participants were performed using the same previous assessment immediately after the conclusion of the 12 sessions and one month after the last session. All

evaluations were carried out by competent neurologists who were unaware of whether the patients were receiving active or sham treatments.

Statistical analysis

Data were collected, coded, updated, and entered into Microsoft Access before being processed with SPSS software version 22 on Windows 7. The *t*-test was applied to compare quantitative data between two independent groups, whereas the paired *t*-test was applied to compare two dependent quantitative data. The Mann–Whitney test was applied to compare two independent groups. When comparing two or more qualitative groups, the Chi-square test is performed. To investigate the association between variables, the bivariate Pearson correlation test was applied. To evaluate the link between quantitative dependent and independent variables and risk factor identification, multiple linear regressions were run. A *p*-value of 0.05 was used to account for statistical significance.

The sample size for this study was calculated utilizing the following assumptions: power 80%, confidence interval 95%, cases-to-control ratio 1:1 based on prior study findings [7] to be 30 cases (15 per group), best increased to 34 to overcome non-response.

Results

The PD patients in this study ranged in age from 52 to 75 years old, with a mean of 61 ± 6.7. It included 21 (52.5%) males and 19 (47.5%) females. The average disease duration was 3 ± 2.2 years, with a range of 1–8 years. As shown in Table 1, PD patients with poor sleep quality according to the PSQI were older and had higher significant scores in the BDI-II and H&Y Staging Scale than those with adequate sleep quality at baseline parameters. Otherwise, no significant difference existed in the other clinical data. As mentioned in Table 2, there was no significant difference in demographic and clinical data at baseline between those who got real and sham rTMS. On the other hand, group (1) patients demonstrated substantially better sleep quality, depression scores, and severity of motor symptoms immediately and 1 month after the rTMS sessions were completed in comparison with the baseline. Contrariwise, no significant differences have been observed in group (2) in these clinical parameters as shown in Table 3.

Table 1 Comparison of demographic and clinical data between the patients with adequate and poor sleep quality at baseline

	***Adequate sleep quality (*n* = 15)**	**+ Poor sleep quality (*n* = 25)**	***p*-value**
Age (yrs) Mean ± SD	60.1 ± 6.5	65.2 ± 6.3	**0.03***
Sex Male:female	8 (53.3%):7 (46.6%)	13 (52%):12 (48%)	0.7
Disease duration (yrs) Mean ± SD	3.2 ± 2.1	4.1 ± 2.6	0.3
Modified Hoehn and Yahr Staging Scale	2.1 ± 0.79	3.7 ± 1.1	**< 0.001***
ESS	2.4 ± 1.85	7 ± 4.24	**0.001***
BDI-II	4.8 ± 3.5	12.7 ± 2.7	**< 0.001***
UPDRS-III	33.6 ± 20.4	40.5 ± 21.6	0.3

BDI-II Beck Depression Inventory-II, *UPDRS-III* Unified Parkinson's Disease Rating Scale, *ESS* Epworth Sleepiness Scale

* Adequate sleep quality: Pittsburgh Sleep Quality Index < 5

\+ Poor sleep quality: Pittsburgh Sleep Quality Index > 5

Table 2 The comparison in demographic and clinical data of the participants at baseline

	***Group (1) *n* = 20**	**Group (2) *n* = 20**	***P* value**
Age (years) Mean ± SD	61.6 ± 7.3	61.1 ± 6.3	0.8
Sex (male: female)	10 (50%):10 (50%)	12 (60%):8 (40%)	0.8
Duration of illness (years) Mean ± SD	3.6 ± 2.3	3.4 ± 2.2	0.8
PSQI Adequate sleep Poor sleep	6 (30%) 14 (70%)	9 (45%) 11 (55%)	0.7
ESS Excessive daytime sleep Normal	16 (80%) 4 (20%)	12 (60%) 8 (40%)	0.7
BDI-II+ Minimal Mild	14 (70%) 6 (30%)	16 (80%) 4 (20%)	0.9
UPDRS-III Mean ± SD	48.4 ± 25.3	41.6 ± 25.3	0.4

PSQI Pittsburgh Sleep Quality Index, *BDI-II* Beck Depression Inventory scale, *ESS* Epworth Sleepiness Scale

* Group (1): PD patients who received real-rTMS, Group (2): PD patients who received sham

\+ Minimal BDI-II:0–13, Mild BDI-II:14–19

Table 3 Effect of rTMS stimulation on clinical parameters of the PD patients

	Baseline	Immediate after rTMS	Follow-up 1 month later	*P* value
Pittsburgh Sleep Quality Index (PSQI)				
[+]Group (1)	**4 ± 1.8**	2.6 ± 1.5	2.6 ± 3.8	**< 0.001**[a,c*]
Group (2)	3.6 ± 1.9	3.4 ± 1.8	3.5 ± 1.8	0.9[b]
Epworth Sleepiness Scale (ESS)				
Group (1)	5.6 ± 3.8	4.5 ± 2.6	4.2 ± 2.5	< 0. 1[a,c]
Group (2)	4.3 ± 3.4	4.2 ± 2.9	4.1 ± 2.9	0.5[a,c]
Beck Depression Inventory Scale (BDI-II)				
Group (1)	6.8 ± 4.5	4.6 ± 3.9	4.6 ± 4	**0.008**[a*]
Group (2)	6.8 ± 5.2	6.6 ± 5	6.6 ± 5	0.9[a,b]
Modified Hoehn and Yahr Staging Scale				
Group (1)	2.6 ± 1.1	2.1 ± 0.86	2.2 ± 0.78	**0.002**[a*]
Group (2)	2.4 ± 1.1	2.2 ± 0.86	2.1 ± 0.86	0.6[a]
UPDRS-III				
Group (1)	48.4 ± 25.3	32.2 ± 20.4	33.6 ± 20.4	**< 0.001**[*a]
Group (2)	41.6 ± 25.3	40.1 ± 22.1	40.5 ± 21.6	0.1[a]

UPDRS-III: Unified Parkinson's disease Rating Scale

a: significance between baseline and immediate, b: significance between immediate and after 1 m, c: significance between baseline and after 1 m

[*] = significant < 0.05, [+]Group (1): PD patients who received real-rTMS, Group (2): PD patients received sham

It was demonstrated that PSQI ($r=0.38$, $p=0.01$), and ESS ($r=0.36$, $p=0.02$), exhibited a positive significant correlation with the age of the patients. However, there was a lack of correlation between the duration of the illness and these clinical variables. Additionally, the follow-up PSQI had a significant positive correlation with the baseline BDI-II ($r=0.88$, $P=0.001$) and baseline the Modified H&Y Staging Scale ($r=0.78$, $P=0.001$) as well as baseline UPDRS-III ($r=0.78$, $p=0.001$) as shown in Fig. 1a–c. Additionally, it was discovered that the follow-up ESS demonstrated a strong positive correlation with the baseline Modified H&Y Staging Scale ($r=0.88$, $p=0.001$), as well as the follow-up ESS showed a positive correlation with the baseline BDI-II ($r=0.87$, $p=0.001$), UPDRS-III ($r=0.85$, $p=0.001$) as shown in Fig. 2a–c.

A multivariate linear regression analysis was performed to investigate the explanatory power of various factors in predicting PSQI improvement. It was illustrated that there was a statistically significant predictor with a *p*-value of 0.01 with age. Otherwise, the other variables showed no significance as shown in Table 4.

Discussion

Sleep issues in Parkinson's disease are among the most noticeable nonmotor symptoms of the illness, affecting patients' quality of life. These sleep issues are derived from the illness's underlying pathology [17]. The PD's pathophysiology which initiates in the brainstem and eventually leads to neuronal degeneration in certain brain centers including the dopaminergic, serotonergic, and cholinergic systems are believed to influence reticular formation, which is involved in sleep and wake control [18].

Aging is an essential factor contributing to the heterogeneous etiology of PD-related sleep disruption. In our study, the older PD patients reported lower sleep quality, as well, there was a significant correlation between the age of the patients and poor sleep quality and excessive daytime sleepiness. Additionally, it was shown that the age of the patients was a significant predictor of improved sleep quality in PD patients following rTMS sessions, which was consistent with Kazmi and colleagues [19], who hypothesized that sleep quality and quantity both declined with advancing age in PD. It was hypothesized that after the age of 30, there was a gradual decrease in sleep slow wave (SWS) activity. Slow-wave sleep activity is thought of as a sign of density of synapses or cortical synapse strength, and decreased SWS in the elderly has been linked with neurodegeneration. Poor glymphatic clearance, endoplasmic reticulum stress, including chaperoning system, and nocturnal brain deoxygenation [20], all of which are hallmarks of neurodegenerative diseases pathophysiology that frequently sets up in old age, may be contributing factors to sleep problems in older PD patients.

In the current study, PD patients with poor sleep quality were substantially more depressed than those with normal sleep quality. Patients suffering from neurodegenerative illnesses may be more susceptible to depression than the general population [21]. One hypothesized explanation for why poor sleep quality is so closely associated with depression severity in PD is dopamine dysfunction. Dopamine levels in the brain rise in healthy individuals after sleep deprivation, possibly as a compensatory mechanism. Dopaminergic dysfunction associated with Parkinson's disease pathology may impair these patients' capacity to adjust to the consequences of sleep deprivation, increasing their risk of depression severity [22].

Repetitive TMS is one of the most extensively applied neurostimulation methods for inducing neural plasticity and, as a result, modulating neuronal activity. High-frequency (HF) rTMS is defined as any frequency over 1 Hz, with a common setting of 10 Hz. The excitatory impact of HF on long-term potentiation has been demonstrated [23]. Low-frequency (LF) rTMS, on the other hand, includes frequencies of 1 Hz and below. When applied constantly, LF rTMS is expected to be inhibitory and result in long-term depression [24].

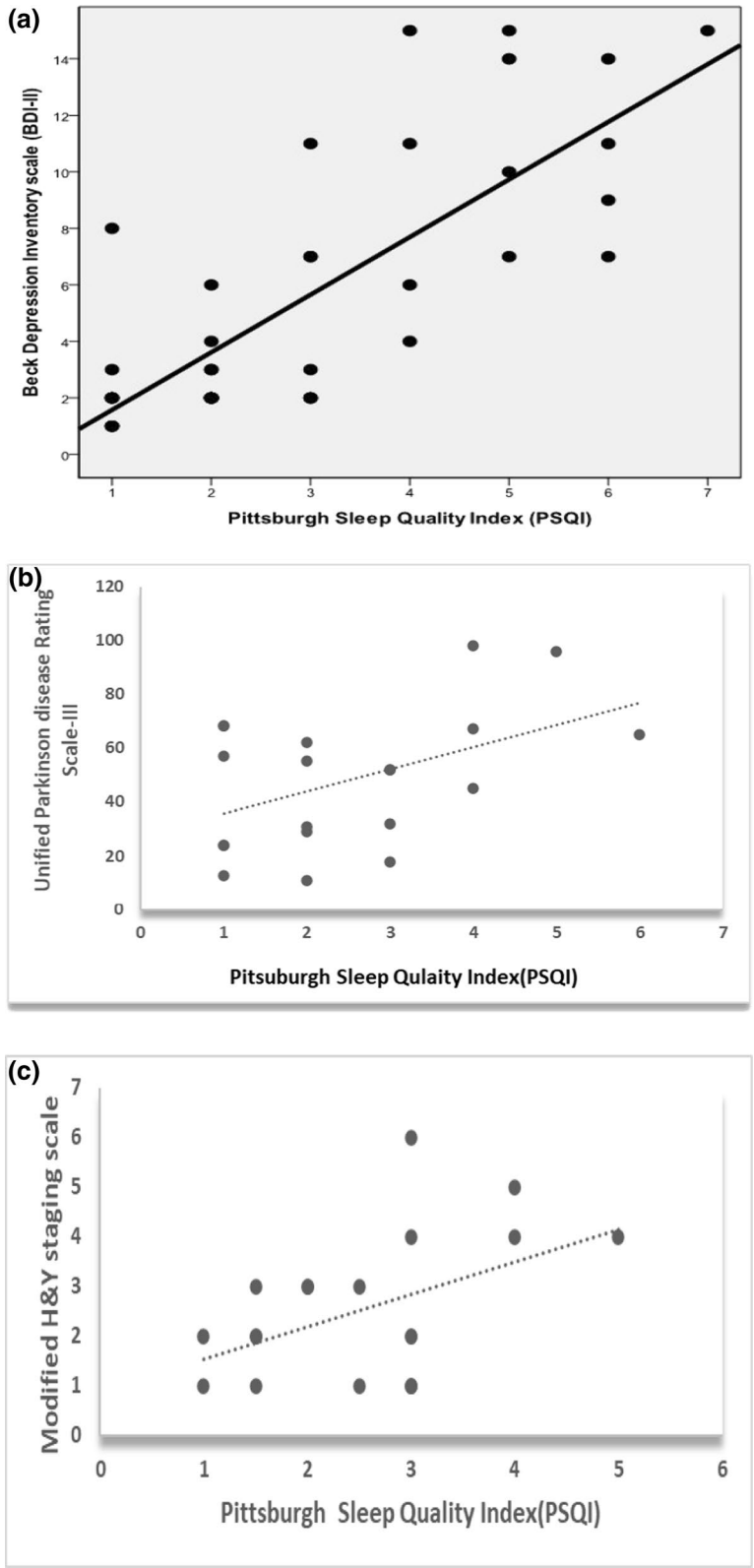

Fig. 1 **a** Correlation between the follow-up Pittsburgh Sleep Quality index with baseline Beck Depression Inventory. **b** Correlation between the follow-up Pittsburgh sleep quality index with baseline Unified Parkinson disease Rating scale. **c** Correlation between the follow-up Pittsburgh sleep quality index with Hoehn and Yahr Staging Scale

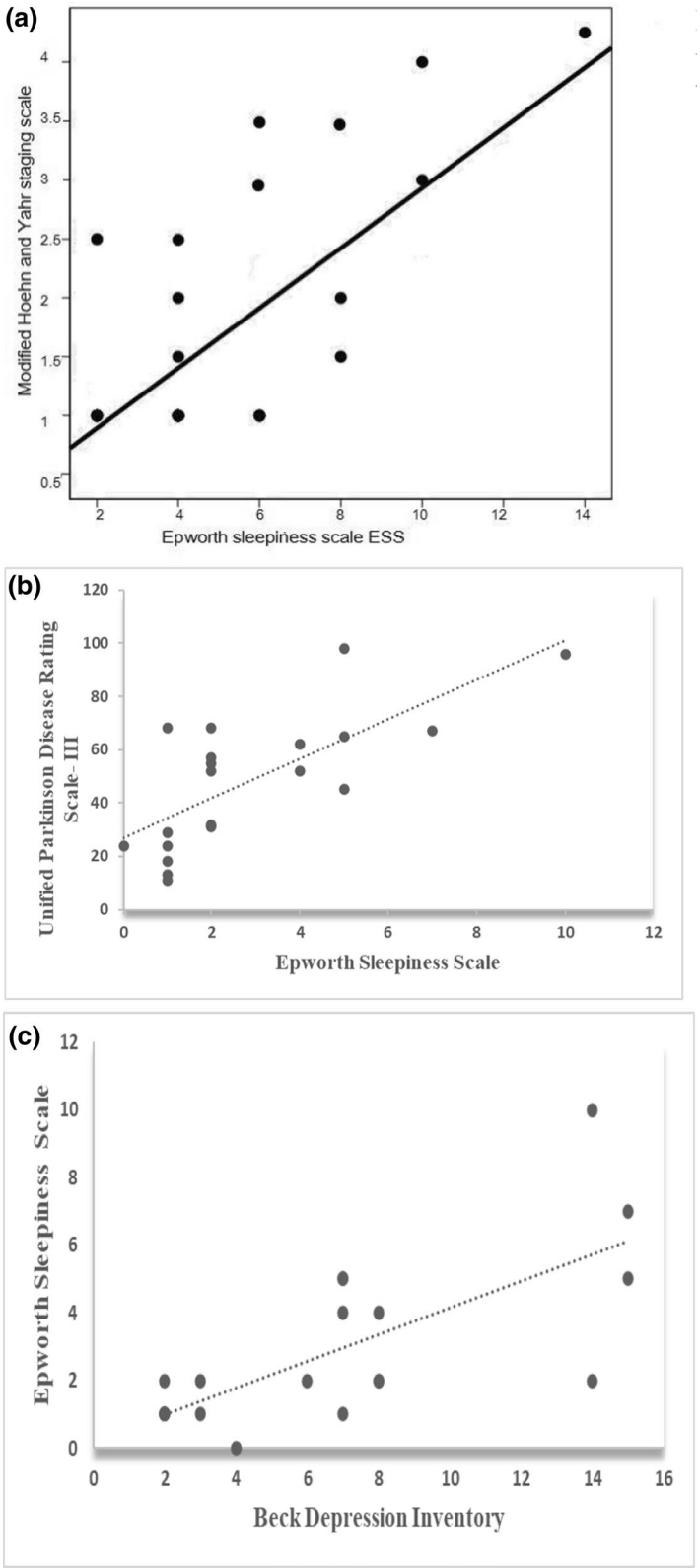

Fig. 2 **a** Correlation between follow-up Epworth Sleepiness Scale with baseline Modified Hoehn Yahr Staging Scale. **b** Correlation between follow-up Epworth Sleepiness Scale with baseline Unified Parkinson Disease Rating Scale. **c** Correlation between follow-up Epworth Sleepiness Scale with baseline Beck Depression Inventory

Table 4 Multivariate linear regression analysis to predict sleep quality

Variables	Un-standardized coefficients		Standardized coefficients	*t*	Sig
	B	Std. error	Beta		
(Constant)	− 4.331	3.283		− 1.319	0.19
Age	0.125	0.047	0.450	2.647	**0.01***
Sex (male)	0.690	0.624	0.185	1.106	0.27
Duration	0.062	0.149	0.073	0.415	0.68
UPDRS-III	− 0.119	0.471	− 0.040	− 0.253	0.80

UPDRS-III: Unified Parkinson's Disease Rating Scale

The frequency and placement of stimulation determine the therapeutic impact of rTMS. It has been proposed that the effect of rTMS on cortical regions is more associated with the functional integration of each area than with frequency settings [25].In this study, it had been found that PD patients who received active HF rTMS over the bilateral parietal cortex noted substantial improvements in subjective sleep quality and excessive daytime sleepiness immediately after the sessions, with a prolonged impact lasting one month. These findings agreed with those of van Dijk and colleagues [8].

Although recommendations for the use of rTMS are established for various diseases, no specific recommendations for its use in sleep disturbances are currently available. As a result, the best procedures and techniques remain unidentified [26]. There has been some research with various protocols that have been proposed to modify sleep disruptions in Parkinson's disease patients [8, 23, 26, 27]. In this work, a high-frequency rTMS technique has been applied across the parietal cortex, a higher-order cortical region that improves subsequent sleep depth by reducing sleep Stage I and increasing sleep Stage IV [8]. However, Huber and coworkers [27] found that 5 Hz rTMS administered to the primary motor cortex significantly boosted slow-wave activity.

This contradiction in results raises a question of how stimulation of the parietal cortex influences sleep quality in PD patients is that, in contrast to the primary motor and premotor cortices, the metabolism of the parietal cortex declines during non-REM sleep [28]. Given that cortical inhibition is decreased by high-frequency TMS, such as the 10 Hz used in our study. The parietal cortex is probably hypofunctional in PD patients who experience sleep disturbances. The use of rTMS may help to partially reverse this parietal hypofunctionality [29].

According to previous research [27, 30], subcortical areas including the caudate nucleus and putamen are affected remotely by cortical rTMS. The therapeutic benefit of parietal rTMS that was observed may be due to the modulation of these subcortical regions which regulate sleep in addition to the hypothalamic–pituitary axis, which is implicated in sleep regulation. Additionally, there is evidence that suggested cortical stimulation by rTMS can trigger the release of dopamine and pineal melatonin, enhance levels of brain serotonin and noradrenaline, as well as serum GABA, which are important neurotransmitters in the sleep–wake cycle, and are consequently accountable for better sleep quality and reduced daytime sleepiness [30].

In contrast to van Dijk and coworkers (2009) [8] who reported no improvement was observed in motor disability with HF rTMS over the parietal cortex, it was demonstrated in this study that the PD patients showed significant improvement in the severity and staging of motor disabilities. There was also a strong correlation between sleep quality, excessive daytime sleepiness, and the severity of motor disabilities as well. Sleep difficulties were shown to be improved by stimulation of the parietal cortex, particularly the primary somatosensory cortex (S1) region, probably secondary to the improvement of the underlying motor disorder. For instance, by altering sensorimotor connection and central sensitization processes by involving GABAergic and glutamatergic circuitries, HF rTMS stimulation of S1 might improve the motor symptoms resulting in reducing its possible irritating effects on sleep [31].

The prefrontal areas have generally been the focus of rTMS research on emotional disorders. However, there is also evidence of incorporating the parietal cortex into emotional disorders [32]. This could support our findings that depressive symptoms in PD patients showed significant improvement after HF rTMS on the parietal cortex. This could be explained by an increase in functional connectivity between the left prefrontal and right parietal cortex by "normalizing" impaired neural networks, as it was noted there was a miscommunication between the right parietal and left prefrontal cortex in depression [33].

It was hypothesized that improved sleep patterns in PD patients with rTMS were caused by the modulation of affected brain areas along pre-existing circuits. In addition to the direct benefits of rTMS, the decrease of sleep disruptions or concomitant motor or mood symptoms might promote healthy circuits [34], Hence improving sleep quality indirectly.

Conclusion

Finally, rTMS stimulation has the potential to enhance a variety of clinical conditions, as HF rTMS over the parietal cortex had shown a significant impact on sleep

quality by the modulation of affected brain areas and by improving concomitant motor and mood manifestations.

Limitation

The shortage of objective sleep quality metrics like polysomnography to track rTMS' impact on various sleep stages and to detect specific sleep disorders like restless legs syndrome or periodic limb movement disorders. Another drawback of this study was the inability of utilization of rTMS on the motor and prefrontal areas to investigate its impact on sleep quality and compare its results to those from rTMS stimulation of the parietal cortex. Moreover, this study did not investigate the impact of rTMS on sleep disorders beyond Parkinson's disease as it is crucial to determine whether rTMS could improve sleep mechanism itself or it is only related to the pathology of PD.

Abbreviations

ADM	Abductor Digiti Minimi
BDI-II	Beck Depression Inventory-II
EMG	Electromyography
ESS	Epworth Sleepiness Scale
GABA	γ-Aminobutyric acid
H &Y staging	Hoehn and Yahr Staging Scale
HF	High-frequency
MMSE	Mini-Mental State Examination
PD	Parkinson's disease
PSQI	Pittsburgh Sleep Quality Index
rTMS	Repetitive transcranial magnetic stimulation
UPDRS-III	Unified Parkinson's Disease Rating Scale

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Author contributions

HS: responsible for analyzing, interpreting the data of the work, and approving the final reversion of the work. MG: responsible for analyzing, and interpreting the data of the work. MM: responsible for data collection, sharing in writing the article. LD: responsible for drafting the work, analyzing, and interpreting the data, writing the article, and communicating with the journal during the manuscript submission, peer review, and publication process. All authors read and approved the final manuscript.

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Availability of data and materials

The dataset is not publicly available due to institutional rules. The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request. The figures used in this manuscript are original.

Declarations

Ethics approval and consent to participate

Faculty of Medicine, Fayoum University Ethical Committee (D-268) had approved the study written informed consent was obtained from all the patients and control volunteers before study initiation.

Consent for publication

Not applicable.

Competing interests

The authors have no conflicts of financial interest to declare concerning this study. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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