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Review Article

EFFECT OF MULTIPLE TRANSCRANIAL DIRECT CURRENT STIMULATION SESSIONS ON COGNITIVE FUNCTION IN PARKINSON'S DISEASE: A SYSTEMATIC REVIEW

Violine Martalia, Aldithya Fakhri, Dheanita Nissrina Andini, Arden Gabrian[1], Aileen Gabrielle[2], Yohana Eka T. Lestari,[3] Pukovisa Prawiroharjo[4]

[1]Faculty of Medicine, Universitas Indonesia
[2]Faculty of Medicine, Universitas Hang Tuah
[3]Faculty of Medicine, Universitas Nusa Cendana
[4]Neurobehavior Division, Department of Neurology, Cipto Mangunkusumo National Central General Hospital, Jakarta, Indonesia

ABSTRACT

Introduction: Cognitive impairment is a common non-motor symptom of Parkinson's disease (PD) that significantly affects quality of life. Transcranial direct current stimulation (tDCS), a non-invasive neuromodulation technique, has been proposed to enhance cognitive function in PD. This study systematically reviews the effects of multiple tDCS sessions on cognitive outcomes in PD patients.
Methods: A systematic search of PubMed, Cochrane, ScienceDirect, and Medline was conducted in accordance with PRISMA guidelines. Randomized controlled trials (RCTs) assessing the impact of tDCS on cognitive function in PD were included. Study quality was evaluated using the RoB 2 tool.
Results: Three RCTs using anodal tDCS over the dorsolateral prefrontal cortex (DLPFC) for 20–25 minutes per session were included. Two studies reported improvements in executive function, attention, memory, and language, with some effects maintained at 3-month follow-up. One study found delayed improvements at 1-month follow-up. However, findings were mixed across studies, especially for memory, language, visuospatial abilities, and global cognition. All studies reported that tDCS was safe and well-tolerated, with only mild, transient side effects.
Discussion: Anodal tDCS may enhance specific cognitive functions, particularly executive function and attention, in PD. However, inconsistent findings across studies likely reflect differences in stimulation protocols and outcome measures.
Conclusion: While tDCS is a safe intervention, its cognitive efficacy in PD remains uncertain. Methodological variability across studies limits generalizability. Further large-scale RCTs using standardized protocols, consistent cognitive measures, and extended follow-up are needed to clarify the role of tDCS in cognitive rehabilitation for PD.

Keywords: Transcranial Direct Current Stimulation, tDCS, Parkinson's Disease, Cognitive Function

INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder affecting over 1% of the global population, typically manifesting later in life with motor symptoms mainly bradykinesia and either resting tremor or rigidity. PD results from the degeneration of dopaminergic neurons in the substantia nigra of the basal ganglia and is predominantly idiopathic.[1] Although motor symptoms are the

hallmark of PD, non-motor manifestations are also prevalent. Cognitive impairment is a common non-motor symptom of PD significantly impacting patients' quality of life.[2]

Cognitive impairment in PD is believed to result from reduced dopamine levels in the brain as it plays a key role in cognitive function of the cortex.[2] In healthy individuals, cortical dopamine enhances working memory, visuospatial abilities, and attentional processing, indicating its crucial role in cognitive function. In PD, the primary pathogenesis involves degeneration of dopaminergic neurons. This leads to over activity of the glutamatergic system that cause neurotoxic damage to surrounding neurons, which explains the decline in cognitive performance.[3,4] Given its significant impact on quality of life, various therapeutic strategies have been explored to preserve cognitive function in patients with PD, including non-invasive brain stimulation techniques.[5]

Transcranial direct current stimulation (tDCS), a non-invasive neuromodulation technique, has been explored as a potential therapy to enhance cognitive function in PD. tDCS is believed to work by stimulating the dorsolateral prefrontal cortex (DLPFC), a region involved in cognitive processing, and is thought to have a positive effect on cognitive function in patients with PD.[2,4] Research has found that tDCS also modulates brain chemistry in a polarity-dependent manner. Anodal tDCS, which involves positive stimulation, has been shown to increase cortical excitability and reduce levels of γ-aminobutyric acid (GABA), the brain’s primary inhibitory neurotransmitter. This reduction occurs through the downregulation of glutamic acid decarboxylase 67 (GAD-67), a key enzyme involved in GABA synthesis. As a result, there is a decrease in inhibitory tone, which may facilitate increased neuronal firing and enhanced cognitive performance. In contrast, cathodal tDCS, which involves negative stimulation, decreases neuronal activity and has been associated with reduced glutamate concentrations, potentially through the suppression of excitatory neurotransmission. This mechanism may help mitigate excitotoxic damage, which is particularly relevant in neurodegenerative conditions such

as PD, where glutamatergic overactivity contributes to neuronal injury and cognitive decline.[4,5]

However, its effectiveness remains inconclusive, particularly regarding the optimal duration of therapy that is both safe and effective. Previous studies have suggested that a single session of tDCS is insufficient to produce meaningful improvements in cognitive function among patients with PD. Moreover, to date, no review has specifically evaluated the effects of multiple session tDCS on cognitive function in this population. Therefore, this study aims to systematically review the impact of repeated tDCS sessions on cognitive function in patients with Parkinson's disease.

MATERIAL AND METHODS

This systematic review was conducted based on the Cochrane Handbook for Systematic Reviews of Interventions 6.2 and is in accordance with the Preferred Items for Systematic Review and Meta-Analysis (PRISMA) guidelines

Search strategy

We conducted a systematic search of PubMed, Cochrane, ScienceDirect, and Medline following PRISMA guidelines. The search strategy utilized a combination of relevant Medical Subject Headings (MeSH) terms and keywords, namely: "Parkinson's Disease", "Parkinson's Disease" [MeSH], "Transcranial Direct Current Stimulation", "tDCS", and "Cognitive Function" [MeSH].

Study eligibility criteria

The studies eligible for inclusion are studies involving Parkinson's Disease patients receiving multiple tDCS sessions compared to sham or placebo. Only studies with study design of randomized controlled trials (RCT) are included. Furthermore, only studies written in English are included.

Methodological quality and risk of bias assessment

Study quality and risk of bias of each selected study were assessed using the RoB 2 tool. Two reviewers independently assessed the risk of bias, and disagreements were resolved through discussion.

RESULT

Search results and study selection

The search across four databases yielded a total of 1,002 articles. From PubMed, 27 records were identified. From the Cochrane Library, 152 articles were retrieved. The Medline database

did not yield any relevant results (n = 0). ScienceDirect yielded 823 results. After title screening, 845 articles were excluded, leaving 157 for abstract screening. Of these, 153 were excluded, and 4 articles were selected for full-text screening. One report was excluded due to the full text being unavailable. All of the three remaining studies met the inclusion criteria and were included in this review. The procedure is illustrated in *Figure 1*.

Study characteristics

The 3 included studies investigated a total of 78 PD patients, consisting of 43 patients who underwent tDCS and 35 patients who underwent sham. The included studies were published between 2014 - 2018. All 3 studies were randomized controlled trials.[2,6,7]

These studies were conducted in several regions, namely Australia, Italy, and USA. All studies applied anodal transcranial direct current stimulation (tDCS) over the dorsolateral prefrontal cortex (DLPFC), with session durations ranging from 20 to 25 minutes. Two studies (Biundo, et al and Lawrence, et al) administered daily tDCS sessions over two weeks, while one study (Doruk, et al) involved a single tDCS session. The stimulation intensity ranged between 1.5 mA and 2 mA, with sham conditions applied in all studies as controls. The characteristics and main findings of the included studies are summarized in *Table 1*.

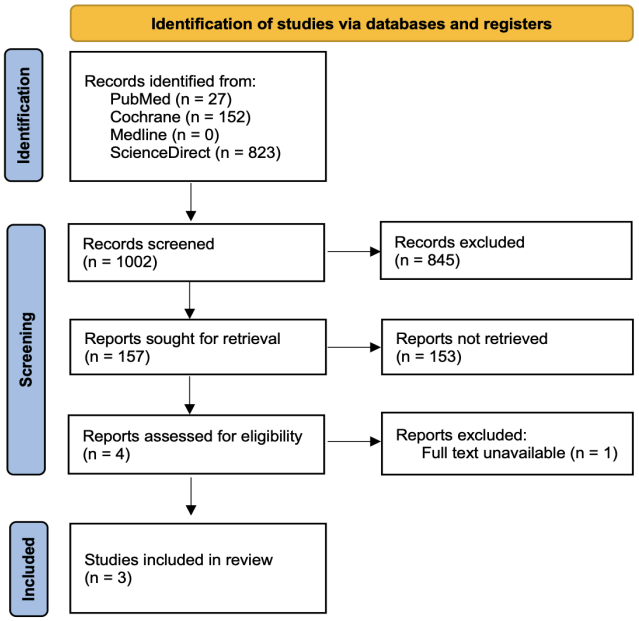

Figure 1. Literature search in accordance with PRISMA guidelines.

Risk of bias assessment

All studies have a low risk of bias in accordance with the RoB 2 tool. *Figure 2* represents the risk of bias assessment of each study using the RoB 2 tool.

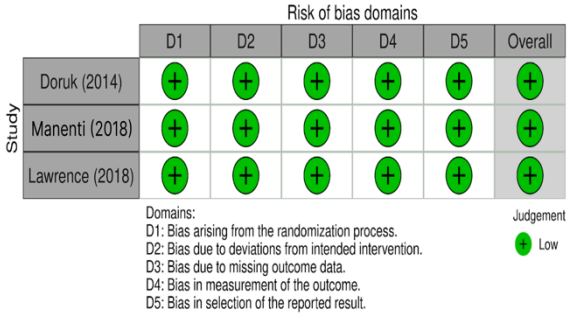

Figure 2. Risk of bias assessment using RoB 2 tool.

Cognitive function outcomes

Cognitive outcomes were assessed across the three studies using a variety of neuropsychological tests, targeting domains such as executive function and attention, memory, language, visuospatial abilities, and global cognitive function.

Executive function, attention, and working memory

In the executive function and attention domain, all three studies found significant improvements in the tDCS groups. Doruk et al. reported significant improvements in TMT-B performance immediately after 10 days of tDCS in all groups, but there are no group differences for the tDCS treatment period based on the ANCOVA model ($p=0.49$, $eta^2=0.02$, percent change $eta^2=7.75$, partial $eta^2=0.03$). However, after the 3-months follow-up, there is a significant group effect, where a comparison of sham tDCS vs both active tDCS groups showed significant difference ($p<0.001$), showing different retention effects. Comparison between the baseline and follow-up period also found significant improvements in both tDCS groups compared to sham ($p=0.03$, effect size for group; $eta^2=0.25$, percent change $eta^2=64.68$, partial $eta^2=0.29$), indicating that the positive effects of tDCS were maintained until the 1-month follow up. This study found no significant group nor time effects for TMT A & B, Wisconsin Card Sorting Test (WCST), Probabilistic Classification Learning (PCL), WMT, Stroop Test, FDS, BDS, 3-back Test.

Manenti et al. performed an ANOVA analysis with the different groups and time after treatment to follow-up as independent variables. This study found a significant main effect of time

for the response flexibility task ($F(2, 40)=8.51$, $p=0.0008$, $\eta2=0.30$, $1-\beta=0.99$) and for the Stroop test ($F(2, 40)=8.35$, $p=0.0009$, $\eta2=0.29$, $1-\beta=0.99$). Reaction times were reported to decrease from baseline to post-treatment assessment for the flexibility task ($p=0.0002$, Cohen's $d=0.53$, $1-\beta=0.67$) and Stroop test ($p=0.009$, Cohen's $d=0.34$, $1-\beta=0.34$), as well as from baseline to 3-month follow-up for the flexibility task ($p=0.031$, Cohen's $d=0.37$, $1-\beta=0.38$) and Stroop test ($p=0.00003$, Cohen's $d=0.64$, $1-\beta=0.82$). This indicates that the treatment immediately improves the test results and that the improvement can be maintained until the 3-months follow up. However, no significant effects on frontal assessment battery (FAB), Stroop test interference effect on errors, trail making test (TMT) part A or B, forward digit span (FDS), backward digit span (BDS), Go/NoGo, and working memory tests were found.

Lawrence et al. also reported a significant effect for the Stroop test in the tDCS group ($F=4.06$, $p=0.02$), as well as standard cognitive training combined with tDCS ($F=35.05$, $p<0.001$). The same study also found significant improvements in the Stockings of Cambridge (SOC) subtest in the standard cognitive training + tDCS group ($p<0.001$) and tailored cognitive training + tDCS group, but there is no significant improvement in neither the tDCS-only group nor cognitive training-only groups compared to control. A significant improvement was also reported for the Letter-Number Sequencing (LNS) test ($p<0.001$) for the tailored cognitive training group ($p=0.002$) and tailore cognitive training + tDCS group ($p=0.01$), but no other groups improved on the LNS. This study reported no significant effects on the Controlled Oral Word Association Task (COWAT) in any group.

Memory

Manenti et al. reported no significant improvement in memory performance, as assessed by the Rey Auditory Verbal Learning Test (RAVLT), either immediately after the intervention or at follow-up. In contrast, Lawrence et al. observed differing results using the Hopkins Verbal Learning Test (HVLT) and Paragraph Recall. A significant interaction effect was found for Paragraph Recall ($F = 2.51$, $p = 0.01$), with notable cognitive improvements observed in the

standard cognitive training group (F = 5.24, p = 0.01), the tDCS-only group (F = 17.82, p < 0.001), and the were observed in any group for HVLT, and no other groups demonstrated gains in Paragraph Recall.

Language

Manenti et al. found a significant effect of time for the phonemic (F(2, 40)=7.35, p=0.002, η^2=0.27, 1-β=0.99) and semantic verbal (F(2, 40)=4.12, p=0.023, η^2=0.017, 1-β=0.99) fluency. The phonemic fluency score increased from baseline to post-treatment assessment (p=0.0005, Cohen's d=0.51, 1-β=0.62) but not from baseline to 3-month follow up, while the semantic verbal fluency improved significantly from baseline to 3-month follow up (p=0.007, Cohen's d=0.44, 1-β=0.51) but not from baseline to post-treatment assessment. For the actions naming abilities, there is a significant effect of time (F(2, 40)=6.34, p=0.004, η2=0.24, 1-β=0.99), with significant increases from baseline to post-treatment assessment (p=0.003, Cohen's d=0.47, 1-β=0.56) and from baseline to 3-month follow up (p=0.004, Cohen's d=0.23, 1-β=0.18). No significant combined tailored cognitive training plus tDCS group (F = 12.09, p < 0.001). No improvements

effects were observed for the object naming test performance. Lawrence et al. also found significant improvements in the language domain, for the similarities test (F=3.25, p=0.001) for the standard cognitive training + tDCS group (F=5.23, p=0.01) and tailored cognitive training + tDCS group (F=17.43, p<0.001). The study did not find any significant improvement on the Boston Naming Test-Short Form (BNT).

Visuospatial abilities

Lawrence et al. reported a significant interaction effect for Judgement of Line Orientation (JLO) (F = 3.76, p < 0.001); however, a significant decline in performance was observed in the standard cognitive training group (F = 6.57, p = 0.0002). Consequently, no intervention groups demonstrated improvement on the JLO task, and similarly, no improvements were found for the Hooper Visual Organization Test (HVOT) across any groups. Consistently, Doruk et al. also found no significant enhancement in visuospatial abilities in any group when assessed using the HVOT.

Global cognition

Manenti et al. reported a significant effect of time on both the total score of the Parkinson's Disease-Cognitive Rating Scale (PD-CRS) [$F(1,20) = 5.87$, $p = 0.025$, $\eta^2 = 0.23$, $1-\beta = 0.99$] and its frontal-subcortical subscale [$F(1,20) = 6.35$, $p = 0.020$, $\eta^2 = 0.24$, $1-\beta = 0.99$], indicating a decline in cognitive gains from the post-intervention phase to follow-up. Specifically, for the active tDCS (AtDCS) plus computerized cognitive training (CCT) group, total PD-CRS scores improved by 12.7% (SD = 1.5) post-treatment and 8.1% (SD = 1.4) at follow-up. The sham tDCS (StDCS) plus CCT group showed a post-treatment gain of 8.6% (SD = 1.2) and 3.8% (SD = 1.4) at follow-up. Frontal-subcortical scores followed a similar trend (AtDCS plus CCT: post-treatment +17.0% SD 2.8, follow-up +10.8% SD 2.6; StDCS plus CCT: post-treatment +19.7% SD 2.6, follow-up +11.4% SD 2.6). Despite these findings, no significant differences were found between groups in global cognitive function as measured by the Mini-Mental Parkinson (MMP). In addition, Lawrence et al. also reported no significant changes in global cognition based on either the Mini-Mental State Examination (MMSE) or the PD-CRS, suggesting divergent findings regarding overall cognitive improvement.

Adverse effects

None of the included studies reported any serious adverse effects related to tDCS. In the study by Doruk et al., the most commonly reported side effects were tingling sensations (50%), sleepiness (55%), and mild headache (22%). Additional side effects included neck pain (11%), skin redness (22%), and difficulty concentrating (22%). However, no unexpected or severe adverse events were observed. In contrast, the studies by Lawrence et al. and Manenti et al. did not report any adverse effects related to the intervention.

Table 1. Summary of Included Randomized Controlled Trials Investigating tDCS Effects on Cognitive Function in Parkinson's Disease

Study (Year)	Sample Size (n)	tDCS Protocol	Stimulation Site	Duration & Frequency	Cognitive Outcomes Measured	Main Findings
Doruk et al. (2014)	18 PD Patients	2 mA, daily Assessment at baseline, at the end of stimulation sessions, and 1-month follow up	Left DLPFC (n=6), Right DLPFC (n=5), Sham (n=7)	20 min/session, for 5 consecutive days (2 weeks total)	Executive function, attention, and working memory: TMT A & B, WCST, PCL, WMT, Stroop Test, FDS, BDS, 3-back Test, CPM. Visuospatial abilities: HVOT.	No significant improvements reported in executive function, attention, and working memory at the end of stimulation sessions, but shows significant improvement in the tDCS groups for the TMT B performance on the 1-month follow up.
Manenti et al. (2018)	22 PD Patients	2 mA, daily (tDCS + CCT or Sham + CCT) Assessment at baseline, at the end of stimulation sessions, and 3-month follow up	Left DLPFC (n=11), Sham (n=11)	25 min/session for 5 consecutive days (2 weeks total)	Executive function, attention, and working memory: FAB, Stroop Test, TMT A & B, FDS, BDS, Go/NoGo, Working Memory, Response Flexibility. Memory: RAVLT. Language: Verbal fluency, Naming objects. Global: MMP, PD-CRS.	Significant improvements in the tDCS group vs. sham were found in the executive function, attention, and working memory domain (response flexibility task and Stroop test) immediately after treatment and on the 3-months follow up, in the language domain (phonemic fluency, semantic verbal fluency, and actions naming abilities) immediately after treatment but not maintained over the 3-months follow up.
Lawrence et al. (2018)	42 PD Patients	1.5 mA, daily (tDCS + CCT or tDCS or Sham + CCT or Sham) Assessment at baseline, at the end of stimulation sessions, and 3-month follow up	Left DLPFC (n=21), Sham (n=17), Loss to follow up (n=4)	20 min/session, 4 sessions across 4 weeks	Executive function, attention, and working memory: COWAT, SOC, Stroop test, LNS. Memory: Paragraph Recall, HVLT. Language: Similarities, BNT. Visuospatial abilities: JLO, HVOT. Global: MMSE, PD-CRS.	Significant improvements in the tDCS groups compared to control were found in the executive function, attention, and working memory domain (Stroop test) immediately after treatment and on the 3-months follow up and in the language domain (Paragraph Recall).

tDCS: transcranial direct current stimulation; DLPFC: dorsolateral prefrontal cortex; TMT A&B: Trail Making Tests A & B, WCST: Wisconsin Card Sorting Test; PCL: Probabilistic Classification Learning; WMT: Working Memory Test; FDS: Forward Digit Span; BDS: Backward Digit Span; MMSE: Mini Mental Status Examination; CCT: computerized cognitive training; MMP: Mini Mental Parkinson, PD-CRS: Parkinson's disease-cognitive rating scale; RAVLT: Rey Auditory Verbal Learning Test, FAB: Frontal Assessment Battery; COWAT: Controlled Oral Word Association Test; SOC: Stockings of Cambridge; LNS: Letter-Number Sequencing; HVLT: Hopkins Verbal Learning Test; BNT: Boston Naming Test; JLO: Judgement of Line Orientation; HVOT: Hooper's Visual Orientation Test; CPM: Colored Progressive Matrices

DISCUSSION

This systematic review evaluated the efficacy of multiple tDCS sessions on cognitive function in PD patients. Findings from the included randomized controlled trials suggest that repeated sessions of anodal tDCS targeting the DLPFC may enhance cognitive performance across multiple domains, including executive function, attention, memory, and language. These effects were particularly evident in protocols implementing daily stimulation over a two to four-week period, as reported in Doruk et al., Manenti et al., and Lawrence et al.[2,6,7]

Mechanisms of Action

The DLPFC is a key hub in cognitive processing, particularly for executive functioning and attention, making it a rational target for neuromodulation. The underlying mechanism of tDCS is thought to involve subthreshold modulation of neuronal membrane potentials, leading to increased cortical excitability and facilitating neuroplastic changes such as long-term potentiation (LTP).[8,9]

Additionally, the neuromodulatory effects of tDCS are polarity-dependent and influence neurotransmitter systems relevant to PD pathology. Anodal tDCS has been shown to reduce levels of GABA via downregulation of the GAD-67 enzyme, resulting in disinhibition and enhanced neuronal firing. Conversely, cathodal tDCS reduces glutamate concentrations and may attenuate excitotoxicity, which is a contributing factor to neurodegeneration in PD. These biochemical effects are further modulated by dopamine, whose dose-dependent role in synaptic plasticity may explain interindividual variability in responsiveness to tDCS, especially in relation to disease severity and pharmacological status.[4,5]

Cognitive Outcomes and Retention Effects

Doruk et al. reported that improvements in executive function, attention, and working memory were not immediately evident after the intervention but became statistically significant at the one-month follow-up, particularly for the TMT-B test performance, suggesting a delayed yet sustained retention effect specific to the tDCS group. In contrast, the sham group showed no such retention, with performance returning to baseline levels. This

finding underscores the potential of tDCS to promote long-term cognitive benefits, particularly in tasks that tap into executive functioning. Notably, the other neuropsychological assessments used in the study failed to show significant changes. This may be attributed to confounding psychiatric variables such as anxiety and depression, which are known to interfere with cognitive test performance. However, TMT-B has shown resilience against such interference, with previous studies showing poor correlation between anxiety and depression with TMT-B scores, suggesting its robustness in clinical evaluations. Additionally, TMT-B has been widely recommended for assessing executive function due to its sensitivity, feasibility, and use in high-quality RCTs.[2] Similarly, Manenti et al. demonstrated cognitive gains in the executive function, attention, and working memory domain (Stroop test and response flexibility task), supporting the findings of Doruk et al. that tDCS can improve executive function and attention in PD patients.[6]

Lawrence et al. further expanded the scope of intervention by comparing six groups, including combinations of standard cognitive training (CT), tailored cognitive training, and tDCS. Their findings suggest that both tDCS alone and CT alone resulted in cognitive improvements, with the most pronounced effect sizes observed in the combined intervention groups. Notably, significant improvements on the Stroop Test were reported in both the tDCS group and the tDCS + standard CT group, indicating some independent benefit of stimulation. However, for more complex executive tasks such as the Stockings of Cambridge (SOC) and Letter-Number Sequencing (LNS), significant improvements were observed only in groups receiving tDCS combined with cognitive training. Specifically, the SOC subtest showed significant enhancement in both the standard cognitive training + tDCS group and the tailored cognitive training + tDCS group, while no significant improvements were found in the tDCS-only or cognitive training-only groups compared to control. Similarly, for the LNS test, significant gains were reported only in the tailored cognitive training group and the tailored cognitive training + tDCS group, with no

improvement observed in other groups. These results indicate that tDCS alone was not sufficient to produce meaningful cognitive benefits in these domains. Instead, the combination of tDCS with structured cognitive interventions appears to be necessary to achieve statistically significant outcomes. This supports the view that tDCS may function best as an adjunctive modality, enhancing the effects of behavioral training rather than acting as a standalone intervention.[7]

Findings on memory outcomes across studies showed notable variability, likely reflecting differences in task sensitivity and intervention protocols. Manenti et al. reported no significant improvements in memory performance, as measured by the RAVLT, either immediately post-intervention or at follow-up. In contrast, Lawrence et al. utilized alternative memory assessments, namely HVLT and Paragraph Recall which yielded mixed results. No significant improvements were observed across any group for HVLT, suggesting similar limitations in sensitivity or possible ceiling effects. However, a significant interaction effect emerged for Paragraph Recall, with post hoc analyses revealing significant improvements in the standard cognitive training group, the tDCS-only group, and the combined tailored cognitive training plus tDCS group. These findings suggest that Paragraph Recall may be a more responsive measure of memory change following cognitive or neuromodulatory interventions in PD. Additionally, the fact that the tDCS-only group showed significant gains reinforces the potential of tDCS to independently enhance specific aspects of memory performance. The variability between memory tasks highlights the importance of selecting outcome measures that are both sensitive and ecologically valid when evaluating cognitive interventions in neurodegenerative populations.[6,7]

While tDCS treatments are anatomically specific—targeting regions such as the DLPFC, which is primarily associated with executive functions—language functions such as phonemic fluency, semantic fluency, action naming, and similarities tests are also closely linked to these cognitive domains. Therefore, stimulation of the DLPFC is thought to indirectly enhance language abilities through improved cognitive processing. Two studies

assessed the effects of tDCS on the language domain of PD patients' cognitive function, reporting mixed results. Manenti et al. found significant improvements in the language domain (phonemic fluency, semantic verbal fluency, and action naming tests) following combined cognitive training and anodal tDCS. Furthermore, these cognitive gains were maintained during a 3-month follow-up period, supporting the notion that tDCS, especially when paired with concurrent cognitive engagement, may foster enduring neural adaptations. However, the study authors emphasized the necessity of longer follow-up durations to determine the true sustainability of these benefits.[6] With language deficits being some of the most frequent cognitive decline in PD from early disease stages because of the associated frontal lobe dysfunctions, this finding shows promising results to mitigate cognitive decline in PD patients.[10,11] This is also consistent with previous studies showing that prefrontal stimulation can improve verbal fluency in both patients with and without PD.[12,13] Interestingly, Lawrence et al. found significant improvements in the language domain measured using the similarities test in the tDCS + standard cognitive training and tDCS + tailored cognitive training groups, but not in the tDCS-only group. This supports the findings of Manenti et al. which demonstrates the efficacy of tDCS in combination with cognitive training in improving cognitive function, especially in the language domain.

Two studies, Lawrence et al. and Doruk et al. assessed the visuospatial abilities of PD patients in the tDCS and non-tDCS groups and found generally no significant increase in visuospatial abilities after receiving tDCS. Doruk et al. found no significant difference in HVOT results across groups. Furthermore, Lawrence et al. also reported no improvements across any intervention groups for the HVOT and JLO task performance. This finding may be attributed to the tDCS stimulation site (left DLPFC) not corresponding to the region associated with visuospatial performance, which has been found to more deeply involve other parts of the brain, such as the right posterior hemisphere, or the posterior cingulate cortex, areas not directly stimulated in any of the studies.

However, there is still some debate regarding which areas of the brain are directly involved with various visuospatial functions.[14,15]

Manenti et al. and Lawrence et al. also tried to assess global cognitive functions of different treatment groups using various tools, with similarly nonsignificant results. Manenti et al. found a significant but negative effect of time on PD-CRS after intervention to follow-up, but no significant group effect. The same study also reported no significant differences in global cognitive function based on Mini-Mental Parkinson (MMP). In addition, Lawrence et al. supported this finding, also reporting no significant changes in the PD-CRS or the MMSE results across groups.

Study Strengths and Limitations

Despite promising results, several limitations must be acknowledged. First, the number of included RCTs was small, with sample sizes ranging from 16 to 20 participants, reducing both statistical power and generalizability. Second, there was substantial heterogeneity in tDCS protocols, including variations in intensity (1.5–2 mA), stimulation duration (20–30 minutes), and session frequency, all of which may influence treatment outcomes and complicate cross-study comparisons. Third, the cognitive assessment tools and outcome domains measured were not standardized across studies.[2,6,7] Additionally, differences in study design further impacted result interpretation. For instance, some studies used cognitive training in conjunction with tDCS or sham stimulation. The inclusion of cognitive training as an adjunct therapy may have confounded the independent effects of tDCS, as suggested in Lawrence et al.'s six-arm design, which allowed for comparisons between tDCS alone, cognitive training alone, and various combinations. This heterogeneity makes it difficult to isolate the efficacy of tDCS from other concurrent interventions. Moreover, short follow-up durations limit conclusions about the long-term maintenance of cognitive gains.

Future Directions

Future research should address these limitations by conducting larger, multicenter RCTs using standardized stimulation protocols. Studies should systematically evaluate individual predictors of response to tDCS, such as disease severity, baseline cognitive

status, neurophysiological biomarkers, and medication regimen. Longer-term follow-up is essential to evaluate the persistence of cognitive improvements beyond the intervention period. Furthermore, there is growing evidence that combining tDCS with structured cognitive training may yield synergistic effects, potentially leading to more robust and sustainable outcomes than either approach alone. Exploring these integrative interventions could inform more effective therapeutic strategies for cognitive rehabilitation in PD.

Safety and Tolerability

Importantly, all included studies reported that tDCS was safe and well-tolerated. The most frequently reported side effects were mild and transient, such as tingling, itching, or redness at the stimulation site. Doruk et al. noted side effects such as tingling (50%), sleepiness (55%), and mild headache (22%), with no unexpected or severe adverse events. Meanwhile, Lawrence et al. and Manenti et al. did not report any significant adverse events related to the intervention. These findings support the feasibility of incorporating tDCS into non-pharmacological intervention programs for cognitive rehabilitation in PD patients.[2,6,7]

This systematic review evaluated the efficacy of multiple tDCS sessions on cognitive function in PD patients. Findings from the included randomized controlled trials suggest that repeated sessions of anodal tDCS targeting the DLPFC may enhance cognitive performance across multiple domains, including executive function, attention, memory, and language. These effects were particularly evident in protocols implementing daily stimulation over a two to four-week period, as reported in Doruk et al., Manenti et al., and Lawrence et al.[2,6,7]

Mechanisms of Action

The DLPFC is a key hub in cognitive processing, particularly for executive functioning and attention, making it a rational target for neuromodulation. The underlying mechanism of tDCS is thought to involve subthreshold modulation of neuronal membrane potentials, leading to increased cortical excitability and facilitating neuroplastic changes such as long-term potentiation (LTP).[8,9] Additionally, the neuromodulatory effects of tDCS are polarity-dependent

and influence neurotransmitter systems relevant to PD pathology. Anodal tDCS has been shown to reduce levels of GABA via downregulation of the GAD-67 enzyme, resulting in disinhibition and enhanced neuronal firing. Conversely, cathodal tDCS reduces glutamate concentrations and may attenuate excitotoxicity, which is a contributing factor to neurodegeneration in PD. These biochemical effects are further modulated by dopamine, whose dose-dependent role in synaptic plasticity may explain interindividual variability in responsiveness to tDCS, especially in relation to disease severity and pharmacological status.[4,5]

Cognitive Outcomes and Retention Effects

Doruk et al. reported that improvements in executive function, attention, and working memory were not immediately evident after the intervention but became statistically significant at the one-month follow-up, particularly for the TMT-B test performance, suggesting a delayed yet sustained retention effect specific to the tDCS group. In contrast, the sham group showed no such retention, with performance returning to baseline levels. This finding underscores the potential of tDCS to promote long-term cognitive benefits, particularly in tasks that tap into executive functioning. Notably, the other neuropsychological assessments used in the study failed to show significant changes. This may be attributed to confounding psychiatric variables such as anxiety and depression, which are known to interfere with cognitive test performance. However, TMT-B has shown resilience against such interference, with previous studies showing poor correlation between anxiety and depression with TMT-B scores, suggesting its robustness in clinical evaluations. Additionally, TMT-B has been widely recommended for assessing executive function due to its sensitivity, feasibility, and use in high-quality RCTs.[2] Similarly, Manenti et al. demonstrated cognitive gains in the executive function, attention, and working memory domain (Stroop test and response flexibility task), supporting the findings of Doruk et al. that tDCS can improve executive function and attention in PD patients.[6]

Lawrence et al. further expanded the scope of intervention by comparing six groups, including combinations

of standard cognitive training (CT), tailored cognitive training, and tDCS. Their findings suggest that both tDCS alone and CT alone resulted in cognitive improvements, with the most pronounced effect sizes observed in the combined intervention groups. Notably, significant improvements on the Stroop Test were reported in both the tDCS group and the tDCS + standard CT group, indicating some independent benefit of stimulation. However, for more complex executive tasks such as the Stockings of Cambridge (SOC) and Letter-Number Sequencing (LNS), significant improvements were observed only in groups receiving tDCS combined with cognitive training. Specifically, the SOC subtest showed significant enhancement in both the standard cognitive training + tDCS group and the tailored cognitive training + tDCS group, while no significant improvements were found in the tDCS-only or cognitive training-only groups compared to control. Similarly, for the LNS test, significant gains were reported only in the tailored cognitive training group and the tailored cognitive training + tDCS group, with no improvement observed in other groups. These results indicate that tDCS alone was not sufficient to produce meaningful cognitive benefits in these domains. Instead, the combination of tDCS with structured cognitive interventions appears to be necessary to achieve statistically significant outcomes. This supports the view that tDCS may function best as an adjunctive modality, enhancing the effects of behavioral training rather than acting as a standalone intervention.[7]

Findings on memory outcomes across studies showed notable variability, likely reflecting differences in task sensitivity and intervention protocols. Manenti et al. reported no significant improvements in memory performance, as measured by the RAVLT, either immediately post-intervention or at follow-up. In contrast, Lawrence et al. utilized alternative memory assessments, namely HVLT and Paragraph Recall which yielded mixed results. No significant improvements were observed across any group for HVLT, suggesting similar limitations in sensitivity or possible ceiling effects. However, a significant interaction effect emerged for Paragraph Recall,

with post hoc analyses revealing significant improvements in the standard cognitive training group, the tDCS-only group, and the combined tailored cognitive training plus tDCS group. These findings suggest that Paragraph Recall may be a more responsive measure of memory change following cognitive or neuromodulatory interventions in PD. Additionally, the fact that the tDCS-only group showed significant gains reinforces the potential of tDCS to independently enhance specific aspects of memory performance. The variability between memory tasks highlights the importance of selecting outcome measures that are both sensitive and ecologically valid when evaluating cognitive interventions in neurodegenerative populations.[6,7]

While tDCS treatments are anatomically specific—targeting regions such as the DLPFC, which is primarily associated with executive functions—language functions such as phonemic fluency, semantic fluency, action naming, and similarities tests are also closely linked to these cognitive domains. Therefore, stimulation of the DLPFC is thought to indirectly enhance language abilities through improved cognitive processing. Two studies assessed the effects of tDCS on the language domain of PD patients' cognitive function, reporting mixed results. Manenti et al. found significant improvements in thelanguage domain (phonemic fluency semantic verbal fluency, and action naming tests) following combined cognitive training and anodal tDCS. Furthermore, these cognitive gains were maintained during a 3-month follow-up period, supporting the notion that tDCS, especially when paired with concurrent cognitive engagement, may foster enduring neural adaptations. However, the study authors emphasized the necessity of longer follow-up durations to determine the true sustainability of these benefits.[6] With language deficits being some of the most frequent cognitive decline in PD from early disease stages because of the associated frontal lobe dysfunctions, this finding shows promising results to mitigate cognitive decline in PD patients.[10,11] This is also consistent with previous studies showing that prefrontal stimulation can improve verbal fluency in both patients with and without PD.[12,13] Interestingly,

Lawrence et al. found significant improvements in the language domain measured using the similarities test in the tDCS + standard cognitive training and tDCS + tailored cognitive training groups, but not in the tDCS-only group. This supports the findings of Manenti et al. which demonstrates the efficacy of tDCS in combination with cognitive training in improving cognitive function, especially in the language domain.

Two studies, Lawrence et al. and Doruk et al. assessed the visuospatial abilities of PD patients in the tDCS and non-tDCS groups and found generally no significant increase in visuospatial abilities after receiving tDCS. Doruk et al. found no significant difference in HVOT results across groups. Furthermore, Lawrence et al. also reported no improvements across any intervention groups for the HVOT and JLO task performance. This finding may be attributed to the tDCS stimulation site (left DLPFC) not corresponding to the region associated with visuospatial performance, which has been found to more deeply involve other parts of the brain, such as the right posterior hemisphere, or the posterior cingulate cortex, areas not directly stimulated in any of the studies. However, there is still some debate regarding which areas of the brain are directly involved with various visuospatial functions.[14,15]

Manenti et al. and Lawrence et al. also tried to assess global cognitive functions of different treatment groups using various tools, with similarly nonsignificant results. Manenti et al. found a significant but negative effect of time on PD-CRS after intervention to follow-up, but no significant group effect. The same study also reported no significant differences in global cognitive function based on Mini-Mental Parkinson (MMP). In addition, Lawrence et al. supported this finding, also reporting no significant changes in the PD-CRS or the MMSE results across groups.

Study Strengths and Limitations

Despite promising results, several limitations must be acknowledged. First, the number of included RCTs was small, with sample sizes ranging from 16 to 20 participants, reducing both statistical power and generalizability. Second, there was substantial heterogeneity in tDCS protocols, including variations in

intensity (1.5–2 mA), stimulation duration (20–30 minutes), and session frequency, all of which may influence treatment outcomes and complicate cross-study comparisons. Third, the cognitive assessment tools and outcome domains measured were not standardized across studies.[2,6,7]

Additionally, differences in study design further impacted result interpretation. For instance, some studies used cognitive training in conjunction with tDCS or sham stimulation. The inclusion of cognitive training as an adjunct therapy may have confounded the independent effects of tDCS, as suggested in Lawrence et al.'s six-arm design, which allowed for comparisons between tDCS alone, cognitive training alone, and various combinations. This heterogeneity makes it difficult to isolate the efficacy of tDCS from other concurrent interventions. Moreover, short follow-up durations limit conclusions about the long-term maintenance of cognitive gains

Future Directions

Future research should address these limitations by conducting larger, multicenter RCTs using standardized stimulation protocols. Studies should systematically evaluate individual predictors of response to tDCS, such as disease severity, baseline cognitive status, neurophysiological biomarkers, and medication regimen. Longer-term follow-up is essential to evaluate the persistence of cognitive improvements beyond the intervention period. Furthermore, there is growing evidence that combining tDCS with structured cognitive training may yield synergistic effects, potentially leading to more robust and sustainable outcomes than either approach alone. Exploring these integrative interventions could inform more effective therapeutic strategies for cognitive rehabilitation in PD.

Safety and Tolerability

Importantly, all included studies reported that tDCS was safe and well-tolerated. The most frequently reported side effects were mild and transient, such as tingling, itching, or redness at the stimulation site. Doruk et al. noted side effects such as tingling (50%), sleepiness (55%), and mild headache (22%), with no unexpected or severe adverse events. Meanwhile, Lawrence et al.

and Manenti et al. did not report any significant adverse events related to the intervention. These findings support the feasibility of incorporating tDCS into non-pharmacological intervention programs for cognitive rehabilitation in PD patients.[2,6,7]

CONCLUSION

This systematic review evaluated the efficacy of anodal tDCS targeting the DLPFC to improve cognitive function in patients with Parkinson's disease, particularly when delivered daily across multiple sessions in a two to four-week period. Cognitive benefits were most consistently observed in executive function and attention, with emerging evidence for improvements in memory and language, especially when tDCS was combined with structured cognitive training. However, the current literature reports mixed findings regarding memory, visuospatial abilities, and global cognitive function improvements in PD patients receiving tDCS. These findings also underscore several limitations, including small sample sizes, protocol variability, and inconsistent outcome measures, which collectively restrict the generalizability of current evidence.

While tDCS appears to be a safe and well tolerated intervention, its efficacy as a standalone treatment according to the currently available studies appears limited, and the greatest gains are likely achieved through synergistic multimodal approaches, particularly when combined with cognitive training. Future studies with standardized protocols, larger cohorts, and longer follow-up periods are warranted to confirm the extent and durability of effects in each cognitive domain, as well as to clarify optimal tDCS stimulation protocols. In conclusion, these findings collectively still regard tDCS as a promising adjunctive tool in the cognitive rehabilitation of PD patients, but further high-quality evidence is needed to inform clinical application

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