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Non-invasive brain stimulation enhances motor and cognitive performances during dual tasks in patients with Parkinson's disease: a systematic review and meta-analysis

Hajun Lee[1], Beom Jin Choi[1] and Nyeonju Kang[1,2,3*]

Abstract

Background Parkinson's disease (PD) induces progressive deficits in motor and cognitive functions as well as impaired dual-task performance requiring both motor and cognitive functions. This systematic review and meta-analysis evaluated the effects of non-invasive brain stimulation (NIBS) on dual-task performance in patients with PD.

Methods 11 studies met the following inclusion criteria: (a) patients with PD, (b) NIBS intervention, (c) comparison with the sham stimulation group, (d) motor and cognitive performance outcomes during dual tasks, and (e) randomized controlled trials with parallel or crossover designs. Individual effect size (i.e., comparison) was quantified by comparing motor and cognitive performances changes during dual tasks between active NIBS and sham stimulation conditions. Thus, higher values of the overall effect size indicate more improvements in either motor or cognitive performances after NIBS. Moreover, moderator variable analyses determined whether NIBS effects on dual-task performances differed depending on targeted brain regions. Finally, meta-regression analyses determined whether NIBS effects on dual-task performances were associated with demographic characteristics.

Results The random-effects model meta-analysis revealed that NIBS significantly improved motor (73 comparisons from 11 studies) and cognitive (12 comparisons from four studies) performances during dual tasks in patients with PD. Specifically, anodal transcranial direct current stimulation protocols on the dorsolateral prefrontal cortex were effective. Moreover, greater improvements in motor performance during dual tasks significantly correlated with decreased age and increased proportion of females, respectively.

Conclusion This meta-analysis suggests that excitatory stimulation on the dorsolateral prefrontal cortex may be effective for improving dual-task performance in patients with PD.

Keywords Parkinson's disease, Dual task, Non-invasive brain stimulation, Transcranial direct current stimulation, Dorsolateral prefrontal cortex

*Correspondence:
Nyeonju Kang
nyunju@inu.ac.kr
[1]Department of Human Movement Science, Incheon National University, Incheon, South Korea
[2]Division of Sport Science, Sport Science Institute & Health Promotion Center, Incheon National University, Incheon, South Korea
[3]Neuromechanical Rehabilitation Research Laboratory, Division of Sport Science & Sport Science Institute, Incheon National University, 119 Academy-ro, Yeonsu-gu, Incheon, South Korea

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Introduction

Parkinson's disease (PD), the second-most common neurodegenerative disorder, normally induces progressive deficits in motor and cognitive functions, as indicated by slower gait speed and impaired executive functions in patients with PD [1–5]. Moreover, patients with PD presented more impairments when performing dual tasks that simultaneously require motor and cognitive task goals than healthy older adults [6–8]. For example, patients with PD exhibited 18% reduction of step length from single-task walking to dual-task walking, whereas healthy older adults showed only 2% decrease in step length [9]. Given that many activities of daily living frequently require dual tasks such as reading text messages on a smartphone while walking, patients with PD may be challenging for increasing independent life without specific rehabilitation protocols that effectively address dual-task impairments [10, 11].

Non-invasive brain stimulation (NIBS) techniques including transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (rTMS) have been explored as intervention protocols for improving dual-task performance due to their potential effects on modulating cortical excitability and facilitating neuroplasticity [12–15]. According to the central capacity sharing model [16], cognitive resources may be divided when concurrently processing multiple stimuli due to a limited capacity. Thus, dual tasks such as using a smartphone while walking can lead to cognitive-motor interference presumably impairing the performance of either one or both tasks [17]. Importantly, patients with PD typically showed impaired gait automaticity so that they may use more cognitive resources for successful locomotion while increasing cognitive-motor interference patterns [18, 19]. For example, although patients with PD revealed greater excitability in the dorsolateral prefrontal cortex (DLPFC) for executive functions, their gait patterns during dual tasks were slower and more variable than those of age-matched healthy older adults [20]. These findings indicated that patients with PD may need more neural resources in the brain (e.g., DLPFC excitability) to compensate for their motor and executive deficits. Potentially, the primary motor cortex (M1) may be an additional key area to preserve motor functions during dual tasks because M1 excitability may advance the cortico-basal ganglia connections affected by striatal dopamine depletion [21–23]. Thus, NIBS protocols targeting these cortical regions may improve dual-task performance by attenuating cognitive-motor interferences. A systematic review and meta-analysis investigating tDCS effects on dual-task performances in older adults reported that anodal tDCS on the DLPFC significantly reduced dual-task cost of gait speed [24]. Taken together, quantifying potential overall effects of NIBS on dual-task performances in patients with PD may provide meaningful information on identifying optimal rehabilitation protocols contributing to increasing their independent life.

A recent systematic review study performed by Lin and colleagues [25] revealed potential positive effects of NIBS protocols on gait speed and timed up and go (TUG) during dual tasks in patients with PD from three studies [14, 26, 27]. Although this study suggested a possibility of improvements in dual-task performances after NIBS protocols, these findings were still insufficient because of the limited number of included studies and no quantitative evidence by conducting data synthesis procedures. Thus, we investigated effects of NIBS on dual-task performances in patients with PD by conducting a systematic review and meta-analysis. Moreover, NIBS effects can vary with different targeted brain areas [28, 29]. Based on these findings, we addressed two leading questions: (1) Do NIBS techniques improve motor and cognitive performances during dual tasks in patients with PD? and (2) Do the effects of NIBS on motor and cognitive performances in patients with PD differ depending on the targeted brain regions?

Methods

Literature search and study inclusion criteria

We conducted the systematic review and meta-analysis consistent with Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines [30]. To formulate convincing eligibility criteria [31], we used Population, Intervention, Comparison, Outcomes, and Study design (PICOS) framework. Specifically, five inclusion criteria included: (1) Population: patients with PD; (2) Intervention: NIBS protocols; (3) Comparison: controls who received sham stimulation; (4) Outcome: motor and cognitive performance during dual tasks; and (5) Study design: studies that included randomized controlled trials (RCT) with either a parallel or crossover design. Moreover, we excluded case studies, animal studies, review articles, and studies that reported insufficient data for calculating effect sizes. Using two databases including PubMed and Web of Science, the literature search was performed from July 12, 2023, to August 14, 2023. For both search engines, we used the following keywords: (PD OR Parkinson's disease OR Parkinson) AND (NIBS OR non-invasive brain stimulation OR tDCS OR transcranial direct current stimulation OR tACS OR transcranial alternating current stimulation OR TMS OR transcranial magnetic stimulation OR rTMS OR repetitive transcranial magnetic stimulation OR tPCS OR

transcranial pulsed current stimulation OR tRNS OR transcranial random noise stimulation) AND (dual-task OR dual task OR concurrent OR walk OR gait OR locomotion OR cognition OR interference).

Data synthesis for meta-analysis

Meta-analysis procedures were conducted using the Comprehensive Meta-Analysis software version 4.0 (Englewood, NJ, USA). Individual effect size (i.e., comparison) and overall effect size (i.e., effect size after data synthesis) were quantified by calculating standardized mean difference (SMD) with a 95% confidence interval (CI). We included multiple comparisons from one study when each comparison could be calculated based on different types of dual tasks, outcome variables, and NIBS protocols (e.g., targeted regions and timing). Higher SMD values indicate more improvements in dual-task performances after applying active NIBS protocols than those for sham stimulation condition. For RCT with a parallel design, individual effect sizes were calculated by comparing mean and standard deviation values of motor and cognitive performances between active and sham stimulation groups. For RCT with a crossover design, we calculated individual effect sizes using a paired analysis that applied the sample size and mean difference values with standard error [32–34]. To synthesize individual effect sizes, we used the random-effects model meta-analysis based on the traditional assumptions that inherent heterogeneity may exist among individual studies because of different experimental characteristics (e.g., participants, study protocols, and outcome measures). This approach may minimize the potential variability of effect sizes by reducing the influence of these methodological differences across individual studies [35].

To estimate the heterogeneity levels across individual effect sizes, we used Higgins and Green's I-squared (I^2) indicating relationship between the distribution of true effects and observed effects [36]. Typically, the 25%, 50%, and 75% values of I^2 denote low, moderate, and high heterogeneity levels, respectively [37]. Moreover, the Egger's regression test was performed to determine whether significant levels of publication bias exist across individual effect sizes. A P-value for the intercept (β_0) of less than 0.05 indicates significant levels of publication bias [38].

Moderator variable analysis

Additional moderator variable analyses were performed to specify effects of NIBS protocols on motor and cognitive performances during dual tasks in patients with PD. First, we investigated how NIBS influenced dual-task performances based on different types of motor functions (i.e., gait speed, cadence, double support time, stride time, stride length, step length, step width, stride time variability, stride length variability, TUG, time to return, and writing amplitude) and cognitive functions (i.e., number of correct generating words and counting). Second moderator analysis specified NIBS effects on dual-task performances according to different targeted brain areas (i.e., DLPFC, supplementary motor area; SMA, M1, and cerebellum). Finally, we conducted additional meta-regression analyses to determine whether the effects of NIBS on motor and cognitive performances were associated with different demographic characteristics (i.e., mean age, proportion of the females, and duration since PD diagnosis).

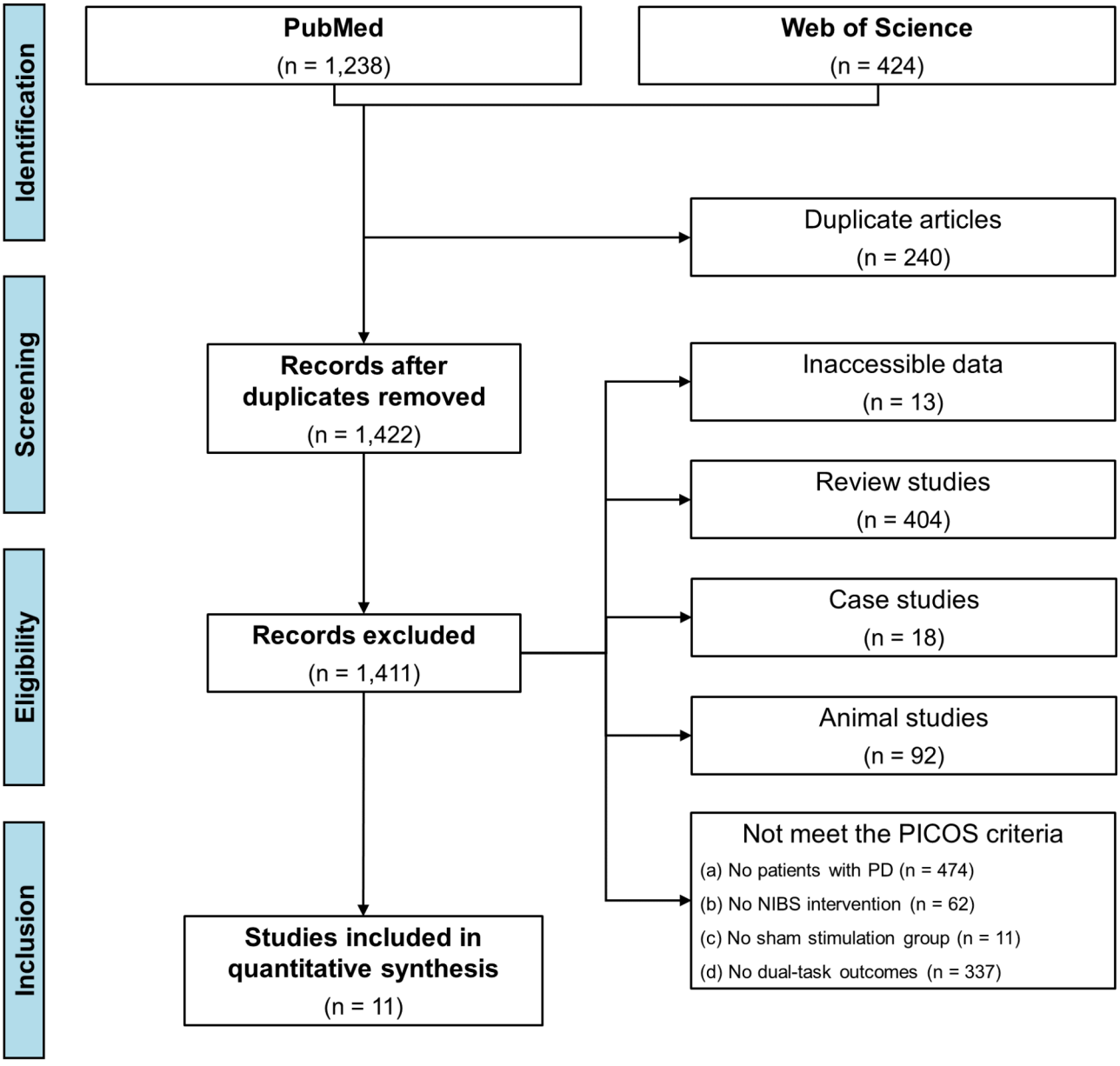
Methodological quality assessment

Using the Cochrane risk of bias assessment tool version 2 [39], two researchers (H.L. and B.J.C.) independently evaluated potential methodological issues based on six specific domains: (1) randomization process (2), timing of identification or recruitment of participants (3), deviations from intended intervention (4), missing outcome data (5), measurement of the outcome, and (6) selection of the reported result [40]. Based on the criteria for algorithms in the Cochrane risk of bias assessment tool [41], we judged the risk of bias for each domain by assigning one of three levels: (1) low risk of bias (2), some concern, and (3) high risk of bias. In the case of any discrepancy between the researchers, one leading researcher (N.K.) made a final decision.

Results

Study identification procedure

Initially, a systematic literature search identified 1,662 studies including 1,238 from the PubMed and 424 from the Web of Science, and then we removed 240 duplicated studies. The title and abstract of 1,422 studies were firstly screened, and 527 studies were excluded because of the following: (1) 404 review articles (2), 92 animal studies (3), 18 case studies, and (4) 13 studies that reported inaccessible contents. Full texts of the remaining 895 studies were carefully reviewed based on our inclusion and exclusion criteria, and 884 studies were further excluded: (1) 474 studies that did not focus on patients with PD (2), 62 studies that did not use NIBS intervention (3), 11 studies that did not involve sham stimulation group, and (4) 337 studies that did not estimate dual-task performances. Finally, 11 studies qualified for this meta-analysis [14, 15, 26, 27, 42–48]. Our study identification procedures are described in Fig. 1.



PICOS Inclusion Criteria	
Population	Patients with PD
Intervention	NIBS protocols including tDCS and rTMS
Comparison	Controls with sham NIBS conditions
Outcome	Dual-task performances including motor and cognition
Study design	RCT with either a crossover or parallel design

Fig. 1 PRISMA flowchart for the study identification procedure. PD = Parkinson's disease; NIBS = non-invasive brain stimulation; tDCS = transcranial direct current stimulation; rTMS = repetitive transcranial magnetic stimulation; RCT = randomized control trials

Demographic information on patients with PD

From the 11 qualified studies, 284 patients with PD participated in experiments (a range of mean age = 50.1–72.8 years and a range of mean duration after PD diagnosis = 3.5–9.3 years). Motor impairments in patients with PD at baseline was mild to moderate [49–51]: (1) a range of mean Hoehn and Yahr scale (H&Y) = 1.7–2.3 and (2) a range of mean unified Parkinson's disease rating scale part III (UPDRS-III) = 15.8–47.7. Cognitive function of the participants was relatively normal [52, 53]: (1) a range of mean mini-mental state examination (MMSE) = 25.5–29.7 and (2) Montreal cognitive assessment (MoCA) = 26.1–28.0. The included studies reported that all patients with PD were on medication state. Table 1 shows specific details on demographic information of patients with PD.

NIBS protocols for dual tasks

For 11 qualified studies, nine studies applied tDCS and two studies used rTMS. For specific brain region of NIBS stimulation, tDCS protocols targeted: (1) DLPFC from five studies (2), M1 from three studies, and (3) three different targeted regions (i.e., DLPFC, M1, and cerebellum) from one study. Two studies that used rTMS protocols stimulated M1 and SMA, respectively. For the stimulation protocol type, nine tDCS studies applied anodal stimulation. For rTMS protocols, one study applied inhibitory stimulation (≤ 1 Hz), whereas another study used both inhibitory and excitatory stimulation (> 5 Hz). For the number of sessions, eight tDCS studies applied a single session and one study administered multiple sessions. Two rTMS studies applied multiple stimulation sessions. For the timing of NIBS protocols, seven tDCS studies used off-stimulation (i.e., tDCS before dual tasks) and two studies administered on-stimulation (i.e., tDCS during dual tasks) and off-stimulation, respectively. Two rTMS studies applied off-stimulation. Specifically, six out of the studies that used off-stimulation provided additional training while administering NIBS protocols: (1) writing figure-8 (2), physical therapy from one study (3), treadmill walking from one study (4), stationary bicycle and golf video game from one study, and (5) dual-task walking from two studies. In Table 2, we describe the specific parameters of NIBS techniques.

Motor and cognitive performances during dual tasks

Nine out of 11 included studies tested following motor performance during dual tasks: (1) gait (e.g., speed and cadence) from four studies (2), TUG from four studies, and (3) time to turn from one study. The remaining one study assessed both gait and TUG, and the other study evaluated writing amplitude. Moreover, three out of four studies estimated following cognitive performance during dual tasks: (1) the number of correct generating words from two studies and (2) the number of correct counting from one study. The remaining one study assessed both the number of correct generating words and counting. Table 3 shows the specific motor and cognitive performances during dual tasks.

Methodological quality assessment results

The Cochrane risk of bias assessment for the 11 qualified studies showed a relatively low risk of methodological biases across three domains: (1) timing of identification or recruitment of participants (2), missing outcome data, and (3) selection of the reported result. However, a relatively moderate risk of methodological biases was confirmed in following three domains: (1) randomization process (2), deviation from intended interventions, and (3) measurements of the outcome. Specifically, four studies failed to mention a specific randomization process and did not report information about the blinding of people who implemented the interventions or assessed performances. The methodological quality assessment for the included studies are described in Fig. 2.

Meta-analytic findings

NIBS effects on motor performances during dual tasks in PD

A random-effects model meta-analysis confirmed that NIBS significantly improved motor performances during dual tasks on 73 comparisons from 11 studies (Fig. 3): $SMD = 0.163$; $SE = 0.055$; 95% CI = 0.056–0.271; $Z = 2.975$; $P = 0.003$. Heterogeneity tests indicated that overall variability of individual effect sizes was relatively moderate ($I^2 = 33.7\%$). Publication bias assessment indicated relatively symmetrical distribution of individual effect size (Egger's $\beta_0 = -0.402$ with $P = 0.395$). These findings indicated that NIBS protocols may slightly improve motor performances during dual tasks with small heterogeneity.

Moreover, a moderator variables analysis showed that NIBS on the DLPFC significantly improved motor performances during dual tasks on 33 comparisons from six studies (Fig. 4): $SMD = 0.298$; $SE = 0.069$; 95% CI = 0.163–0.433; $Z = 4.317$; $P < 0.001$; $I^2 = 35.5\%$; Egger's $\beta_0 = 2.048$ with $P = 0.003$. Importantly, the six studies that reported overall positive effects used tDCS protocols. However, NIBS on the M1 failed to report significant effects on motor performances during dual tasks on 32 comparisons from five studies (Additional file 1): $SMD = -0.014$; $SE = 0.094$; 95% CI = −0.199–0.171; $Z = -0.145$; $P = 0.885$; $I^2 = 27.8\%$; Egger's $\beta_0 = -5.525$ with $P < 0.001$. These findings suggested that tDCS protocols targeted the DLPFC may

Table 1 Participants characteristics

Study	Study Design	Total (*N*)	Age (yrs)	Gender	Disease Duration (yrs)	LEDD (mg)	Motor Function		Cognitive Function	
							H&Y	UPDRS-3	MMSE	MoCA
Broeder 2023	Parallel	Trt: 20	62.9 ± 8.3	3 F, 17 M	3.5 (2.8, 8.0)	588.4 ± 379.0	2.0 (2.0, 3.0)	23.4 ± 12.1	NA	28.0 (25.3, 29.0)
		Con: 19	63.5 ± 8.5	5 F, 14 M	6.0 (4.0, 9.0)	748.8 ± 381.8	2.0 (2.0, 3.0)	29.1 ± 12.1		28.0 (25.0, 29.0)
Bueno 2023	Parallel	Trt 1: 12	63.9 ± 11.9	5 F, 7 M	5.1 ± 4.1	786.6 ± 707.1	2.2 ± 0.7	36.7 ± 14.7	25.5 ± 3.9	NA
		Trt 2: 12	60.8 ± 10.6	3 F, 9 M	5.2 ± 4.1	654.2 ± 350.3	2.0 ± 0.3	29.5 ± 18.6	28.3 ± 2.0	
		Con: 13	69.6 ± 6.2	5 F, 8 M	6.5 ± 5.3	651.2 ± 460.6	1.9 ± 0.3	28.5 ± 15.7	27.2 ± 2.5	
Chung 2020	Parallel	Trt 1: 17	62.1 ± 5.7	8 F, 9 M	7.5 ± 4.9	512.5 ± 359.9	2.2 ± 0.4	27.1 ± 9.6	NA	NA
		Trt 2: 17	62.7 ± 6.8	7 F, 10 M	5.2 ± 3.4	484.2 ± 336.4	2.2 ± 0.3	27.9 ± 10.5		
		Con: 16	62.1 ± 5.7	9 F, 7 M	6.9 ± 3.3	493.3 ± 523.9	2.3 ± 0.3	29.7 ± 10.6		
Criminger 2018	Crossover	Total: 16	68.1 ± 9.8	4 F, 12 M	8.7 ± 9.8	'ON' state	NA	23.4 ± 9.7	NA	NA
Lench 2021	Parallel	Trt: 12	66.6 ± 7.5	5 F, 7 M	8.7 ± 7.1	1074.4 ± 493.9	2.3 ± 0.4	16.8 ± 4.1	29.1 ± 1.2	NA
		Con: 8	64.5 ± 8.9	1 F, 7 M	8.0 ± 5.6	1304.4 ± 757.3	2.3 ± 0.3	15.8 ± 6.0	28.4 ± 1.7	
Mishra 2021	Crossover	Total: 20	67.8 ± 8.3	6 F, 14 M	4.8 ± 3.8	'ON' state	1.9 ± 0.9	NA	NA	26.1 ± 2.2
Mishra 2022	Crossover	Total: 20	67.8 ± 8.3	6 F, 14 M	4.8 ± 3.8	'ON' state	1.9 ± 0.9	NA	NA	26.1 ± 2.2
Putzolu 2018	Crossover	FOG: 10	70.1 ± 3.8	4 F, 6 M	9.3 ± 5.5	'ON' state	NA	20.1 ± 8.4	29.0 ± 1.9	NA
		Non-FOG: 10	72.8 ± 6.9	5 F, 5 M	7.2 ± 5.2		NA	22.9 ± 8.1	29.1 ± 0.9	
Schabrun 2016	Parallel	Trt: 8	72.0 ± 4.9	0 F, 8 M	6.9 ± 4.4	730.0 ± 341.0	NA	47.7 ± 7.5	29.0 ± 0.8	NA
		Con: 8	63.0 ± 11.0	2 F, 6 M	4.6 ± 3.9	523.0 ± 398.0	NA	37.7 ± 9.8	29.7 ± 0.5	
Swank 2016	Crossover	Total: 10	68.7 ± 10.2	2 F, 8 M	7.9 ± 7.1	'ON' state	NA	37.0 ± 12.9	NA	NA
Wong 2022	Parallel	Trt 1: 9	54.2 ± 4.1	1 F, 8 M	7.8 ± 5.7	592.1 ± 208.2	1.9 ± 0.6	33.2 ± 13.1	28.1 ± 1.8	NA
		Trt 2: 9	50.1 ± 2.4	3 F, 6 M	6.2 ± 3.3	603.9 ± 357.3	1.7 ± 0.5	25.6 ± 17.0	28.9 ± 1.8	
		Trt 3: 9	61.3 ± 7.9	7 F, 2 M	4.1 ± 3.3	468.2 ± 212.1	2.1 ± 0.6	24.2 ± 9.9	27.3 ± 2.2	
		Con: 9	58.3 ± 8.0	6 F, 3 M	8.3 ± 12.3	426.1 ± 243.7	1.8 ± 0.7	23.4 ± 14.7	28.9 ± 2	

Data is mean ± standard deviations or median (1st quartile, 3rd quartile)

Abbreviation. LEDD = levodopa equivalent daily dose; H&Y = Hoehn and Yahr scale; UPDRS-3 = unified Parkinson's disease rating scale; MMSE = mini-mental state examination; MoCA = Montreal cognitive assessment; Trt = treatment; Con = control; FOG = freezing of gait; F = female; M = male

produce slight enhancements in motor performances during dual tasks with small heterogeneity.

NIBS effects on cognitive performances during dual tasks in PD

A random-effects model meta-analysis found that NIBS significantly enhanced cognitive performances during dual tasks on 12 comparisons from four studies (Fig. 5): $SMD = 0.375$; $SE = 0.110$; 95% CI = 0.161–0.590; Z = 3.427; $P = 0.001$. Importantly, the four studies that reported overall positive effects used tDCS protocols. Heterogeneity tests showed that overall variability of individual effect sizes was relatively moderate ($I^2 = 36.3\%$). Publication bias assessment showed a no significant publication bias across individual effect sizes (Egger's $\beta_0 = 2.047$ with $P = 0.070$). These findings implied that tDCS protocols may moderately improve cognitive performances during dual tasks with small heterogeneity.

Moreover, moderator variables analysis reported that NIBS on the DLPFC significantly improved cognitive performances during dual tasks on eight comparisons from three studies (Fig. 6): $SMD = 0.283$; $SE = 0.099$; 95% CI = 0.089–0.478; Z = 2.860; $P = 0.004$; $I^2 = 20.9\%$; Egger's $\beta_0 = -0.061$ with $P = 0.985$. Importantly, the three studies that reported overall positive effects used tDCS protocols. These findings showed tDCS protocols on the DLPFC may lead to small enhancements in cognitive performances during dual tasks with minimal heterogeneity.

Meta-regression analyses

The random-effects meta-regression analyses revealed that greater improvements in motor performances during dual tasks after NIBS were significantly associated with decreased age ($Y = 1.61 - 0.02X$; $P = 0.004$; Fig. 7A) and increased proportion of females in total patients with PD ($Y = 0.00 + 0.58X$; $P = 0.026$; Fig. 7B), respectively. However, the amount of duration since PD diagnosis was not significantly associated with improvements in motor performances during dual tasks after NIBS ($Y = 0.10 + 0.01X$; $P = 0.727$). The meta-regression analyses found no significant relationships between improvements in cognitive performances during dual tasks after NIBS and following demographic characteristics: (1) age ($Y = -9.13 + 0.14X$; $P = 0.052$) (2), proportion of females in total patients with PD ($Y = 0.80 - 1.77X$; $P = 0.075$), and (3) duration since PD diagnosis ($Y = 0.17 + 0.04X$; $P = 0.686$).

Discussion

This meta-analysis investigated effects of NIBS techniques including tDCS and rTMS on motor and cognitive performances during dual tasks in patients with PD. The findings revealed that NIBS protocols significantly enhanced motor and cognitive performances during dual tasks. Specifically, these improvements were observed when tDCS stimulated the DLPFC regions. Moreover, the meta-regression analyses revealed that greater improvements in motor performances during dual tasks after NIBS protocols were significantly associated with decreased age and increased proportion of females in patients with PD, respectively.

The meta-analytic findings demonstrated that tDCS protocols increasing DLPFC excitability improved motor performances during dual tasks in patients with PD. Successful walking in well-functioning people is typically based on the automaticity allowing the motor system to quickly and efficiently coordinate movements with minimal cognitive involvement [54]. However, individuals with impaired automaticity such as older adults and patients with stroke may require more cognitive resources (e.g., executive control involving conscious processing of information for organizing, managing, and controlling movements) for executing gait performances [55, 56]. Several studies reported impaired automaticity during gait performances in patients with PD due to dopamine depletion in the posterior putamen, a sensorimotor region of the striatum that potentially acquires, stores, and facilitates automated motor skills [18, 57–59]. However, patients with PD who exhibited greater DLPFC excitability showed no significant impairments in normal gait performances as compared with those for age-matched controls [20]. Given that the DLPFC is important for executive functions [60], these findings indicated that patients with PD may be dependent on executive control processing during normal locomotion to compensate for their impaired automaticity [61–63]. Importantly, dual tasks such as walking with subtraction or generating words normally increase cognitive workload [64]. Perhaps, dual tasks for patients with PD may attenuate executive resources being applied to compensate for impaired automaticity consequently interfering with gait performances [20]. A recent meta-analysis demonstrated that anodal tDCS on the DLPFC reduced dual-task cost on gait speed in older adults, suggesting that increasing DLPFC excitability may improve executive control associated with gait [24]. Taken together, brain stimulation for facilitating DLPFC excitability may contribute to locomotion improvements during dual tasks in patients with PD by maintaining neural resource levels for executive control processing on gait.

In addition to improved motor performance, applying tDCS protocols targeting the DLPFC facilitated cognitive improvements during dual tasks in patients

Table 2 Specific parameters of NIBS protocols

Study	Group	NIBS	Stimulation Site	Intensity	Session	Timing	Duration	Surface	Additional Training
Broeder 2023	Trt	tDCS	M1	1 mA	1	Off	20 min	35 cm^2	Writing figure-8
Bueno 2023	Trt 1	tDCS	$M1_{Cz}$	2 mA	1	Off	20 min	NA	Physical therapy
	Trt 2		$M1_{C3-Cz-C4}$						
Chung 2020	Trt 1	rTMS	M1	1 Hz, 80% of RMT	12	Off	600 pulses	NA	Treadmill walking
	Trt 2			25 Hz, 80% of RMT					
Criminger 2018	Trt 1	tDCS	DLPFC	2 mA	1	Off	20 min	15 cm^2	Resting
	Trt 2								Stationary bicycle
	Trt 3								Golf video game
Lench 2021	Trt	rTMS	SMA	1 Hz, 110% of RMT	10	Off	1200 pulses	NA	Dual-task walking
Mishra 2021	Trt	tDCS	DLPFC	2 mA	1	On	30 min	35 cm^2	Resting
						Off			
Mishra 2022	Trt	tDCS	DLPFC	2 mA	1	On	30 min	35 cm^2	Resting
						Off			
Putzolu 2018	Trt	tDCS	DLPFC	1.5 mA	1	Off	20 min	25 cm^2	Resting
Schabrun 2016	Trt	tDCS	M1	2 mA	9	Off	20 min	35 cm^2	Dual-task walking
Swank 2016	Trt	tDCS	DLPFC	2 mA	1	Off	20 min	NA	Resting
Wong 2022	Trt 1	tDCS	DLPFC	2 mA	1	Off	20 min	35 cm^2	Resting
	Trt 2		M1						
	Trt 3		Cerebellum						

Abbreviation. NIBS = non-invasive brain stimulation; tDCS = transcranial direct current stimulation; rTMS = repetitive transcranial magnetic stimulation; Trt = treatment; M1 = primary motor cortex; DLPFC = dorsolateral prefrontal cortex; SMA = supplementary motor area; RMT = resting motor threshold; min = minute

Table 3 Specific motor and cognitive performances during dual tasks

Study	Motor Performance	Cognitive Performance	Dual Task
Broeder 2023	DTC-writing amplitude	NA	Writing figure-8 patterns while counting low and high tones
Bueno 2023	Speed, Cadence, Step length, Step width	NA	Walking while counting backwards by three
Chung 2020	TUG	NA	TUG test while counting backwards by three
Criminger 2018	TUG	NA	TUG test while carrying a full cup of water TUG test while counting backwards by three
Lench 2021	Time to turn	NA	TUG test while counting backwards by seven
Mishra 2021	Speed, DTC-speed	Number of correct generated words, DTC-number of correct generated words	Walking while generating words starting from a given alphabet
Mishra 2022	TUG, DTC-TUG	Number of correct generated words	TUG test while generating words starting from a given alphabet
Putzolu 2018	DTC-speed, DTC-step length, DTC-double support time, DTC-stance time	NA	Walking while counting backwards by seven
Schabrun 2016	Speed, Cadence, Stride length, Double support time, TUG	Number of correct generated words, Number of correct backward counts	Walking while counting backwards by three Walking while generating words starting from a particular letter Walking while conversation TUG test while counting backwards by three TUG test while generating words starting from a particular letter
Swank 2016	TUG, DTC-TUG	Number of correct backward counts, DTC-number of correct backward counts	TUG test while carrying a full cup of water TUG test while counting backwards by three
Wong 2022	Speed, Cadence, Stride length, Stride time, Stride length variability, Stride time variability, DTC-speed	NA	Walking while counting backwards by three

Abbreviation. TUG = timed up and go; DTC = dual-task cost

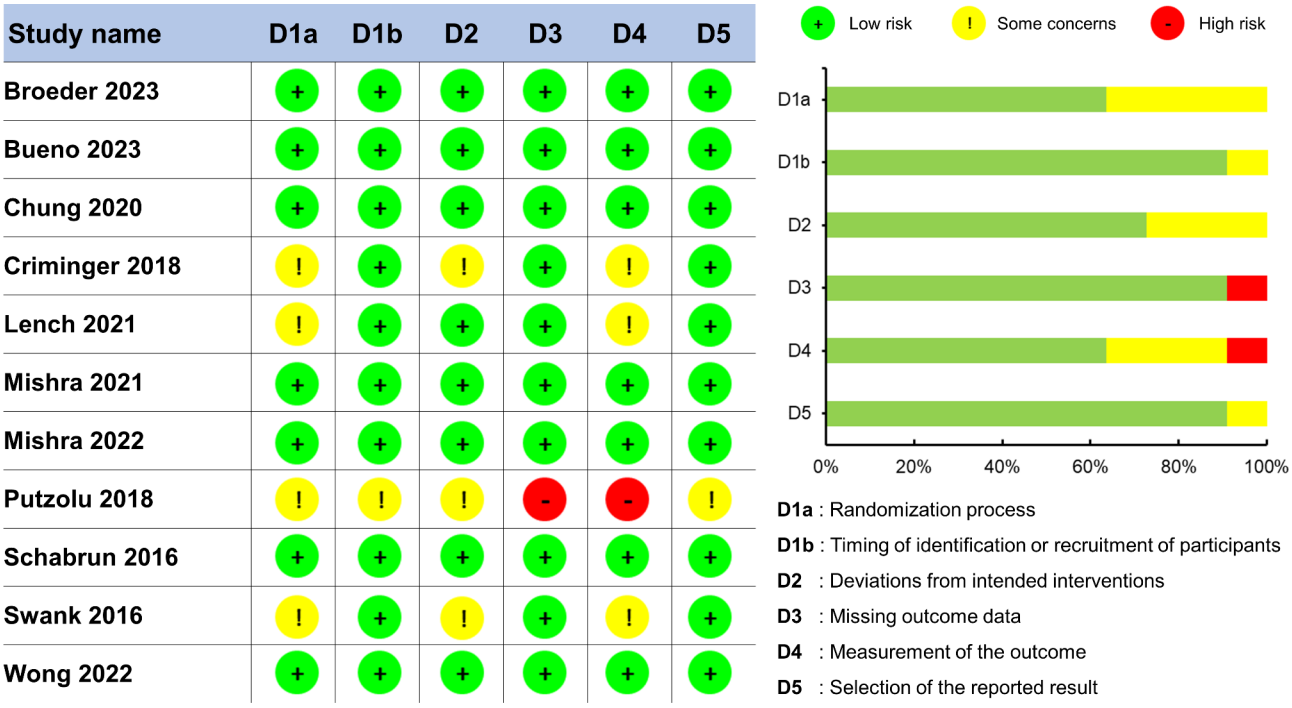
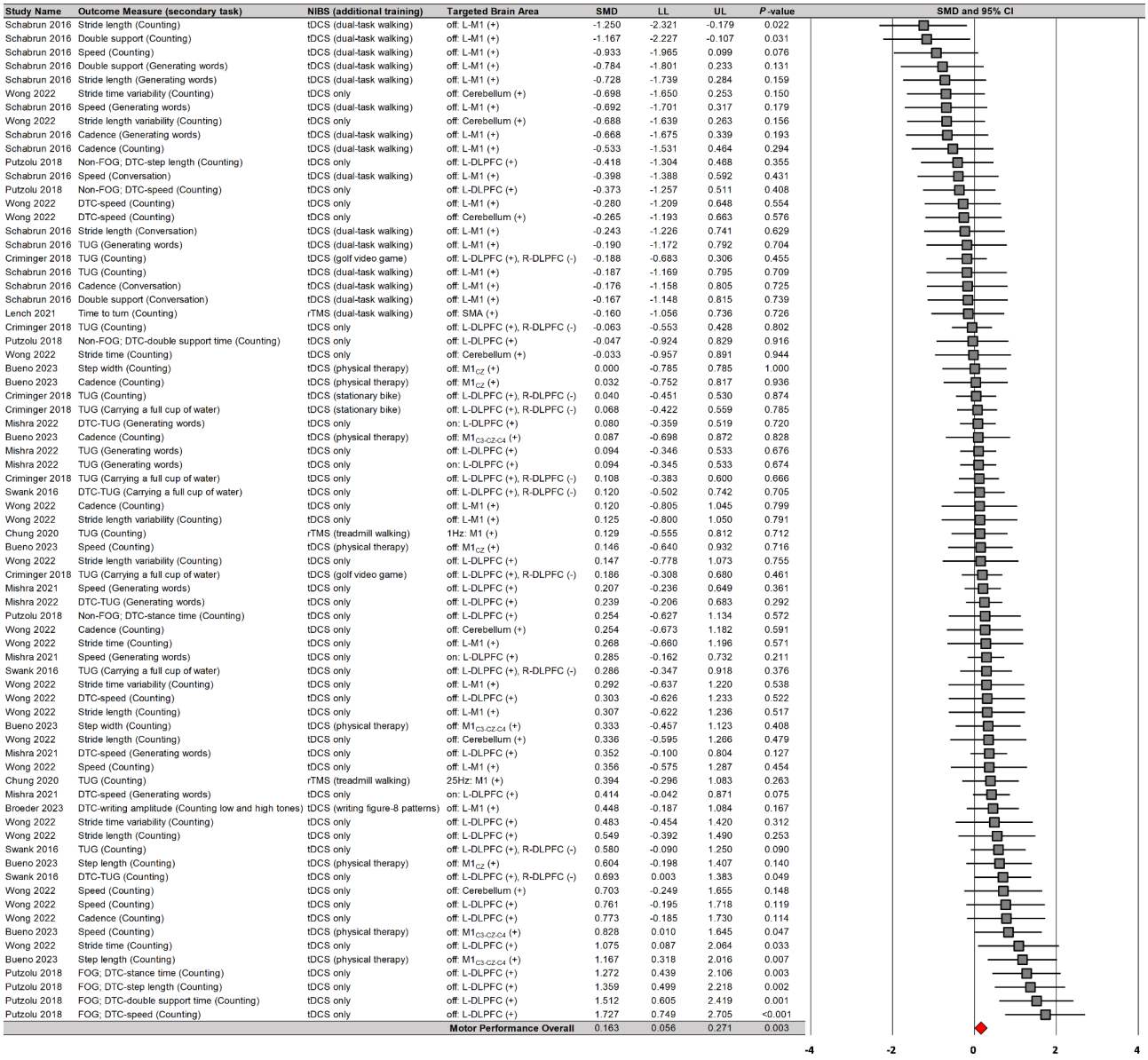


Fig. 2 Methodological quality assessment using Cochrane risk-of-bias tool



Study Name	Outcome Measure (secondary task)	NIBS (additional training)	Targeted Brain Area	SMD	LL	UL	*P*-value
Schabrun 2016	Stride length (Counting)	tDCS (dual-task walking)	off: L-M1 (+)	-1.250	-2.321	-0.179	0.022
Schabrun 2016	Double support (Counting)	tDCS (dual-task walking)	off: L-M1 (+)	-1.167	-2.227	-0.107	0.031
Schabrun 2016	Speed (Counting)	tDCS (dual-task walking)	off: L-M1 (+)	-0.933	-1.965	0.099	0.076
Schabrun 2016	Double support (Generating words)	tDCS (dual-task walking)	off: L-M1 (+)	-0.784	-1.801	0.233	0.131
Schabrun 2016	Stride length (Generating words)	tDCS (dual-task walking)	off: L-M1 (+)	-0.728	-1.739	0.284	0.159
Wong 2022	Stride time variability (Counting)	tDCS only	off: Cerebellum (+)	-0.698	-1.650	0.253	0.150
Schabrun 2016	Speed (Generating words)	tDCS (dual-task walking)	off: L-M1 (+)	-0.692	-1.701	0.317	0.179
Wong 2022	Stride length variability (Counting)	tDCS only	off: Cerebellum (+)	-0.688	-1.639	0.263	0.156
Schabrun 2016	Cadence (Generating words)	tDCS (dual-task walking)	off: L-M1 (+)	-0.668	-1.675	0.339	0.193
Schabrun 2016	Cadence (Counting)	tDCS (dual-task walking)	off: L-M1 (+)	-0.533	-1.531	0.464	0.294
Putzolu 2018	Non-FOG; DTC-step length (Counting)	tDCS only	off: L-DLPFC (+)	-0.418	-1.304	0.468	0.355
Schabrun 2016	Speed (Conversation)	tDCS (dual-task walking)	off: L-M1 (+)	-0.398	-1.388	0.592	0.431
Putzolu 2018	Non-FOG; DTC-speed (Counting)	tDCS only	off: L-DLPFC (+)	-0.373	-1.257	0.511	0.408
Wong 2022	DTC-speed (Counting)	tDCS only	off: L-M1 (+)	-0.280	-1.209	0.648	0.554
Wong 2022	DTC-speed (Counting)	tDCS only	off: Cerebellum (+)	-0.265	-1.193	0.663	0.576
Schabrun 2016	Stride length (Conversation)	tDCS (dual-task walking)	off: L-M1 (+)	-0.243	-1.226	0.741	0.629
Schabrun 2016	TUG (Generating words)	tDCS (dual-task walking)	off: L-M1 (+)	-0.190	-1.172	0.792	0.704
Criminger 2018	TUG (Counting)	tDCS (golf video game)	off: L-DLPFC (+), R-DLPFC (-)	-0.188	-0.683	0.306	0.455
Schabrun 2016	TUG (Counting)	tDCS (dual-task walking)	off: L-M1 (+)	-0.187	-1.169	0.795	0.709
Schabrun 2016	Cadence (Conversation)	tDCS (dual-task walking)	off: L-M1 (+)	-0.176	-1.158	0.805	0.725
Schabrun 2016	Double support (Conversation)	tDCS (dual-task walking)	off: L-M1 (+)	-0.167	-1.148	0.815	0.739
Lench 2021	Time to turn (Counting)	rTMS (dual-task walking)	off: SMA (+)	-0.160	-1.056	0.736	0.726
Criminger 2018	TUG (Counting)	tDCS only	off: L-DLPFC (+), R-DLPFC (-)	-0.063	-0.553	0.428	0.802
Putzolu 2018	Non-FOG; DTC-double support time (Counting)	tDCS only	off: L-DLPFC (+)	-0.047	-0.924	0.829	0.916
Wong 2022	Stride time (Counting)	tDCS only	off: Cerebellum (+)	-0.033	-0.957	0.891	0.944
Bueno 2023	Step width (Counting)	tDCS (physical therapy)	off: $M1_{CZ}$ (+)	0.000	-0.785	0.785	1.000
Bueno 2023	Cadence (Counting)	tDCS (physical therapy)	off: $M1_{CZ}$ (+)	0.032	-0.752	0.817	0.936
Criminger 2018	TUG (Counting)	tDCS (stationary bike)	off: L-DLPFC (+), R-DLPFC (-)	0.040	-0.451	0.530	0.874
Criminger 2018	TUG (Carrying a full cup of water)	tDCS (stationary bike)	off: L-DLPFC (+), R-DLPFC (-)	0.068	-0.422	0.559	0.785
Mishra 2022	DTC-TUG (Generating words)	tDCS only	on: L-DLPFC (+)	0.080	-0.359	0.519	0.720
Bueno 2023	Cadence (Counting)	tDCS (physical therapy)	off: $M1_{C3\text{-}CZ\text{-}C4}$ (+)	0.087	-0.698	0.872	0.828
Mishra 2022	TUG (Generating words)	tDCS only	off: L-DLPFC (+)	0.094	-0.346	0.533	0.676
Mishra 2022	TUG (Generating words)	tDCS only	on: L-DLPFC (+)	0.094	-0.345	0.533	0.674
Criminger 2018	TUG (Carrying a full cup of water)	tDCS only	off: L-DLPFC (+), R-DLPFC (-)	0.108	-0.383	0.600	0.666
Swank 2016	DTC-TUG (Carrying a full cup of water)	tDCS only	off: L-DLPFC (+), R-DLPFC (-)	0.120	-0.502	0.742	0.705
Wong 2022	Cadence (Counting)	tDCS only	off: L-M1 (+)	0.120	-0.805	1.045	0.799
Wong 2022	Stride length variability (Counting)	tDCS only	off: L-M1 (+)	0.125	-0.800	1.050	0.791
Chung 2020	TUG (Counting)	rTMS (treadmill walking)	1Hz: M1 (+)	0.129	-0.555	0.812	0.712
Bueno 2023	Speed (Counting)	tDCS (physical therapy)	off: $M1_{CZ}$ (+)	0.146	-0.640	0.932	0.716
Wong 2022	Stride length variability (Counting)	tDCS only	off: L-DLPFC (+)	0.147	-0.778	1.073	0.755
Criminger 2018	TUG (Carrying a full cup of water)	tDCS (golf video game)	off: L-DLPFC (+), R-DLPFC (-)	0.186	-0.308	0.680	0.461
Mishra 2021	Speed (Generating words)	tDCS only	off: L-DLPFC (+)	0.207	-0.236	0.649	0.361
Mishra 2022	DTC-TUG (Generating words)	tDCS only	off: L-DLPFC (+)	0.239	-0.206	0.683	0.292
Putzolu 2018	Non-FOG; DTC-stance time (Counting)	tDCS only	off: L-DLPFC (+)	0.254	-0.627	1.134	0.572
Wong 2022	Cadence (Counting)	tDCS only	off: Cerebellum (+)	0.254	-0.673	1.182	0.591
Wong 2022	Stride time (Counting)	tDCS only	off: L-M1 (+)	0.268	-0.660	1.196	0.571
Mishra 2021	Speed (Generating words)	tDCS only	on: L-DLPFC (+)	0.285	-0.162	0.732	0.211
Swank 2016	TUG (Carrying a full cup of water)	tDCS only	off: L-DLPFC (+), R-DLPFC (-)	0.286	-0.347	0.918	0.376
Wong 2022	Stride time variability (Counting)	tDCS only	off: L-M1 (+)	0.292	-0.637	1.220	0.538
Wong 2022	DTC-speed (Counting)	tDCS only	off: L-DLPFC (+)	0.303	-0.626	1.233	0.522
Wong 2022	Stride length (Counting)	tDCS only	off: L-M1 (+)	0.307	-0.622	1.236	0.517
Bueno 2023	Step width (Counting)	tDCS (physical therapy)	off: $M1_{C3\text{-}CZ\text{-}C4}$ (+)	0.333	-0.457	1.123	0.408
Wong 2022	Stride length (Counting)	tDCS only	off: Cerebellum (+)	0.336	-0.595	1.266	0.479
Mishra 2021	DTC-speed (Generating words)	tDCS only	off: L-DLPFC (+)	0.352	-0.100	0.804	0.127
Wong 2022	Speed (Counting)	tDCS only	off: L-M1 (+)	0.356	-0.575	1.287	0.454
Chung 2020	TUG (Counting)	rTMS (treadmill walking)	25Hz: M1 (+)	0.394	-0.296	1.083	0.263
Mishra 2021	DTC-speed (Generating words)	tDCS only	on: L-DLPFC (+)	0.414	-0.042	0.871	0.075
Broeder 2023	DTC-writing amplitude (Counting low and high tones)	tDCS (writing figure-8 patterns)	off: L-M1 (+)	0.448	-0.187	1.084	0.167
Wong 2022	Stride time variability (Counting)	tDCS only	off: L-DLPFC (+)	0.483	-0.454	1.420	0.312
Wong 2022	Stride length (Counting)	tDCS only	off: L-DLPFC (+)	0.549	-0.392	1.490	0.253
Swank 2016	TUG (Counting)	tDCS only	off: L-DLPFC (+), R-DLPFC (-)	0.580	-0.090	1.250	0.090
Bueno 2023	Step length (Counting)	tDCS (physical therapy)	off: $M1_{CZ}$ (+)	0.604	-0.198	1.407	0.140
Swank 2016	DTC-TUG (Counting)	tDCS only	off: L-DLPFC (+), R-DLPFC (-)	0.693	0.003	1.383	0.049
Wong 2022	Speed (Counting)	tDCS only	off: Cerebellum (+)	0.703	-0.249	1.655	0.148
Wong 2022	Speed (Counting)	tDCS only	off: L-DLPFC (+)	0.761	-0.195	1.718	0.119
Wong 2022	Cadence (Counting)	tDCS only	off: L-DLPFC (+)	0.773	-0.185	1.730	0.114
Bueno 2023	Speed (Counting)	tDCS (physical therapy)	off: $M1_{C3\text{-}CZ\text{-}C4}$ (+)	0.828	0.010	1.645	0.047
Wong 2022	Stride time (Counting)	tDCS only	off: L-DLPFC (+)	1.075	0.087	2.064	0.033
Bueno 2023	Step length (Counting)	tDCS (physical therapy)	off: $M1_{C3\text{-}CZ\text{-}C4}$ (+)	1.167	0.318	2.016	0.007
Putzolu 2018	FOG; DTC-stance time (Counting)	tDCS only	off: L-DLPFC (+)	1.272	0.439	2.106	0.003
Putzolu 2018	FOG; DTC-step length (Counting)	tDCS only	off: L-DLPFC (+)	1.359	0.499	2.218	0.002
Putzolu 2018	FOG; DTC-double support time (Counting)	tDCS only	off: L-DLPFC (+)	1.512	0.605	2.419	0.001
Putzolu 2018	FOG; DTC-speed (Counting)	tDCS only	off: L-DLPFC (+)	1.727	0.749	2.705	<0.001
			Motor Performance Overall	0.163	0.056	0.271	0.003

Fig. 3 NIBS effects on motor performances during dual tasks. NIBS = non-invasive brain stimulation; tDCS = transcranial direct current stimulation; rTMS = repetitive transcranial magnetic stimulation; DLPFC = dorsolateral prefrontal cortex; M1 = primary motor cortex; SMA = supplementary motor area; L = left; R = right; DTC = dual-task cost; FOG = freezing of gait; TUG = timed up and go

with PD. These findings indicate that increasing DLPFC excitability may enhance dual-task performance including both motor and cognitive tasks. Beneficial effects of NIBS protocols that targeted the DLPFC on dual-task performances appeared in healthy young adults and patients with stroke [65, 66]. DLPFC regions are typically associated with executive functions including shifting and inhibitory control [67, 68]. Furthermore, executive functions may be related to the ability to successfully perform dual tasks [69]. For example, better shifting may decrease task-switch costs and inhibitory control may suppress inappropriate responses consequently contributing to efficient allocation of attention during dual tasks [70]. Importantly, patients with PD often showed impaired executive functions because deficits in the striatal dopamine interfere with normal transmission of information through the frontostriatal circuits leading to dorsolateral frontal-lobe dysfunction [71, 72]. Thus, excitatory stimulation on the DLPFC may improve executive functions of patients with PD by increasing dopamine levels [73–77] via the meso-cortico-limbic pathway and local effects on the nigrostriatal pathway [78–80]. In fact, patients with PD revealed lower functional connectivity patterns across cortico-subcortical areas including DLPFC, caudate, and motor networks [81,

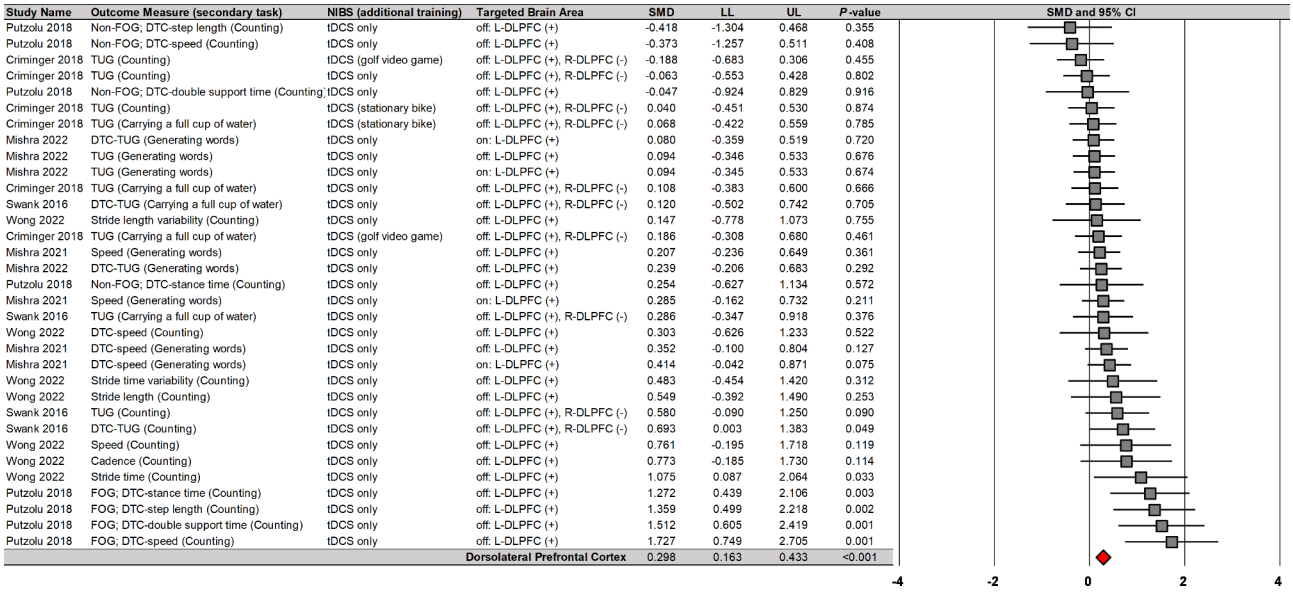


Fig. 4 NIBS effects on motor performances during dual tasks based on stimulation site. NIBS = non-invasive brain stimulation; tDCS = transcranial direct current stimulation; DLPFC = dorsolateral prefrontal cortex; L = left; R = right; DTC = dual-task cost; FOG = freezing of gait; TUG = timed up and go

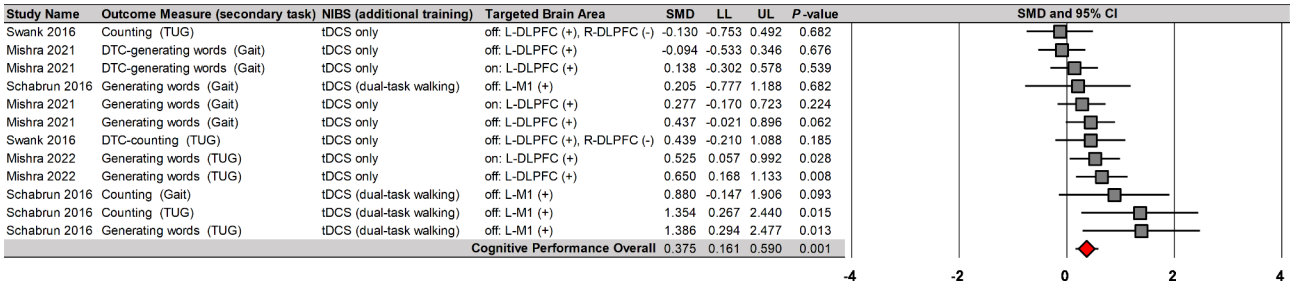


Fig. 5 NIBS effects on cognitive performances during dual tasks. NIBS = non-invasive brain stimulation; tDCS = transcranial direct current stimulation; DLPFC = dorsolateral prefrontal cortex; M1 = primary motor cortex; L = left; R = right; DTC = dual-task cost; TUG = timed up and go

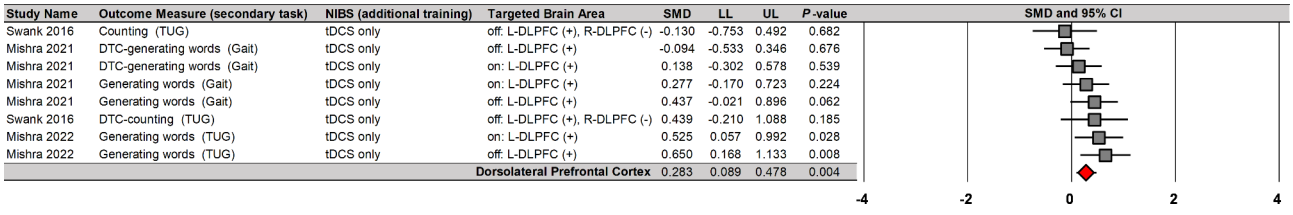


Fig. 6 NIBS effects on cognitive performances during dual tasks based on stimulation site
NIBS = non-invasive brain stimulation; tDCS = transcranial direct current stimulation; DLPFC = dorsolateral prefrontal cortex; L = left; R = right; DTC = dual-task cost; TUG = timed up and go

82], whereas NIBS protocols upregulating DLPFC patterns increased functional connectivity across these areas [83, 84]. Taken together, given that patients with PD typically revealed both gait impairments as well as mild cognitive deficits [85, 86], applying NIBS for increasing DLPFC excitability may facilitate improvements in dual-task performances contributing to independent daily living.

Meta-regression analyses revealed that effects of NIBS on motor performances during dual tasks increased with lower age and greater proportion of females for patients with PD. Previous pharmacological studies argued that neuroplasticity facilitated by NIBS protocols may be related to the glutamatergic system [87–91]. Glutamate is the primary excitatory neurotransmitter allowing influx of Ca^{2+} associated with neuroplasticity via increased sensitivity of the synapse [92–94]. Given that aging normally decreases glutamatergic receptors and glutamate concentration in brain areas such as the frontal, parietal, and

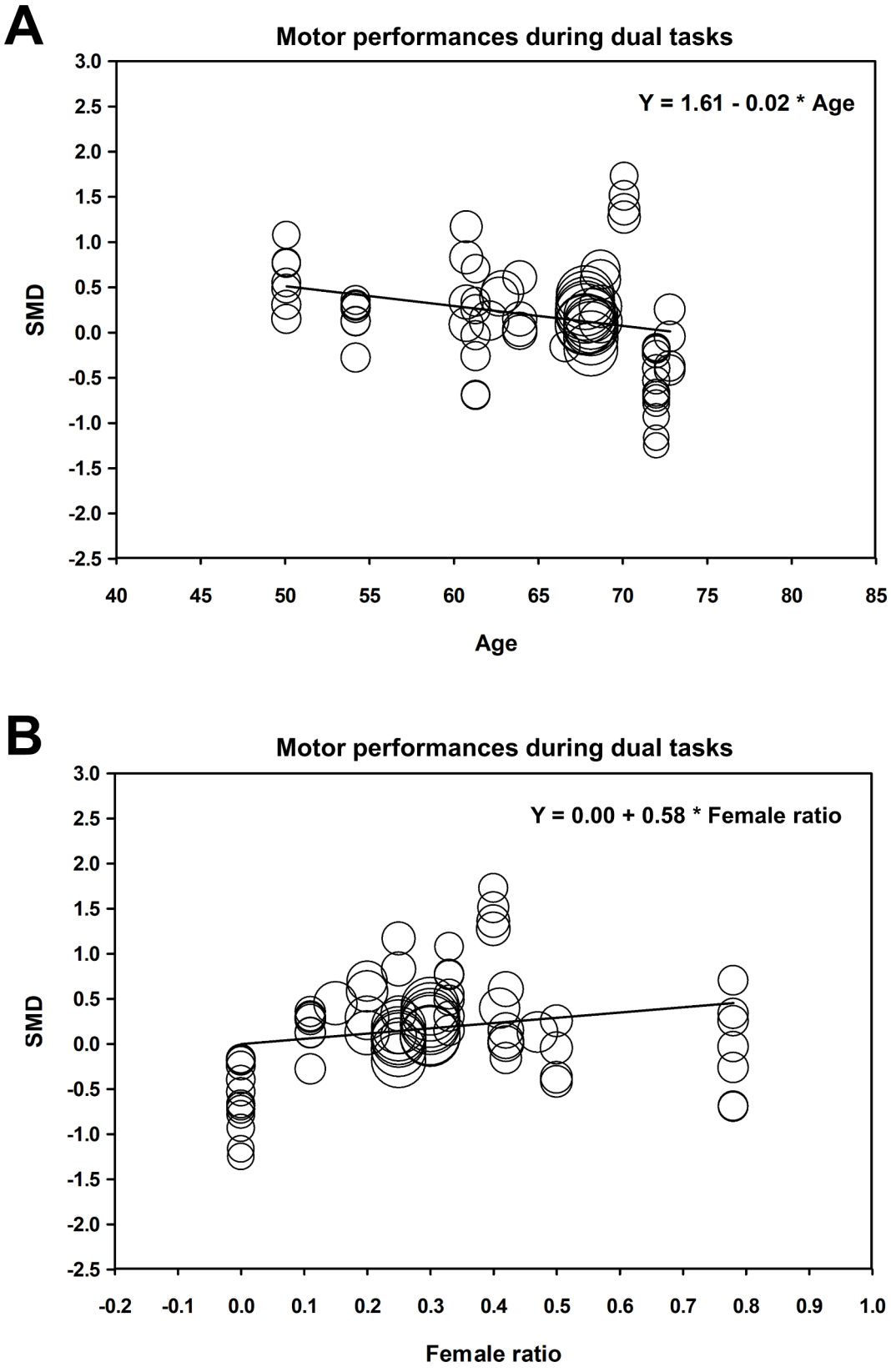


Fig. 7 NIBS effects on motor performances during dual tasks versus age (**A**) and female ratio (**B**). SMD = standardized mean difference

temporal cortical regions [95, 96], positive effects of NIBS may be greater for younger patients with PD because of better brain neuroplasticity [97–100]. Moreover, estrogen may protect dopaminergic neurons that presumably induce relatively lower symptom severity in women with PD than men [101–104]. Given that patients with PD who had lower symptom severity showed more neuroplasticity patterns facilitated by brain stimulation [105], women with PD may receive greater therapeutic effects of NIBS protocols due to the neuroprotective effects of estrogen.

Although the current meta-analysis revealed potential effects of NIBS on dual-task performance in patients with PD, these findings should be cautiously interpreted. First, significant positive effects on both motor and cognitive performances during dual tasks were only observed in tDCS studies that targeting the DLPFC, and we found no rTMS studies. Given that potential neurophysiological changes may differ between tDCS and rTMS protocols [106, 107], our findings are still limited to tDCS effects. Thus, additional studies should determine whether rTMS protocols on the DLPFC improve dual-task performances in patients with PD. Importantly, improved cognitive performances during dual tasks after NIBS protocol are still tentative because of prior suggestion that at least five studies may be required for increasing validity of data synthesis [108]. Given that small number of studies may influence reliability of the results, more studies are necessary to determine positive effects of NIBS on cognitive function during dual tasks. In addition, seven out of 10 total studies focused on transient effects of NIBS by providing a single session of stimulation. Given that multiple sessions of NIBS protocols may result in cumulative effects [109, 110], additional studies should investigate long-term effects of NIBS on dual-task performances in patients with PD by administering more sessions of stimulation. Finally, neurophysiological mechanisms underlying NIBS effects on dual-task performance in patients with PD are still inconclusive. Future studies using neuroimaging techniques should investigate how brain activation patterns are changed during and after different NIBS protocols for improving dual-task performance in patients with PD.

Conclusion

This systematic review and meta-analysis found positive effects of NIBS on dual-task performances in patients with PD. Specifically, applying tDCS on the DLPFC effectively improved motor and cognitive performances during dual tasks. Furthermore, the meta-regression analysis identified a significant relationship between greater improvements in motor performance during dual tasks after NIBS and younger age as well as a higher proportion of females in patients with PD. These findings suggest that NIBS protocols increasing DLPFC excitability may be a viable option for improving dual-task performance in patients with PD.

Abbreviations

PD	Parkinson's disease
NIBS	Non-invasive brain stimulation
tDCS	Transcranial direct current stimulation
rTMS	Repetitive transcranial magnetic stimulation
DLPFC	Dorsolateral prefrontal cortex
SMA	Supplementary motor area
M1	Primary motor cortex
TUG	Timed up and go
PRISMA	Preferred reporting items for systematic reviews and meta-analysis
RCT	Randomized control trials
SMD	Standardized mean difference
CI	Confidence interval
H&Y	Hoehn and Yahr scale
UPDRS-III	Unified Parkinson's disease rating scale part III
MMSE	Mini-mental state examination
MoCA	Montreal cognitive assessment

Supplementary Information

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Supplementary Material 1

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Conceptualization: H.L.; Systematic review and meta-analysis: H.L.; Writing - original draft: H.L. and B.J.C.; Writing—review and editing: N.K.; Supervision: N.K. All authors have read and agreed to the published version of the manuscript.

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Data availability
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Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
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Competing interests
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