Magna Neurologica Vol. 4, No. 2, July 2026

https://journal.uns.ac.id/magna-neurologica
DOI: 10.20961/magnaneurologica.v4i2.3441
e-ISSN 2985-3729 p-ISSN 2963-6027

MAGNA NEUROLOGICA

REVIEW ARTICLE **OPEN ACCESS**

REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (rTMS) AS A NON-INVASIVE NEUROMODULATION FOR THE SPECTRUM OF NON-MOTOR SYMPTOMS IN PARKINSON'S DISEASE: A SYSTEMATIC REVIEW

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Article History:
Received: April 1, 2026
Accepted: May 12, 2026
Published: July 15, 2026

Cite this as:
Paramadina I, Futana NP, Sulistyani. Repetitive Transcranial Magnetic Stimulation (rTMS) as a Non-Invasive Neuromodulation for the Spectrum of Non-Motor Symptoms in Parkinson's Disease: A Systematic Review. Magna Neurologica 4(2) July 2026: 155-164. 10.20961/magnaneurologica.v4i2.3441

ABSTRACT

Background: Non-motor symptoms are an essential component of Parkinson's disease (PD) and represent a major contributor to disability and quality of life. Repetitive transcranial magnetic stimulation (rTMS) has been explored as a non-invasive adjunctive therapy; however, evidence remains heterogeneous and limited to specific symptom domains.
Objective: This systematic review aimed to synthesize randomized controlled trial (RCT) evidence on the efficacy and safety of rTMS for non-motor symptoms in PD.
Methods: RCTs published between 2017 and 2026 were identified from PubMed, Nature Portfolio, and SpringerLink. Twelve studies with PD were included, comparing active rTMS with sham. Outcomes encompassed sleep disturbances, depression, anxiety, pain, apathy, constipation, and cognitive impairment. Risk of bias was evaluated using Cochrane RoB 2.0.
Results: Twelve RCTs (566 patients) with PD were included. rTMS showed the most consistent benefits for sleep disturbances and depressive symptoms, particularly with low-frequency stimulation targeting the right dorsolateral prefrontal cortex (DLPFC). Evidence for anxiety, pain, apathy, and cognitive outcomes was moderate and variable, with effects dependent on stimulation parameters and cortical targets; cognitive benefits were largely confined to executive domains. Preliminary evidence suggested a potential emerging role for rTMS in improving constipation via prefrontal modulation of the gut–brain axis. Overall, rTMS was well tolerated, with only mild and transient adverse events reported and no serious safety concerns.
Conclusion: rTMS is a safe and well-tolerated neuromodulation approach with potential domain-specific benefits for non-motor symptoms in PD, particularly sleep and depression. This review contributes to the current understanding of symptom-targeted rTMS applications in PD.

Keywords: non-motor symptoms, parkinson's disease, Repetitive Transcranial Magnetic Stimulation (rTMS)

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder in which non-motor symptoms (NMS), including cognitive impairment, depression, anxiety, and sleep disturbances, substantially contribute to disability and reduced quality of life.[1,2] These NMS, particularly executive/attention deficits and mood and sleep disturbances, further increase the disease burden, and improvements in NMS correlate with better quality of life.[2–4] While dopaminergic therapy effectively alleviates motor symptoms, its benefits on NMS are often limited, and additional pharmacological treatments show only moderate efficacy with potential side effects.[1,3] This therapeutic gap has driven interest in non-pharmacological approaches. Repetitive

transcranial magnetic stimulation (rTMS) is a non-invasive neuromodulation technique that modulates cortical excitability and network plasticity in a frequency-dependent manner.[5,6]

Recent randomized controlled trials (RCTs) suggest that rTMS may improve several NMS in PD. Although several recent systematic reviews and meta-analyses have evaluated rTMS in PD, most have focused on selected symptom domains or specific stimulation approaches. Consequently, evidence regarding the broader therapeutic role of rTMS across the spectrum of NMS remains clinically fragmented due to heterogeneity in stimulation targets, protocols, and outcome measures.[1–3,5,6] In addition, emerging evidence on novel applications of rTMS, including pain and gastrointestinal dysfunction, has not been comprehensively synthesized. Therefore, this systematic review aimed to provide an updated and clinically integrated synthesis of RCT evidence on the efficacy and safety of rTMS across non-motor symptom domains in PD.

Methods

Research Design

This study was a systematic review of RCTs assessing the efficacy and safety of rTMS for NMS in PD, conducted in accordance with PRISMA 2020 guidelines. Eligible studies were RCTs involving adult patients with PD that compared rTMS with sham stimulation and reporting at least one validated non-motor outcome measure. Non-randomized studies and studies not relevant to the research question were excluded from the review. Overall, studies that did not meet methodological criteria or lacked sufficient outcome data were also excluded from analysis.

Data Sources

Literature searches were conducted in PubMed, Springer, and Nature Portfolio using MeSH and free-text terms related to PD, rTMS, and NMS with Boolean operators. Reference lists were also screened. Only English-language studies were included.

Data Collection

After removing duplicates, two reviewers independently screened studies and assessed full texts based on eligibility criteria, with disagreements resolved by a third reviewer. Data were extracted by three reviewers using a standardized form covering study characteristics, participants, interventions, outcomes, and adverse events.

Data Analysis

Study selection was reported using a PRISMA flowchart. Risk of bias was assessed independently by two reviewers using the Cochrane RoB 2.0 tool, classifying studies as low risk, some concerns, or high risk.

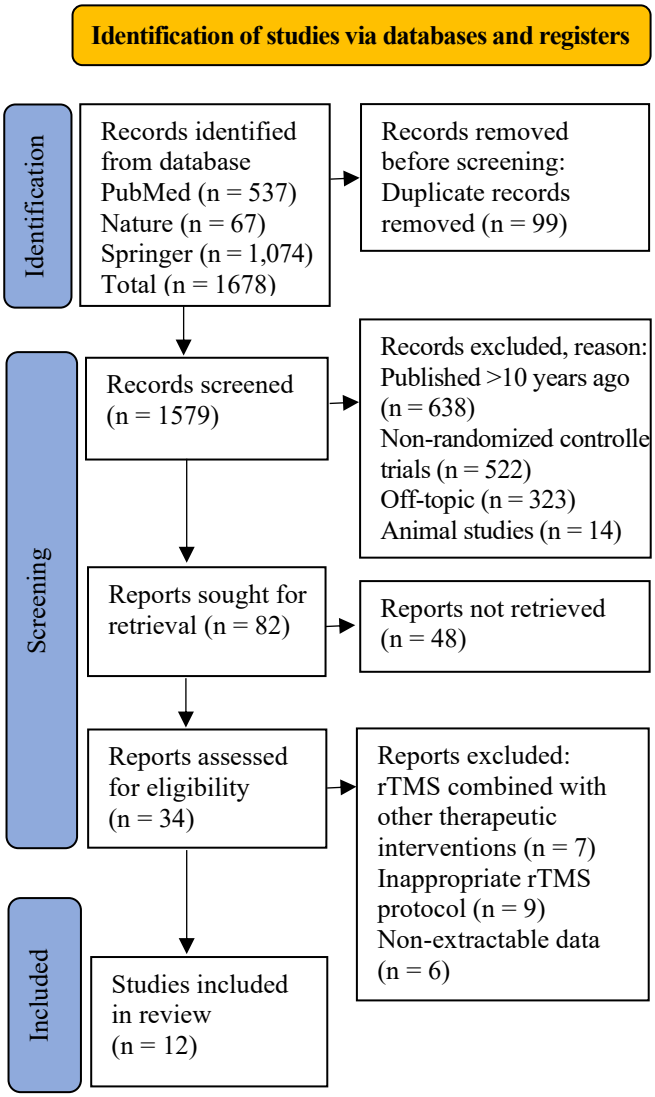

Figure 1. PRISMA 2020 flow diagram illustrating the study selection process

Results

A total of 1,678 records were identified through systematic database searches. After removing 99 duplicate records, 1,579 studies remained and were screened based on their titles and abstracts. Of these, 1,497 records were excluded as they did not meet the predefined eligibility criteria or were not relevant to the study objectives. Thirty-four full-text articles were retrieved and assessed in detail for eligibility. Among these, 22 studies were excluded because rTMS was combined with other therapeutic interventions that could confound the interpretation of treatment effects, because inappropriate or non-standard rTMS protocols were used, or because outcome data were insufficient, incomplete, or could not be adequately extracted for analysis. Ultimately, 12 randomized controlled trials met all inclusion criteria and were included in the final systematic review (Figure 1).

Table 1. Characteristics of the included studies

Author, Year (References)	PD Criteria	H&Y	Country	Sample size	Mean/ Median Age (years)	Sex (M/F)	PD Duration	rTMS target	Frequency (Hz)	Intensity (%)	Session, Duration
Barboza 2024[7]	UK Brain Bank	1–3	Brazil	25	55.2 ± 9.5	11/14	9.3 ± 7.8	PSI	10	80% RMT	12 sessions/ 8 weeks
Wu 2024[8]	MDS criteria	1–2.5	China	67	64.0	34/29	5.0 (median)	Right DLPFC	1	80% RMT	10 session/ 10 days
Bo 2025[9]	UK Brain Bank	≤3	China	58	51.3 ± 7.3	31/27	4.6 ± 2.2	Left DLPFC	5	100% MT	14 sessions/ 14 days
Shaheen 2023[10]	UK Brain Bank	1–3	Egypt	40	61 ± 6.7	21/19	3.0 ± 2.2	Bilateral parietal cortex	10	100% MT	12 sessions/ 3-4 weeks
Wei 2021[11]	MDS criteria	1–2.5	China	100	65.8 ± 6.8	48/52	4.7 ± 1.0	Right DLPFC	10	110% MT	20 sessions/ 2 weeks
Khedr 2024[12]	UK Brain Bank	2–3	Egypt	24	61.8 ± 3.5	10/14	6.7 ± 3.8	M1	20	80% RMT	10 sessions/ 2 weeks
Li 2020[13]	UK Brain Bank	NR	China	48	61.6 ± 7.6	NR	NR	Right DLPFC	10	110% MT	20 sessions/ 2 weeks
Feng 2025[14]	MDS criteria	1–3	China	80	68.6 ± 8.1	44/36	NR	Right DLPFC	1	90% RMT	10 sessions/ 10 days
Zhang 2022[15]	UK Brain Bank	1–2	China	25	65.4 ± 9.1	15/10	39 vs 19.5 months	Right DLPFC	1	90% RMT	10 sessions/ 10 days
Yokoe 2018[16]	UK Brain Bank	2–3	Japan	19	69.1 ± 8.4	7/12	9.5 ± 3.2	M1, SMA, DLPFC	10	100% RMT	3 sessions/ 3 days
Wei 2022[17]	MDS criteria	1–2.5	China	60	61.7 ± 8.0	33/27	4.9 ± 1.7	Left DLPFC	5	110% RMT	20 sessions/ 2 weeks
Khedr 2020[18]	UK Brain Bank	2–3	Egypt	20	62.5 ± 12.2	NR	NR	Bilateral parietal cortex	20	70% RMT	10 sessions/ 2 weeks

Abbreviations: DLPFC, dorsolateral prefrontal cortex; F, female; M, male; H&Y, hoehn and yahr; Hz, hertz; MDS, Movement Disorder Society; MT, motor threshold; M1, primary motor cortex; NR, not reported; PD, parkinson's disease; PSI, posterior-superior insula; RCT, randomized controlled trial, RMT, resting motor threshold; rTMS, repetitive transcranial magnetic stimulation; SMA, supplementary motor area; UK, United Kingdom.

Study characteristics

Table 1 describes 12 RCTs (n=566) in PD (mainly Hoehn & Yahr 1–3). rTMS targets mainly involved the dorsolateral prefrontal cortex (DLPFC), also parietal cortex, primary motor cortex (M1), and posterior-superior insula (PSI). Stimulation protocols varied (1–20 Hz, 70–110% motor threshold, 3–20 sessions over 3 days to 8 weeks).

Risk of bias in included studies

Using the Cochrane RoB 2.0 tool, most studies showed some concerns about bias (Figure 2). One study had a low risk of bias,[12] while three studies were assessed as high risk.[9,14,17] The high-risk judgments were primarily related to inadequate reporting of the randomization process, insufficient allocation concealment, and concerns regarding selective outcome reporting or incomplete outcome data. In particular, some studies did not clearly describe sequence generation or blinding procedures, while others reported limited information regarding predefined outcomes and follow-up completeness. The other domains were mostly low risk, indicating moderate methodological quality overall.

Assessment of non-motor symptoms Pain

Two RCTs assessed the effects of rTMS on pain in PD. Significant pain reduction was observed following high-frequency (HF-rTMS) targeting the right M1 and DLPFC, with Numeric Rating Scale scores (NRS) decreasing by 3.79 points post-intervention and remaining reduced at 2- and 4-months follow-up compared with sham stimulation ($p < 0.001$).[13] In contrast, there was no significant overall difference between PSI rTMS and sham stimulation in achieving ≥30% pain reduction; however, post-hoc analysis

showed significantly higher response rates and lower pain intensity in patients with nociceptive pain receiving active rTMS,[7] suggesting that treatment response may depend on pain subtype (Table 2).

Sleep Disturbances

Seven RCTs assessed the effects of rTMS on sleep disturbances in PD using subjective (PSQI, PDSS, ESS) and objective (PSG) measures. Low-frequency (LF-rTMS) targeting the DLPFC was associated with the most consistent benefits. Significantly greater reductions in PSQI scores with rTMS compared with sham stimulation both post-intervention (−2.4 ± 3.1 vs. −0.2 ± 2.5; $p < 0.001$) and at three-month follow-up ($p = 0.004$), along with an increase in the proportion of REM sleep on PSG ($p = 0.043$).[8] Similar improvements in PSQI and ESS scores after right DLPFC rTMS were reported ($p < 0.01$).[14,15] In contrast, HF-rTMS targeting the bilateral parietal cortex produced less consistent subjective benefits, with no significant differences in PDSS scores, although improvements in PSG such as sleep latency and wake after sleep onset (WASO) were observed.[12,18]

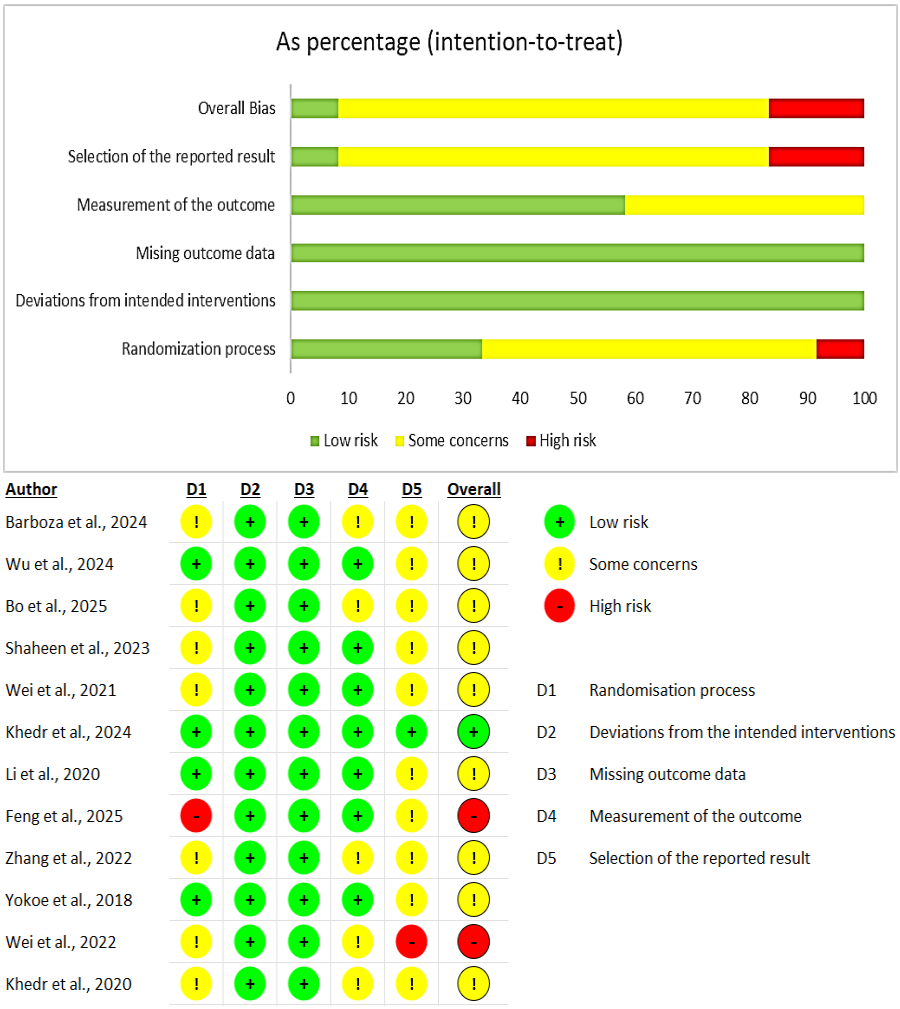

Figure 2. Assessment of the risk of bias score using the Cochrane risk of bias tool 2.0

Anxiety

Three RCTs assessed anxiety outcomes using HAMA or BAI. LF-rTMS targeting M1 or right DLPFC significantly reduced anxiety scores ($p < 0.05$)[13,14] whereas HF-rTMS targeting the right DLPFC showed no significant effect,[11] suggesting frequency- and target-dependent anxiolytic effects.

Apathy

Two RCTs assessed apathy outcomes. One study reported a significant reduction in apathy scores after rTMS compared with sham stimulation ($p = 0.005$),[11] while another found no significant benefit after multi-target stimulation,[16] suggesting that treatment effects depend on stimulation target and protocol.

Depression

Seven RCTs evaluated the effects of rTMS on depression in PD using validated rating scales. Most studies reported significant antidepressant effects, particularly with right DLPFC stimulation, demonstrating greater reductions in depression scores than sham stimulation and effects that persisted for up to one month.[13–15] In contrast, two studies found no significant benefit over sham stimulation, possibly due to shorter intervention duration or heterogeneity in stimulation targets.[11,16]

Table 2. Outcomes: The role of rTMS as a Non-Invasive Neuromodulation Strategy for the Spectrum of Non-Motor Symptoms in Parkinson's Disease

Author, Year (References)	rTMS target	Frequency/ Intensity	Session/ Duration	Outcome measure	Main result
Pain					
Li 2020[13]	M1	10 Hz/ 110% MT	20 sessions/ 2 weeks	NRS	rTMS significantly reduced pain intensity compared with sham stimulation ($p < 0.001$), with a mean NRS reduction of −3.79 after intervention, −3.25 at 1 week, and −3.17 at 4 weeks.
Barboza 2024[7]	PSI	10 Hz/ 80% RMT	12 sessions/ 8 weeks	NRS, MPQ-SF, BPI, NPSI	No significant differences were found between rTMS and sham stimulation for pain intensity, quality, or impact (NRS $p = 0.23–0.26$; MPQ-SF $p = 0.869$; BPI $p = 0.891$; NPSI $p = 0.260$). Significant responses were only observed in the nociceptive pain subgroup (post hoc analysis).
Sleep Disturbances					
Wu 2024[8]	Right DLPFC	1 Hz/ 80% RMT	10 sessions/ 10 days	PSQI, REM sleep % (PSG)	rTMS decreased PSQI more than sham stimulation after intervention (−2.4 ± 3.1 vs −0.2 ± 2.5; $p < 0.001$) and at 3 months (−2.0 ± 2.8 vs −0.9 ± 3.0; $p = 0.004$), and increased REM sleep (13.6%→17.8%; $p = 0.043$) with a greater change in REM sleep than sham stimulation (+5.75 ± 10.02% vs −1.09 ± 6.64%; $p = 0.036$).
Shaheen 2023 [10]	Bilateral parietal cortex	10 Hz/ 100% MT	12 sessions/ 3-4 weeks	PSQI	PSQI scores decreased significantly in the rTMS group (4.0 ± 1.8 to 2.6 ± 1.5; $p < 0.001$), whereas no significant change was observed in the sham group ($p = 0.9$)
Khedr 2024[12]	Bilateral parietal cortex	20 Hz/ 80% RMT	10 sessions/ 2 weeks	PDSS	PDSS scores did not differ significantly between rTMS and sham groups pre–post intervention (real rTMS −7.5 ± 4.6 vs sham −5.1 ± 4.0; $p = 0.190$).
Feng 2025[14]	Right DLPFC	1 Hz/ 90% RMT	10 sessions/ 10 days	PSQI, PDSS	Subjective sleep quality improved significantly in the rTMS group, with PSQI decreasing from 14.42 ± 3.27 to 11.50 ± 3.49 and PDSS increasing from 92.58 ± 30.91 to 100.65 ± 29.74 (both $p < 0.001$).
Khedr 2020[18]	Bilateral parietal cortex	20 Hz/ 70% RMT	10 sessions/ 2 weeks	PDSS, PSG (SL, WASO)	No significant difference between groups in PDSS scores ($p = 0.1902$). However, rTMS significantly reduced sleep latency compared with sham stimulation ($p = 0.049$) and was associated with reduced wakefulness, REM sleep, WASO, and wakefulness after continuous sleep compared with sham stimulation.
Li 2020 [13]	M1	10 Hz/ 110% MT	20 sessions/ 2 weeks	PDSS	rTMS significantly improved PDSS scores compared with sham ($p < 0.001$), with the greatest effect at follow-up 2 (−2.75; 95% CI −3.89 to −1.61).
Zhang 2022[15]	Right DLPFC	1 Hz/ 90% RMT	10 sessions/ 10 days	ESS, PSQI	rTMS improved ESS at day 10 (15.65 ± 17.18%; $p = 0.008$) and 1 month (16.72 ± 14.33%; $p < 0.001$), as well as PSQI (20.20 ± 22.43%; $p = 0.004$).
Anxiety					
Li 2020 [13]	M1	10 Hz/ 110% MT	20 sessions/ 2 weeks	HAMA	rTMS significantly reduced anxiety scores compared with sham from follow-up 1 (−0.71 points) to follow-up 3 (−0.79 points) ($p = 0.013$).
Feng 2025[14]	Right DLPFC	1 Hz/ 90% RMT	10 sessions/ 10 days	HAMA	In the rTMS group, anxiety scores decreased significantly from 24.88 ± 10.34 to 16.25 ± 6.36 ($p < 0.001$), while no change was observed in the sham stimulation group.
Wei 2021[17]	Right DLPFC	10 Hz/ 110% MT	20 sessions/ 2 weeks	BAI	HF-rTMS did not significantly affect anxiety scores in PD, with no difference between rTMS and sham groups ($p > 0.05$).
Apathy					
Wei 2021[17]	Right DLPFC	10 Hz/ 110% MT	20 sessions/ 2 weeks	SAS	SAS scores decreased significantly in the rTMS group compared with the sham group ($Z = −2.449$; $p = 0.014$), with between-group analyses indicating greater improvement in apathy in the rTMS group ($p = 0.005$).
Yokoe 2018[16]	M1, SMA, DLPFC	10 Hz/ 100% RMT	3 sessions/ 3 days	AES	rTMS applied to M1, SMA, or DLPFC did not result in significant improvement in apathy symptoms in patients with Parkinson's disease ($p > 0.05$).

Table 2. Outcomes: The role of rTMS as a Non-Invasive Neuromodulation Strategy for the Spectrum of Non-Motor Symptoms in Parkinson's Disease

Author, Year (References)	rTMS target	Frequency/ Intensity	Session/ Duration	Outcome measure	Main result
Depression					
Li 2020[13]	Right DLPFC	10 Hz/ 110% MT	20 sessions/ 2 weeks	HAMD	Depression improved significantly in the rTMS group compared with sham ($p = 0.009$), with the greatest reduction at 2-week follow-up (mean difference −0.96 (95% CI −1.33 to −0.59)
Feng 2025[14]	Right DLPFC	1 Hz/ 90% RMT	10 sessions/ 10 days	HAMD	Depression improved significantly in the rTMS group, with HAMD scores decreasing from 19.76 ± 8.79 to 19.08 ± 7.11 ($p < 0.001$), while the sham stimulation group showed worsening depression.
Wei 2021[17]	Right DLPFC	10 Hz/ 110% MT	20 sessions/ 2 weeks	HAMD	No significant difference in HAMD scores between the rTMS and sham groups ($p > 0.05$).
Yokoe 2018[16]	M1, SMA, DLPFC	10 Hz/ 100% RMT	3 sessions/ 3 days	MADRS-S, SDS	MADRS-S and SDS analyses showed no significant differences between the intervention (M1, SMA, DLPFC) and sham groups ($p > 0.05$).
Zhang 2022[15]	Right DLPFC	1 Hz/ 90% RMT	10 sessions/ 10 days	HRDS	Depression improved significantly with rTMS, with meaningful reductions in HRDS at day 10 (28.77 ± 20.08%; $p = 0.004$) and at 1 month post-therapy (17.97 ± 22.81%; $p = 0.009$).
Shaheen 2023[10]	Bilateral parietal cortex	10 Hz/ 100% MT	12 sessions/ 3-4 weeks	BD-II	BDI-II scores decreased significantly in the rTMS group (6.8 ± 4.5 to 4.6 ± 3.9; $p = 0.008$), with no significant change observed in the sham group
Khedr 2024[12]	Bilateral parietal cortex	20 Hz/ 80% RMT	10 sessions/ 2 weeks	BD-II	BDI-II scores decreased significantly following rTMS (14.87 ± 6.35 to 8.87 ± 5.85; $p = 0.001$)
Cognitive Impairment					
Wei 2021[17]	Right DLPFC	10 Hz/ 110% MT	20 sessions/ 2 weeks	MoCA	There was no significant difference in cognitive function between groups (26.60 ± 2.75 vs 27.77 ± 2.58; $p > 0.05$).
Zhang 2022[15]	Right DLPFC	1 Hz/ 90% RMT	10 sessions/ 10 days	MoCA	Cognitive function in the rTMS group improved significantly at day 10 (8.25 ± 11.53%; $p = 0.015$) and at 1 month post-therapy (9.07 ± 8.28%; $p = 0.002$).
Wu 2024[8]	Right DLPFC	1 Hz/ 80% RMT	10 sessions/ 10 days	MoCA	MoCA scores increased significantly in the rTMS group, with the median rising from 25.0 (22.8–27.0) to 26.0 (25.0–28.0) after the intervention ($p < 0.001$), while no significant improvement was observed in the sham group.
Wei 2022[17]	Left DLPFC	5 Hz/ 110% RMT	20 sessions/ 2 weeks	MoCA, WCST, SI	MoCA scores were not significantly different (26.60 ± 2.75 vs 27.77 ± 2.58; $p > 0.05$), but executive functions improved with rTMS: WCST category (5.57 ± 2.18 vs 3.90 ± 1.71; $p = 0.001$) and SI reaction time (27.81 ± 9.57 vs 48.04 ± 14.68 ms; $p < 0.001$), while other tests were not significant.
Constipation					
Bo 2025[9]	Left DLPFC	5 Hz/ 100% MT	14 sessions/ 14 days	CSS, SBM, CSBM, BSS	rTMS improved constipation compared with sham stimulation: lower day 14 CSS (4.03±1.01 vs 6.23±1.03; $p < 0.001$), response ($\Delta CSS \geq 3$: 86.2% vs 62.1%; $p = 0.027$), SBM (3.83±0.15 vs 3.57±0.17; $p < 0.001$), CSBM (4.67±0.04 vs 4.16±0.06; $p < 0.001$), and BSS (3.42±0.39 vs 3.19±0.33; $p = 0.019$).

Abbreviations: AES, Apathy Evaluation Scale; BAI, Beck Anxiety Inventory; BDI-II/BD-II, Beck Depression Inventory-II; BPI, Brief Pain Inventory; BSS, Bristol Stool Scale; CSBM, Complete Spontaneous Bowel Movements; CSS, Constipation Scoring System; DLPFC, Dorsolateral Prefrontal Cortex; ESS, Epworth Sleepiness Scale; HAMA, Hamilton Anxiety Rating Scale; HAMD, Hamilton Depression Rating Scale; HRDS, Hamilton Rating Scale for Depression; MADRS-S, Montgomery–Åsberg Depression Rating Scale (Self-rated); MoCA, Montreal Cognitive Assessment; MPQ-SF, McGill Pain Questionnaire–Short Form; NPSI, Neuropathic Pain Symptom Inventory; NRS, Numeric Rating Scale; PDSS, Parkinson's Disease Sleep Scale; PSG, Polysomnography; PSQI, Pittsburgh Sleep Quality Index; REM, Rapid Eye Movement; SAS, Starkstein Apathy Scale; SBM, Spontaneous Bowel Movements; SDS, Self-rating Depression Scale; SI, Stroop Interference; SL, Sleep Latency; WASO, Wake After Sleep Onset; WCST, Wisconsin Card Sorting Test

Cognitive impairment

Five RCTs evaluated cognition using the MoCA and executive function tests. rTMS showed heterogeneous effects on global cognition but more consistent improvements in executive function, particularly with DLPFC stimulation. Significant MoCA improvements were reported in some studies,[8,16] while others demonstrated benefits only in executive measures such as WCST and Stroop.[17]

Constipation

One RCT evaluated constipation outcomes. rTMS targeting the left DLPFC significantly improved constipation severity, bowel frequency, and stool form compared with sham stimulation ($p < 0.001$).[9]

Adverse Event

Across all included studies, rTMS was well tolerated in PD with no serious adverse events reported.[9–12,14–16,18] Adverse events were mild and transient (e.g., headache, dizziness, tinnitus, nausea, local discomfort) and comparable to sham stimulation.[13] with rare discontinuations and no seizures or major complications.[7,8]

Discussion

As a non-invasive neuromodulation technique, rTMS modulates cortical excitability and promotes neuroplasticity through synaptic changes, functional connectivity, and cortical subcortical network regulation.[19–21] Clinical effects are highly dependent on the target and stimulation parameters, favoring network-based mechanisms over purely focal effects.[22] Across studies, the most consistent improvements were reported for sleep and mood symptoms, particularly with LF-rTMS targeting the right DLPFC, while effects on cognition, anxiety, and pain appeared more protocol- and domain-specific. Although generally well tolerated, large, well-designed trials incorporating further neurophysiological/connectivity biomarkers are needed to optimize symptom-targeted rTMS applications.[23,24]

Pain is common in PD and is often associated with other NMS.[25] It is multifactorial, involving dopaminergic and non-dopaminergic dysfunction, and includes musculoskeletal, neuropathic, and fluctuation-related subtypes.[26,27] HF-rTMS over the M1 shows analgesic effects, mainly for musculoskeletal pain, likely via modulation of corticospinal excitability, descending inhibitory pathways, and neuroplasticity.[13,28] PSI stimulation showed less consistent effects but may be beneficial for nociceptive pain, consistent with the insula's role in sensory-affective pain processing.[29]

Sleep disturbances are common in PD and impair quality of life, reflecting neurodegeneration outside the nigrostriatal pathway involving the brainstem and hypothalamic sleep-wake regulatory nuclei.[30] This review suggests that rTMS provides relatively consistent benefits for sleep disturbances in PD, particularly with LF-rTMS targeting the right DLPFC. These benefits may be mediated through modulation of cortical excitability and synaptic plasticity within sleep-regulating networks. Reduced cortical hyperarousal and restoration of right DLPFC activity may also contribute.[28,31–34] However, the heterogeneity of protocols and outcomes suggests the need for larger, standardized trials.

Patients with PD-related depression may benefit from rTMS. This review suggests that both HF-rTMS and LF-rTMS applied to the DLPFC, as well as HF-rTMS targeting the parietal cortex, may reduce depression scores compared with the sham stimulation group. Mechanistically, HF-rTMS left prefrontal stimulation may enhance monoaminergic neurotransmission, while low-frequency right prefrontal stimulation may reduce cortical hyperactivity and negative affect.[35,36] rTMS may also improve mood by enhancing neuroplasticity and normalizing dysfunctional emotion regulatory networks, with effects comparable to antidepressant pharmacotherapy, potentially involving modulation of the frontoparietal network.[1,10,37]

Anxiety in PD often coexists with depression. This review suggests that LF-rTMS targeting the right DLPFC, as well as HF-rTMS over M1, may alleviate anxiety symptoms in PD, although findings remain inconsistent. Given its broad connection with limbic, frontal, and parietal networks, the right DLPFC may have anxiolytic effects by modulating frontal-limbic circuits and dopaminergic transmission in subcortical regions.[38,39] M1 stimulation may indirectly relieve anxiety by boosting cortical-striatal and sensorimotor networks, consequently promoting motor well-being and body perception.[40] Overall, variation in stimulation targets and settings likely drives the different findings, consistent with guidelines highlighting protocol-dependent effects of rTMS.[28]

Apathy is a problematic NMS in PD, associated with fronto-striatal-limbic dysfunction and often resistant to dopaminergic treatment. Only two RCTs in this analysis explored rTMS for apathy, with inconsistent findings, as right DLPFC stimulation reduced apathy in one study.[11] consistent with the involvement of the DLPFC in motivation through connections to the ventral striatum and mesocortical dopaminergic system.[41,42] In contrast, short-duration multi-target stimulation exhibited little benefit,16 suggesting that prolonged and concentrated prefrontal modulation may be necessary. Given the overlap with depression and anxiety, future research should apply an integrated neuropsychiatric framework.[43]

Cognitive impairment in PD usually impacts executive function, attention, and working memory due to disruption of fronto-striatal circuits.[44,45] This review suggests that rTMS, particularly DLPFC stimulation, may provide selective cognitive benefits in PD, with more consistent improvements reported in executive function and working memory than in global cognition or motor cortex-targeted stimulation.[44] These benefits likely reflect increased prefrontal network efficiency and synaptic plasticity.[28] Variability in outcomes is likely related to differences in stimulation parameters, intervention duration, and baseline cognitive severity, with repeated-session protocols and milder impairments potentially associated with better responses.[28,45]

Constipation is an NMS in PD that may precede the onset of motor symptoms, suggesting early gut involvement.[46] Evidence regarding the effects of rTMS on constipation remains limited due to the small number of available trials.[9] PD-related constipation is associated with gut-brain axis dysfunction involving enteric signaling, vagal pathways, immune-endocrine mechanisms, and changes in the gut microbiota.[47] Therefore, the observed benefits of rTMS may be mediated indirectly through modulation of autonomic and afferent–efferent pathways within the gut–brain axis, although further mechanistic and clinical studies are still required.[9]

Conclusion

This systematic review suggests that rTMS appears to be a safe and well-tolerated intervention for non-motor symptoms in Parkinson's disease, with the most consistent improvements reported for sleep disturbances and depression, particularly with DLPFC stimulation. Evidence for other NMS remains variable and appears strongly dependent on stimulation targets and protocol characteristics. Overall, rTMS shows potential as a symptom-specific neuromodulation strategy; however, larger and methodologically robust studies are needed to confirm its clinical efficacy and optimize treatment protocols.

Acknowledgment

We would like to thank the Faculty of Medicine, Universitas Muhammadiyah Surakarta, and the Department of Neurology for their support throughout this research. We also appreciate all those who contributed to the review process and the authors of the original studies included in this paper.

Declaration of Interests

The authors report no financial or personal relationships that could have influenced the work presented in this study.

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