The Role of Repetitive Transcranial Magnetic Stimulation for Enhancing the Quality of Life in Parkinson's Disease: A Systematic Review

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Abstract

Background: Parkinson's disease (PD) is a neurodegenerative disorder which greatly affects patients' quality of life. Despite an exponential increase in PD cases, not much attention has been paid to enhancing their quality of life (QoL). Thus, this systematic review aims to summarize the available literature for the role of repetitive transcranial magnetic stimulation (rTMS) intervention to improve QoL of PD patients. **Methods:** Literature review was carried out using PubMed, Embase, Web of Science and Scopus databases. The key search words were, "*rTMS AND Parkinson AND QoL*", "*rTMS AND Parkinson AND Quality of Life*". Cochrane Collaboration software *Revman* 5.3 was used to assess the quality of studies. **Results:** Over 707 studies were identified out of which 5 studies were included which consisted of 160 subjects, 89 male and 71 female, with mean age of 65.04 years. PD type varied from idiopathic PD, rigid, akinetic, tremor dominant to mixed type. The overall risk of bias across the studies was low and unclear with high risk of bias in *incomplete outcome data* domain in one study. **Conclusions:** The efficacy of rTMS as an adjunct intervention to enhance QoL of PD patients is uncertain due to dire lack of research in this area. The findings of the present review would help researchers conduct a well-defined, randomized, controlled trial by overcoming the present limitations associated with rTMS intervention to improve QoL of PD patients.

Keywords: Behaviour, cognition, emotion, health, neuropsychology

Introduction

Parkinson's disease (PD) is a neurodegenerative disorder that hampers greatly with activities of daily living (ADL). In 2016, 6.1 million individuals had PD globally.[1] This number is estimated to double by 2030.[2] The underlying physiological mechanisms of the disease involves the degeneration of dopaminergic neurons in the substantia nigra region of the brain.[3-5] It is characterized by tremors, rigidity, bradykinesia, and instability of posture.[4,6-8] Non-motor[9] and motor symptoms adversely affect patients' quality of life (QoL).[10]

Repetitive transcranial magnetic brain stimulation (rTMS) is effective,[11] non-invasive, and alters the excitatory levels of different brain areas.[12] The excitability produced by high-frequency stimulation may be associated with long-term potentiation.[7] It is safe, painless, and inexpensive.[7]

Combining rTMS with existing interventions seems to be promising in neuromodulation.[5] As compared to antiparkinsonian medications, rTMS has a long-term effect (up to 20 weeks from rTMS stimulation[11]) on cognition, mood, motor symptoms, and QoL with minimal side effects.[13] Longer duration rTMS sessions have long-lasting benefits.[14,15]

Health-related QoL refers to an individual's perception of the impact of an illness on his/her social, psychological, and physical domains of life. Issues such as gait,[16,17] dysphagia,[18] sleep problems[19], and depression,[20] impair QoL significantly and markedly restrict ADL.[21] While QoL decreases with impaired motor symptoms,[22] it is more severely affected by neuropsychological symptoms like cognition and mood.[23] Thus, QoL is gradually becoming the focus of attention in research. There is a need for multidisciplinary interventions to enhance the well-being and QoL of patients with PD.[24,25]

Research on rTMS intervention as an adjunct therapy[16,26] for enhancing the QoL of patients with PD is required for holistic rehabilitation.[27] No research has been undertaken in this topic for systematic review so far, to the best of our knowledge. Therefore, the primary objective is to carry out a review to assess the role of rTMS intervention on the QoL of patients

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with PD while the secondary objective is to observe whether other factors contribute towards increased QoL.

Methods

A literature search from inception to the mentioned date was carried out using the following sources – *PubMed* (27 studies; 17/06/19), *Embase* (37 studies; 27/05/19), *Web of Science* (16 studies; 21/06/19), and *Scopus* (626 studies; 16/09/19). The key search words were, "*rTMS AND Parkinson AND QoL*", "*rTMS AND Parkinson AND Quality of Life*". The details of the included studies are described in Table 1. Cochrane Collaboration software *Revman 5.3*[28] and the guidelines by *Higgins and Altman* were used to assess the risk of bias[29] as described in Table 3 (online only: supplementary material).vw

Selection criteria

Studies with rTMS and sham intervention on humans with QoL assessment tools were included.

Studies were excluded if they were, reviews of previous studies (256), meta-analysis (13), without rTMS (69) or sham (4) intervention, not measuring QoL (16), editorials (6), articles (18), duplicates (74), case reports (2), chapters (53), books (36), not in English (16), not based on PD population (132), based on animal subjects (2), or was an on-going study (1), consensus (1), had multiple interventions (1) (online only: Supplementary material). Since the study design is a systematic review, no ethics committee approval was required.

Population

Studies recruited patients with PD as classified by the UK PDS Brain Bank criteria[30-32] for diagnosing PD by Calne *et al.* (1992)[33] and the Queen Square Brain Bank Criteria by Lees *et al.* (2009).[34]

Intervention

Studies included determined the role of rTMS intervention on patients with PD.

Comparison

Studies compared *rTMS* with *sham* group, which utilizes a sham coil that only generates sound instead of the magnetic field generated by the rTMS coil.

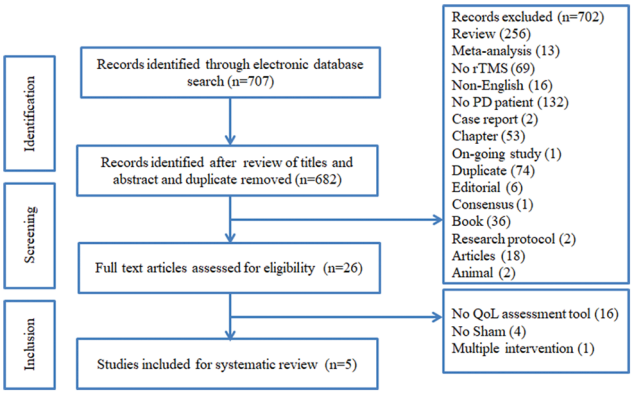

Figure 1: PRISMA flow chart for systematic review

Outcome

Included studies used QoL assessment tools to evaluate patients with PD post the rTMS intervention.

Data extraction

Two reviewers, PS and AN extracted the data individually [see Table 1]. Any disagreements between the reviewers were resolved through discussions and mutual consensus amongst all authors. The papers were read thoroughly to critically analyze the studies.

Results

Electronic search in *PubMed*, *Embase*, *Web of Science,* and *Scopus* databases identified over 707 studies out of which, five were included. A total number of 160 subjects were present with, 47 in sham group, 88 in experimental group, and 25 subjects belonged to both groups. The included studies consisted of, open-label,[30] two pilots,[33,34] crossover[33], and multicenter[32] study. No significant demographic difference across groups and baseline clinical characteristics was observed in two studies.[30,31] However, it differed in other studies due to the low sample size.[33,34] A summary of included and excluded studies is provided in Tables 1 and 2 (online only: supplementary information),

Figure 2: Risk of bias summary: review authorsæ judgement about each risk of bias item for included studies

respectively. The study flow diagram is illustrated in Figure 1.

As mentioned above, *Revman 5.3* software[28] was used to assess the risk of bias across seven domains[29] (*Refer to* Figures 2 and 3). Within the trails - the studies by Dias,[30] Makkos,[31] Yokoe,[33] and Randver *et al*.[34], had *low or unclear risk of bias* for all key domains. However, Brys *et al*.[32] demonstrated *high risk of bias* in the domain of '*incomplete outcome data'*. Across the trails, there was *low to uncertain risk of bias* in all domains, in all studies except one study,[32] which had *high risk of bias* in *incomplete outcome data* domain.

Patient characteristics

A total number of 89 male and 71 female subjects participated in the studies with an average age of 65.04 years. PD type consisted of idiopathic[30,32] or rigid, akinetic, tremor dominant, mixed type.[31] Several patients with PD had comorbid depression.[31,32,34]

Sample size

Studies provided no information regarding sample size calculation,[30,31,33,34] except one study,[32] which had an initial sample size of 160 (81.7% power) subjects. However, this sample size was halved and the study was terminated prematurely, which reduced the statistical power and effect size and thus, resulted in inconclusive results.

rTMS parameters

Most of the studies focused on stimulating the dorsolateral prefrontal cortex (DLPFC)[30,32-34] followed by the primary motor area (M1)[31-33] and supplementary motor area (SMA).[33] The frequency of rTMS sessions ranged from 5 Hz[31] to 15 Hz[30] with 10 Hz[32,33] being the most common. The pulses ranged from 600[31] to 6000.[34] All studies used figure- eight coil except one study,[31] which used a circular coil. Most of the rTMS sessions lasted for 10 days[31-33] however, one study gave the intervention for 6 consecutive weeks.[34] Parkinson's disease questionnaire (PDQ-39) was the most common tool[31-34] and voice-related QoL (V-RQOL)[30] was also used. No adverse side effects of rTMS were reported[30,31,33,34] apart from mild, transient head and neck ache.[32]

Factors affecting QoL

Only one study[30] recognized speech issues as significantly affecting the QoL of patients with PD and addressed V-RQOL as the primary objective. Whereas, in other studies[31-33] QoL was a secondary outcome measure and not the primary concern. Additionally, a study[34] noted that, along with the motor symptoms, neuropsychological issues may adversely affect the QoL of patients with PD.

Findings

As compared to sham, the following changes were observed in rTMS group: mean scores of V-RQOL increased from 26.67 (male) and 27.50 (female) to 51.25 (male) and 51.50 (female). A significant subjective improvement was observed in the emotional domain of V-RQOL.[30] Another study[31] established improvement in mobility, emotional well-being, and ADL domains of PDQ-39. The scores improved from a median of 25.4 [interquartile range (IQR): 18.5–35.4) to 16.9 (IQR: 4.5–20.0). Its efficacy was maintained in the 30-days follow-up (16.9 vs. 24.2 points). Another study[34] measured PDQ-39 at baseline (1 week before) and then after 3 weeks and 6 weeks. In a study of 6 patients, following changes in the PDQ-39 subscales were noticed: an improvement in mobility subscale was observed in subject 3 after 3rd week and in subject 5 after 6th week. However, after the 6th week, the scores of the subjects returned to the previous level and became worse in some cases. In ADL subscale, subject 5 reported a beneficial effect after 6th week and subject 6 after 3rd week. However, the scores of subject 6 decreased. The total score demonstrated a decrease from the baseline, up to 3rd week. After 6th week, the total score returned to baseline or stayed the same for most of the subjects, however, subject 5 showed steady improvements in scores. Conversely, two studies[32,33] could not establish any difference in PDQ-39 scores between sham and rTMS groups.

Interesting findings

The study by Dias *et al*.[30] established a correlation between subjective improvement of speech and improvement in depression. A correlation between voice intensity and motor improvement as assessed by Unified Parkinson's Disease Rating Scale (UPDRS) was also established. It is probable that the increased scores of V-RQOL resulted indirectly due to enhanced voice intensity and motor symptoms. Additionally, in a study,[31] significant improvement in QoL was observed in 'mobility', 'emotional well-being', and 'ADL' domains. Furthermore, four studies had to be excluded since, they were without sham intervention, which could have provided greater insight into the present research question.

Quality assessment of included studies

Figure 3: Risk of bias graph: review of authors' judgment about each risk of bias item presented as percentages across all included studies.

Discussion

Research in rTMS interventions to enhance QoL of patients with PD is required since the disease is drastically rising.[2] Overall, the risk of biases across the studies ranged from low to unclear suggesting that, the present biases are unlikely to alter the results seriously. However, a study[32] demonstrated a high risk of bias in the domain of *incomplete outcome data*.

Several limitations as outlined in the aforementioned studies should be addressed to improve future research.

There is a lack of sham group to negate the placebo effect.[19] The placebo effect in rTMS intervention is particularly pronounced for mood symptoms that create confusion in determining the efficacy of rTMS intervention.[34] The fact that placebo induced improvement can be observed in one domain but not the other gives us insight into the selectivity of placebo effect.

The issue of low sample size persists due to low confidence in the safety of the procedure, lack of rTMS professionals,[33] alterations in PD course, overall disease burden, high patient drop-outs, non-consenting patients, and strict contraindications for rTMS. Reduced sample size leads to poor generalization and decreased effect size, which results in inconclusive results and large discrepancy between individual differences.[34]

Mood and voice improvement via rTMS may be confounded with antidepressants since enhanced mood due to anti-depressants can also result in voice improvements.[27] Moreover, decreased scores on measures assessing the efficacy of rTMS intervention, may be attributed to - 'regression to mean', spontaneous recovery, placebo effect, better palliative care, healthier lifestyle,[34] illness duration, and medical adherence.[32] There is also a lack of systematic data collection clearly outlining the medical regimen of the patients, their symptoms of fluctuation and consistency of pre and post-assessment during off/on periods.[32] Since patients with PD are prone to motor fluctuations during the daytime, based on the timing of their medications, motor symptoms should be assessed at fixed intervals.[32]

The efficacy of rTMS varies due to its heterogeneous stimulation protocols.[31] The studies suggest that its effectiveness is dependent on patients' age, illness duration and severity, rTMS pulses, frequency, sessions, coil type, and intensity.[30] Furthermore, the stimulation parameters are restricted to existing literature. While this is mandatory for patients' safety, it limits the exploration of other efficient parameters. For instance, a study[34] mentioned that, in elderly, the stimulation intensity required to produce a significant effect may be higher than the existing guidelines.

Moreover, there is a lack of standardized reporting guidelines that may be followed to collate results of multiple studies. This is required to perform systematic reviews and meta-analysis easily and provide clearer results that can be generalized.

Limitation

Data could not be extracted for meta-analysis because of insufficient information to pool the data. The corresponding authors of relevant studies were contacted, however, no reply, except one, was received (till second follow-up). Additionally, the email address of one author[30] was non-existent. Publication bias could not be assessed since it requires at least 10 studies. Lastly, studies in non-English languages were not accessed.

Conclusions

The role of rTMS intervention in PD population, for enhancing QoL is unclear and controversial. This review provides insight to conduct well-defined, randomized, controlled, multicenter trials and highlights present limitations that need to be addressed while designing future neuro-psychological rTMS interventions to enhance QoL of patients with PD.

Future directions

Research protocols that address the aforementioned limitations should be prepared. The discrepancy between female to male subjects ratio should be reduced and the various PD symptoms should be addressed. A consensus in the standardized classification protocol for PD is also required to ensure that the clinical characteristics of patients do not vary largely to impact the outcome of the interventions. Different rTMS protocols should be observed to assess their efficacy and standardization for safety. Precautions like earbuds and sturdy neck support should be taken to avoid head and neck aches. Cognitive, mood, speech, and motor symptoms should be focused upon to enhance QoL. Symptom-specific QoL measures are required and should be used as primary assessment tools in rTMS studies.

Additional research is required to observe the effectiveness of focalized vs. multifocal stimulation (for assessing the extent of synergic effect) and unilateral vs. bilateral stimulation. The duration of sessions along with the wash-out period and durability of rTMS effects also needs clarity. A deeper understanding of the underlying neurophysiological mechanisms, in the case of multifocal stimulations is also required. Multicenter studies should be designed to overcome low sample size issues and thus increase the power of the study. Lastly, it is speculated that providing neuropsychological interventions along with rTMS intervention, would greatly enhance the QoL of patients with PD.

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Conflicts of interest

There are no conflicts of interest.

References

1. GBD 2016 Parkinson's disease Collaborators. Global, regional, and national burden of Parkinson's disease, 1990–2016: A systematic analysis for the Global Burden of Disease Study. The Lancet Neurology 2016;11:939-53.
2. Loius CS. Epidemiology of Parkinson's disease. Neurology Asia 2013;18:231-8.
3. Aftanas LI, Gevorgyan MM, Zhanaeva SY, Dzemidovich SS, Kulikova KI, Al'perina EL, *et al.* Therapeutic effects of repetitive transcranial magnetic stimulation (rTMS) on neuroinflammation and neuroplasticity in patients with Parkinson's disease: A placebo-controlled study. Bull Exp Biol Med 2018;165:195-9.
4. Lefaivre SC, Brown MJN, Almeida QJ. Cerebellar involvement in Parkinson's disease resting tremor. Cerebellum Ataxias 2016;3:13.
5. González-García N, Armony JL, Soto J, Trejo D, Alegría MA, Drucker-Colín R. Effects of rTMS on Parkinson's disease: A longitudinal fMRI study. J Neurol 2011;258:1268-80.
6. Yang YR, Tseng CY, Chiou SY, Liao KK, Cheng SJ, Lai KL, *et al*. Combination of rTMS and treadmill training modulates corticomotor inhibition and improves walking in Parkinson disease: A randomized trial. Neurorehabil Neural Repair 2012;27:79-86.
7. Otomune H, Mihara M, Hattori N, Fujimoto H, Kajiyama Y, Konaka K, *et al*. Involvement of cortical dysfunction in frequent falls in patients with Parkinson's disease. Parkinsonism Relat Disord 2019;64:169-74.
8. Obeso I, Cerasa A, Quattrone A. The effectiveness of transcranial brain stimulation in improving clinical signs of hyperkinetic movement disorders. Front Neurosci 2016;9:486.
9. Maruo T, Hosomi K, Shimokawa T, Kishima H, Oshino S, Morris S, *et al.* High-frequency repetitive transcranial magnetic stimulation over the primary foot motor area in Parkinson's disease. Brain Stimul 2013;6:884-91.
10. Oonk NG, Movig KL, Munster EM, Koehorst-Ter Huurne K,

van der Palen J, Dorresteijn LD. The effect of a structured medication review on quality of life in Parkinson's disease: The study protocol. Contemp Clin Trials Commun 2019;13:100308.
11. Shirota Y, Ohtsu H, Hamada M, Enomoto H, Ugawa Y. Supplementary motor area stimulation for Parkinson disease: A randomized controlled study. Neurology 2013;80:1400-5.
12. Kim SJ, Paeng SH, Kang SY. Stimulation in supplementary motor area versus motor cortex for freezing of gait in Parkinson's disease. J Clin Neurol 2018;14:320-6.
13. Málly J, Geisz N, Dinya E. Follow up study: The influence of rTMS with high and low frequency stimulation on motor and executive function in Parkinson's disease. Brain Res Bull 2017;135:98-104.
14. Kim MS, Chang WH, Cho JW, Youn J, Kim YK, Kim SW, *et al*. Efficacy of cumulative high-frequency rTMS on freezing of gait in Parkinson's disease. Restor Neurol Neurosci 2015;33:521-30.
15. Hamada M, Ugawa Y, Tsuji S. High-frequency rTMS over the supplementary motor area for treatment of Parkinson's disease. Mov Disord 2008;23:1524-31.
16. Dagan M, Herman T, Mirelman A, Giladi N, Hausdorff JM. The role of the prefrontal cortex in freezing of gait in Parkinson's disease: Insights from a deep repetitive transcranial magnetic stimulation exploratory study. Exp Brain Res 2017;235:2463-72.
17. Mancini M, Fling BW, Gendreau A, Lapidus J, Horak FB, Chung K, *et al*. Effect of augmenting cholinergic function on gait and balance. BMC Neurol 2015;15:264.
18. Michou E, Hamdy S, Harris M, Vania A, Dick J, Kellett M, *et al*. Characterization of corticobulbar pharyngeal neurophysiology in dysphagic patients with Parkinson's disease. Clin Gastroenterol Hepatol 2014;12:2037-45.e4.
19. van Dijk KD, Møst EI, Van Someren EJ, Berendse HW, van der Werf UD. Beneficial effect of transcranial magnetic stimulation on sleep in Parkinson's disease. Mov Disord 2009;24:878-84.
20. Shin HW, Youn YC, Chung SJ, Sohn YH. Effect of high-frequency repetitive transcranial magnetic stimulation on major depressive disorder in patients with Parkinson's disease. J Neurol 2016;263:1442-8.
21. Gorecka-Mazur A, Furgala A, Krygowska-Wajs A, Pietraszko W, Kwinta B, Gil K. Activities of daily living and their relationship to health-related quality of life in patients with Parkinson disease after subthalamic nucleus deep brain stimulation. World Neurosurg 2019;125:e552-62.
22. Pinto C, Salazar AP, Marchese RR, Stein C, Pagnussat AS. The effects of hydrotherapy on balance, functional mobility, motor status, and quality of life in patients with Parkinson disease: A systematic review and meta-analysis. PMR 2019;11:278-91.
23. Erro R, Picillo M, Vitale C, Amboni M, Moccia M, Santangelo G, *et al.* The non-motor side of the honeymoon period of Parkinson's disease and its relationship with quality of life: A 4-year longitudinal study. Eur J Neurol 2016;23:1673-9.
24. Wu YR, Chang CW, Fan JY, Chang BL. Anxiety and levodopa equivalent daily dose are potential predictors of sleep quality in patients with Parkinson disease in Taiwan. Front Neurol 2019;10:340.
25. Marumoto K, Yokoyama K, Inoue T, Yamamoto H, Kawami Y, Nakatani A, *et al.* Inpatient enhanced multidisciplinary care effects on the quality of life for Parkinson disease: A quasi-randomized controlled trial. J Geriatr Psychiatry Neurol 2019;32:186-94.
26. Málly J, Farkas R, Tóthfalusi L, Stone TW. Long-term follow-up study with repetitive transcranial magnetic stimulation (rTMS) in Parkinson's disease. Brain Res Bull 2004;64:259-63.
27. Takahashi K, Kamide N, Suzuki M, Fukuda M. Quality of life in people with Parkinson's disease: The relevance of social relationships and communication. J Phys Ther Sci 2016;28:541-6.
28. Review Manager (RevMan) [Computer Program] Version 5.3. Copenhagen: The Nordic Cochrane Centre; Cochrane Collaboration. 2014.
29. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, *et al.* The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
30. Dias AE, Barbosa ER, Coracini K, Maia F, Marcolin MA, Fregni F. Effects of repetitive transcranial magnetic stimulation on voice and speech in Parkinson's disease. Acta Neurol Scand 2006;113:92-9.
31. Makkos A, Pál E, Aschermann Z, Janszky J, Balázs E, Takács K, *et al.* High-frequency repetitive transcranial magnetic stimulation can improve depression in Parkinson's disease: A randomized, double-blind, placebo-controlled study. Neuropsychobiology 2016;73:169-77.
32. Brys M, Fox MD, Agarwal S, Biagioni M, Dacpano G, Kumar P, *et al.* Multifocal repetitive TMS for motor and mood symptoms of Parkinson disease: A randomized trial. Neurology 2016;87:1907-15.
33. Yokoe M, Mano T, Maruo T, Hosomi K, Shimokawa T, Kishima H, *et al.* The optimal stimulation site for high-frequency repetitive transcranial magnetic stimulation in Parkinson's disease: A double-blind crossover pilot study. J Clin Neurosci 2018;47:72-8.
34. Randve R, Davel K, Toomsoo T. High-frequency repetitive transcranial magnetic stimulation to the left dorsolateral prefrontal cortex of patients with Parkinson's disease and treatment-resistant depression: A pilot study. Neurocase 2019;25:80-90.

Table 1: Summary of research on rTMS interventions on patients with PD and its effectiveness on their quality of life

Author	Design	Sample	Medication	Patient Characteristic (Mean)	Clinical Characteristics	Location	Intensity	Frequency (Hz)
Dias *et al.*, (2006)	Randomized, double-blind controled clinical trial, open study	N=30 EG -19; CG - 11	EG - placebo medication; CG - fluoxetine 20 mg; L-dopa	EG - 64.89, Yrs, 27M, 13 F, ID – 6.9	HYS - 1.9, idiopathic PD	L-DLPFC	110% MT,	15
Makkos *et al.*, (2016)	Randomized, Double-Blind, Placebo-Controlled Study	N=44 EG - 23; CG - 21	L-dopa-equivalent dosage, dopamine agonist	66.5 Yrs, 24M, 20F, ID - 5.5	HYS - 2.4, on & off meds, with depression, PD type, n Rigid-akinetic Tremor-dominant Mixed-type	M1	90% RMT	5
Randver *et al.*, (2019)	single-blind randomized controlled trial Pilot study	N=6	Levodopa-equivalent daily dose	61.3 yrs (11.89); 3M, 3F; ID-5.2 (1.72) Yrs	Moderate to severe depression; HYS-2.5-3 PD type - INP	L-DLPFC	80% RMT	10
Yokoe *et al.*, (2018)	randomized, double-blind, placebo-controlled crossover study	N=19	All patients were currently receiving dopaminergic replacement therapy	8M, 11F; 69.1 (8.4) Yrs, ID - 9.5 (3.2), PD type - INP	HYS - 3.5 (0.6)	M1, DLPFC, SMA	100% RMT	10
Brys *et al.*, (2016)	Multicenter, double-blind, sham-controlled, parallel-group study	N=M1 + DLPFC -20, M1-14, DLPFC-12, DS-15	Antidepressants	M1 + DLPFC-64.9 (8) yrs, M1-59.6 (12.6) yrs, DLPFC-64.6 (12.3), DS-64 (7.4) Yrs; 24F, 27M; ID: M1 + DLPFC-7.3 (5.6), M1-8.4 (5.2), DLPFC - 7.7 (4.2), DS - 4.5 (2.2)	With depression, PD type - Idiopathic	B-M1, L-DLPFC	INP	10

Author	Pulses	Coil	rTMS protocol	QoL Tool	Other Tools	Result	Key Findings	Side Effects
Dias *et al.*, (2006)	3000	F8	10 daily sessions during a 2- week period, administered Monday to Friday. At each session, a train of 75 stimuli was delivered for 5s followed by a 10s interval.	V-RQOL	SE-ADL, UPDRS, BDI, HDRS, acoustic and perceptual analysis of voice features	Mood amelioration and subjective improvement of the V-RQOL	5 Hz rTMS of M1-mouth area is associated with a significant improvement of voicing, characterized by an improvement in voice intensity and fundamental frequency.	Did not observe any rTMS-related side effects in any group.
Makkos *et al.*, (2016)	600-300 on right and 300 on left side	Circular coil	12 trains of 10 s with an intertrain interval of 20 s) for 10 consecutive days	PDQ-39	MADRS, MDS-UPDRS	PDQ-39 (from 25.4 to 16.9)	Out of the 8 domains of PDQ-39, significant improvement in mobility, emotional well-being and ADL	Did not observe any rTMS-related side effects in any group.
Randver *et al.*, (2019)	6000	F8	5 s and interval between trains of 25 s, 500 impulses per session, two sessions per week for a period of six consecutive weeks, amounting to a total of 12 sessions	PDQ-39	MoCA, TMT-A, B, WAIS, BDI, EST-Q, UPDRS, SE-ADL	Total score on PDQ-39 demonstrated a decrease from the baseline, up to the third week. However, after the sixth week, the total score returned to the base line or stayed the same for most of the subjects however, subject 5 showed steady improvement in scores.	Those with more pronounced anxiety show better results after rTMS. It may be that rTMS the depressive effects are part of an underlying anxiety disorder. This may be a direct representation of depression in PD being qualitatively different from “pure” major depressive disorder	Judging by a VAS before and after brain stimulation, the stimulation procedure was well tolerated by the subjects and without any major side effects.

Contd...

Table 1: Contd...

Author	Pulses	Coil	rTMS protocol	QoL Tool	Other Tools	Result	Key Findings	Side Effects
Yokoe *et al*., (2018)	1000	F8	pulse trains lasted 5 s with an inter-train interval of 25 s. 10 trains were delivered on both sides,	PDQ-39	AES, MADRS-S, UPDRS-II, SDS, self-assessment motor test, VAS, 10-m walk test outcome	Changes in the PDQ-39 motor and non-motor scores from before and after the rTMS stimulations were similar to those observed in the patients who received the sham stimulation.	Application of HF-rTMS over the M1 and SMA significantly improved the motor symptoms in the PD patients but did not alter the mood disturbances. Compared with the sham stimulations, significant changes were observed in the UPDRS-III total scores after the stimulation over the M1 and SMA	One patients experienced headache during DLPFC stimulation session that spontaneously resolved. Strength of unplesantness was similar regardless of the site and the type of stimulation. No serious adverse effects.
Brys *et al*., (2016)	2000 - DLPFC; 1000-M1	F8	50 trains of 40 stimuli at 10 Hz for 10 days and 25 minutes each for DLPFC, 12.5 minutes for M1	PDQ-39	UPDRS, HAM-D, DBI-II, CAS, MoCA, CGIS,	There was no difference in change of the PDQ-39 between the M1 and double-sham groups.	There was no correlation found between changes in UPDRS and PDQ-39 in M1 rTMS group	68% of completers reported adverse events, most commonly headache and neck pain, which were mild and transient. One serious adverse event (ischemic stroke) occurred in a patient receiving active rTMS (deemed unrelated to the study). The distribution of adverse events was similar in the active TMS groups (25 of 46) and the DS group (9 of 15).

* N - no. of subject, EG: experimental group, CG: control group, M: male, F: female, PD: Parkinson's disease, HYS: Hoehn & Yahr Scale, LDLPFC: left dorsolateral pre-frontal cortex, MT: motor threshold, F8:figure eight coil, s: seconds, V-RQoL: voice-related quality of life, SE-ADL: Schwab & England Activities of Daily living, UPDRS: Unified Parkinson's Rating Scale, HDRS: Hamilton Depression Rating Scale, M1:primary motor area, rTMS: repetitive transcranial magnetic stimulation, ID: illness duration, Hz: hertz, RMT: resting motor threshold, PDQ-39:Parkinson's disease questionnaire, MADRS: Montgomery and Asberg Depression Rating Scale, MoCA: Montreal Cognitive Assessment, TMT: Trail making test A/B version, BDI: Beck depression Inventory, EST-Q: Emotional state questionnaire, VAS: visual analog scale, SDS: Self-Rating Depression Scale, HF: high frequency, SMA: sensory motor area, DS: double sham, INP: information not provided.

Table 3: Assessment of Risk of Bias

Bias	STUDY 1 Dias *et al*., (2006)		STUDY 2 Makkos *et al*., (2016)		STUDY 3 Randver *et al*., (2019)		STUDY 4 Yokoe *et al*., (2018)		STUDY 5 Brys *et al*., (2016)	
	Authors' Judgement	Support for judgement	Authors' Judgement	Support for judgement	Authors' Judgement	Support for judgement	Authors' Judgement	Support for judgement	Authors' Judgement	Support for judgement
Random sequence generation	L	"Patients were assigned to one of the two groups according to a computer-generated randomization list."	L	"Patients were randomly assigned to groups using an automated stratified procedure."	U	"Block randomization was used"	L	"Independent statistician generated the random allocation sequence."	U	"Participants were randomized in a 1:1:1:1 fashion to receive rTMS over the bilateral M1, left DLPFC, both, or neither (sham rTMS)."
Allocation concealment	U	Randomization list was created using automated stratified procedure but further description of allocation was not included.	U	Randomization list was created using automated stratified procedure but further description of allocation was not included.	L	Further description of allocation method was not included.	U	Further description of allocation method was not included.	U	Randomization list was created using automated stratified procedure but further description of allocation was not included.
Blinding of participants and researchers	L	Double-blind	L	Double-blind	L	"All rTMS procedures were performed by a rTMS-trained clinical neuropsychologist (R.R.) who was not blind to the stimulation group. The assessing neurologist (T.T.) was blind in regard to the stimulation group, as was the subject."	L	Double-blind	L	Double-blind
Blinding of outcome assessment	U	No information relating to whether the intended blinding was effective.	L	"Effectiveness of blinding was measured by the number of patients at whom either the patient or the examiner expected an active stimulation. It was observed to be effective."	U	No information relating to whether the intended blinding was effective.	L	"At the end of each of the treatment sessions, none of the patients were able to identify which type of rTMS (sham/real) they received."	L	"Only 49% of participants correctly guessed the stimulation status (real vs sham), confirming the efficacy of the blinding method used."
Incomplete outcome data	L	No attrition and exclusions were reported.	L	"Out of 46 patients, 2 dropped out in the Sham group. (One moved out of the city and the other developed superficial thrombophlebitis) This is a reasonable attrition and not expected to affect results. Only the data	L	"Only 6 patients were present. Subject 3 (S3) could not participate in all of the assessments in Week 6 due to health problems not associated with the study".	L	No attrition and exclusions were reported.	H	"The analysis included all patients who completed the primary study end point visit and were not excluded from analysis."

Contd...

Table 3: Contd...

Bias	STUDY 1 Dias *et al*., (2006)		STUDY 2 Makkos *et al*., (2016)		STUDY 3 Randver *et al*., (2019)		STUDY 4 Yokoe *et al*., (2018)		STUDY 5 Brys *et al*., (2016)	
	Authors' Judgement	Support for judgement	Authors' Judgement	Support for judgement	Authors' Judgement	Support for judgement	Authors' Judgement	Support for judgement	Authors' Judgement	Support for judgement
				of patients who completed the study protocol were analysed. There were no significant differences between the baseline characteristics of the actively treated and sham-treated groups.						
Selective reporting	L	All pre-specified outcomes were reported.	L	All pre-specified outcomes were reported.	L	All pre-specified outcomes were reported.	L	No selective outcomes reported.	L	No selective outcomes reported.
Other bias	L	No important concerns about bias present, which are not covered in the other domains in the tool.	L	No important concerns about bias present, which are not covered in the other domains in the tool.	U	"Our results cannot be extrapolated to other PD patient subgroups, and we cannot draw any conclusions with respect to the specificity of our results in the PD patient population. The decrease in scores observed in some patients may be attributable to spontaneous recovery, regression to the mean, placebo effect, and a general palliative effect due to compassionate care of any kind, or other unknown (and uncontrolled) factors." "Due to the clinically complex characteristics of the subject sample and lack of specific stimulation guidelines, we focused on individual scores and case reports rather than relying on group comparisons."	L	No important concerns about bias present, which are not covered in the other domains in the tool.	L	No important concerns about bias present, which are not covered in the other domains in the tool.

*L-Low risk, U-Unclear risk, H-High risk