Cognitive Training and Noninvasive Brain Stimulation for Cognition in Parkinson's Disease: A Meta-analysis

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Abstract

Background. Many people with Parkinson's disease (PD) experience cognitive decline. It is not known whether cognitive training or noninvasive brain stimulation are effective at alleviating cognitive deficits in PD. *Objective.* To examine cognitive training and non-invasive brain stimulation interventions for cognition in PD. *Methods.* An extensive search was conducted of published and unpublished studies in online databases. Studies were selected if they were controlled trials examining standard (not individualized) or tailored (individualized) cognitive training, repetitive transcranial magnetic stimulation (rTMS), or transcranial direct current stimulation (tDCS) in PD, with outcomes measured by standardized neuropsychological tests. *Results.* Fourteen controlled trials met inclusion criteria. For executive function, the pooled effect size (Hedges' *g*) for cognitive training (standard and tailored combined) was small (*g* = 0.42) but statistically significant (95% CI 0.15-0.68). The pooled effect for standard cognitive training (alone) was medium (*g* = 0.51) and significant (95% CI 0.16-0.85). For attention/working memory, small pooled effect sizes were found when combining standard and tailored cognitive training (*g* = 0.23; 95% CI 0.02-0.44) and for standard cognitive training alone (*g* = 0.29; 95% CI 0.04-0.53), both significant. For memory, small but significant pooled effect sizes were also found when combining standard and tailored cognitive training and for standard cognitive training alone. *Conclusions.* The results suggest that standard and tailored cognitive training may improve executive function, attention/working memory, and memory in PD. Future studies must adopt randomized controlled trial designs to explore the therapeutic potential of these interventions.

Keywords

Parkinson's disease, mild cognitive impairment, memory, executive function, attention/working memory

Introduction

While Parkinson disease (PD) is classified as a movement disorder, approximately 30% of people with PD experience cognitive symptoms that negatively affect quality of life.[1] Five domains of cognition are potentially vulnerable to mild cognitive impairment in PD: long-term memory, attention/working memory, visuospatial abilities, executive function, and language.[2,3] While there is limited evidence supporting pharmacological treatment for people with comorbid cognitive impairments in PD,[4] nonpharmacological interventions are being considered as potential therapeutic techniques for improving cognition.[5]

Evidence suggests that standard (not individualized) cognitive training and tailored (individualized) cognitive training appears to improve cognition in PD.[6,7] Likewise, repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) may also improve cognition in PD.[8,9] However, a recent review of

nonpharmacological intervention in PD (predominantly for executive functions), reported a lack of methodological rigor, which reduced the quality of the results.[5]

rTMS studies in PD have varied by intervention length (1-12 sessions), stimulation frequency (0.2-50 Hz), target locations (dorsolateral prefrontal or motor cortices), and approach to stimulation: intermittent theta-burst or

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repetitive TMS.[10-15] Consequently, studies administering a lower frequency (eg, 5 Hz) of rTMS over the left dorsolateral prefrontal cortex (affecting executive function) will likely produce different cortical effects compared with a higher frequency (eg, 50 Hz) of rTMS over the motor cortices (affecting motor function). Most studies have also assessed cognitive domains as secondary outcomes, rather than targeting interventions primarily toward improvement of cognition.[13,16] For tDCS, more consistent methodology has been adopted (eg, 2 mA stimulation of prefrontal cortices) but findings are limited by lack of controlled designs.[8,17]

Furthermore, many studies have not included controlled designs,[8,17] albeit recent, placebo-controlled trials have adopted more stringent methodological designs and these still support cognitive training and brain stimulation for improving cognition in PD.[18,19] In addition, a recent meta-analysis of cognitive training in PD found improvements in working memory, processing speed, and executive function.[20] Research, however, needs to examine the independent therapeutic effects of standard and tailored cognitive training[21] and whether rTMS or tDCS are viable nonpharmacological interventions for improving cognition in PD. The present study builds on the recent meta-analysis of cognitive training, by examining the efficacy of controlled trials of standard cognitive training, tailored cognitive training, tDCS, and rTMS studies in PD and provides a synthesis of current results with recommendations for future, nonpharmacological interventions.

Method

This meta-analysis was conducted in accordance with the Preferred Reporting of Systematic Reviews and Meta-Analyses (PRISMA) statement (see Supplementary Table S1).[22]

Search Strategy and Study Selection

Key words (eg, cognitive training OR tDCS OR rTMS; see Supplementary Table S2) were systematically searched in online databases for published articles (eg, MEDLINE, PubMed, Wiley Online Library) and gray literature (e.g., OpenGrey, NTIS). Search parameters were from first date of publication to May 27, 2016. Reference lists were also searched. Studies were included in the meta-analysis if (1) they recruited participants with idiopathic PD diagnosed by a neurologist or geriatrician using the United Kingdom's Parkinson's Disease Society Brain Bank Clinical Criteria; (2) they evaluated rTMS, tDCS, or cognitive training interventions; (3) they used a controlled design; (4) primary outcomes were measured by standardized neuropsychological tests; and (5) data were provided to calculate an effect size (means, SDs, *t* or *F* values, and probability values). One

author (B.J.L) systematically screened article titles and abstracts in line with selection criteria and identified preliminary articles for inclusion. Two authors (B.J.L and A.M.L) independently screened selected articles to determine the final studies for inclusion. Any disagreements were resolved through discussion.

Data Extraction and Risk of Bias Assessment

The data extracted from each study included participants, interventions, comparisons, outcomes, and study design (PICOS). Cognitive outcomes were categorised in accordance with the Movement Disorder Society (MDS) Task Force recommendations for cognitive domains: executive function, attention/working memory, memory, visuospatial abilities, language, and global cognition.[23] Outcomes assessing processing speed (not addressed by the MDS Task Force) were categorized within the "attention/working memory" domain. Pre- and post-intervention means and standard deviations were extracted for cognitive outcomes. Where outcome means and standard deviations were not reported, probability values for between-group comparisons based on post-intervention outcomes were extracted to compute effect sizes. The Cochrane Collaboration tool was used to assess risk of bias among studies included in this meta-analysis.[24] The risk of bias assessment tool classifies individual studies as having low, high, or unclear risk of bias across 6 domains; sequence generation, allocation concealment, blinding, selective reporting, and other biases.[24]

Statistical Analysis and Publication Bias

Comprehensive Meta-Analysis (CMA) version 3.3.070 was used to complete data analyses.[25] The change score method from pre- to post-intervention was used to calculate the absolute magnitude of change for intervention and control groups. Effect sizes for each outcome were then computed as Hedge's *g*.[25] Cognitive domain effect sizes were calculated by computing the mean effect within each domain and adjusting the mean variance by 0.8 to correct for intercorrelation among outcomes.[25] Domain effect sizes and adjusted variances were then pooled using a random-effects model, with 95% confidence intervals.[25,26] Egger's regression asymmetry test and the fail-safe N were used to assess publication bias.[27,28] For studies with 2 or more intervention groups but 1 control group, the control group was divided into the same number of groups.[25] This ensured that each participant's data were analyzed only once.

Heterogeneity Analysis

Heterogeneity was explored using Cochrane's Q and I^2 statistics. A statistically significant Q statistic suggests a difference between an observed and true effect.[29] However, the

Q statistic may overestimate this difference in small sample sizes. If Q was significant, the I^2 statistic was used as an estimate of the percentage of variation across the samples due to heterogeneity. Values for I^2 are expressed as a percentage, with suggested values of 25% (low), 50% (moderate), and 75% (high) used to categorize levels of heterogeneity.[29]

Results

Search Results

In total, 13 162 titles and abstracts were systematically screened in online databases. Seventy-one studies examined nonpharmacological interventions in PD. Fifty-seven were excluded as they were not rTMS, tDCS, or cognitive training interventions (13), multiple interventions (eg, cognitive training combined with physical exercise) (4), study protocols (3), case studies (2), not assessing cognition with standardised outcomes (9), not all participants diagnosed with PD (1), provided insufficient data to be meta-analyzed (eg, conference abstracts and authors did not respond to follow-up) (6), or not controlled trials (17). Two additional studies were excluded as we were unsuccessful in obtaining missing data from the authors. Since one of these excluded studies was the only tDCS study to be considered in this meta-analysis, it was therefore not possible to examine tDCS (see Figure 1).

Study Characteristics

Fourteen controlled trials met inclusion criteria (see Table 1): 3 rTMS,[9,11,12] 3 tailored cognitive training,[6,30,31] and 8 standard cognitive training studies.[7,19,32-37] Articles were published from 2006 to 2014, with all but one published in the past 5 years. Petrelli et al[19] provided data for 2 comparisons, comparing structured and unstructured training groups against a single control group.

Assessment of Risk of Bias

Two studies had low risk,[19,35] 5 high risk,[6,31,32,34,37] and 7 unclear risk of bias.[7,9,11,12,30,33,36] Of the 5 studies with high risk, 3 did not use a randomization sequence for allocating participants,[6,32,34] 3 did not blind outcome assessments,[31,34 37] and 1 did not conceal participant group allocation.[34] Of the 7 studies with unclear risk, 5 did not clearly describe the randomization sequence generation,[7,9,30,33,36] 3 did not sufficiently describe blinding of outcome assessments,[11,12,33] and 2 did not adequately describe concealment of group allocation.[33,36] Only 3 of the cognitive training studies were double-blind.[19,32,35] However, double-blinding is difficult to achieve in such intervention studies.[24]

Executive Function

Ten studies assessed executive functions pre- and posttreatment. Supplementary Figure S1 shows a forest plot of effect sizes, 95% confidence limits, and heterogeneity results, revealing that there was a significant, small benefit of combined cognitive training on executive outcomes.[38] A medium and statistically significant pooled effect for executive function was found for standard cognitive training alone. No other effects were significant (Table 2).

Attention and Working Memory

Ten cognitive intervention studies and 1 rTMS study explored effects on attention/working memory (see Table 2 and Supplementary Figure S2). Therefore, only cognitive training pooled effect sizes were calculated. Small and statistically significant effects for combined and standard cognitive training improving attention/working memory were identified.

Memory

Six studies examined the effect of cognitive training on memory. No rTMS studies assessed memory. Meta-analysis revealed a small effect of combined and standard cognitive training on memory: both statistically significant (see Table 2 and Supplementary Figure S3).

Visuospatial Abilities, Language, and Global Cognition

Four studies examined the effect of cognitive training (3 standard and 1 tailored) on visuospatial abilities in PD, but pooled effects were not significant (see Table 2 and Supplementary Figure S4). Four standard and 1 tailored cognitive training study, and 1 rTMS study examined effects on global cognition in PD. Meta-analysis revealed no significant effects (see Table 2 and Supplementary Figure S5). No controlled studies examined language impairment.

Publication Bias

Publication bias statistics were calculated for significant, pooled effect sizes by cognitive domain. Despite a nonsignificant Egger's regression for combined cognitive training effects on executive function, $P = .25$, only 14 nonsignificant results would be required to render this effect zero, suggesting publication bias. Likewise, Egger's regression for standard cognitive training effects on executive function was not significant ($P = .54$), but needing only 7 nonsignificant results suggests publication bias. Likewise, for attention/working memory Egger's regression was not significant for combined ($P = .77$) or standard training ($P = .58$) but
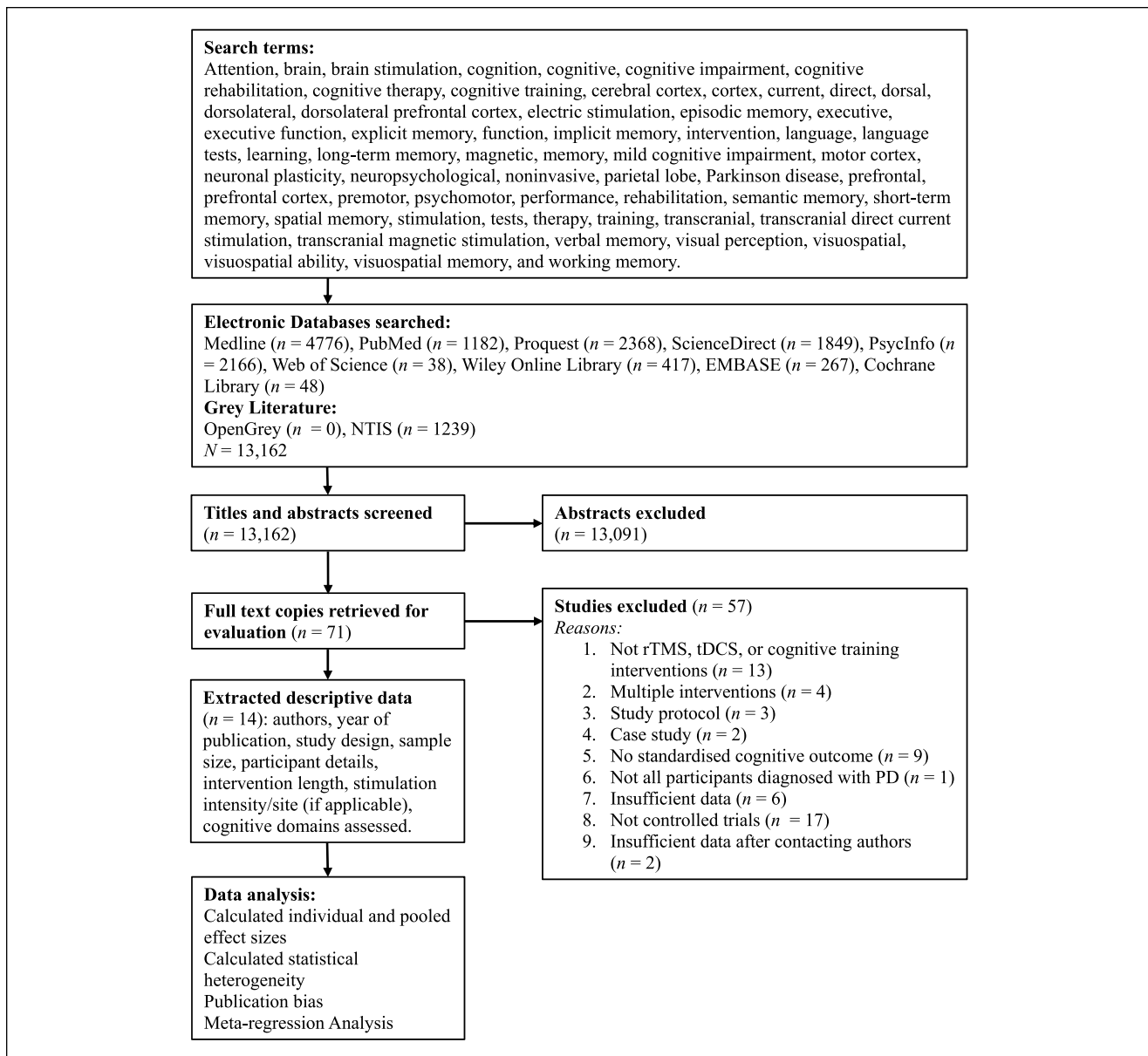
Search terms:
Attention, brain, brain stimulation, cognition, cognitive, cognitive impairment, cognitive rehabilitation, cognitive therapy, cognitive training, cerebral cortex, cortex, current, direct, dorsal, dorsolateral, dorsolateral prefrontal cortex, electric stimulation, episodic memory, executive, executive function, explicit memory, function, implicit memory, intervention, language, language tests, learning, long-term memory, magnetic, memory, mild cognitive impairment, motor cortex, neuronal plasticity, neuropsychological, noninvasive, parietal lobe, Parkinson disease, prefrontal, prefrontal cortex, premotor, psychomotor, performance, rehabilitation, semantic memory, short-term memory, spatial memory, stimulation, tests, therapy, training, transcranial, transcranial direct current stimulation, transcranial magnetic stimulation, verbal memory, visual perception, visuospatial, visuospatial ability, visuospatial memory, and working memory.

Electronic Databases searched:
Medline ($n = 4776$), PubMed ($n = 1182$), Proquest ($n = 2368$), ScienceDirect ($n = 1849$), PsycInfo ($n = 2166$), Web of Science ($n = 38$), Wiley Online Library ($n = 417$), EMBASE ($n = 267$), Cochrane Library ($n = 48$)
Grey Literature:
OpenGrey ($n = 0$), NTIS ($n = 1239$)
$N = 13,162$

Titles and abstracts screened ($n = 13,162$) → **Abstracts excluded** ($n = 13,091$)

Full text copies retrieved for evaluation ($n = 71$) → **Studies excluded** ($n = 57$)
Reasons:
1. Not rTMS, tDCS, or cognitive training interventions ($n = 13$)
2. Multiple interventions ($n = 4$)
3. Study protocol ($n = 3$)
4. Case study ($n = 2$)
5. No standardised cognitive outcome ($n = 9$)
6. Not all participants diagnosed with PD ($n = 1$)
7. Insufficient data ($n = 6$)
8. Not controlled trials ($n = 17$)
9. Insufficient data after contacting authors ($n = 2$)

Extracted descriptive data ($n = 14$): authors, year of publication, study design, sample size, participant details, intervention length, stimulation intensity/site (if applicable), cognitive domains assessed.

Data analysis:
Calculated individual and pooled effect sizes
Calculated statistical heterogeneity
Publication bias
Meta-regression Analysis

Figure 1. PRISMA (Preferred Reporting of Systematic Reviews and Meta-Analyses) flowchart of search results.

fail-safe Ns of 2, for both, suggest publication bias. Finally, for memory, Egger's regression was significant for combined cognitive training ($P = .01$) and only 3 nonsignificant results would be needed to undermine this significant pooled effect. Also for memory, Egger's regression for standard cognitive training effects was not significant ($P = .27$), yet a low fail-safe N (N = 1) suggests publication bias.

Sensitivity Analyses

Petrelli et al[19] reported means and standard error values adjusted for covariates and not raw data, Sammer et al[31] did not report pre/post data and effect sizes were computed

using probability values from postintervention outcomes, and Ell[33] conducted a short cognitive training intervention (8 minutes) compared with the longer interventions included in this meta-analysis. Therefore, 3 sensitivity analyses were conducted to determine if removing these studies would significantly affect pooled effect estimates (see Table 3).

Discussion

This meta-analysis is the first to provide distinct, pooled effect sizes for standard (not individualized) and tailored (individualized) cognitive training and rTMS interventions for cognition in PD. When considered together, standard

Table 1. Characteristics of Controlled Trials Included in Meta-analysis.

Intervention	First Author (Year)	n	Mean Age (Years)	Male (%)	Duration of Illness (Years)	Education (Years)	Intervention Length (Hours)	Cognitive Status	Stimulation Intensity/Site	Cognitive Domain Assessed					
										G	EF	A/WM	M	V	L
rTMS	Pal (2010)[9]	22	68	50	6.25	—	.30	No CI	5Hz / Left DLPFC	×		×			
	Benninger (2011)[11]	26	63.85	69	8.65	—	.08	n.a	50Hz / MI and DLPFC		×				
	Benninger (2012)[12]	26	64.1	77	8.95	—	.08	n.a	50Hz / MI		×	×			
Standard CT	Nombela (2011)[34]	20	60.65	50	8.10	7.60	45.63	CI	n.a	×	×	×			
	Paris (2011)[7]	28	65.09	53.80	7.60	9.69	9	CI (50%)	n.a	×		×	×	×	
	Pompeu (2012)[36]	32	67.40	53.13	—	—	7	No CI	n.a	×					
	Ell (2013)[33,a]	36	66.13	—	4.70	16.33	.13	No CI	n.a		×				
	Edwards (2013)[37]	73	68.78	62.07	6.94	15.15	20	No CI	n.a			×			
	Costa (2014)[32]	17	68.50	—	9.10	10.90	9	CI	n.a		×	×			
	Petrelli (2014)[19]	65	69.05	43.08	5.63	13.17	18	No CI	n.a	×	×	×	×		
	Pena (2014)[35]	44	67.84	61.36	6.50	10.40	36	No CI	n.a			×	×		
Tailored CT	Sammer (2006)[31]	26	69.65	—	—	—	5	No CI	n.a		×	×			
	Naismith (2013)[6]	50	66.70	70.50	7.05	14.45	14	No CI	n.a		×	×	×		
	Cerasa (2014)[30]	15	59.70	—	3.35	8	12	No CI	n.a		×	×	×	×	
Mean		34	66.10	58.99	6.90	11.74	12.59	n.a	n.a						

Abbreviations: rTMS, repetitive transcranial magnetic stimulation; CT, cognitive training; CI, cognitive impairment; DLPFC, dorsolateral prefrontal cortex; MI, primary motor cortex; n.a, not applicable; —, not reported; G, global cognition; EF, executive functions; A/WM, attention and working memory; M, memory; V, visuospatial abilities; L, language.
aOnly participants with Parkinson's disease.

Table 2. Effect Sizes With Heterogeneity Statistics for Cognitive Outcomes in Cognitive Training and rTMS Studies.

| Outcome | Intervention | Study | Effect Size Statistics | | | | | Heterogeneity Statistics | | |
| | | | | 95% CI | | | | | | |
			Hedge's g	Lower	Upper	Z	p	Cochrane's Q (df)	p	I^2
Executive function										
	Standard CT	Paris (2013)	0.85	0.15	1.56	2.36	0.02			
		Ell (2013)	0.87	−0.06	1.80	1.84	0.07			
		Costa (2014)	0.56	−0.30	1.43	1.28	0.20			
		Petrelli (2014)–1	0.38	−0.32	1.10	1.07	0.28			
		Petrelli (2014)–2	0.01	−0.74	0.72	−.02	0.98			
		Pooled effect (standard CT)	0.51	0.16	0.85	2.86	0.004	3.56 (4)	0.47	0.00
	Tailored CT	Sammer (2006)	0.73	−0.002	1.48	1.96	0.05			
		Naismith (2013)	−0.01	−0.60	0.59	−0.02	0.98			
		Cerasa (2014)	0.30	−0.66	1.26	0.62	0.54			
		Pooled effect (tailored CT)	0.30	−0.16	0.76	1.28	0.20	2.37 (2)	0.31	15.49
		Pooled effect (combined standard and tailored CT)	0.42	0.15	0.68	3.07	0.002	6.54 (7)	0.48	0.00
	rTMS	Benninger (2011)	0.42	−0.33	1.18	1.10	0.27			
		Benninger (2012)	0.37	−0.38	1.12	0.96	0.34			
		Pooled effect (rTMS)	0.40	−0.14	0.93	1.46	0.15	0.01 (1)	0.92	0.00
Attention/Working memory										
	Standard CT	Nombela (2011)	−0.33	−1.38	0.72	−0.62	0.54			
		Paris (2013)	0.54	−0.13	1.22	1.58	0.11			
		Edwards (2013)	0.30	−0.16	0.76	1.28	0.20			
		Pena (2014)	0.20	−0.34	0.73	0.71	0.48			
		Costa (2014)	0.46	−0.41	1.33	1.03	0.30			
		Petrelli (2014)–1	0.51	−0.17	1.19	1.46	0.14			
		Petrelli (2014)–2	0.07	−0.63	0.76	0.18	0.85			
		Pooled effect (standard CT)	0.29	0.04	0.53	2.31	0.02	2.95 (6)	0.82	0.00
	Tailored CT	Sammer (2006)	0.00	−0.70	0.70	0.00	1.00			
		Naismith (2013)	0.02	−0.54	0.59	0.08	0.94			
		Cerasa (2014)	0.39	−0.55	1.33	0.82	0.41			
		Pooled effect (tailored CT)	0.08	−0.32	0.48	0.40	0.69	0.52 (2)	0.77	0.00
		Pooled effect (combined standard and tailored CT)	0.23	0.02	0.44	2.18	0.03	4.22 (9)	0.90	0.00
	rTMS	Pal (2010)	0.34	−0.42	1.11	0.88	0.38			
		Pooled effect (rTMS)	—	—	—	—	—	—	—	—
Memory										
	Standard CT	Paris (2013)	0.37	−0.30	1.04	1.09	0.28			
		Pena (2014)	0.42	−0.13	0.96	1.51	0.13			
		Petrelli (2014)–1	0.33	−0.33	0.98	0.98	0.33			
		Petrelli (2014)–2	0.24	−0.43	0.91	0.70	0.49			
		Pooled effect (standard CT)	0.35	0.03	0.66	2.17	0.03	0.17 (3)	0.98	0.00
	Tailored CT	Naismith (2013)	0.38	−0.19	0.95	1.30	0.19			
		Cerasa (2014)	0.03	−0.85	0.91	0.06	0.95			
		Pooled effect (tailored CT)	0.28	−0.20	0.76	1.13	0.26	0.43 (1)	0.51	0.00
		Pooled effect (combined standard and tailored CT)	0.33	0.06	0.59	2.44	0.02	0.67 (5)	0.99	0.00
Visuospatial function										
	Standard CT	Paris (2013)	0.76	0.05	1.48	2.10	0.04			
		Petrelli (2014)–1	0.09	−0.62	0.80	0.25	0.80			
		Petrelli (2014)–2	0.11	−0.62	0.83	0.28	0.78			
		Pooled effect (standard CT)	0.32	−0.12	0.76	1.44	0.15	2.22 (2)	0.33	10.08

(continued)

Table 2. (continued)

Outcome	Intervention	Study	Effect Size Statistics					Heterogeneity Statistics		
			Hedge's g	95% CI		Z	*p*	Cochrane's Q (df)	*p*	I^2
				Lower	Upper					
	Tailored CT	Cerasa (2014)	−0.15	−1.10	0.81	−0.30	0.77			
		Pooled effect (combined standard and tailored CT)	0.25	−0.13	0.63	1.28	0.20	2.99 (3)	0.39	0.00
Global cognition										
	Standard CT	Pompeu (2012)	0.04	−0.63	0.72	0.12	0.90			
		Paris (2013)	0.39	−0.31	1.08	1.09	0.28			
		Petrelli (2014)−1	0.48	−0.20	1.17	1.38	0.17			
		Petrelli (2014)−2	0.39	−0.31	1.08	1.08	0.28			
		Pooled effect (standard CT)	0.32	−0.02	0.67	1.83	0.07	0.93 (3)	0.82	0.00
	Tailored CT	Cerasa (2014)	0.28	−0.68	1.24	0.57	0.57			
		Pooled effect (combined standard and tailored CT)	0.32	−0.01	0.64	1.91	0.06	0.94 (4)	0.92	0.00
	rTMS	Pal (2010)	−0.17	−0.98	0.64	−0.42	0.68			
		Pooled effect (rTMS)	—	—	—	—	—	—	—	—

Abbreviations: CT, cognitive training; rTMS, repetitive transcranial magnetic stimulation.

Table 3. Changes in Pooled Effects Sizes Following Sensitivity Analyses.

Study Removed	Outcome		Original Effect Size			Change in Effect Size		
			Hedge's g	95% CI		Hedge's g	95% CI	
				Lower	Upper		Lower	Upper
Petrelli (2014)	Executive function							
		Pooled effect (standard CT)	0.51	0.16	0.85	0.77	0.30	1.24
		Pooled effect (combined CT)	0.42	0.15	0.68	0.50	0.19	0.81
	Attention/Working memory							
		Pooled effect (standard CT)	0.29	0.04	0.53	0.29	0.004	0.57
		Pooled effect (combined CT)	0.23	0.02	0.44	0.22	−0.01	0.45
	Memory							
		Pooled effect (standard CT)	0.35	0.03	0.66	0.40	−0.02	0.82
		Pooled effect (combined CT)	0.33	0.06	0.59	0.35	0.03	0.66
	Visuospatial function							
		Pooled effect (standard CT)	0.32	−0.12	0.76	0.76	0.05	1.48
		Pooled effect (combined CT)	0.25	−0.13	0.63	0.37	−0.52	1.25
	Global cognition							
		Pooled effect (standard CT)	0.32	−0.02	0.67	0.21	−0.28	0.70
		Pooled effect (combined CT)	0.32	−0.01	0.64	0.22	−0.21	0.66
Sammer (2006)	Executive function							
		Pooled effect (tailored CT)	0.30	−0.16	0.76	0.08	−0.43	0.58
		Pooled effect (combined CT)	0.42	0.15	0.68	0.37	0.08	0.66
	Attention/Working memory							
		Pooled effect (tailored CT)	0.08	−0.32	0.48	0.12	−0.36	0.60
		Pooled effect (combined CT)	0.23	0.02	0.44	0.25	0.04	0.47
Ell (2014)	Executive function							
		Pooled effect (standard CT)	0.51	0.16	0.85	0.45	0.07	0.82
		Pooled effect (combined CT)	0.42	0.15	0.68	0.38	0.10	0.65

Abbreviation: CT, cognitive training.

and tailored cognitive training studies appear to improve executive function, albeit only by a small amount. When analyzed separately, perhaps because of the small number of studies, executive function was no longer improved by tailored cognitive training, but standard cognitive training appeared to have a more moderate effect. This nonsignificant effect for tailored cognitive training may represent a type II error, given that a small effect size was observed but only three tailored cognitive training studies were included in this meta-analysis. There were insufficient studies for a formal comparison of the relative effects of standard and tailored cognitive training. Thus, more controlled trials of tailored cognitive training are needed to determine if this modality is more or less efficacious than a standard (non-individualized) intervention. Executive function did not appear to improve in the 2 rTMS studies investigated.[11,12] Given that preliminary results of rTMS trials[13] report improvements in cognition in PD, more detailed exploration of this therapeutic technique is required.

People with PD and cognitive impairment demonstrate deficits in attention/working memory.[39] When considered together, attention/working memory was improved by standard and tailored cognitive training and by standard training alone. This finding conflicts with those of Leung et al[20] who reported a medium and significant effect for working memory, but a small and non-significant negative effect for attention. Unlike this meta-analysis, however, Leung et al[20] included one study that had a large negative effect on attention.[40] This study compared computerized cognitive training (intervention group) to computerized sport-related video gaming (control group). But sport-related video games have improved cognition in older adults,[41] which Zimmermann et al[40] also reported. Inclusion of this study in the previous meta-analysis led to inclusion of a large negative effect for cognitive training on attention, but inversely included a large positive effect for computerized sport-related gaming on attention (rather than an effect favoring a control group). The current meta-analysis excluded this study to ensure only controlled comparisons were included in pooled effects, and this approach found positive effects for combined and standard cognitive training improving attention/working memory in PD.

Only one controlled rTMS study examined attention/working memory in PD, reporting no significant changes.[9] However, several noncontrolled rTMS studies have shown improvements in cognition.[14-16,42] Before concluding whether rTMS is or is not helpful in alleviating cognitive deficits in PD, more controlled rTMS studies are needed.

While the primary cognitive impairments in PD are characterized by frontal dysfunction, memory impairment is also common.[43] Both standard and combined standard and tailored cognitive training offered small improvements in memory. This corresponds with a meta-analysis of memory training in healthy older adults, which found significant memory improvements posttraining.[44]

Inconsistent with studies in mild cognitive impairment,[45] standard and combined cognitive training did not appear to produce improvements in global cognition—despite all studies reporting a positive effect of cognitive training on global cognition. Compared with larger cognitive training trials improving all cognitive domains in healthy older adults,[46] the studies included in this meta-analysis may have been underpowered (ie, small N), which resulted in nonsignificant effects. Future studies need to recruit larger samples to ensure sufficient statistical power in cognitive training trials in PD.

Because of the heterogeneous nature of cognitive impairment in PD, individuals may demonstrate deficits in visuospatial and language domains.[39] There was no impact of cognitive training on visuospatial abilities across the 4 studies examined in this analysis. No controlled studies evaluated language impairment. Although language deficits are rare in PD,[47] future studies should include standardized neuropsychological assessment of these domains.[23]

In addition to the cognitive outcomes, sensitivity analyses examined whether removing the covariate adjusted results of Petrelli et al[19] affected corresponding effect estimates. Several changes suggest that this study's adjusted results had a large impact on attention/working memory, visuospatial, memory and global cognition effects.[19] Pooling effect sizes with adjusted results may not, however, demonstrate an accurate effect of standard cognitive training on these cognitive domains in PD. Adjusting results for the effect of covariates will likely underrepresent the true effect of an intervention (eg, cognitive training), by accounting for a proportion of variance in outcome variables. Sensitivity analyses also examined whether removing Sammer et al's[31] effect sizes (computed with probability statistics) or Ell's[33] results from a short cognitive training intervention, would affect pooled effect estimates. No changes in statistical significance of effects were observed.

For rTMS, methodological differences between studies may have resulted in the nonsignificant effect for executive function. Benninger et al[11] administered 50-Hz intermittent theta burst rTMS over the primary motor and dorsolateral prefrontal cortices, whereas Benninger et al[12] applied 50-Hz rTMS over primary motor cortices. Compared with the short-term effects found in rTMS studies, intermittent theta burst rTMS has been shown to increase the duration of synaptic plasticity by delivering 3 shorter pulses of stimulation (every 200 ms) to specific neuronal groups.[48] Conversely, earlier studies delivered longer stimulation (20-30 minutes) and showed significant improvements in cognition in PD.[9,13,16] Length and frequency of stimulation may, therefore, produce variable effects on synaptic connections and associated cognitive functions. Moreover, Benninger et al[12] assessed executive function but stimulated primary motor cortices not associated with executive function improvement. Having said this, rTMS is relatively nonfocal, often activating a combination of cortical systems that may have

interacting effects.[48] In their earlier study, Benninger et al[11] used the 5-cm rule to target the dorsolateral prefrontal cortex, which provides widespread stimulation across motor and prefrontal sites.[49] Consequently, rTMS over primary motor cortices may activate broader cortical systems that impact prefrontal areas (thus affecting executive function). Despite these differences, both studies reported positive effects in support of rTMS for improving cognition in PD. Future studies should build on these preliminary results by exploring the therapeutic potential of this noninvasive intervention for people with cognitive impairment and PD.

A lack of sensitivity of executive function and attention/working memory measures for detecting change in PD may also have contributed to the null rTMS pooled effect sizes. For Pal et al,[9] the Trail Making Test–Part A (TMT-A) was 1 of 3 outcomes used to compute an attention/working memory effect.[50] However, a meta-analysis comparing TMT-A performance between people with frontal deficits to those with posterior deficits found no significant difference between groups.[51] This suggests that the TMT-A is not sensitive to differences between frontal and nonfrontal cognitive impairments, yet impairments in PD are associated with deficits in prefrontal (dorsolateral and ventrolateral) cortices.[52] In addition, both rTMS[11,12] studies assessing executive function used the Frontal Assessment Battery (FAB).[53] The FAB has, however, low sensitivity (66.3%) in detecting executive function impairments related to dementia in PD.[54] These limiting factors may account for the nonsignificant executive function and attention/working memory effect estimates and must be acknowledged when interpreting the results.

Methodological heterogeneity of cognitive training interventions also limited this meta-analysis. Jean et al[55] recommend 6 to 20 cognitive training sessions (up to 15 hours) completed within 12 weeks, to be most effective, when compared with longer and more costly interventions. However, studies ranged between 8 minutes (computer-based rule learning task[33]) and 45 hours (Sudoku puzzle every day for 6 months[34]). Having said this, removing Ell[33] from pooled effects resulted in no changes in corresponding effect estimates and recent cognitive training studies have implemented more homogenous interventions (9-18 hours).[19,32,35] Type of cognitive training (eg, single-participant vs group-based training, or computer vs paper/pencil tasks) also varied between studies. Seven studies[7,30,32-34,36,37] administered training to participants individually, whereas 3 studies[6,19,35] conducted group-based training. Compared with participants who complete cognitive training alone, group based training has shown greater efficacy in healthy older adults by providing additional benefits, including trainer supervision, encouragement in performance, and social interaction among participants.[46] In addition, most trials included in this meta-analysis administered computer-based cognitive training[6,30,32,37] (compared with paper/

pencil tasks) and there is an ever-growing body of research in support of computer-based interventions in PD[56] and other neurodegenerative disorders (eg, Alzheimer's disease[57]). Furthermore, several studies[7,9,30,33,36] did not adequately describe their randomization sequence generation and 3 studies[6,32,34] did not randomize participants to intervention and control groups. Methodological limitations in controlled trials undermine the validity and generalizability of results, while perpetuating uncertainty for an intervention's potential to alleviate symptoms for people with PD. Future trials need to build on current scientific evidence to establish the most efficacious parameters (eg, length, frequency, and type of training) for cognitive interventions in PD, and conduct randomized controlled trials in accordance with the CONSORT (Consolidated Standards of Reporting Trials) statement to provide reliable and externally valid evidence of these nonpharmacological interventions.[58]

It is also important to note that only 2 studies in this meta-analysis included participants with cognitive impairment. Administering cognitive training, tDCS, or rTMS to people with PD and normal cognition may result in a ceiling effect of the therapeutic potential of these interventions to improve cognition. Future studies should therefore examine the potential of these interventions for people with cognitive deficits (eg, mild cognitive impairment and dementia) in PD.

The literature relating to the impact of either rTMS or tDCS in PD on cognitive function is limited, and very few studies employed a controlled design. In addition to a small N, there was evidence of bias within trials and bias in publication for combined and standard cognitive training effects on executive function, attention/working memory, and memory. Although violation of Rosenthal's fail-safe N suggests included studies may not be a true representation of the population effect, 13 162 studies were systematically searched in published and unpublished databases and only 14 met inclusion criteria. This extensive search, inclusive of gray literature, suggests these significant fail-safe N results may not be an accurate indication of publication bias.

This study highlights the need for randomized controlled trials of cognitive training (standard and tailored), rTMS, and tDCS for improving cognition in PD. Future interventions need to compare standard (not individualized) and tailored (individualized) cognitive training, and examine whether combining cognitive training with brain stimulation further improves cognition in PD. Studies should also compare interventions between participant groups with varying severity of cognitive impairment, to provide insight into which stages of disease progression are most likely to benefit from cognitive training and brain stimulation. Furthermore, previous studies report associations between cognitive decline and impaired activities of daily living, depression, and quality of life in PD.[36,59-62] Future clinical trials should therefore include these variables as primary

outcomes to explore the potential of these nonpharmamcological interventions for improving neuropsychiatric and practical domains.

This meta-analysis builds on previous results to provide the first individual pooled effect sizes for standard and tailored cognitive training and brain stimulation interventions for cognition in PD. Despite the significant prevalence of cognitive impairment in PD, there is a considerable lack of empirical evidence to support the improvement of cognitive functioning. An extensive literature search uncovered 14 controlled trials, 3 rTMS, 3 tailored cognitive training, and 8 standard cognitive training. The only controlled trial of tDCS did not provide sufficient data for inclusion. Based on the available studies, there is evidence to support the use of standard and tailored cognitive training for improving executive function, attention/working memory, and memory in PD. Although limited by available studies, the results of this meta-analysis provide a promising starting point for future nonpharmacological interventions in PD.

Acknowledgments

Declaration of Conflicting Interests

Funding

References

1. Litvan I, Aarsland D, Adler CH, et al. MDS task force on mild cognitive impairment in Parkinson's disease: critical review of PD-MCI. *Mov Disord*. 2011;26:1814-1824.

2. Kehagia AA, Barker RA, Robbins TW. Neuropsychological and clinical heterogeneity of cognitive impairment and dementia in patients with Parkinson's disease. *Lancet Neurol*. 2010;9:1200-1213.

3. Lawrence BJ, Gasson N, Loftus AM. Prevalence and subtypes of mild cognitive impairment in Parkinson's disease. *Sci Rep*. 2016;6:e33929.

4. Goldman JG, Weintraub D. Advances in the treatment of cognitive impairment in Parkinson's disease. *Mov Disord*. 2015;30:1471-1489.

5. Hindle JV, Petrelli A, Clare L, Kalbe E. Nonpharmacological enhancement of cognitive function in Parkinson's disease: a systematic review. *Mov Disord*. 2013;28:1034-1049.

6. Naismith SL, Mowszowski L, Diamond K, Lewis SJ. Improving memory in Parkinson's disease: a healthy brain ageing cognitive training program. *Mov Disord*. 2013;28:1097-1103.

7. París AP, Saleta HG, de la Cruz Crespo Maraver M, et al. Blind randomized controlled study of the efficacy of cognitive training in Parkinson's disease. *Mov Disord*. 2011;26:1251-1258.

8. Boggio PS, Ferrucci R, Rigonatti SP, et al. Effects of transcranial direct current stimulation on working memory in patients with Parkinson's disease. *J Neurol Sci*. 2006;249:31-38.

9. Pal E, Nagy F, Aschermann Z, Balazs E, Kovacs N. The impact of left prefrontal repetitive transcranial magnetic stimulation on depression in Parkinson's disease: a randomized, double-blind, placebo-controlled study. *Mov Disord*. 2010;25:2311-2317.

10. Benninger DH, Lomarev M, Wassermann EM, et al. Safety study of 50 Hz repetitive transcranial magnetic stimulation in patients with Parkinson's disease. *Clin Neurophysiol*. 2009;120:809-815.

11. Benninger DH, Berman B, Houdayer E, et al. Intermittent theta-burst transcranial magnetic stimulation for treatment of Parkinson disease. *Neurology*. 2011;76:601-609.

12. Benninger DH, Iseki K, Kranick S, Luckenbaugh DA, Houdayer E, Hallett M. Controlled study of 50-Hz repetitive transcranial magnetic stimulation for the treatment of Parkinson disease. *Neurorehabil Neural Repair*. 2012;26:1096-1105.

13. Boggio PS, Fregni F, Bermpohl F, et al. Effect of repetitive TMS and fluoxetine on cognitive function in patients with Parkinson's disease and concurrent depression. *Mov Disord*. 2005;20:1178-1184.

14. Epstein CM, Evatt ML, Funk A, et al. An open study of repetitive transcranial magnetic stimulation in treatment-resistant depression with Parkinson's disease. *Clin Neurophysiol*. 2007;118:2189-2194.

15. Furukawa T, Izumi S, Toyokura M, Masakado Y. Effects of low-frequency repetitive transcranial magnetic stimulation in Parkinson's disease. *Tokai J Exp Clin Med*. 2009;34:63-71.

16. Fregni F, Santos CM, Myczkowski ML, et al. Repetitive transcranial magnetic stimulation is as effective as fluoxetine in the treatment of depression in patients with Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 2004;75:1171-1174.

17. Pereira JB, Junqué C, Bartrés-Faz D, et al. Modulation of verbal fluency networks by transcranial direct current stimulation (tDCS) in Parkinson's disease. *Brain Stimul*. 2013;6:16-24.

18. Doruk D, Gray Z, Bravo GL, Pascual-Leone A, Fregn F. Effects of tDCS on executive function in Parkinson's disease. *Neurosci Lett*. 2014;582:27-31.

19. Petrelli A, Kaesberg S, Barbe MT, et al. Effects of cognitive training in Parkinson's disease: a randomized controlled trial. *Parkinsonism Relat Disord*. 2014;20:1196-1202.

20. Leung IH, Walton CC, Hallock H, Lewis SJ, Valenzuela M, Lampit A. Cognitive training in Parkinson disease: a systematic review and meta-analysis. *Neurology*. 2015;85:1843-1851.

21. Walton CC, Naismith SL, Lampit A, Mowszowski L, Lewis SJ. Cognitive training in Parkinson's disease: a theoretical perspective. *Neurorehabil Neural Repair*. 2017;31:207-216.

22. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med*. 2009;151:264-269.

23. Litvan I, Goldman JG, Troster AI, et al. Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. *Mov Disord*. 2012;27:349-356.

24. Higgins JP, Green S. *Cochrane Handbook for Systematic Reviews of Interventions*. 5th ed. Chichester, England: Wiley; 2008.

25. Borenstein M, Hedges LV, Higgins JP, Rothstein HR. *Introduction to Meta-Analysis*. Chichester, England: Wiley; 2011.

26. Hedges L, Vevea JL. Fixed-and random-effects models in meta-analysis. *Psychol Methods*. 1998;3:486-504.

27. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315:629-634.

28. Rosenthal R. The file drawer problem and tolerance for null results. *Psychol Bull*. 1979;86:638-641.

29. Huedo-Medina TB, Sánchez-Meca J, Marín-Martínez F, Botella J. Assessing heterogeneity in meta-analysis: Q statistic or I^2 index? *Psychol Methods*. 2006;11:193-206.

30. Cerasa A, Gioia MC, Salsone M, et al. Neurofunctional correlates of attention rehabilitation in Parkinson's disease: an explorative study. *Neurol Sci*. 2014;35:1173-1180.

31. Sammer G, Reuter I, Hullmann K, Kaps M, Vaitl D. Training of executive functions in Parkinson's disease. *J Neurol Sci*. 2006;248:115-119.

32. Costa A, Gioia MC, Salsone M, et al. Prospective memory performance of patients with Parkinson's disease depends on shifting aptitude: evidence from cognitive rehabilitation. *J Int Neuropsychol Soc*. 2014;20:717-726.

33. Ell SW. Targeted training of the decision rule benefits rule-guided behavior in Parkinson's disease. *Cog Affect Behav Neurosci*. 2013;13:830-846.

34. Nombela C, Bustillo PJ, Castell PF, Sanchez L, Medina V, Herrero MT. Cognitive rehabilitation in Parkinson's disease: evidence from neuroimaging. *Front Neurol*. 2011;2:82.

35. Pena J, Ibarretxe-Bilbao N, Garcia-Gorostiaga I, Gomez-Beldarrain MA, Diez-Cirarda M, Ojeda N. Improving functional disability and cognition in Parkinson disease. *Neurology*. 2014;83:2167-2174.

36. Pompeu JE, Mendes FA, Silva KG, et al. Effect of Nintendo Wii™-based motor and cognitive training on activities of daily living in patients with Parkinson's disease: a randomised clinical trial. *Physiotherapy*. 2012;98:196-204.

37. Edwards JD, Hauser RA, O'Connor ML, Valdes EG, Zesiewicz TA, Uc EY. Randomized trial of cognitive speed of processing training in Parkinson disease. *Neurology*. 2013;81:1284-1290.

38. Cohen J. A power primer. *Psychol Bull*. 1992;112:155-159.

39. Cholerton BA, Zabetian CP, Wan JY, et al. Evaluation of mild cognitive impairment subtypes in Parkinson's disease. *Mov Disord*. 2014;29:756-764.

40. Zimmermann R, Gschwandtner U, Benz N, et al. Cognitive training in Parkinson disease: cognition-specific vs nonspecific computer training. *Neurology*. 2014;82:1219-1226.

41. Basak C, Boot WR, Voss MW, Kramer AF. Can training in a real-time strategy video game attenuate cognitive decline in older adults? *Psychol Aging*. 2008;23:765-777.

42. Srovnalova H, Marecek R, Rektorova I. The role of the inferior frontal gyri in cognitive processing of patients with Parkinson's disease: a pilot rTMS study. *Mov Disord*. 2011;26:1545-1548.

43. Domellof M, Ekman U, Forsgren L, Elgh E. Cognitive function in the early phase of Parkinson's disease, a five-year follow-up. *Acta Neurol Scand*. 2015;132:79-88.

44. Zehnder F, Martin M, Altgassen M, Clare L. Memory training effects in old age as markers of plasticity: a meta-analysis. *Restor Neurol Neurosci*. 2009;27:507-520.

45. Li H, Li J, Li N, Li B, Wang P, Zhou T. Cognitive intervention for persons with mild cognitive impairment: a meta-analysis. *Ageing Res Rev*. 2011;10:285-296.

46. Lampit A, Hallock H, Valenzuela M. Computerized cognitive training in cognitively healthy older adults: a systematic review and meta-analysis of effect modifiers. *PLoS Med*. 2014;11:e1001756.

47. Goldman JG, Holden S, Bernard B, Ouyang B, Goetz CG, Stebbins GT. Defining optimal cutoff scores for cognitive impairment using Movement Disorder Society Task Force criteria for mild cognitive impairment in Parkinson's disease. *Mov Disord*. 2013;28:1972-1979.

48. Huang YZ, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC. Theta burst stimulation of the human motor cortex. *Neuron*. 2005;45:201-206.

49. Pascual-Leone A, Wassermann EM, Grafman J, Hallett M. The role of the dorsolateral prefrontal cortex in implicit procedural learning. *Exp Brain Res*. 1996;107:479-485.

50. Reitan RM. *Trail Making Test: Manual for Administration and Scoring*. Tempe, AZ: Reitan Neuropsychology Laboratory; 1992.

51. Demakis GJ. Frontal lobe damage and tests of executive processing: a meta-analysis of the category test, Stroop test, and trail-making test. *J Clin Exp Neuropsychol*. 2004;26:441-450.

52. Lewis SJ, Dove A, Robbins TW, Barker RA, Owen AM. Cognitive impairments in early Parkinson's disease are accompanied by reductions in activity in frontostriatal neural circuitry. *J Neurosci*. 2003;23:6351-6356.

53. Dubois B, Slachevsky A, Litvan I, Pillon B. The FAB: a frontal assessment battery at bedside. *Neurology*. 2000;55:1621-1626.

54. Kaszás B, Kovacs N, Balas I, et al. Sensitivity and specificity of Addenbrooke's cognitive Examination, Mattis Dementia Rating Scale, Frontal Assessment Battery and Mini Mental State Examination for diagnosing dementia in Parkinson's disease. *Parkinsonism Relat Disord*. 2012;18:553-556.

55. Jean L, Bergeron ME, Thivierge S, Simard M. Cognitive intervention programs for individuals with mild cognitive impairment: systematic review of the literature. *Am J Geriatr Psychiatry*. 2010;18:281-296.

56. Kalbe E, Kessler J. Task force WANTED: many reasons to promote research on cognitive rehabilitation to prevent, delay,

and treat cognitive dysfunctions in patients with Parkinson's disease. *Parkinsonism Relat Disord*. 2014;21:166-167.

57. Tappen RM, Hain D. The effect of in-home cognitive training on functional performance of individuals with mild cognitive impairment and early-stage Alzheimer's disease. *Res Gerontol Nurs*. 2014;7:14-24.

58. Boutron I, Moher D, Altman DG, Schulz KF, Ravaud P. Extending the CONSORT statement to randomized trials of nonpharmacologic treatment: explanation and elaboration. *Ann Intern Med*. 2008;148:295-309.

59. Klepac N, Trkulja V, Relja M, Babić T. Is quality of life in non-demented Parkinson's disease patients related to cognitive

performance? A clinic-based cross-sectional study. *Eur J Neurol*. 2008;15:128-133.

60. Lawrence BJ, Gasson N, Loftus AM. Activities of daily living, depression, and quality of life in Pakinson's disease. *PLoS One*. 2014;9:e102294.

61. Lawson RA, Yarnall AJ, Duncan GW, et al. Cognitive decline and quality of life in incident Parkinson's disease: the role of attention. *Parkinsonism Relat Disord*. 2016;27:47-53.

62. Muslimović D, Post B, Speelman JD, Schman B, de Haan RJ. Determinants of disability and quality of life in mild to moderate Parkinson disease. *Neurology*. 2008;70:2241-2247.