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Effect of transcranial direct current stimulation on learning in older adults with and without Parkinson's disease: A systematic review with meta-analysis

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ABSTRACT

Older adults with and without Parkinson's disease show impaired retention after training of motor or cognitive skills. This systematic review with meta-analysis aims to investigate whether adding transcranial direct current stimulation (tDCS) to motor or cognitive training versus placebo boosts motor sequence and working memory training. The effects of interest were estimated between three time points, i.e. pre-training, post-training and follow-up. This review was conducted according to the PRISMA guidelines (PROSPERO: CRD42022348885). Electronic databases were searched from conception to March 2023. Following initial screening, 24 studies were eligible for inclusion in the qualitative synthesis and 20 could be included in the meta-analysis, of which 5 studies concerned motor sequence learning (total n = 186) and 15 working memory training (total n = 650). Results were pooled using an inverse variance random effects meta-analysis. The findings showed no statistically significant additional effects of tDCS over placebo on motor sequence learning outcomes. However, there was a strong trend showing that tDCS boosted working memory training, although methodological limitations and some heterogeneity were also apparent. In conclusion, the present findings do not support wide implementation of tDCS as an add-on to motor sequence training at the moment, but the promising results on cognitive training warrant further investigations.

1. Introduction

The persistence of learning outcomes after a period without practice has been defined as the process of retention (Kantak and Winstein 2012). Older adults frequently present with motor and/or cognitive impairments, which affect retention (Hedden and Gabrieli 2004, King et al. 2013). These deficits are even greater in people with Parkinson's disease (PwPD) (Marinelli et al. 2017). Impaired cortico-striatal function as a result of ageing and exaggerated by dopamine-deficiency in PwPD may partly explain these retention deficits (King et al. 2013, Marinelli et al. 2017). Equally, the prefrontal circuits involved in executive function may impact the ability to preserve learning gains (Wu and Hallett 2005). As ageing and Parkinson's disease can be viewed as related and partially overlapping processes (Coleman and Martin 2022), we studied these as part of a continuum. Therefore, in this study we investigated whether relearning of motor and/or cognitive skills can be enhanced by transcranial direct current stimulation (tDCS), ultimately facilitating independence in daily life in both older adults and PwPD.

Non-invasive brain stimulation techniques such as tDCS have the potential to enhance the susceptibility for learning (Buch et al. 2017, Coffman et al. 2014). tDCS comprises an electrical current of 1–4 mA applied to the scalp with at least two electrodes (Nitsche and Bikson 2017, Nitsche and Paulus 2000). The most common explanation for tDCS effects is the depolarization of membrane potentials of cortical neurons, which are brought closer to their intrinsic threshold for eliciting action potentials (Nitsche and Paulus 2000). Recent study showed that specific tDCS-protocols enhanced cortical excitability, creating prolonged after-effects not witnessed after sham stimulation in healthy young individuals (Agboada et al. 2020). The online (improvements seen during training) and offline effects (improvements seen after training) of tDCS may thus eventually facilitate long-term memory formation (Kronberg et al. 2017).

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Recently, we found in a randomized clinical trial that when adding tDCS to writing training in PwPD, practice effects were greater at 24-hour retention compared to training plus sham (Broeder et al. 2023). However, when considering the wider spectrum of learning studies involving both PwPD and healthy people, the effects of tDCS-augmentation seemed mixed and highly task-dependent (Reis et al. 2015, Reis et al. 2009, Saucedo Marquez et al. 2013). Only two systematic reviews focused on the effects of tDCS + training. Beretta et al. 2020 found synergistic effects for cognition and upper limb function when adding tDCS to training in PwPD (Beretta et al. 2020), although a meta-analysis was not performed and retention not studied. Hashemirad et al. 2016 showed favorable effects for multiple sessions of tDCS + training on the acquisition and retention of motor sequence learning (MSL) based on just two studies in older adults (Hashemirad et al. 2016). In both reviews, endpoints with or without tDCS were pooled at different time points of learning. Therefore, the isolated effects of tDCS as a possible booster of learning are at present largely unknown. The current systematic review aimed to address this gap by investigating the current state of the art on the effects of tDCS added to training in older adults and PwPD. As it is possible that tDCS can rescue some age-related but not disease-related impairments or vice versa, we also distinguished between these subgroups in an exploratory analysis.

To reduce heterogeneity and allow for a meta-analytic approach, we strictly selected studies with placebo control, comparable anodal tDCS procedures and clearly defined learning studies in two specific motor and cognitive categories. First, we investigated whether tDCS applied to the primary motor cortex (M1) during MSL would be beneficial. Second, we examined whether tDCS of the prefrontal cortex (PFC) during cognitive training would help working memory (WM). WM represents a component of executive function providing a temporary representation of the information needed for goal-directed behavior, and as such is highly relevant for learning and rehabilitation (D'Esposito 2007). The primary research question was whether tDCS, when added to MSL- or WM-training, resorted in better learning outcomes than sham + training. We compared three specific contrasts: 1) pre-post; 2) pre-retention and 3) post-retention. We hypothesized that tDCS + training would have a superior effect on training outcomes at all three time points as compared to sham + training.

2. Methods

This study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al. 2009) and registered in the International Prospective Register Of Systematic Reviews (PROSPERO CRD42022348885) while formal screening of studies against eligibility criteria was ongoing.

2.1. Search strategy

We performed electronic database searches in March 2022 and 2023 (update) using PubMed, CINAHL, EMBASE, Web of Science, The Cochrane Library and the Physiotherapy Evidence Database (PEDro). We searched for records published online from inception of these databases without any date restrictions. Search terms were based on the population (Parkinson's disease, healthy aging) and intervention (transcranial direct current stimulation, motor or cognitive training). The electronic search strategy for each database can be found in Appendix A.

2.2. Study selection

Based on the following eligibility criteria we selected: (1) Prospective randomized controlled trials, including parallel-group or cross-over designs; (2) studies on humans without neurological disorders older than 60 (i.e. mean age of sample) or diagnosed with idiopathic Parkinson's disease; and (3) studies with samples of minimal 10 participants across groups. We also selected (4) interventional studies of anodal tDCS added to motor or cognitive training regardless of the number of training sessions, as even a single session could trigger short-term retention (Broeder et al. 2023). Other criteria were: (5) studies with sham-stimulation added to the same training protocol as tDCS; (6) studies reporting MSL or WM outcomes; (7) studies with coherence between training and outcomes (i.e. motor-motor, cognitive-cognitive); (8) studies with post-intervention outcomes without applying tDCS, capturing true 'offline' effects and (9) studies in peer-reviewed journals. Two reviewers (BV and AM/CH/KP, see acknowledgements) independently screened the results against the above-described criteria (see Fig. 1). Disagreements regarding study eligibility were resolved through discussion between the reviewers. A senior researcher (AN) approved the final list of included studies.

2.3. Risk of bias assessment

Two reviewers (BV and KP) independently assessed the internal validity of the studies using the Study Quality Assessment Tool for Controlled Intervention Studies of the National Heart, Lung, and Blood Institute (NIH) (National Heart, Lung, and Blood Institute 2021). This tool consists of 14 questions regarding randomization, treatment allocation, blinding, group similarity at baseline, dropout, adherence, avoidance of other interventions, outcome measures, power, pre-specification of outcomes and intention-to-treat. Inconsistencies were resolved through a third moderator (FH). Additionally, we visually explored funnel plots for publication bias.

2.4. Data extraction

Two reviewers (BV and AM) extracted the data independently using a standardized form (see Appendix B). Discrepancies were resolved via discussion. In case of missing data, the corresponding author was contacted by email. A reminder email was sent after two weeks to non-responders.

2.5. Data synthesis

For the meta-analysis, motor sequence reaction times (in milliseconds) and working memory accuracy (number of correct responses) were the primary outcomes of interest. If at least two studies with available results were identified, pooling was carried out using an inverse variance random effects meta-analysis in Review Manager (*RevMan*, *Version* 5.4.1, *The Cochrane Collaboration*, 2020). We used this approach to counter the possible effects of heterogeneity in effect sizes due to varying populations, intervention protocols and statistical designs across the included studies.

In a first step, we compared mean values at baseline between intervention and control groups for each outcome using either an independent samples *t*-test or a Mann-Whitney *U* test. This revealed comparable groups at baseline ($p > 0.05$) for each outcome. Hence, standardized mean differences between intervention and control groups with 95% confidence intervals and two-sided p-values for each study were calculated between two or three time points (pre-post, pre-follow-up and post-follow-up). If not reported, standard deviations of the aforementioned changes were either provided by the authors upon request ($n = 10$), or imputed based on a weighted correlation between the reported standard deviations of the included studies for the same time points ($n = 10$) (Higgins et al. 2011). Next, the overall effect size across studies was quantified. An effect size of 0.2 was interpreted as a small effect, 0.5 a moderate effect and 0.8 a large effect (Cohen 2013). P-values < 0.05 were considered statistically significant. Heterogeneity between studies was explored using the χ^2- and I^2-statistics. A significant χ^2 ($p < 0.05$) and an I^2-value greater than 50% were considered as representative of substantial heterogeneity (Higgins et al. 2003), in which case a leave-one-out sensitivity analysis was conducted. We also conducted a

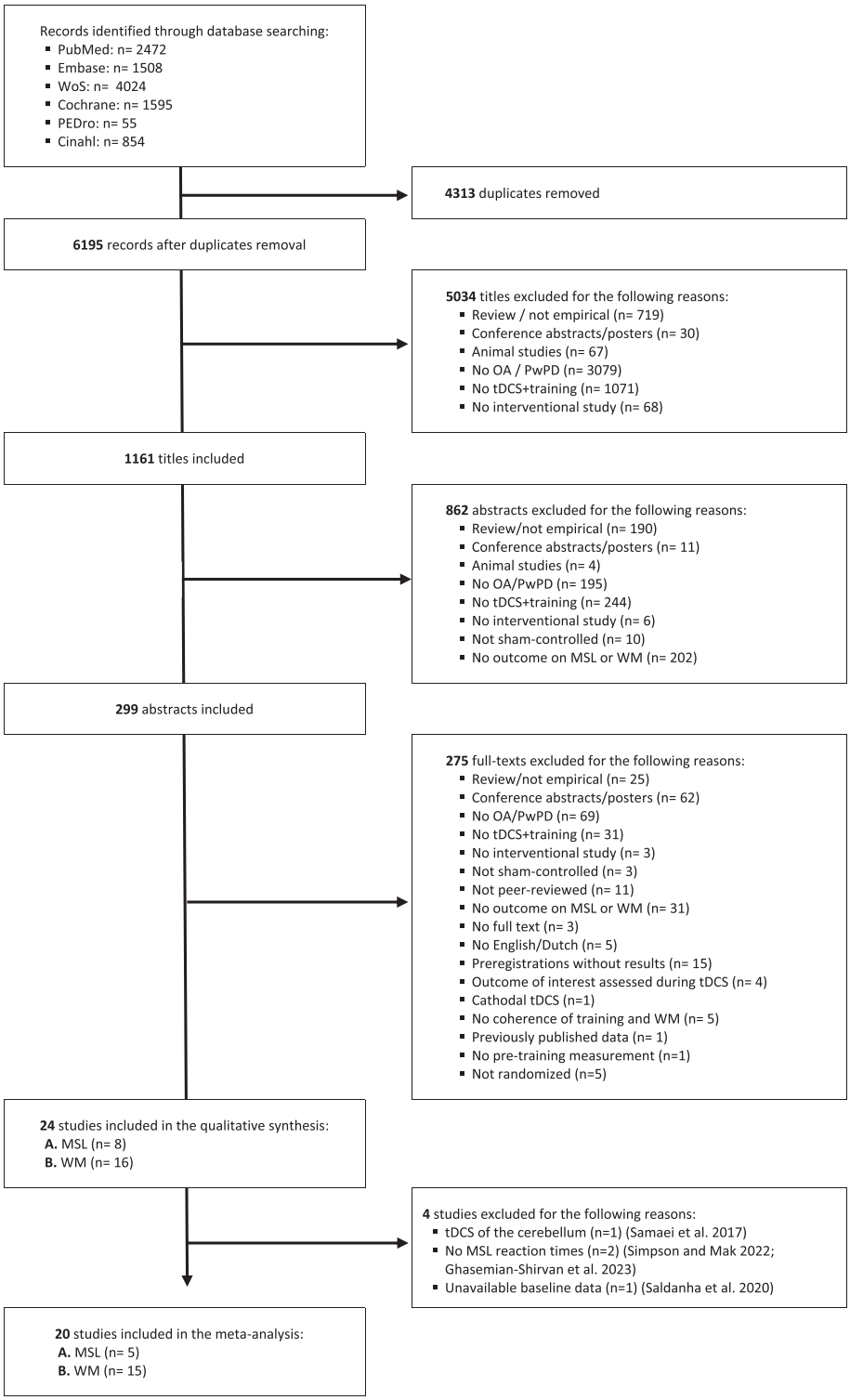

Fig. 1. Flow chart. Abbreviations: MSL - motor sequence learning; OA - older adults; PwPD - patients with Parkinson's disease; tDCS - transcranial direct current stimulation; WM - working memory.

qualitative analysis on all studies, whereby we calculated the % of studies with significantly favorable results comparing tDCS + training compared to sham + training.

3. Qualitative synthesis

3.1. Search results

A total of 5710 non-duplicate studies were screened according to the eligibility criteria, resulting in 24 studies included in the qualitative synthesis (Fig. 1). The details of these studies are described in Table 2.

Table 1
Risk of bias assessment of included studies.

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Score
Motor sequence learning															
Ghasemian-Shirvan 2023	Y	?	?	Y	Y	Y	Y	Y	?	?	Y	Y	N	N	8
Abedi 2022	Y	Y	Y	N	Y	Y	Y	Y	?	?	Y	Y	N	Y	10
Greeley 2022	Y	?	?	?	?	Y	Y	Y	?	?	Y	N	N	N	5
Simpson and Mak 2022	Y	Y	Y	N	N	N	Y	Y	N	Y	N	N	N	N	6
Firouzi 2020	Y	?	?	N	N	Y	?	?	?	?	Y	N	N	N	3
King 2020	Y	?	?	Y	?	Y	Y	Y	Y	?	N	N	Y	N	7
Dumel 2018	Y	?	?	N	?	Y	?	?	?	?	Y	N	N	?	3
Samaei 2017	Y	?	?	Y	?	Y	Y	Y	?	?	N	Y	Y	N	7
Working memory															
Antonenko 2022	Y	Y	Y	N	Y	?	Y	Y	N	?	Y	N	Y	Y	9
Assecondi 2022	Y	?	?	N	?	Y	Y	Y	?	Y	Y	N	Y	N	7
Au 2022	Y	?	?	Y	?	?	Y	Y	Y	?	Y	N	N	N	6
Teixeira-Santos 2022	Y	Y	Y	N	Y	Y	Y	Y	?	?	Y	Y	N	Y	10
Krebs 2021	Y	?	?	Y	?	Y	Y	N	?	?	Y	N	Y	N	6
Horne 2021	Y	?	N	?	?	Y	Y	Y	Y	?	Y	Y	Y	N	8
Simko 2021	Y	?	?	Y	?	Y	?	?	?	?	Y	N	N	N	4
Saldanha 2020	Y	Y	Y	N	N	N	?	?	N	?	Y	N	Y	N	5
Nissim 2019 (1)	Y	?	?	Y	Y	Y	?	?	?	?	Y	N	Y	?	6
Nissim 2019 (2)	Y	?	?	Y	Y	Y	?	?	?	?	Y	N	Y	?	6
Manenti 2018	Y	Y	Y	Y	?	Y	Y	Y	Y	Y	Y	Y	N	Y	12
Nilsson 2017	Y	?	?	Y	Y	?	Y	Y	?	?	Y	Y	N	N	7
Stephens 2016	Y	?	?	?	?	Y	Y	Y	Y	?	Y	N	N	Y	7
Jones 2015	Y	?	?	N	N	?	Y	Y	?	?	Y	N	N	Y	5
Nilsson 2015	Y	?	?	N	?	Y	Y	Y	Y	?	Y	N	N	N	6
Park 2014	Y	?	?	Y	?	Y	?	?	?	?	Y	N	N	?	4

Q1: Described as randomized; Q2: Adequate randomization; Q3: Allocation concealment; Q4: Blinding of persons receiving and providing the intervention; Q5: Blinding of person assessing the outcomes; Q6: Similarity of groups at baseline; Q7: Overall dropout; Q8: Differential dropout between groups; Q9: Adherence; Q10: Avoiding other interventions; Q11: Outcome measures assessment; Q12: Power calculation; Q13: Prespecified outcomes; Q14: Intention-to-treat analysis

3.2. Study samples

Twenty-one studies comprised older adults (Abedi et al. 2022, Antonenko et al. 2022, Assecondi et al. 2022, Au et al. 2022, Dumel et al. 2018, Ghasemian-Shirvan et al. 2023, Greeley et al. 2022, Horne et al. 2021, Jones et al. 2015; King et al. 2020; Krebs et al. 2021, Nilsson et al. 2015, Nilsson et al. 2017, Nissim et al. 2019, Nissim et al. 2019, Park et al. 2014, Saldanha et al. 2020, Samaei et al. 2017, Simko et al. 2021, Stephens and Berryhill 2016, Teixeira-Santos et al. 2022), while three studies investigated PwPD (Firouzi et al. 2021, Manenti et al. 2018, Simpson and Mak 2022). Two of those examined PwPD with mild cognitive impairment (Firouzi et al. 2021, Manenti et al. 2018). Sample sizes varied from 10 to 65 participants, of which 456 participants underwent tDCS and 471 participants sham. Intervention group sizes ranged from 8 to 32, with a mean age between 61.6 and 77.1 years, and control group sizes ranged from 8 to 31, with a mean age between 61.3 and 77.1 years. For PwPD, Hoehn and Yahr stages in the ON medication phase ranged from 1.6 to 2.6 in the intervention and control groups. The Unified Parkinson Disease Rating Scale part III scores ON medication varied from 24.4 to 41.0 in the intervention and from 22.7 to 39.0 in the control group.

3.3. Study designs

Eighteen studies consisted of parallel groups (Abedi et al. 2022, Antonenko et al. 2022, Assecondi et al. 2022, Au et al. 2022, Dumel et al. 2018, Greeley et al. 2022, Horne et al. 2021, Jones et al. 2015, King et al. 2020, Krebs et al. 2021, Manenti et al. 2018, Nilsson et al. 2017, Nissim et al. 2019, Park et al. 2014, Samaei et al. 2017, Simpson and Mak 2022, Stephens and Berryhill 2016, Teixeira-Santos et al. 2022), while the remaining studies applied a cross-over design (Firouzi et al. 2021, Ghasemian-Shirvan et al. 2023, Nilsson et al. 2015, Nissim et al. 2019, Saldanha et al. 2020, Simko et al. 2021). For the cross-over studies, the results prior and post cross-over were considered since a wash-out period was taken into account. Total study periods ranged from 2 h to 12 months.

3.4. Study quality

A detailed quality assessment can be found in Table 1. All studies were described as randomized, which was an inclusion criterion (item 1). However, only five studies reported computerized randomizations (items 2 and 3). Twelve studies were double-blind (participant and tDCS provider), while nine were single-blind (participant only) (item 4). Blinding of the person providing tDCS was often achieved by using the operation mode of the tDCS apparatus. Most studies ($n = 18$) demonstrated similar baseline characteristics for intervention and control groups (item 6). Seventeen studies reported an overall dropout rate at endpoint lower than 20% (item 7), of which 16 studies maintained their differential dropout rate between groups below 15% (item 8). Only 7/24 studies reported that their sample size had at least 80% power (item 12). Nine studies presented a clear hypothesis pre-specifying their primary outcome and comparator (item 13). Six studies reported that all randomized participants were analyzed according to their assigned group (item 14). Overall, the majority of studies ($n = 21$) showed high risk of bias on at least 5 items. The three studies with the highest methodological quality were Abedi et al. 2022, Teixeira-Santos et al. 2022 and Manenti et al. 2018. A sum score is provided in Table 1 for interpretation purposes, taking into account that even studies with a relatively high score can still have a single 'fatal' flaw affecting the interpretation of the outcomes.

3.5. Descriptors of study interventions

3.5.1. Transcranial direct current stimulation (tDCS)

The studies investigating MSL administered 1–2 mA anodal tDCS to the M1, except for the study of Samaei et al. targeting the cerebellum (Samaei et al. 2017). tDCS electrode sizes varied from 25 to 46 cm^2,

Table 2
Systematic overview of characteristics of included studies per outcome.

Study (First author(s) year)	Design	Population	Groups	tDCS1. Anode/cathode location 2. Intensity 3. Electrode size 4. Current density 5. Duration 6. Number of sessions	Training 1. Type 2. Moment 3. Medication status (PD-specific)	N	Age (Years)	Sex (M,F)	HY stage (PD-specific)	UPDRS-III (PD-specific)	LEDD in mg (PD-specific)	Assessment (without tDCS) 1. Time points 2. Medication status (PD-specific)
Motor sequence learning												
Ghasemian-Shirvan 2023	Cross-over	OA	A	1. M1/contralateral supraorbital area 2. 2 mA 3. 35 cm^2 4. 0.06 mA/cm^2 5. 21.8 ± 1.2 min 6. 1 session	1. SRTT 2. During tDCS/Sham	25	72.1 ± 5.9	11, 14	NA	NA	NA	1. 24 h follow-up
			C	Sham		25	72.1 ± 5.9	11, 14	NA	NA	NA	
Abedi 2022	Parallel groups	OA	A	1. M1/contralateral supraorbital area 2. 1 mA 3. 25 cm^2 4. 0.04 mA/cm^2 5. 20 min 6. 5 sessions	1. SRTT 2. During tDCS/Sham	14	69.8 ± 4.0	9, 5	NA	NA	NA	1. 24 h and 1 week follow-up
			C	Sham		14	70.1 ± 3.7	7, 7	NA	NA	NA	
Greeley 2022	Parallel groups	OA	A	1. M1/contralateral orbitofrontal area 2. 2 mA 3. 25 cm^2 4. 0.08 mA/cm^2 5. 20 min 6. 2 sessions	1. SRTT 2. During tDCS/Sham	12	72.8 ± 6.9	6, 6	NA	NA	NA	1. 24 to 72 h follow-up
			C	Sham		12	68.5 ± 4.5	5, 7	NA	NA	NA	
Simpson and Mak 2022	Parallel groups	PwPD	A	1. M1/contralateral orbitofrontal area 2. 2 mA 3. 35 cm^2 4. 0.06 mA/cm^2 5. 20 min 6. 1 session	1. SRTT 2. During tDCS/Sham 3. ON	8	65.0 ± 6.0	5, 3	2.0 ± 0.0	41.0 ± 5.0	783.0 ± 288.0	1. End of treatment 2. ON
			C	Sham		8	66.0 ± 8.0	4, 4	2.0 ± 1.0	39.0 ± 10.0	850.0 ± 241.0	
Firouzi 2020	Cross-over	PwPD-MCI	A	1. M1/contralateral orbitofrontal area 2. 2 mA 3. 46,02 cm^2 4. 0.04 mA/cm^2 5. R 6. 1 session	1. SRTT 2. During tDCS/Sham 3. ON	11	77.1 ± NR	8, 3	2.6 ± 0.5	24.4 ± 4.3	784.3 ± 592.6	1. End of treatment and 1 week follow-up 2. NR
			C	Sham		11	77.1 ± NR	8, 3	2.6 ± 0.5	24.4 ± 4.3	784.3 ± 592.6	

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Table 2 (*continued*)

Study (First author(s) year)	Design	Population	Groups	tDCS1. Anode/cathode location 2. Intensity 3. Electrode size 4. Current density 5. Duration 6. Number of sessions	Training 1. Type 2. Moment 3. Medication status (PD-specific)	N	Age (Years)	Sex (M,F)	HY stage (PD-specific)	UPDRS-III (PD-specific)	LEDD in mg (PD-specific)	Assessment (without tDCS) 1. Time points 2. Medication status (PD-specific)
King 2020	Parallel groups	OA	A	1. M1/contralateral orbitofrontal area 2. 1 mA 3. 25 cm^2 4. 0.04 mA/cm^2 5. 15 min 6. 1 session	1. SRTT 2. Before tDCS/Sham	20	67.8 ± 5.5	11, 9	NA	NA	NA	1. End of treatment
			C	Sham		20	67.3 ± 4.5	11, 9	NA	NA	NA	
Dumel 2018	Parallel groups	OA	A	1. M1/contralateral supraorbital area 2. 2 mA 3. 45 cm^2 4. 0.04 mA/cm^2 5. 20 min 6. 5 sessions	1. SRTT 2. During tDCS/Sham	18	61.6 ± 5.9	9, 9	NA	NA	NA	1. 24 h and 12 weeks follow-up
			C	Sham		19	61.3 ± 6.8	9, 10	NA	NA	NA	
Samaei 2017	Pararllel groups	OA	A	1. Cerebellum/right arm 2. 2 mA 3. 25 cm^2 4. 0.08 mA/cm^2 5. 20 min 6. 1 session	1. SRTT 2. During tDCS/Sham	15	69.4 ± 5.1	4, 11	NA	NA	NA	1. End of treatment and 48 h follow-up
			C	Sham		15	68.0 ± 5.6	3, 12	NA	NA	NA	
Working memory												
Antonenko 2022	Parallel groups	OA	A	1. Left dlpfc/right supraorbital area 2. 1 mA 3. 20 cm^2 4. 0.05 mA/cm^2 5. 20 min 6. 9 sessions	1. CT (tablet, computer) 2. During tDCS/Sham	24	NR	NR	NA	NA	NA	1. End of treatment and 1 month follow-up
			C	Sham		27	NR	NR	NA	NA	NA	
Assecondi 2022	Parallel groups	OA	A	1. Dlpfc/ contralateral supraorbital area 2. 2 mA 3. NR 4. NR 5. 20 min 6. 5 sessions	1. WM training (computer, 20 min) 2. During tDCS/Sham	14	67.5 ± 6.2	7, 7	NA	NA	NA	1. 48 h follow-up
			C	Sham		14	68.4 ± 6.1	7, 7	NA	NA	NA	
Au 2022	Parallel groups	OA	A	1.Left dlpfc/right supraorbital area 2.2 mA 3.35 cm^2 4.0.06 mA/cm^2 5.25 min 6.5 sessions	1. WM training (tablet) 2. During tDCS/Sham	24	NR	NR	NA	NA	NA	1. End of treatment and 3 months follow-up

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Table 2 (*continued*)

Study (First author(s) year)	Design	Population	Groups	tDCS1. Anode/cathode location 2. Intensity 3. Electrode size 4. Current density 5. Duration 6. Number of sessions	Training 1. Type 2. Moment 3. Medication status (PD-specific)	N	Age (Years)	Sex (M,F)	HY stage (PD-specific)	UPDRS-III (PD-specific)	LEDD in mg (PD-specific)	Assessment (without tDCS) 1. Time points 2. Medication status (PD-specific)
			C	Sham		28	NR	NR	NA	NA	NA	
Teixeira-Santos 2022	Parallel groups	OA	A	1. Left dlpfc/right supraorbital area 2. 2 mA 3. 35 cm^2 4. 0.06 mA/cm^2 5. 20 min 6. 5 sessions	1. WM training 2. During tDCS/Sham	18	67.6 ± 5.1	4, 14	NA	NA	NA	1. End of treatment and 2w follow-up
			C	Sham		18	68.7 ± 7.0	5, 13	NA	NA	NA	
Krebs 2021	Parallel groups	OA	A	1. Left dlpfc/right supraorbital area 2. 2 mA 3. 35 cm^2 4. 0.06 mA/cm^2 5. 20 min 6. 10 sessions	1. CT (computer, 50 min) 2. During tDCS/Sham	17	75.0 ± NR	9, 8	NA	NA	NA	1. End of treatment and 6m and 12m follow-up
			C	Sham		22	70.5 ± NR	12, 10	NA	NA	NA	
Horne 2021	Parallel groups	OA	A	1. Left prefrontal cortex/right supraorbital area 2. 2 mA 3. 25 cm^2 4. 0.08 mA cm^2 5. 20 min 6. 5 sessions	1. Decision-making training 2. During tDCS/Sham	30	NR	NR	NA	NA	NA	1. End of treatment and 3 months follow-up
			C	Sham		31	NR	NR	NA	NA	NA	
Simko 2021	Cross-over	OA	A	1. Left DLPFC/right middle frontal gyrus 2. 2 mA 3. 25 cm^2 4. 0.08 mA/cm^2 5. 20 min 6. 1 session	1. WM training 2. During tDCS/Sham	25	68.8 ± 4.7	8, 17	NA	NA	NA	1. End of treatment
			C	Sham		25	68.8 ± 4.7	8, 17	NA	NA	NA	
Saldanha 2020	Cross-over	OA	A	1. Left dlpfc/right supraorbital area 2. 2 mA 3. 25 cm^2 4. 0.08 mA/cm^2 5. 30 min 6. 1 session	1. N-back task with flankers 2. During tDCS/Sham	10	63.8 ± 2.6	0, 30	NA	NA	NA	1. End of treatment
			C	Sham		10	63.8 ± 2.6	0, 30	NA	NA	NA	
Nissim 2019 (1)	Parallel groups	OA	A	1. Bilateral dlpfc 2. 2 mA 3. 35 cm^2 4. 0.06 mA/cm^2 5. 20 min 6. 10 sessions	1. CT (computer, 40 min) 2. During tDCS/Sham	14	73.6 ± 7.8	7, 7	NA	NA	NA	1. End of treatment

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Table 2 (*continued*)

Study (First author(s) year)	**Design**	**Population**	**Groups**	**tDCS**1. Anode/cathode location 2. Intensity 3. Electrode size 4. Current density 5. Duration 6. Number of sessions	**Training** 1. Type 2. Moment 3. Medication status (PD-specific)	**N**	**Age (Years)**	**Sex (M,F)**	**HY stage (PD-specific)**	**UPDRS-III (PD-specific)**	**LEDD in mg (PD-specific)**	**Assessment (without tDCS)** 1. Time points 2. Medication status (PD-specific)
			C	Sham		14	73.8 ± 7.1	6, 8	NA	NA	NA	
Nissim 2019 (2)	Cross-over	OA	A	1. Bilateral dlpfc 2. 2 mA 3. 35 cm^2 4. 0.06 mA/cm^2 5. 12 min 6. 1 session	1. N-back WM task 2. During tDCS/Sham	16	71.8 ± 7.3	10, 6	NA	NA	NA	1. End of treatment
			C	Sham		16	71.8 ± 7.3	10, 6	NA	NA	NA	
Manenti 2018	Parallel groups	PwPD-MCI	A	1. Left dlpfc/right supraorbital area 2. 2 mA 3. 35 cm^2 4. 0.06 mA/cm^2 5. 25 min 6. 10 sessions	1. CT (computer) 2. During tDCS/Sham 3. ON	11	65.5 ± 6.4	5, 6	1.6 ± 0.8	26.0 ± 10.3	618.6 ± 304.4	1. End of treatment and 3 months follow-up 2. ON
			C	Sham		11	63.8 ± 7.1	7, 4	1.9 ± 0.5	22.7 ± 7.8	559.8 ± 306.5	
Nilsson 2017	Parallel groups	OA	A	1. Left dlpfc/right supraorbital area 2. 2 mA 3. 35 cm^2 4. 0.06 mA/cm^2 5. 25 min 6. 20 sessions	1. WM training (40 min) 2. During tDCS/Sham	32	69.3 ± 2.7	16, 16	NA	NA	NA	1 week follow-up
			C	Sham		33	69.6 ± 3.0	11, 22	NA	NA	NA	
Stephens 2016	Parallel groups	OA	A	1. Right prefrontal cortex/left cheek 2. 2 mA 3. 35 cm^2 4. 0.06 mA/cm^2 5. 15 min 6. 5 sessions	1. WM training (45 min) 2. During tDCS/Sham	30	68.6 ± NR	13, 17	NA	NA	NA	1. 1 month follow-up
			C	Sham		30	69.9 ± NR	14, 16	NA	NA	NA	
Jones 2015	Parallel groups	OA	A	1. Prefrontal cortex/ contralateral cheek 2. 1.5 mA 3. 35 cm^2 4. 0.04 mA/cm^2 5. 10 min 6. 10 sessions	1. WM training 2. During tDCS/Sham	18	63.9 ± 4.3	NR	NA	NA	NA	1. End of treatment and 1 month follow-up
			C	Sham		18	64.3 ± 5.3	NR	NA	NA	NA	
Nilsson 2015	Cross-over	OA	A	1. Left dlpfc/contralateral supraorbital area 2. 2 mA 3. 35 cm^2 4. 0.06 mA/cm^2 5. 25 min 6. 1 session	1. WM training 2. During tDCS/Sham	30	69.0 ± 7.0	16, 14	NA	NA	NA	1. End of treatment

(*continued on next page*)

Table 2 (*continued*)

Study (First author(s) year)	Design	Population	Groups	tDCS1. Anode/cathode location 2. Intensity 3. Electrode size 4. Current density 5. Duration 6. Number of sessions	Training 1. Type 2. Moment 3. Medication status (PD-specific)	N	Age (Years)	Sex (M,F)	HY stage (PD-specific)	UPDRS-III (PD-specific)	LEDD in mg (PD-specific)	Assessment (without tDCS) 1. Time points 2. Medication status (PD-specific)
			C	Sham		30	69.0 ± 7.0	16, 14	NA	NA	NA	
Park 2014	Parallel groups	OA	A	1. Prefrontal cortex/non-dominant arm 2. 2 mA 3. 25 cm^2 4. 0.08 mA/cm^2 5. 30 min 6. 10 sessions	1. CT (computer) 2. During tDCS/Sham	20	70.1 ± 3.4	7, 13	NA	NA	NA	1. End of treatment and 1 month follow-up
			C	Sham		20	69.4 ± 3.1	6, 14	NA	NA	NA	

Abbreviations: A - active tDCS group; C - control group; CT - cognitive training; dlpfc - dorsolateral prefrontal cortex; HY - Hoehn and Yahr; LEDD – Levodopa equivalent daily dose; M1 - primary motor cortex; MCI - mild cognitive impairment; NA - not applicable; NR - not reported; OA - older adults; PD - Parkinson's disease; PwPD - people with Parkinson's disease; SRTT - serial reaction time task; tDCS - transcranial direct current stimulation; UPDRS-III – Unified Parkinson's disease rating scale - part III; WM - working memory

resulting in current densities of 0.04–0.08 mA/cm^2. The majority of interventions comprised one session of 15–20 min of tDCS added to training (Firouzi et al. 2021, Ghasemian-Shirvan et al. 2023, King et al. 2020, Samaei et al. 2017, Simpson and Mak 2022). Abedi et al., Dumel et al. and Greeley et al. offered multiple sessions of 20 min of tDCS + training (Abedi et al. 2022, Dumel et al. 2018, Greeley et al. 2022). tDCS duration was not reported by Firouzi et al. (Firouzi et al. 2021). Seven studies administered tDCS simultaneously with training (Abedi et al. 2022, Dumel et al. 2018, Firouzi et al. 2021, Ghasemian-Shirvan et al. 2023, Greeley et al. 2022, Samaei et al. 2017, Simpson and Mak 2022), while King et al. postponed tDCS to immediately post-training (King et al. 2020). The studies reporting on WM investigated anodal tDCS applied to the PFC. Current intensities were set at 1–2 mA and electrodes were sized 20–35 cm^2. Current densities ranged from 0.04 to 0.08 mA/cm^2. TDCS was administered simultaneously with training, comprising 1–20 sessions of 10–30 min. No study applied high-definition tDCS. Generally, sham-tDCS consisted of 10–60 s of stimulation preceded and followed by a 10–30 s ramp up and down of current at the beginning of the sham period. Some studies also incorporated this at the end of sham (Assecondi et al. 2022, Au et al. 2022, Jones et al. 2015, Manenti et al. 2018).

3.5.2. *Training*

All MSL studies used unimanual serial reaction time tasks (SRTTs) of 4–12 items as the trained task. The SRTTs were practiced with the dominant right hand in the studies of Ghasemian-Shirvan et al. 2023, Abedi et al. 2022, Greeley et al. 2022, King et al. 2020 (experiment 2) and Dumel et al. 2018; and with the non-dominant left hand in experiment 1 of King et al. 2020. In Firouzi et al. 2020, the disease-dominant hand of PwPD was addressed. All SRTTs were trained with the same hand and finger(s) as employed during assessment. Most SRTTs used the four fingers except the thumb (Dumel et al. 2018, Ghasemian-Shirvan et al. 2023, Greeley et al. 2022, King et al. 2020, Simpson and Mak 2022), while three SRTTs only employed the index finger (Abedi et al. 2022, Firouzi et al. 2021, Samaei et al. 2017). The number of training sessions equaled the number of stimulation sessions (i.e. 1 to 5), since they were paired. PwPD were trained in the ON phase of the medication cycle (Firouzi et al. 2021, Simpson and Mak 2022). Five studies assessing WM offered computerized cognitive training covering various cognitive subdomains (Krebs et al. 2021, Manenti et al. 2018, Nissim et al. 2019, Nissim et al. 2019, Park et al. 2014). In eleven studies WM was specifically trained (Antonenko et al. 2022, Assecondi et al. 2022, Au et al. 2022, Horne et al. 2021, Jones et al. 2015, Nilsson et al. 2015, Nilsson et al. 2017, Saldanha et al. 2020, Simko et al. 2021, Stephens and Berryhill 2016, Teixeira-Santos et al. 2022). The number of training sessions equaled the number of stimulation sessions (i.e. 1 to 20). PwPD were trained in ON (Manenti et al. 2018).

3.5.3. *Outcomes*

All MSL studies used SRTTs that were identical to their trained version. Post-measurements were performed in 4/8 studies between 5 min to 8 h after the intervention, while follow-up measurements in 6/8 studies between 24 h and 3 months after the intervention. The longest intervention (5 days) was followed by the longest follow-up period (3 months) (Dumel et al. 2018). Similarly for WM, the same tasks were employed for assessment and training in nine studies (Antonenko et al. 2022, Au et al. 2022, Horne et al. 2021, Jones et al. 2015, Nilsson et al. 2015, Nilsson et al. 2017, Saldanha et al. 2020, Simko et al. 2021, Stephens and Berryhill 2016). In case of broad cognitive training and testing (Assecondi et al. 2022, Krebs et al. 2021, Manenti et al. 2018, Nissim et al. 2019, Nissim et al. 2019, Park et al. 2014, Teixeira-Santos et al. 2022), specific WM outcomes were selected based on their coherence with the trained task. The most prevalent outcomes were: backward corsi blocks (Krebs et al. 2021), digit span backward (Manenti et al. 2018, Teixeira-Santos et al. 2022), and n-back tasks (Assecondi et al. 2022, Nissim et al. 2019, Nissim et al. 2019, Park et al. 2014). Post

assessments without tDCS were performed in 13/16 studies. Outcomes were generally measured 5 min post intervention, however Krebs et al. 2021 reported a post measurement period of 0–6 weeks. Eleven studies performed follow-up measurements between 48 h and 12 months following the intervention (Antonenko et al. 2022, Assecondi et al. 2022, Au et al. 2022, Horne et al. 2021, Jones et al. 2015, Krebs et al. 2021, Manenti et al. 2018, Nilsson et al. 2017, Park et al. 2014, Stephens and Berryhill 2016, Teixeira-Santos et al. 2022).

3.6. Main findings

Fig. 2 maps the reported findings of all studies per subdomain. As for MSL, only 1/5 studies showed a statistical difference in favor of tDCS + training compared to sham + training for acquisition. At retention, 2/6 studies exhibited a favorable effect of tDCS. Regarding WM, a minority of studies at post (3/13) and 3/11 at retention indicated that tDCS was beneficial for learning.

4. Meta-analyses

The results of the meta-analyses are presented as forest plots in Figs. 3-4 and included 20/24 studies. Funnel plots are presented in Appendix C and generally show symmetrical distributions.

4.1. Motor sequence learning

Five studies comprising 107 participants were included in the meta-analysis on MSL. The results of three studies were excluded because the cerebellum was targeted (Samaei et al. 2017) or reaction times were not assessed (Simpson and Mak 2022) or unavailable (Ghasemian-Shirvan et al. 2023). The results including the outcomes of the study targeting the cerebellum (Samaei et al. 2017) can be found in the Supplementary Materials. Fig. 3 A-B display the results for pre-post (A) and pre-retention (B) contrasts. No meta-analysis was performed for post-retention, due to insufficient studies ($n = 1$).

Tests for the overall effect showed no significant differences between the intervention and control groups for changes in MSL from pre-post ($Z = 0.01$, $p = 0.99$, ES [95% CI] = 0.00 [−0.60; 0.61]) and from pre-retention ($Z = 0.71$, $p = 0.48$, ES [95% CI] = 0.40 [−0.71; 1.51]). I^2 exceeded 50% for both contrasts. Leaving out the findings of experiment 1 of King et al. 2020 from the pre-post analysis and Abedi et al. 2022 from the pre-retention analysis reduced heterogeneity to $I^2 = 0\%$. Results remained non-significant (Pre-post: $Z = 1.11$, $p = 0.27$, ES [95% CI] = −0.29 [−0.81; 0.23] and pre-retention: $Z = 0.98$, $p = 0.32$, ES [95% CI] = −0.22 [−0.65; 0.21]). Sub-analyses including older adults only showed non-significant findings (see Supplementary Materials). While insignificant, the effects of tDCS were, however, in a positive direction for the pre-post contrast, unlike that for the pooled groups ($Z = 0.51$, $p > 0.05$, ES[95%CI] = 0.19 [−0.54; 0.91]).

4.2. Working memory

Fifteen studies comprising 318 and 332 participants in the intervention and control groups, were included in the meta-analysis on WM. The findings of Saldanha et al. 2020 were excluded as baseline data were unavailable. For Stephens et al. 2016 and Nilsson et al. 2015, results of the 2 mA tDCS group were included. Fig. 4 A-C display the results for pre-post (A), pre-retention (B), and post-retention (C) contrasts, illustrating some non-significant trends in favor of tDCS.

Tests for the overall effect showed a significant difference between the intervention and control groups in change of WM from pre-post ($Z = 2.13$, $p = 0.03$, ES [95% CI] = 0.51 [0.04; 0.97]). However, $\chi 2$ was significant and $I^2 = 84\%$, indicating significant heterogeneity. Leaving out the study of Simko et al. 2021, reduced heterogeneity to $I^2 = 31\%$ and the results became non-significant ($Z = 1.84$, $p = 0.07$, ES [95% CI] = 0.21 [−0.01; 0.44]). We found no significant difference between the intervention and control groups from pre-retention ($Z = 1.63$, $p = 0.10$, ES [95% CI] = 0.14 [−0.03; 0.32]) and from post-retention ($Z = 1.78$, $p = 0.08$, ES [95% CI] = 0.19 [−0.02; 0.40]). Statistical heterogeneity was low for these contrasts. As such, small beneficial effects of tDCS-boosted training over sham were found ($ES = 0.20$) for pre-post and post-retention differences, which were nearly significant. Sub-analyses for older adults only showed non-significant findings (see Supplementary Materials).

5. Discussion

This systematic review with meta-analysis assessed, for the first time, the effects of tDCS combined with motor or cognitive training to improve MSL and WM from pre-post, pre-retention and post-retention. The meta-analysis revealed a trend for a surplus effect of tDCS at acquisition and retention after WM training. In contrast to our

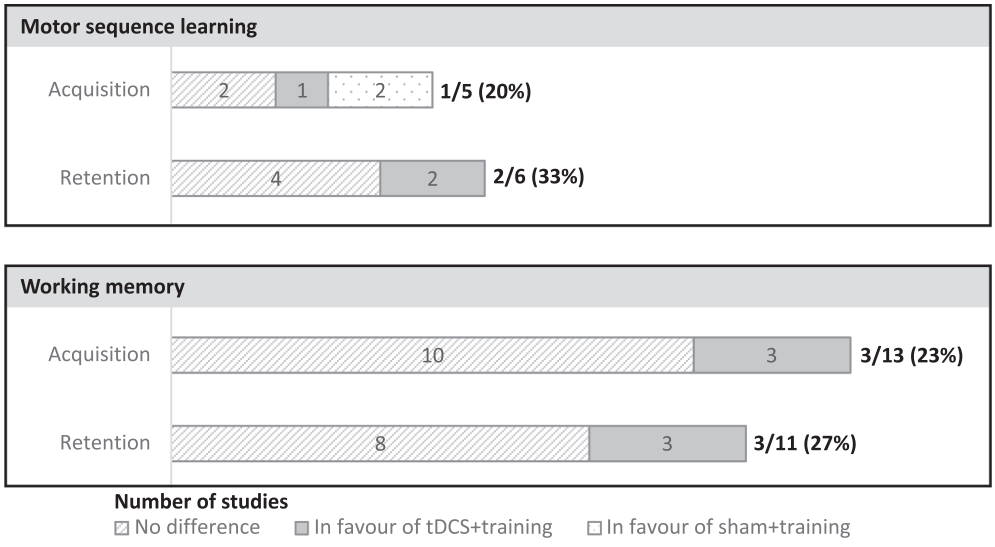

Fig. 2. Reported findings of included studies assessing differences in motor sequence learning and working memory at acquisition and retention in older adults with and without Parkinson's disease Data are presented as: Number of studies with statistically significant differences in favor of tDCS + training ($p < 0.05$) /Total studies (%). Abbreviation: tDCS - transcranial direct current stimulation.

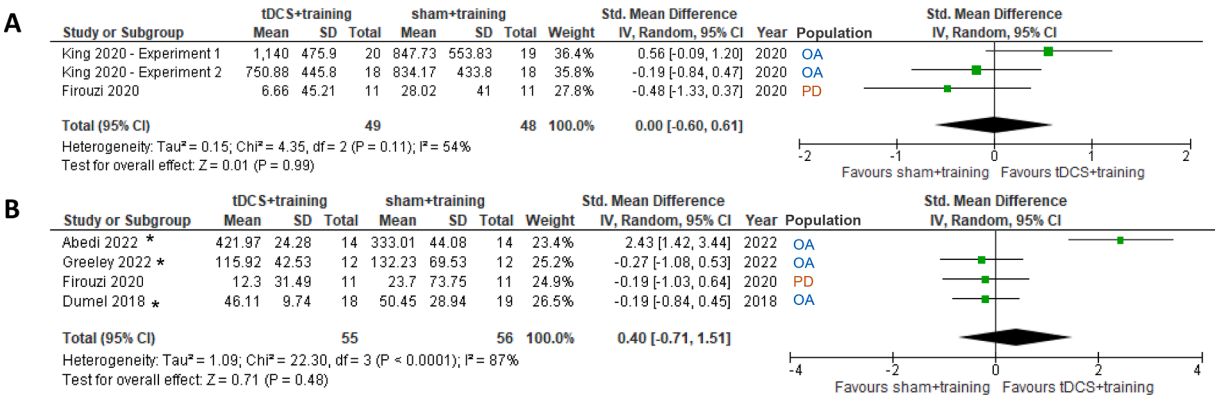

Fig. 3. Metaviews of the effect of training combined with transcranial direct current stimulation showing changes in motor sequence learning A) fr om pre to post intervention and B) from pre to follow-up, pooling older adults with and without Parkinson's disease. Abbreviations: OA - older adults; PD – Parkinson's disease; tDCS - transcranial direct current stimulation. *Multiple intervention sessions.

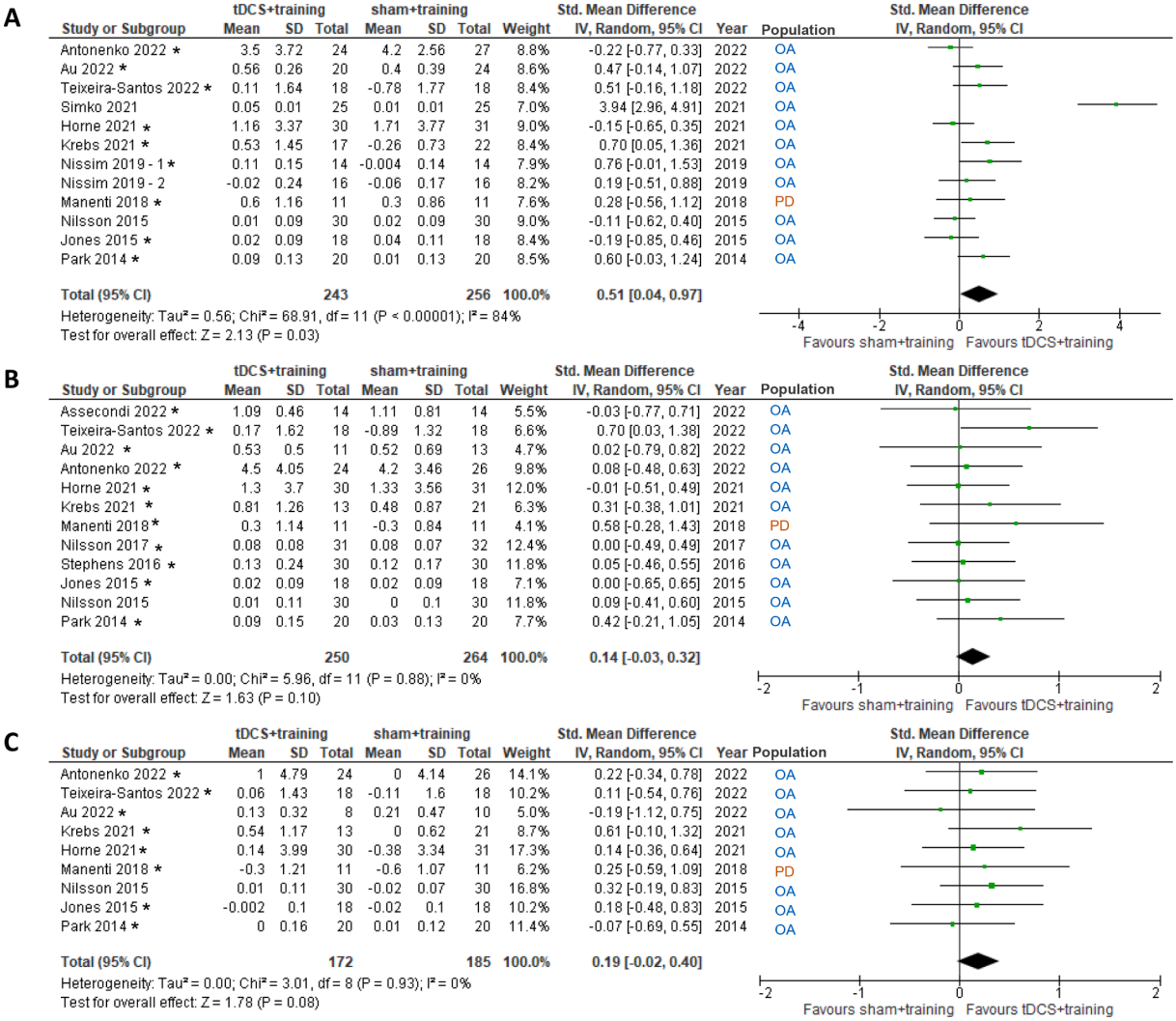

Fig. 4. Metaviews of the effect of training combined with transcranial direct current stimulation showing changes in working memory A) from pre to post intervention B) from pre to follow-up C) from post intervention to follow-up, pooling older adults with and without Parkinson's disease. Abbreviations: OA - older adults; PD – Parkinson's disease; tDCS - transcranial direct current stimulation. *Multiple intervention sessions.

hypothesis, no significant difference between tDCS + training and sham + training was found in the motor domain. Most of the included studies were of poor methodological quality. Therefore, on the basis of this review no firm recommendation for the clinical use of tDCS during training can be put forward.

The small effects of tDCS-boosted training on WM but not on MSL could be explained by the number of studies included in the meta-analysis, which was particularly low for MSL. Overall, the individual

studies showed that the supplementary effects of tDCS on top of training were small and variable and therefore the statistical power to detect these changes was crucial. By including randomized sham-controlled studies with offline measurements only (tested without tDCS), we intended to probe the add-on effects of tDCS in a clean fashion, justifying the exclusion of studies which did not comply with this criterion. However, this approach reduced power.

In this review, we pooled tDCS-studies on motor and cognitive training thereby treating advancing age and neurodegenerative disease as part of a spectrum (Coleman and Martin 2022). Indeed, both expressions of neurodegeneration change the brain's architecture and its cortical electrophysiological response (Chen et al. 2022, Habich et al. 2020, Pieperhoff et al. 2022). Although atrophy patterns are similar in older adults and PwPD, cortical thickness is reduced to a greater extent in PwPD (Zeighami et al. 2015). Evidence also suggests that the thickness of the skull and cerebrospinal fluid, which impact the magnitude of the electric field at the cortical level (Laakso et al. 2015, Opitz et al. 2015), change with age (Yamada et al. 2023, Van Hoornweder et al. 2023). These changes could have attenuated electric fields to a variable extent in PwPD and in older adults. As such, pooling may have enlarged the heterogeneity of the response to tDCS with a particular impact on MSL as only 5 studies were considered in this domain. When analyzing older adults only, tDCS + training showed an insignificant but positive effect on the acquisition of MSL, while no effect was apparent for the pooled groups. Area-specific changes in baseline excitation and inhibition of cortical neurons, which differ in older adults versus PwPD, may also have played a role in these findings (Ammann et al. 2020, Habich et al. 2020). Stagg et al. 2011 showed that the responsiveness of the neurotransmitter gamma-aminobutyric acid was modified by anodal tDCS of M1 and correlated with motor learning capacity in young healthy people (Stagg et al. 2011). Our findings in older adults and PwPD do not replicate these findings, which could be attributed to the above-mentioned structural and functional changes in M1, overruling this gamma-aminobutyric acid responsiveness to tDCS.

The lack of effect on MSL may also be attributed to the conventional tDCS montages consisting of large rectangular electrodes placed over the motor cortex (anode) and contralateral supraorbital area (cathode). According to modelling studies, this montage may fail to induce its peak current density in M1, thereby missing the target (Faria et al. 2011). To counteract this limitation, the use of electrode montages ensuring higher stimulation focality (Alam et al. 2016, Edwards et al. 2013) may be warranted to reach the intended brain region.

Employing tDCS to enhance a dynamic learning process may have been another reason for the mixed findings of this review and for the discrepancy between motor and cognitive training. The engagement of brain areas involved in learning are not only task-specific but also change with ongoing practice (Dahms et al. 2020). Possibly, the timing and frequency of stimulation generate different effects in motor and cognitive task learning. For instance, several studies found that the PFC is activated during tasks that require WM processing (Blumenfeld and Ranganath 2006, Ranganath and D'Esposito 2005). This early involvement was suggested to lead to a strategic organization of neural encoding eventually facilitating long-term memory formation (Blumenfeld and Ranganath 2006). As such, it seems appropriate to stimulate PFC at the onset of WM training, which is underscored by our findings. In contrast, M1 is activated once a motor sequence is learned, thereby engaging in the delayed recall of acquired motor sequences (Dahms et al. 2020). As a result, it is possible that stimulating M1 during early learning, when it is not yet optimally engaged, did not improve MSL. This brings up the question whether the stimulation timing of M1 during the learning process needs to be delayed or whether multiple sessions of tDCS are needed to gain optimal effects. Ho et al. 2016 showed that repeated sessions of M1 tDCS resulted in a cumulative increase in cortical excitability (Ho et al. 2016). In this review, only a small number of studies (n = 3) offered multiple tDCS-boosted MSL training sessions (Abedi et al. 2022, Dumel et al. 2018, Greeley et al. 2022) and therefore a comparison between single and multiple sessions could not be made.

Despite our efforts to maximize comparability between studies, some heterogeneity across studies was inevitable, especially regarding the timing of the outcomes assessment (i.e. intervention and follow-up durations). Additionally, pre-training MSL was not always assessed in the absence of tDCS (Dumel et al. 2018, Firouzi et al. 2021), which may have led to an underestimation of the tDCS benefit in the motor domain.

6. Future research

Based on our results, tDCS applied to the PFC constitutes a promising tool to complement cognitive rehabilitation at least for the acquisition phase. However, future studies should be conducted to gauge the offline effects of multiple sessions of tDCS + training at retention. More tDCS + training studies in PwPD are needed to be able to better compare studies between older adults with and without this disease. Studies contrasting conventional with high-definition montages, the latter providing a higher stimulation focality (Alam et al. 2016, Edwards et al. 2013), are needed to address whether a larger effect on learning can be attained. Finally, to improve the internal validity and responsiveness of tDCS studies to the add-on effects of training, preregistrations with sample size calculations on pre-specified outcomes are imperative (see guidelines by Buch et al. 2017).

7. Conclusions

This systematic review cautiously supports the hypothesis that tDCS combined with cognitive training led to superior WM outcomes as compared to sham, which was not the case for MSL. This is an important finding as tDCS-devices are easy and safe to use, relatively cheap and portable making them suitable for different rehabilitation settings. Most of the studies pertained to older adults and only three addressed PwPD, of which two included PwPD with mild cognitive impairment. This may explain also why no positive tDCS effects were found in PwPD, unlike in the recent study of Broeder et al. (Broeder et al. 2023). The present findings can therefore not be generalized to the wider population of PwPD and could also be task-specific. Given these drawbacks and the methodological poor quality of the evidence found, we conclude that the current results do not endorse a wide implementation of tDCS as an accessory to rehabilitation at this point in time. Our findings do support further work to ascertain whether tDCS applied to the PFC is helpful to enhance cognitive training and whether this can lead to clinically relevant benefits.

CRediT authorship contribution statement

Britt Vandendoorent: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Visualization, Project administration. **Evelien Nackaerts:** Conceptualization, Methodology, Writing – original draft, Project administration. **Demi Zoetewei:** Formal analysis, Investigation. **Femke Hulzinga:** Formal analysis, Investigation. **Moran Gilat:** Conceptualization, Methodology, Writing – review & editing, Supervision. **Jean-Jacques Orban de Xivry:** Conceptualization, Methodology, Writing – review & editing, Supervision, Project administration, Funding acquisition. **Alice Nieuwboer:** Conceptualization, Methodology, Writing – review & editing, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendices. Supplementary material

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