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# Repetitive transcranial magnetic stimulation improves cognition, depression, and walking ability in patients with Parkinson's disease: a meta-analysis

Mingchen Wang<sup>1,2</sup>, Wenyu Zhang<sup>3</sup> and Wanli Zang<sup>4\*</sup>

## Abstract

**Objective** To evaluate the efficacy of repetitive transcranial magnetic stimulation (rTMS) on cognitive function, depression, and walking ability in patients with Parkinson's disease.

**Methods** A comprehensive search was conducted in PubMed, Web of Science, Embase, Cochrane Library, China National Knowledge Infrastructure (CNKI), Chinese Biomedical Literature Database (CBM), VIP Database, and Wanfang Database. Randomized controlled trials (RCTs) on rTMS treatment in Parkinson's disease patients were retrieved, covering the period from the inception of each database to July 2024. The quality of the included studies was assessed using the Cochrane risk of bias tool. Two researchers independently screened the literature, extracted data, and assessed the risk of bias in the studies. Data synthesis and analysis were performed using RevMan 5.4 and Stata 17.0 software.

**Results** A total of 15 studies were included. The meta-analysis revealed that rTMS significantly improved the MOCA score (MD = 2.98, 95% CI 2.08, 3.88,  $P = 0.000$ ), TUGT score (SMD = -0.72, 95% CI -1.43, 0.00,  $P = 0.048$ ), FOG-Q score (SMD = -0.54, 95% CI -0.97, -0.11,  $P = 0.01$ ), and UPDRS-III score (SMD = -0.66, 95% CI -0.84, -0.47,  $P = 0.000$ ) in Parkinson's disease patients, and also alleviated depressive symptoms as measured by the HAMD (SMD = -0.43, 95% CI -0.72, -0.13,  $P = 0.004$ ).

**Conclusions** rTMS can improve cognitive function, depressive symptoms, and walking ability in patients with Parkinson's disease.

**Keywords** Walking ability, Cognitive function, Repetitive transcranial magnetic stimulation, Gait, Meta-analysis

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## Introduction

Parkinson's disease (PD) is a neurodegenerative disorder primarily affecting middle-aged individuals, characterized by the gradual loss of dopaminergic neurons in the substantia nigra pars compacta. The motor symptoms of PD include bradykinesia, tremor, rigidity, and gait disturbances, with freezing of gait (FOG) being one of the most debilitating gait disturbances associated with the disease. A study involving 990 PD patients reported a FOG incidence of 32% [1], which severely impairs mobility, increases the risk of falls [2], and leads to a decline in quality of life [3]. Non-motor symptoms of PD manifest as cognitive impairment, depressive symptoms, visual dysfunction, and even cardiovascular autonomic dysfunction [4–9], all of which significantly exacerbate the suffering of PD patients. Various pharmacological treatments are available for both motor and non-motor symptoms of PD, primarily involving levodopa therapy [4, 10] to alleviate symptoms. However, these medications sometimes fail to provide the desired effects and may even induce motor complications, particularly levodopa-induced dyskinesias during long-term treatment [11, 12]. Therefore, exploring alternative and promising therapeutic approaches for PD, such as non-invasive brain stimulation (NIBS) [13], is essential. Current evidence has identified various neuroimaging markers and their related neuropathological mechanisms in PD, which appear to contribute to both motor and non-motor dysfunctions [14–16].

rTMS, a form of NIBS, has demonstrated neuromodulatory effects [13]. During rTMS intervention, a coil generates a magnetic field that penetrates the scalp and skull, thereby altering cortical excitability. Different rTMS frequencies elicit distinct effects: high-frequency rTMS ( $\geq 5$  Hz) induces cortical excitation, while low-frequency rTMS ( $\leq 1$  Hz) produces inhibitory effects; longer stimulation durations may result in prolonged effects [17, 18]. Additionally, various target sites are available for rTMS intervention, including the primary motor cortex (M1) for motor symptoms, as well as the dorsolateral prefrontal cortex (DLPFC), supplementary motor area (SMA), and, in some cases, the cerebellum [19, 20].

Gait disturbances are typically characterised by slow movements, an unstable gait and an increased risk of falls, which have a significant impact on patients' functional independence and quality of life. With regard to gait disturbances in PD, some studies have indicated that rTMS may represent a potential therapeutic approach [21]. Although PD is a neurodegenerative disease with predominantly motor symptoms, its non-motor symptoms, such as cognitive deficits and depressive symptoms, also have a significant impact on patients' quality of life. In recent years, rTMS has been identified as a potential treatment for alleviating these non-motor symptoms.

A number of studies have demonstrated that rTMS has a substantial ameliorative effect on depressive symptoms in patients with Parkinson's disease [22]. For example, a meta-analysis conducted by Lesenskyj et al. [23] on the treatment of depression associated with Parkinson's disease demonstrated that rTMS significantly reduced depression scores and positively affected patients' mood states. Furthermore, a study by Chen et al. demonstrated that rTMS was capable of enhancing mood-related cognitive performance, which subsequently led to an improvement in patients' overall mental health [24]. With regard to cognitive impairment, a recent meta-analysis indicated that rTMS exhibited some efficacy in improving executive function and working memory [25]. This evidence provides support for the hypothesis that rTMS may represent an effective strategy for the treatment of non-motor symptoms in Parkinson's disease.

However, there are still some shortcomings in the current research on the use of rTMS in the treatment of cognition, depression and walking ability in PD. First, the results of existing studies on the effects of rTMS on walking ability vary widely [21, 26, 27], with some studies finding that rTMS did not have significant effects on improving gait imbalance and reducing the risk of falling [28]. Second, studies have varied widely in treatment parameters (e.g., frequency, stimulation site, and duration), limiting the comparability and consistency of results. In addition, findings on the specific effects of rTMS on cognitive function have been inconsistent [29, 30], with some studies failing to establish significant causal relationships, suggesting that our understanding of the cognitive benefits of rTMS is incomplete. Therefore, there is a need to comprehensively synthesise and analyse the efficacy of transcranial magnetic stimulation on cognitive function, depression and walking ability by assessing multiple scales.

The current study synthesises the latest research findings and comprehensively examines the different effects of rTMS in improving cognitive impairment, depressive symptoms and walking ability and identifies potential influencing factors through heterogeneity analysis. In addition, this analysis will use a systematic quality assessment method to ensure the scientific validity and reliability of the included studies. This will provide deeper insights for future clinical applications and lay the foundation for the development of personalised treatment plans.

## Methods

This study has been registered with PROSPERO, registration number No. CRD42023410954.

### Literature search

A comprehensive search was conducted in both English databases (PubMed, Embase, Cochrane Library, Web of Science) and Chinese databases (Wanfang, CNKI, VIP, CBM) up until July 1, 2024, to identify randomized controlled trials (RCTs) related to rTMS intervention in Parkinson's disease.

English search strategy: (transcranial magnetic stimulation[MeSH Terms]) AND (Parkinson's disease[MeSH Terms]) OR (idiopathic Parkinson's disease).

Chinese search strategy: (pajinsenbing OR pajinsen-zonghezhen) AND (chongfujingluciciji).

### Inclusion criteria

1. Study Type: Randomized controlled trials (RCTs) examining the effects of rTMS on patients with PD.
2. Study Population: Patients who meet the international diagnostic criteria for Parkinson's disease, have a confirmed PD diagnosis with stable disease progression (e.g., stabilized by levodopa or other anti-Parkinson medications or stable after drug withdrawal with no other interventions), are aged 18 years or older, and are of any gender.
3. Intervention: The experimental group received rTMS either alone or combined with other basic treatments (e.g., conventional training, pharmacotherapy). The control group received sham rTMS or was combined with other basic treatments.
4. Outcomes: Motor improvement was measured by the motor sections of the Unified Parkinson's Disease Rating Scale (UPDRS Part III, also known as UPDRS-III) and the Movement Disorder Society-Sponsored Revision of the UPDRS (MDS-UPDRS Part III). The primary assessment indicators for walking ability included the FOG-Q and the TUGT.
5. Non-motor outcomes included cognitive improvement and antidepressant effects, with cognitive improvement measured by the Montreal Cognitive Assessment (MoCA) scale and antidepressant effects measured by the Hamilton Depression Rating Scale (HDRS, also sometimes abbreviated as HRSD or HAMD in other articles).
6. Studies should include the mean values and standard deviations (SD) of the aforementioned scales before and after the intervention in both the rTMS intervention group and the sham control group.

### Exclusion criteria

1. Duplicate studies;
2. Non-randomized controlled trials;

3. Studies in which the subjects were not Parkinson's disease patients or the intervention in the treatment group was not rTMS;
4. Studies where the full text could not be obtained, data could not be extracted, or data were missing.

### Data extraction

The process included the following steps: Two researchers independently conducted the initial screening by reviewing the titles, abstracts, and study types to remove duplicates. A second round of screening was performed based on full-text information and inclusion criteria. If discrepancies arose between the two researchers' screening results, a third researcher would adjudicate the final inclusion. The final selected studies were included in the meta-analysis.

Extracted variables included: (1) Study design; (2) Demographic characteristics (including the number of patients, country, age, disease duration); (3) Mean scores and standard deviations of the following scales: (I) Cognitive scales, including MoCA; (II) Depression scales, including HAMD; (III) Walking ability scales, including FOG-Q, TUGT, and UPDRS-III; (4) rTMS parameters (frequency, intensity, site, and treatment duration). If a study had multiple rTMS intervention groups with different frequencies, these groups were treated as separate studies in our analysis. Summary data were independently extracted by two researchers from these RCTs.

### Quality assessment of included studies

The quality of the included studies was evaluated using the Cochrane Handbook 5.1.0 criteria [31], which include the generation of random sequences, allocation concealment, blinding of researchers and subjects, blind assessment of outcomes, completeness of outcome data, selective reporting of results, and other biases. According to the quality assessment criteria, the risk of bias was categorized into three levels: "unclear risk," "low risk," and "high risk." Two researchers independently assessed the quality of the studies and cross-checked their results. In case of disagreement, a third researcher determined the final risk level.

### Statistical analysis

Meta-analysis was performed using RevMan 5.4 and Stata 17.0 statistical software. Data for continuous variables were expressed as mean differences (MD) or standardized mean differences (SMD) with 95% confidence intervals. Heterogeneity among studies was assessed using the  $I^2$  statistic and  $P$ -value: If  $I^2 < 50\%$  and  $P > 0.1$ , heterogeneity among studies was considered low, and a fixed-effects model was used; If  $I^2 \geq 50\%$  and  $P \leq 0.1$ , heterogeneity was considered high, and a random-effects model was adopted. Subgroup analysis and sensitivity

analysis were conducted using Stata 14.0 software to explore sources of heterogeneity in outcome indicators. Egger's test was used to assess publication bias for studies with five or more included studies; Funnel plots were used for bias assessment in studies with ten or more included studies. Statistical significance was indicated by a  $P$ -value of less than 0.05, with  $P \geq 0.05$  indicating no significant difference.

#### GRADE evidence quality assessment

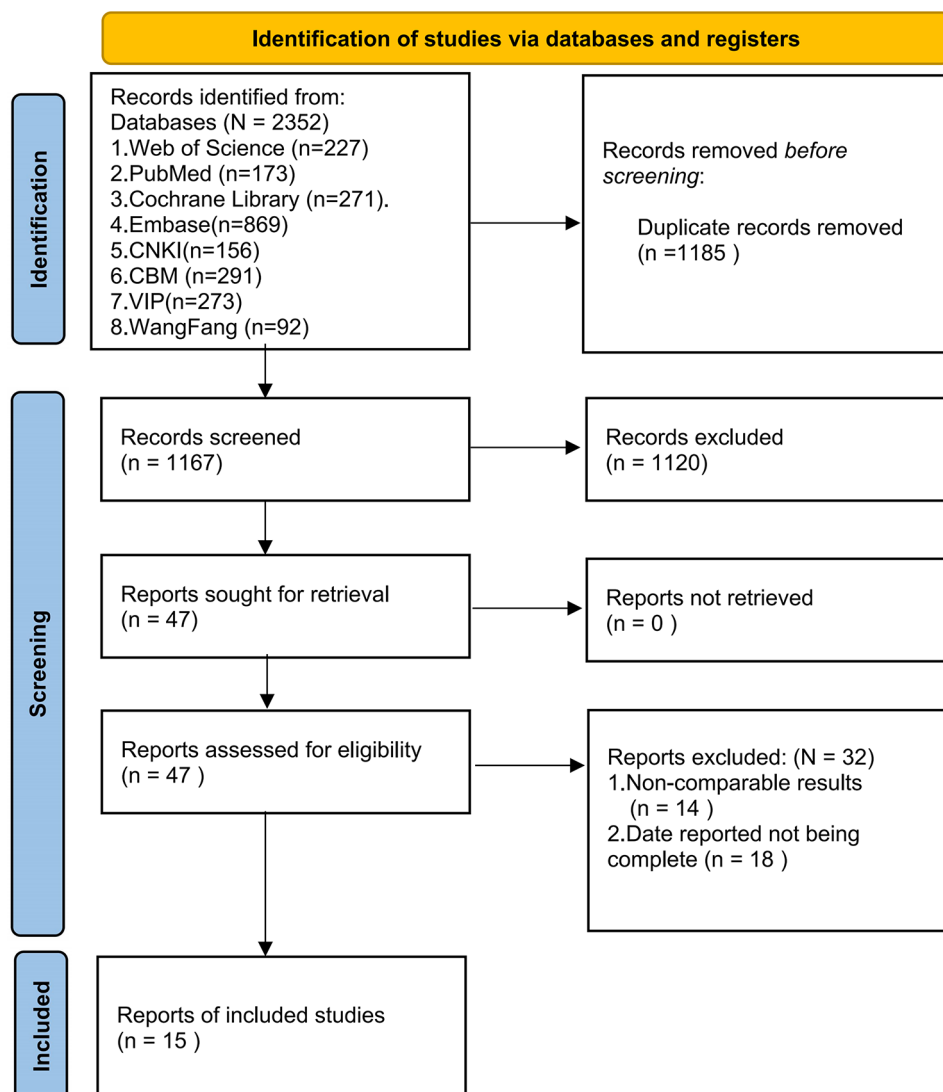
The evidence quality for outcome indicators with three or more studies was assessed using the GRADE method. The quality of evidence was rated considering risk of bias, inconsistency, imprecision, indirectness, and publication bias, and was categorized into four levels: high, moderate, low, and very low.

#### Results

A total of 2,352 related studies were retrieved. After preliminary screening, 1,185 duplicate studies were excluded. Subsequently, 1,120 studies were further excluded based on their titles and abstracts. After reviewing the full texts according to the inclusion and exclusion criteria, an additional 32 studies were excluded. Ultimately, 15 studies were included. The detailed process and results of literature screening are presented in Fig. 1.

#### Characteristics of included studies

A total of 15 studies were included, with 9 studies in Chinese [32–40] and 6 in English [41–46], involving a total of 789 PD patients. In most studies, the average age of patients was over 50 years, and the average disease duration was over 3 years. Cognitive function analysis was performed on 175 patients, FOG-Q analysis on 90



**Fig. 1** Literature screening flowchart

patients, TUGT analysis on 178 patients, HAMD analysis on 201 patients, and UPDRS III analysis on 489 patients. Among these studies, 11 [32, 35–39, 41, 43–46] used high-frequency ( $\geq 5$  Hz) rTMS to treat Parkinson's disease, 1 study [34] used low-frequency ( $\leq 1$  Hz) rTMS, and 3 studies [33, 40, 42] used both low and high-frequency rTMS. Nine studies targeted the DLPFC, six targeted M1, one targeted both M1 and DLPFC, and one study did not provide stimulation intensity information. Most patients in these studies had stable medication regimens before and during treatment. Detailed information on patient and rTMS variables used in these studies can be found in Table 1.

### Quality assessment of included studies

Among the 15 included studies, 10 studies [33–35, 37, 41–46] mentioned randomization and provided specific methods, while 5 studies [36, 38–40] did not specify the methods used, and one study [32] had a un risk in the randomization process. Four studies [33, 35, 37, 41] provided detailed descriptions of allocation concealment, while the remaining 9 did not mention it. 9 studies [33, 35, 37, 41–46] blinded both researchers and subjects, one study [34] blinded only the researchers, and the remaining five studies [32, 36, 38–40] did not mention blinding methods. All 15 studies reported complete data, and all 15 studies reported their results without mentioning any other biases. Details are shown in Fig. 2.

### Meta-analysis

#### Baseline consistency test

In this paper, all outcome indicators were tested for consistency at baseline, i.e. there was no significant difference between the baseline scores of the control and baseline groups before the effect sizes were combined post-intervention (See Table 2).

#### Effect of rTMS on MOCA in PD patients

Three studies [34, 36, 38] reported MOCA as an outcome measure. The study by Zhuang et al. used low-frequency (1 Hz) stimulation, focusing on the right DLPFC, for a shorter treatment course (10 days), while the study by Li and Dong et al. used high-frequency (5 Hz) stimulation and was performed on both DLPFCs for a longer treatment course (4 weeks). The heterogeneity test indicated no heterogeneity ( $I^2=0\%$ ,  $P=0.544$ ), so a fixed-effects model was used for analysis. Meta-analysis showed that transcranial magnetic stimulation significantly improved cognitive function in patients with Parkinson's disease after the intervention (MD=2.98, 95% CI 2.08 to 3.88,  $P=0.000$ ) (See Table 3; Fig. 3A).

#### Effect of rTMS on HAMD in PD patients

Four studies [34, 35, 40, 43] provided HAMD outcome data. The meta-analysis indicated that rTMS significantly alleviated depressive symptoms in PD patients (SMD=-0.43, 95% CI -0.72 to -0.13,  $P=0.004$ ). The heterogeneity test showed low heterogeneity ( $P=0.14$ ,  $I^2=43\%$ ), so a fixed-effects model was used for analysis. Subgroup analysis was conducted by rTMS frequency and stimulation site to explore the sources of heterogeneity in HAMD outcomes. The results indicated that the effect of rTMS on HAMD in PD patients was not influenced by stimulation frequency or site, and no sources of heterogeneity were found in either subgroup (See Table 3. Figs. 3B. and 4)..

#### Walking ability

**Effect of rTMS on TUGT in PD patients** Five studies [33, 37, 42, 44, 46] evaluated TUGT as an outcome measure. The meta-analysis showed that there was a statistically significant difference between the experimental group and the control group in TUGT (SMD=-0.72, 95% CI -1.43 to 0.00,  $P=0.048$ ). The heterogeneity test indicated high heterogeneity ( $I^2=81\%$ ,  $P=0.000$ ); to further explore the sources of heterogeneity, subgroup analysis was conducted by rTMS frequency, stimulation site, and intervention measures. The results indicated that the effect of rTMS on TUGT in PD patients was related to the stimulation site (See Table 3; Figs. 3C and 5).

**Effect of rTMS on FOG-Q in PD patients** Three studies [37, 44, 45] evaluated FOG-Q as an outcome measure. The heterogeneity test indicated no heterogeneity ( $P=0.497$ ,  $I^2=0\%$ ), so a fixed-effects model was used for analysis. The meta-analysis showed that rTMS significantly improved freezing of gait in PD patients (SMD=-0.54, 95% CI -0.97 to -0.11,  $P=0.01$ ) (See Table 3; Fig. 3D).

**Effect of rTMS on UPDRS III in PD patients** Eleven studies [32–34, 36, 37, 39–41, 43, 44, 46] provided UPDRS III outcome data. The meta-analysis indicated that rTMS significantly improved UPDRS III scores in PD patients (SMD=-0.66, 95% CI -0.84 to -0.47,  $P=0.000$ ). The heterogeneity test showed low heterogeneity ( $I^2=35\%$ ,  $P=0.083$ ), and a fixed-effects model was used for analysis (See Table 3; Fig. 3E).

#### Publication bias

Egger's test was used to assess publication bias for outcome indicators with five or more studies, and funnel plots were used for bias assessment for outcome indicators with ten or more studies. The results showed no publication bias for cognitive function (MOCA,

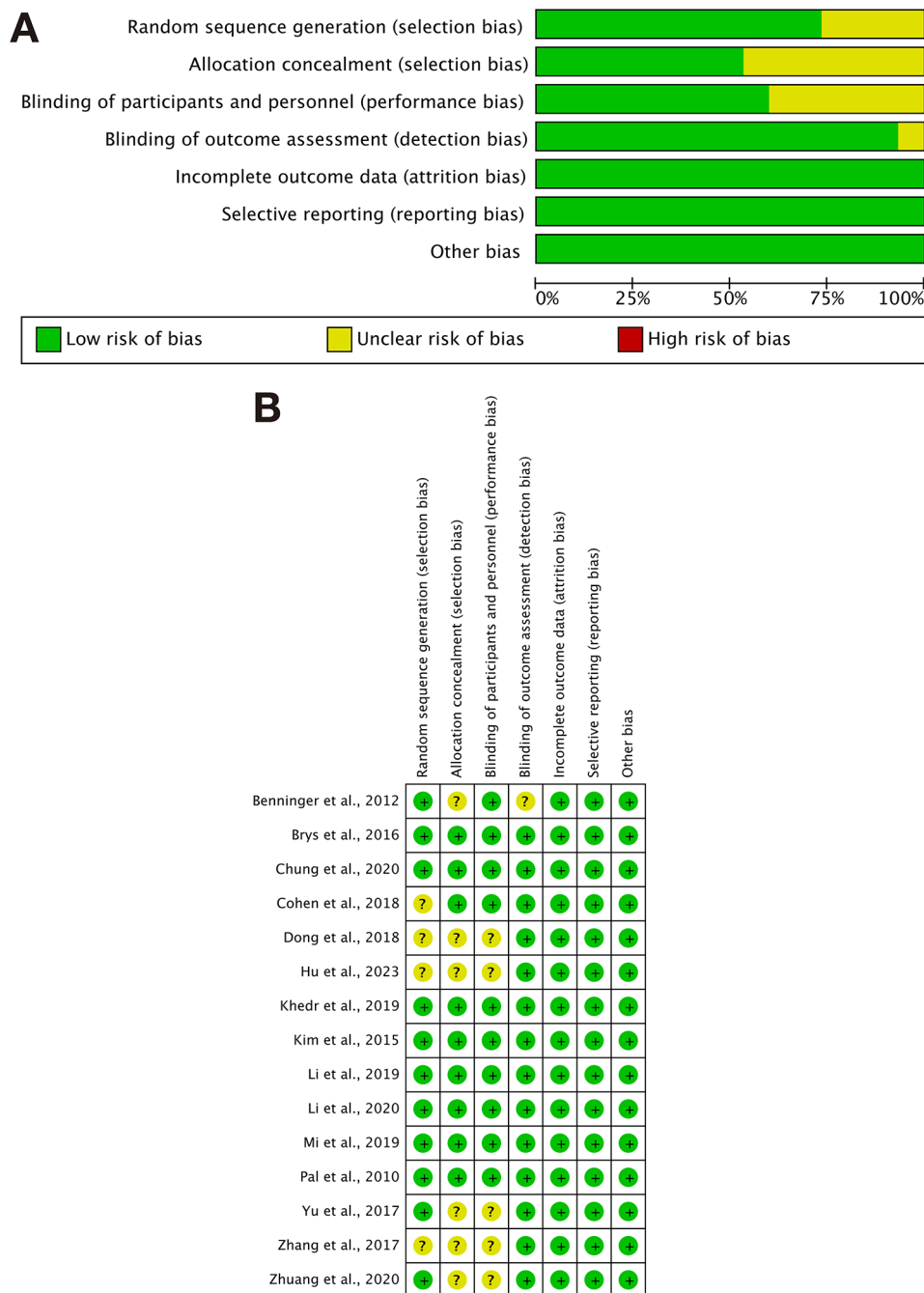
**Table 1** Characteristics of included literatures

Re-searcher and Year	Country	Sample Size (C/T)	Sam-Age (C/T)	Disease Duration (C/T)	Interventions (C/T)	Stimulation Frequency	Stimulation Intensity	Stimulation Site	Treatment Duration	Outcome Measures					
										Cognition	Depression	Walking Ability			
Zhuang et al. 2020 [34]	China	14/19	61.57 ± 13.25/ 60.58 ± 9.21	68.57 ± 45.29 M 70.37 ± 52.26 M	①/rTMS	1 Hz	110%RMT	Right DLPFC	20 min/d, 10d	MOCA	HAMD	-	UPDRSIII	-	
Hu et al. 2023 [32]	China	47/47	68.13 ± 5.41/ 68.13 ± 5.41	4.21 ± 0.69 4.30 ± 0.71	②/③/rTMS	5 Hz	80%MT	Bilatera DLPFC	5 times/week, 2 week	-	-	-	UPDRSIII	-	
Chen et al. 2014 [40]	China	18/21	66.61 ± 8.00/ 65.81 ± 9.38 , 63.19 ± 8.16	6.22 ± 3.96 5.88 ± 5.29	①/rTMS	1 Hz/5Hz	100%RMT	M1	1 times/d, 10d	-	HAMD	-	UPDRSIII	-	
Yu et al. 2017 [39]	China	30/31	60.16 ± 10.14/ 60.32 ± 9.63	2.62 ± 0.86 2.33 ± 0.74	②/③/rTMS	5 Hz	100%MEP	Bilatera DLPFC	1 times/d, 10d	-	-	-	UPDRSIII	-	
Li et al. 2019 [36]	China	41/41	54.54 ± 3.51/ 54.51 ± 3.49	3.12 ± 0.53 3.13 ± 0.55	②/③/④/rTMS	5 Hz	80%MT	Bilatera DLPFC	1 times/d, 5 d /w, 4w	MoCA	-	-	UPDRSIII	-	
Dong et al. 2018 [38]	China	30/30	65.83 ± 11.57	7.3 ± 2.4	②/③/rTMS	5 Hz	80%MT	Bilatera DLPFC	1 times/d, 5 d /w, 4w	MoCA	-	-	-	-	
Li et al. 2020 [35]	China	24/24	61.46 ± 8.40/ 61.67 ± 6.92	6.46 ± 5.17 5.48 ± 3.69	①/rTMS	20 Hz	80%RMT	M1	20 min/d	-	HAMD	-	-	-	
Chung et al. 2020 [33]	Hong Kong	16/17	62.1 ± 5.7/ 62.1 ± 5.7 62.7 ± 6.8	6.9 ± 3.3 7.5 ± 4.9	①/rTMS	1 Hz/25Hz	80%RMT	M1	20 min/times, 5 times/d	-	-	-	TUGT	UPDRSIII	
Mi et al. 2019 [37]	China	10/20	65.60 ± 8.68/ 62.65 ± 10.56	7.40 ± 4.83 9.15 ± 5.82	①/rTMS	10 Hz	46.0 ± 6.8%/ 45.6% ± 6.7%	SMA	1 times/d, 5d/w, 2w	-	-	-	TUGT	UPDRSIII	FOG-Q
Khedr et al. 2019 [41]	United Kingdom	11/19	57.4 ± 10.0/ 60.7 ± 8.8	6.5 ± 3.7 5.7 ± 3.9	①/rTMS	20 Hz	90%RMT	M1	10 times/d, 5d/w	-	-	-	UPDRSIII	-	
Cohen et al. 2018 [42]	United Kingdom	21/21	66.8 ± 8.1/ 64.4 ± 6.8	5.6 ± 3.7 4.7 ± 3.4	①/rTMS	1/10Hz	110%/ 100%RMT	M1/DLPFC	1 times/d, 12w	-	-	-	TUGT	-	

**Table 1** (continued)

Re-searcher and Year	Country	Sample Size (C/T)	Age (C/T)	Disease Duration (C/T)	Interventions (C/T)	Stimulation Frequency	Stimulation Intensity	Stimulation Site	Treatment Duration	Outcome Measures			
										Cognition	Depression	Walking Ability	
Bryson et al. 2016 [43]	United Kingdom	15/12	64.0 ± 7.4/ 64.6 ± 12.3	4.5 ± 2.2 7.7 ± 4.2	⊙/rTMS	10 Hz	-	Left DLPFC	2,000times/d, 10d	-	HAMD	-	UPDRSIII
Kim et al. 2015 [44]	South Korea	17	64.5 ± 8.4	7.8 ± 4.9	⊙/rTMS	10 Hz	90%RMT	M1	5times/w	-	-	TUGT	UPDRSIII FOG-Q
Pal et al. 2010 [46]	United Kingdom	10/12	67.5(57.0,72.0)/ 68.5(59.5,70.0)	6.5(3.75–10.5) 6.0(3.0–9.5)	⊙/rTMS	5 Hz	90%RMT	Left DLPFC	600times/d, 10 d	-	-	TUGT	UPDRSIII
Benninger et al. 2012 [45]	United States	13/13	63.7 ± 8.3/ 64.5 ± 9.1	9.3 ± 6.8 8.6 ± 4.1	⊙/rTMS	50 Hz	80%AMT	M1	1times/d, 4d/w, 2w	-	-	-	FOG-Q

Notes: T represents the Experimental Group; C represents the Control Group; M1 refers to the Primary Motor Cortex; SMA stands for the Supplementary Motor Area; PFC indicates the Prefrontal Cortex; MT refers to the Motor Threshold; AMT denotes the Active Motor Threshold; RMT is the Resting Motor Threshold. M: month The interventions are categorized as follows: ⊙ Sham Stimulation, ⊕ Conventional Anti-Parkinson Medication ⊗ Cognitive Training



**Fig. 2** Risk assessment chart. **A** Risk of bias graph. **B** Risk of bias summary

**Table 2** Baseline test score table

	Outcome measures	Study (Patient)	SMD(95%CI)	P-value of the intervention effect	Heterogeneity
Cognitive function	MOCA	3(n= 175)	0.103,(-0.195;0.401)	P=0.496	I <sup>2</sup> =0%, P=0.544
Depressive symptoms	HAMD	4(n= 168)	0.071,(-0.219;0.362)	P=0.631	I <sup>2</sup> =2.6%, P=0.392
Walk ability	FOG-Q	3(n=90)	0.023,(-0.398;0.444)	P=0.915	I <sup>2</sup> =0%, P=0.967
	TUGT	5(n= 178)	-0.182,(-0.470;0.106)	P=0.216	I <sup>2</sup> =4%, P=0.108;
	UPDRSIII	11(n=489)	-0.03,(-0.203;0.142)	P=0.730	I <sup>2</sup> =0%, P=0.993



**Table 3** Meta-analysis results

Outcome measures		Study (Patient)	SMD/MD (95%CI)	P-value of the intervention effect	Heterogeneity	Publication bias
Cognitive function	MOCA	3(n=175)	2.98,(2.08;3.88)	$P=0.000$	$I^2=0\%$ , $P=0.87$	
Depressive symptoms	HAMD	4(n=186)	-0.43,(-0.72;-0.13)	$P=0.004$	$I^2=43\%$ , $P=0.14$	
	Intervention Frequency					
	≥ 5 Hz	2(n=114)	-0.19,(-0.73; 0.35)	$P=0.50$	$I^2=51\%$ , $P=0.13$	
	≤ 1 Hz	2(n=72)	-0.88,(-1.37; -0.39)	$P=0.0005$	$I^2=0\%$ , $P=0.42$	
	Stimulation Site			$P=0.361$		
	DLPFC	2(n=60)	-0.23,(-0.76;0.30)	$P=0.39$	$I^2=82\%$ , $P=0.02$	
	M1	2(n=126)	-0.52,(-0.88;-0.16)	$P=0.004$	$I^2=0\%$ , $P=0.74$	
Walk ability	FOG-Q	3(n=90)	-0.54,(-0.97;-0.11)	$P=0.01$	$I^2=0\%$ , $P=0.01$ ;	
	TUGT	5(n=178)	-0.72,(-1.43; 0.00)	$P=0.048$	$I^2=81\%$ , $P=0.000$	Egger's test, $P=0.243$
	Stimulation Site					
	M1	3(n=83)	-0.54,(-1.60; 0.52)	$P=0.32$	$I^2=0\%$ , $P=0.85$	
	DLPFC	2(n=64)	1.19,(0.77; 1.61)	$P<0.00001$	$I^2=0\%$ , $P=0.68$	
	SMA	1(n=30)	-5.8,(-7.95;-3.65)	$P<0.00001$	-	
	UPDRSIII	11(n=489)	-0.66,(-0.84; -0.47)	$P=0.000$	$I^2=35\%$ , $P=0.083$	Egger's test, $P=0.976$

$P=0.070>0.05$ ), TUGT ( $P=0.243>0.05$ ), and UPDRS III ( $P=0.976>0.05$ ), indicating negative results (See Fig. 6).

#### Evidence credibility

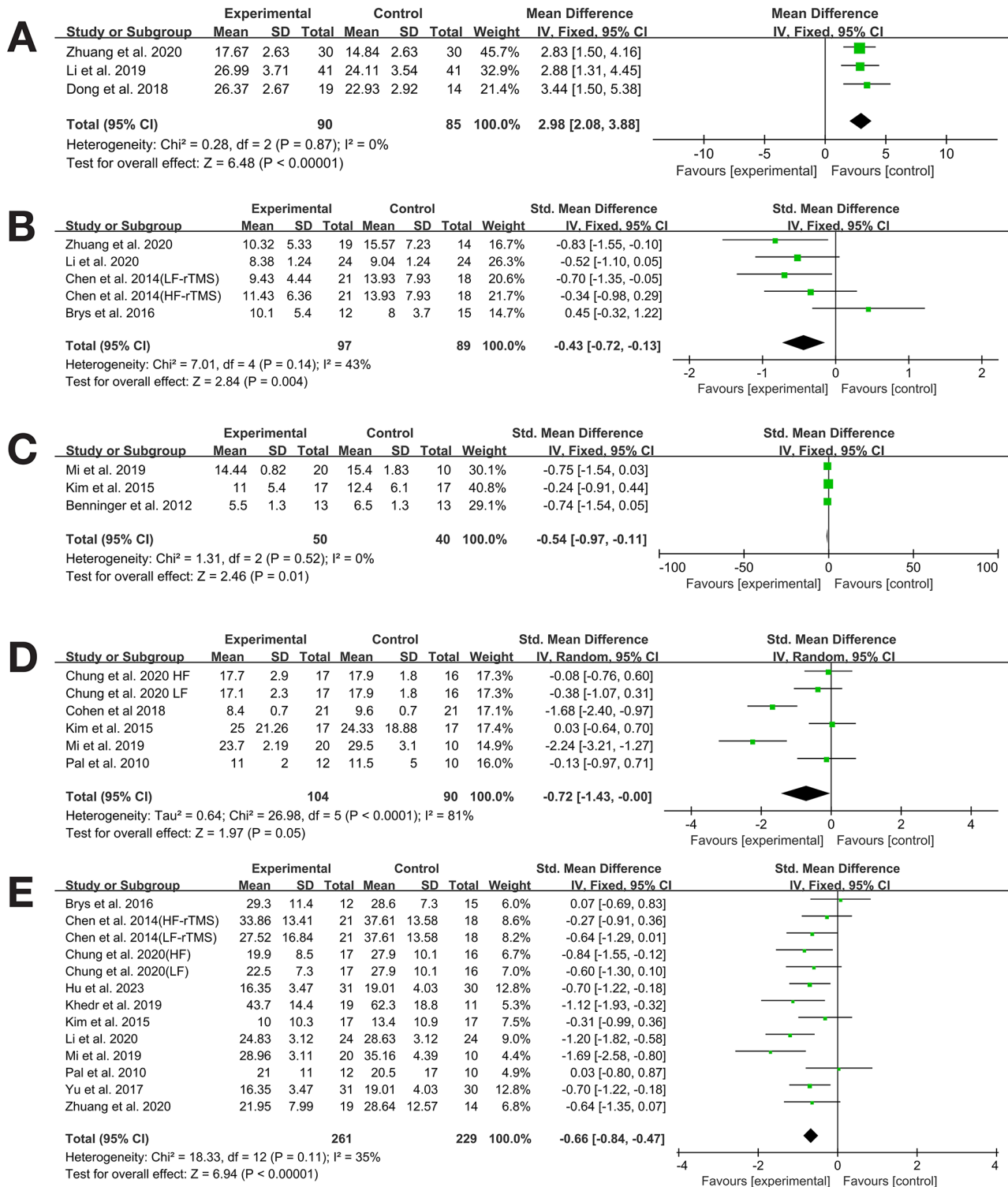
The GRADE quality of evidence was assessed for studies that included MOCA scores, HAMD scores, TUGT scores, FOG-Q scores, and UPDRS III scores (See Table 4).

#### Discussion

The risk of cognitive impairment in PD increases as the disease progresses. This study assessed the efficacy of rTMS on cognitive function in PD patients by examining the differences in MOCA scores before and after rTMS intervention. Overall, the effects of rTMS were positive. The effective mechanisms of rTMS in improving cognitive function in PD patients lie mainly in promoting neuroplasticity and reorganisation of functional networks in the brain. rTMS is able to improve neural conduction and promote synaptic plasticity by modulating the neural excitability of specific brain regions, which can lead to improvements in cognitive domains such as executive function, attention and working memory [47]. Studies have shown that rTMS stimulation targeting the frontal and motor cortex improves neural activity related to attention and decision making and promotes functional connectivity of the prefrontal cortex with other brain regions [48]. In addition, the application of high-frequency (e.g., 10–20 Hz) rTMS, which is commonly used to activate cortical functions and strengthen neural networks, especially in tasks related to motor control and cognitive processing, can significantly improve patients' cognitive performance [49]. In contrast, low frequency

(e.g.1 Hz) rTMS is used to inhibit overactive brain regions and help balance the relationship between inhibition and activation [50], which also plays an important role in cognitive interventions in PD.

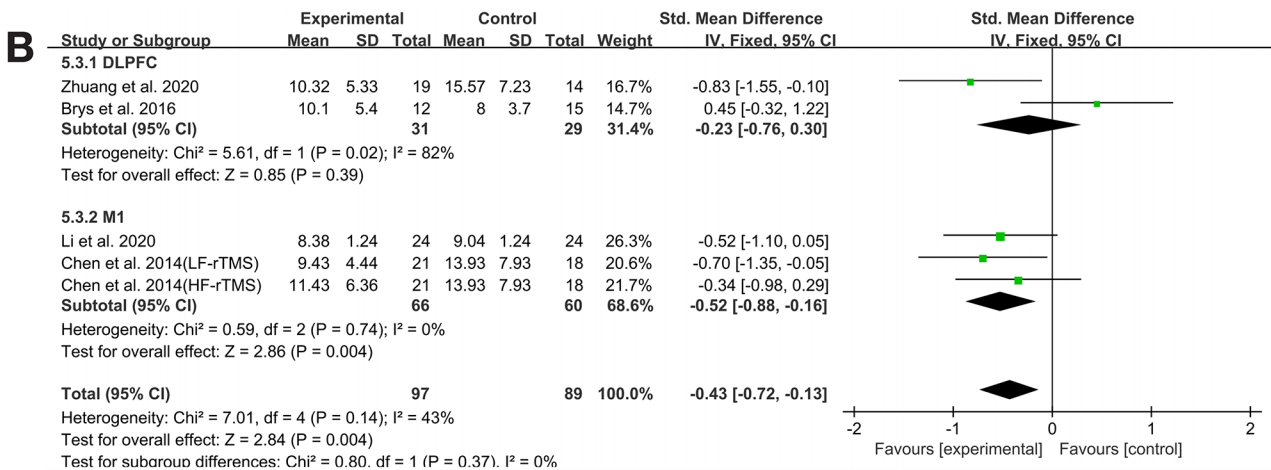
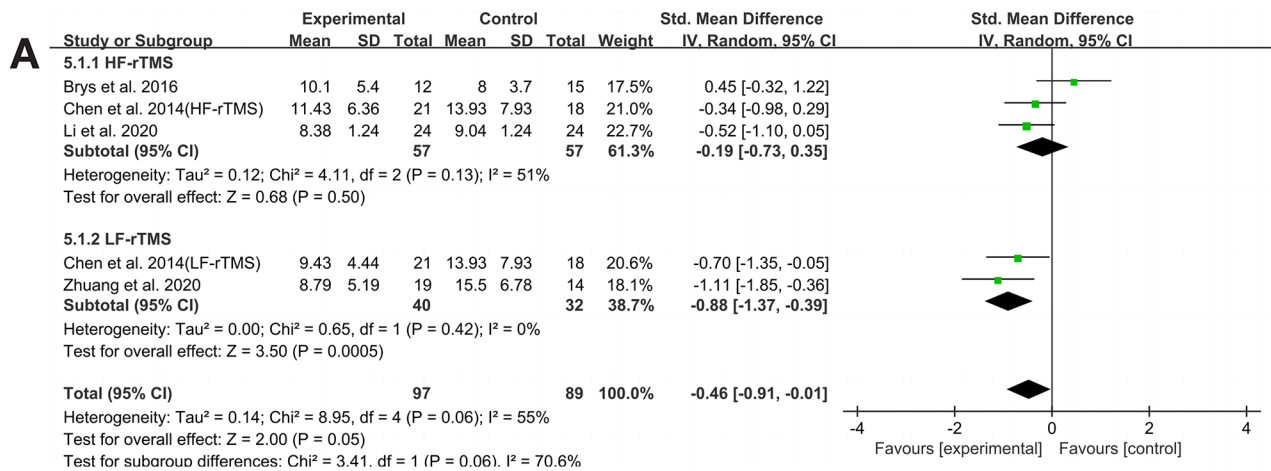
Depression has the highest prevalence among non-motor symptoms in PD, affecting 20–50% of patients, and most antidepressants have limited efficacy [51]. In this study, four studies showed significant effect sizes on depression scales (SMD=-0.43), supporting the potential antidepressant effects of active rTMS over sham rTMS in PD patients. However, subgroup analysis by rTMS frequency and stimulation site showed no differences. Multiple reviews and meta-analyses have indicated that rTMS intervention can reduce depression scale scores, suggesting a potential antidepressant effect [48, 52]. Studies have shown that high-frequency stimulation of the left prefrontal lobe increases its neural activity, thereby increasing the release of neurotransmitters such as dopamine and serotonin, which has been directly linked to improvements in depressive symptoms [53]. In addition, low-frequency stimulation can be used to inhibit hyperactivity in the right prefrontal lobe, a mechanism that is also important in regulating mood and suppressing negative thinking [54]. Other studies have also found that TMS can help remodel patients' functional brain networks by promoting neuroplasticity and strengthening synaptic connections [55]. Depressed patients often show abnormalities in functional brain connectivity, such as dysregulation between the default mode network and the emotion regulation network. The use of TMS may help to restore the coordination of these networks and improve the brain's ability to regulate emotions, thereby improving the patient's overall mental health. Additionally, some



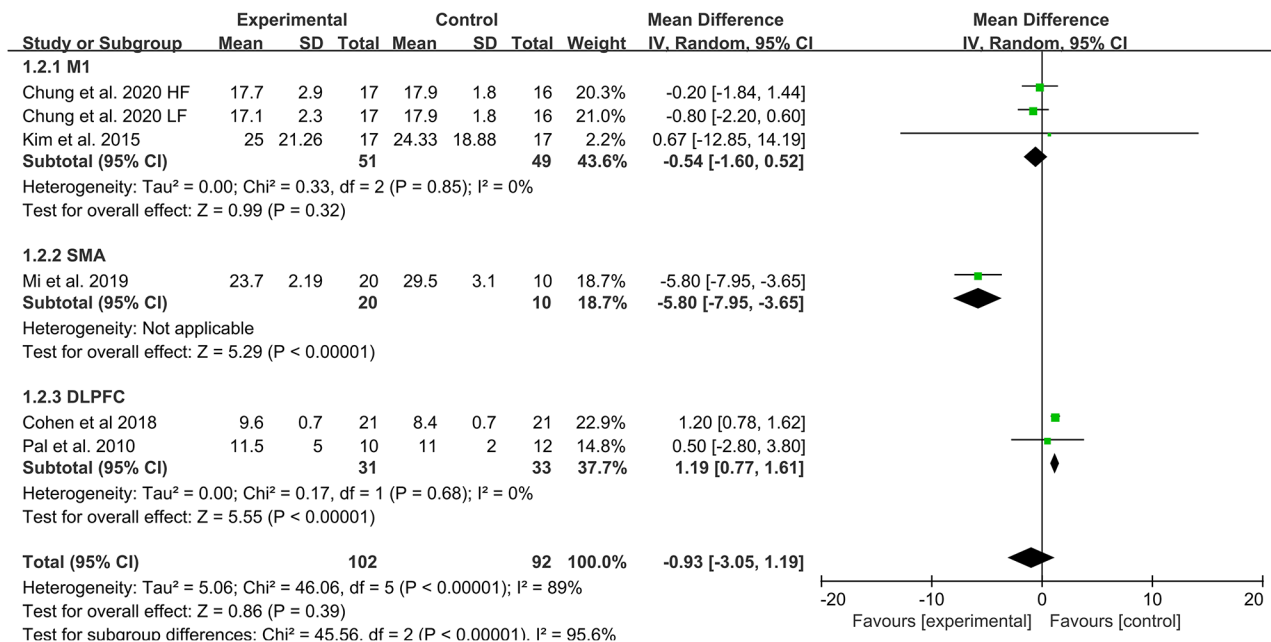
**Fig. 3** Meta-analysis results. **A** MOCA. **B** HAMD. **C** TUGT. **D** FOG-Q. **E** UPDRSIII

studies have shown that rTMS intervention exhibits antidepressant-like effects similar to oral medications such as selective serotonin reuptake inhibitors (SSRIs) used in clinical antidepressant treatment [56]. To our knowledge,

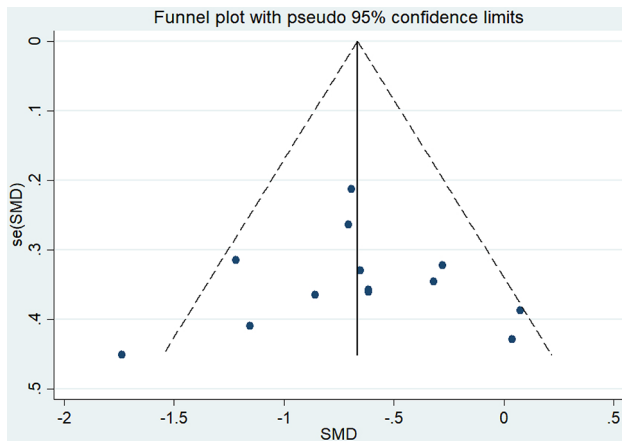
rTMS intervention may be used not only for treating PD-related depression but also for other types of depression. Therefore, we believe that rTMS is effective in treating depression, with the DLPFC being a potential target.



**Fig. 4** HAMD subgroup analysis



**Fig. 5** TUGT subgroup analysis



**Fig. 6** UPDRSIII funnel plot

However, the appropriate stimulation site (left or right DLPFC, unilateral or bilateral) and frequency require further study.

The TUGT is a more sensitive method for assessing functional mobility and gait stability in the elderly, and it is clinically significant for the diagnosis and treatment of gait disturbances in PD. Five studies [33, 37, 42, 44, 46] in this paper used TUGT as an outcome measure, showing a significant difference between the rTMS group and the sham stimulation group, with the rTMS group performing better. This suggests that rTMS can improve TUGT ability in PD patients. However, the heterogeneity among studies was high for this measure ( $P=0.000$ ,  $I^2=81\%$ ). To further investigate the source of heterogeneity, subgroup analysis was conducted, which indicated that different stimulation sites might affect TUGT outcomes. Treatment effects were better when M1 was selected as the stimulation site compared to DLPFC and SMA. Freezing of gait (FOG) is one of the common symptoms of PD, and its improvement helps reduce the risk of falls, enhance walking ability, and improve quality of life. Based on data from three studies [37, 44, 45] using FOG-Q as an outcome measure, the results showed a significant reduction in FOG-Q scores, indicating that rTMS significantly

improved FOG in PD patients. Mi [37] reported that HF-rTMS of the SMA could improve FOG in PD, while Kim [44] reported that HF-rTMS of the leg primary motor cortex (M1-LL) in the dominant hemisphere also improved FOG. Due to the small number of studies in our research, we did not further analyze the stimulation sites. Therefore, future research is needed to determine whether different stimulation sites for HF-rTMS can better improve FOG. Eleven studies [32–34, 36, 37, 39–41, 43, 44, 46] used UPDRS III as an outcome measure, and the results showed that the rTMS group was significantly better than the control group in improving motor function in PD patients, consistent with the conclusions of Li et al. [57]. Overall, rTMS can effectively improve walking function in PD patients compared to the control group. By stimulating specific regions of the motor cortex, TMS can effectively enhance the brain's control of lower limb movement while improving coordination and stability during movement. Studies have shown that high-frequency rTMS stimulation of the primary motor cortex increases neural excitability in this region, which in turn improves stride length and gait smoothness [58], and that gait deficits are mainly due to basal ganglia dysfunction and incoordination of the motor control network [59]. In addition, TMS may promote neuroplasticity by improving cortical functional connectivity. Compared to normal gait, patients with PD often show abnormalities in motor network connectivity, which can lead to gait instability and reduced stride length. TMS stimulation can reintegrate functional networks between motor-related brain regions, thereby improving brain motor control and gait performance [60]. In particular, coordinated stimulation of different brain regions (e.g. combined stimulation of the cerebellum and motor cortex) can synchronise the improvement of gait and static balance. Although TMS has been shown to be effective in improving gait disorders in PD patients, the optimisation of stimulation parameters (e.g. stimulation frequency, intensity and number of repetitions) and their effects on long-term outcomes need to be thoroughly investigated.

**Table 4** GRADE quality of evidence assessment of included studies

Outcome Measures	Number of Studies	Sample Size	Limitations	Inconsistency	Indirectness	Imprecision	Publication Bias	Evidence Quality
MOCA Score	3	175	0	0	0	Downgraded by One Grade (b)	0	Moderate
HAMD Score	4	186	0	0	0	Downgraded by One Grade (b)	0	Moderate
TUGT Score	5	178	0	Downgraded by One Grade (a)	0	Downgraded by One Grade (b)	0	Low
FOG-Q Score	3	90	0	0	0	Downgraded by One Grade (b)	0	Moderate
UPDRS III Score	11	489	0	Downgraded by One Grade (a)	0	0	0	Moderate

Note: a: The confidence intervals of different studies have poor overlap, with a high  $I^2$  value and a low  $P$ -value in the heterogeneity test; b: The sample size is too small, resulting in a wide confidence interval and poor overlap of confidence intervals; c: Publication bias is present

In addition, combining TMS with other rehabilitation tools (e.g., physical therapy or medication) may further enhance the effect of gait improvement.

This study has some limitations. First, this meta-analysis did not further analyze the specific stimulation sites for rTMS intervention on cognition. We acknowledge that the lack of this separate evaluation is one of the limitations of our study, and future clinical research and meta-analyses should consider this. Second, due to the lack of high-quality randomized controlled trials on non-motor symptoms, we could not further evaluate the efficacy of rTMS on various aspects of cognition. Therefore, unlike other reviews and meta-analyses, we did not further analyze changes in various cognitive domains. Third, we did not assess other non-motor symptoms that might be early PD symptoms, such as sleep disorders, although Babiloni et al. [61] demonstrated the potential positive effects of rTMS intervention on sleep disorders. Fourth, although this study focused mainly on rTMS intervention, several new TMS protocols, such as theta burst stimulation (TBS), paired associative stimulation (PAS), and other types of NIBS, including transcranial direct current stimulation (tDCS), are rapidly developing and deserve attention. These new protocols introduce innovative methods for modulating cortical excitability, and future network meta-analyses should further compare the efficacy of these methods in improving PD symptoms to select the optimal protocol.

## Conclusion

rTMS significantly improves cognitive function, depressive symptoms, and walking ability in Parkinson's disease patients. Different stimulation sites may influence TUGT outcomes, while the improvement of depressive symptoms is not affected by stimulation frequency or site.

## Abbreviations

PD	Parkinson's Disease
FOG	Freezing of Gait
rTMS	Repetitive Transcranial Magnetic Stimulation
M1	Primary Motor Cortex
DLPFC	Dorsolateral Prefrontal Cortex
SMA	Supplementary Motor Area
UPDRS	Unified Parkinson's Disease Rating Scale
MDS-UPDRS	Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale
FOG-Q	Freezing of Gait Questionnaire
TUGT	Timed Up and Go Test
MoCA	Montreal Cognitive Assessment
HAMD (or HDRS, HRSD)	Hamilton Depression Rating Scale
SMD	Standardized Mean Difference
MD	Mean Difference
I <sup>2</sup>	Inconsistency Index (for heterogeneity in meta-analysis)
GRADE	Grading of Recommendations, Assessment, Development, and Evaluations

## Author contributions

M.W. and W.Z. contributed to data analysis and wrote the original draft. W.Z. collected the data and conducted the literature review. M.W. and W.Z.

contributed to reviewing and editing the manuscript. W.Z. supervised the project, and W.Z. handled project administration. All authors reviewed and approved the final manuscript.

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## Data availability

No datasets were generated or analysed during the current study.

## Declarations

### Ethical approval and consent to participate

This article contains no studies with human participants or animals performed by any authors.

### Consent for publication

Not applicable.

### Competing interests

The authors declare no competing interests.

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