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Systematic Review

Effect of Dual-Site Transcranial Direct-Current Stimulation on Post-Stroke Cognitive Impairment and Dementia: A Systematic Review and Meta-Analysis

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Abstract

Introduction: Transcranial direct-current stimulation (tDCS) is a neuromodulation with no consensus on its effect in restoring cognitive function following stroke. To determine if dual-site tDCS attenuates post-stroke cognitive impairment and dementia (PSCID), a systematic-review and meta-analysis were carried out.

Methods: Five databases (PubMed/Medline, EMBASE, Web of Science, Scopus, and Cochrane Library) were searched from inception to January 2025.. Two reviewers independently conducted study screening, data extraction, and quality assessment. The Cochrane Risk of Bias 2.0 (RoB 2) tool was used for RCTs, and JBI checklists for case series and reports. A total of 296 participants were included across 17 studies. Standardized mean difference (SMD) was used as the pooled statistic using random-effects models, with Hartung-Knapp-Sidik-Jonkman (HKSJ) sensitivity analyses. Quantitative meta-analysis was performed for domains with at least three studies (aphasia, neglect, attention); other domains (global cognition, executive function, working memory) were assessed qualitatively. This review was not prospectively registered.

Results: The meta-analysis included twelve studies, out of the 17 included in the systematic-review. The qualitative results reported improvements in global cognition, working memory, and executive function following tDCS application. The quantitative results demonstrated a pooled effect for aphasia using the random-effects model (SMD: 1.965, 95% CI: 0.950-2.979, $P<0.001$, I^2: 82.42%; HKSJ: SMD: 1.266, 95% CI: 0.560-1.972, $P<0.001$). However, no significant effects were identified for attention (random-effects SMD: 1.702, 95% CI: -0.07-3.474, $P=0.06$, I^2: 88.51%; HKSJ: SMD: 1.355, 95% CI: -0.087-2.798, $P=0.065$) or neglect (random-effects SMD: -1.041, 95% CI: -2.209-0.126, $P=0.08$, I^2: 64.73%; HKSJ: SMD: -0.658, 95% CI: -2.165-0.849, $P=0.391$). GRADE certainty of evidence was rated as VERY LOW for all domains due to risk of bias, serious inconsistency, and imprecision. Evidence for global cognition, executive function, and working memory remains inconclusive due to insufficient studies.

Conclusions: Dual-site tDCS may have beneficial effects in PSCID, with a pooled improvement observed for aphasia. However, no significant effects were found for attention or neglect. Substantial heterogeneity, small sample sizes, and moderate-to-high ROB limit the robustness and generalizability of findings. Overall, current evidence is insufficient to support definitive clinical effectiveness, highlighting the need for high-quality randomized trials.

Introduction

Stroke is the second leading cause of death globally, accounting for over 13 million new cases annually.[1] Two-thirds of stroke survivors experience a cognitive deficiency or deterioration that impairs their ability to conduct daily activities and lowers their quality of life.[2,3]

Studies show that around 80% of stroke patients experience post-stroke cognitive impairment and dementia

(PSCID), which significantly affects the patients' self-care ability and participation in society.[3,4] Accordingly, there exists an urge to address PSCID meticulously. Evidence indicates that lesions affecting significant brain regions (e.g., the hippocampus, medial prefrontal cortex, and cingulate cortex) as well as white matter lesions and cerebral microbleeds are the main causes of PSCID.[5]

In this light, a variety of techniques have been used to ameliorate post-stroke cognitive impairment (PSCI), including brain stimulation, cognitive training, and pharmaceutical therapies.[6,7] Transcranial direct current stimulation (tDCS) is one of the most utilized non-invasive brain stimulation (NIBS) techniques.[8] In tDCS, cortical activity can be modulated by applying a low-intensity electrical current (typically between 1 and 2 mA) with two or more electrodes on the scalp. The electrical current between the electrodes causes cortical excitability to rise below the anode and decrease below the cathode (transcranial route).[9] Recent evidence also supports their acute impact on brain activity modulation via affecting brainstem pathways involving trigeminal nuclei, locus coeruleus (LC), and raphe nuclei (RNs) (transcutaneous route).[10-12]

There are three methods to apply tDCS: bilateral simultaneous anodal and cathodal tDCS stimulation, and anodal or cathodal tDCS stimulation alone.[13] Bilateral, bihemispheric, or dual-site tDCS has been shown to exert positive effects on a number of cognitive domains[14-18], and motor functions.[19-22] Moreover, dual-site tDCS has been shown to be more effective than single anodal or cathodal one in numerous motor[19,21] and cognitive functions.[23,24]

The effect of single tDCS following stroke has been assessed in a number of systematic reviews.[25-27] Further, a recent systematic review and network meta-analysis suggested that anodal tDCS over the affected dorsolateral prefrontal cortex (DLPFC) attenuated memory impairment following PSCID.[28] Nevertheless, conclusive evidence regarding the impact of dual-site tDCS on PSCID is lacking.

This systematic review and meta-analysis was conducted to assess the available evidence about the impact of dual-site tDCS on cognitive domains such as global cognition, attention, working memory, neglect, aphasia, and executive function in patients with PSCID.

Methods

Protocol Registration

This systematic review and meta-analysis was not prospectively registered in a protocol registry (e.g., PROSPERO). The absence of preregistration introduces a potential risk of selective outcome reporting and post-hoc methodological decisions, which is acknowledged as a limitation. To mitigate this risk, we adhered strictly to the PRISMA 2020 guidelines (Table S1)[29], prespecified our PICO framework, inclusion/exclusion criteria, and analytic plan before data extraction, and transparently reported all analyses conducted.

Literature Search

Five different databases, including PubMed (Medline), EMBASE, Web of Science, Scopus, and the Cochrane Library were searched independently for the studies meeting inclusion criteria. The search was conducted from database inception to January 2025. Full electronic search strategies for all databases, including field tags, Boolean logic, filters, date limits, and exact search dates, are provided in Table S2.

The systematic review question was informed by the "PICO" framework.[30] Regarding the study question, the study population (P) for searching was hemorrhagic or ischemic stroke accompanied by cognitive impairment. The intervention (I) was either dual-site tDCS stimulation or dual-site tDCS stimulation plus an additional cognitive component. The comparison group (C) was either a control group or a control plus additional component group. The included outcomes (O) were categorized into six cognitive domains including attention, neglect, aphasia, working memory, executive function, and global cognition.

Appropriate free terms combined with medical subject headings (MeSH) were used as the retrieval strategy: The search formula was structured as:

(stroke OR cerebrovascular accident OR CVA OR brain ischemia OR cerebral hemorrhage OR cerebral infarction OR cerebral stroke OR brain vascular accident) AND (noninvasive brain stimulation OR transcranial direct current stimulation OR transcranial stimulation OR tDCS AND dual-site transcranial direct current stimulation OR dual site-tDCS OR bilateral transcranial direct current stimulation OR bilateral tDCS OR bihemispheric transcranial direct current stimulation OR bihemispheric tDCS OR bicephalic transcranial direct current stimulation OR bicephalic tDCS). The findings were cross-checked once the two researchers (ME, HSP) had finished their separate searches. Disagreements were resolved through discussion with a third researcher (SSE). Relevant reviews and reference lists of all articles were examined for potentially eligible studies.

Inclusion and exclusion criteria

Studies meeting the specified criteria were incorporated into the systematic review. I) Research concentrating on individuals diagnosed with hemorrhagic or ischemic stroke accompanied by cognitive impairment; II) Research comparing dual-site tDCS stimulation with a control group receiving either sham or no stimulation (when the intervention included an additional component, such as cognitive training, the comparison was made between intervention plus cognitive training and sham plus cognitive training); III) Research that presents outcomes from neuropsychological and cognitive assessments, along with adequate details to calculate effect size statistics; IV) Randomized controlled trials, case series or case-report studies. Case reports and case series were included in the systematic review for qualitative synthesis only and were not included in the quantitative meta-analysis due to their inherent methodological limitations and lack of comparator groups. The certainty of evidence derived

from these designs was considered lower than that from RCTs. There were no limitations on the study duration, age, gender, ethnicity, follow-up period, or severity of the illness.

We excluded all non-English articles from our study. Non-English articles were excluded due to resource constraints for translation and verification of methodological quality. We acknowledge that this exclusion may introduce language bias and potentially limit the generalizability of findings, as positive results may be overrepresented in English-language publications. Articles that employed a healthy population as a control, studies with no full text accessible, conference papers, reviews, meta-analyses, animal studies, and articles analyzing other outcomes as well as research evaluating the effects of single-mode (anodal or cathodal) tDCS were not included in this study. Grey literature (e.g., theses, conference abstracts) was not included due to the lack of peer review and insufficient methodological detail required for risk of bias assessment. This limitation is discussed in the Limitations section. Due to insufficient data, we excluded results supported by fewer than three studies from that section of the meta-analysis.

Outcomes measures

For each identified study, we included pre- and post-assessments of cognitive function for the active and sham groups. To facilitate cross-comparisons, cognitive outcomes were categorized into domains. The systematic review focused on six cognitive domains including attention, neglect, aphasia, working memory, executive function, and global cognition. The Mini-Mental State Exam (MMSE) and the Montreal Cognitive Assessment (MoCA) were the primary tools used to assess cognitive function. The Seoul Computerized Neuropsychological Test (SCNT) and RehaCom software modules were used to assess subsets of attention and working memory. Aphasic test subsets included picture description, naming, reading, and repetition. Behavioral inattention (neglect) subtests were the line bisection test and star cancellation. Also, measures of verbal working memory, verbal fluency, the Stroop color-word test (SCWT), the Wisconsin card sorting test (WCST), and verbal working memory were used for executive function.

Data extraction

A standardized data collection form was employed to extract data from the selected articles. The following information was extracted: Author names, year of publication, study design, sample size, age, gender, educational level, stroke phase, stimulation type, stimulation intensity and duration, target and references electrode regions, assessed cognitive domains, type of stroke (ischemic or hemorrhagic), length of the test phase, length of follow-up, type of cognitive tests used in the study, cognitive outcome(s) and general effect of dual-site tDCS were extracted from the included publications. Data from eligible studies were retrieved twice (ME and HSP), and any differences in opinions were addressed through discussion.

Risk of bias assessment

For randomized controlled trials, the Cochrane guidelines and their bias risk assessment tool were used, assessing the following domains: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result.[31]

For case series and case reports, the Joanna Briggs Institute (JBI) Critical Appraisal Checklists (version 2020) were used, with study-specific criteria applied. Judgment rules for each domain were prespecified: 'low risk' indicated adequate methods and low susceptibility to bias; 'high risk' indicated serious methodological flaws; 'unclear' indicated insufficient information to judge.

In terms of other study designs, standardized JBI critical appraisal instruments were applied..Eligible studies were critically appraised using the standardized JBI critical appraisal tool for case series and case reports. The chosen studies were divided into three quality categories according to their scores. A score above 80% was classified as high quality, a score ranging from 60% to 80% as medium quality, and a score below 60% as low quality. Each of the included studies underwent independent assessment by two authors. Any discrepancies in bias assessment or justifications were addressed through discussion with the other authors, and consensus was reached until a final agreement was obtained. The ROB was rated as low, unclear, or high for each item. All studies were included in this systematic review and meta-analysis regardless of the quality assessment results. However, sensitivity analyses were performed excluding studies with high ROB and case series to assess the robustness of findings. Risk of bias assessments directly informed GRADE certainty ratings; studies with high ROB contributed to downgrading of evidence certainty.

Certainty of Evidence Assessment

Using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) framework, the certainty of evidence was assessed for each cognitive domain outcome. Certainty was rated as HIGH, MODERATE, LOW, or VERY LOW based on risk of bias, inconsistency, indirectness, imprecision, and publication bias.

Statistical analysis

Meta-analyses were conducted using Comprehensive Meta-Analysis (CMA, version 2; Biostat, Englewood, NJ) and R (version 4.3.2) with the metafor package (version 4.2-0). When at least three studies assessed the cognitive domains of interest, the domains were included in the meta-analysis. The standardized mean difference (SMD) with 95% confidence intervals (CI) was used as the pooled effect measure because different neuropsychological scales were used to assess the same cognitive domains across studies; therefore, pooling raw mean differences was not appropriate.

The random-effects model was chosen a priori based

on the expectation of between-study heterogeneity due to anticipated variations in stroke phase (subacute vs. chronic), tDCS parameters (intensity, duration, number of sessions), electrode montages, outcome measurement tools, and co-interventions. This conceptual rationale informed the choice of the random-effects model regardless of the observed I^2 statistic. The DerSimonian and Laird (DL) estimator was used for between-study variance (tau^2).

The I^2 statistic was applied to assess the heterogeneity of the data and stratified to 25%, 50%, or 75%, groups as low, modest, and high, respectively. In addition to I^2, tau^2 (between-study variance) and, where at least five studies were available, prediction intervals were reported to characterize the distribution of true effects. For HKSJ re-analyses, the rma.uni function with method = "DL" was used, applying the Hartung-Knapp adjustment for the confidence interval. The HKSJ method provides more conservative estimates and is particularly appropriate for meta-analyses with few studies, as it adjusts for uncertainty in the estimation of between-study variance and reduces the risk of false-positive findings.

Trim and fill analyses as well as funnel plots were used to quantify publication bias.[32,33] Funnel plots and trim-and-fill analyses were performed despite the limited number of studies per outcome (3-7 studies). We acknowledge that these methods have limited power and reliability with such small numbers of studies; therefore, conclusions regarding publication bias should be interpreted with caution. The observed asymmetry may reflect small-study effects, heterogeneity, or true lack of effect rather than publication bias. This limitation is discussed in the Limitations section..[32,33]

Since the number of included studies and sample sizes are small and varied among the studies, we reanalyzed the data using more conservative analyses with the Hartung, Knapp, Sidik, and Jonkman (HKSJ) method, using R (metafor package).

Sensitivity analyses were performed to evaluate the influence of source of heterogeneity or low-quality studies on outcomes.

In cases where a publication presented information on more than one outcome, all involving the same participants, we calculated an overall effect for all outcomes while taking bias into account.[34] The following was used to measure the mean for different outcomes reported for a single cognitive domain:

$$\bar{Y} = \frac{I}{m} / (\sum_{j}^{m} \mathrm{Yj}) \quad (1)$$

$$\bar{Y} = \frac{1}{m} \sum Y \quad (1)$$

where "Y" is the mean for effect sizes from various outcomes and "m" is the number of means.

However, the cumulative variance of these means was estimated as,

$$V_{\bar{Y}} = (1/m)^2 \, var = \sum_{j=1}^{m} (\mathrm{Yj}) = (1/m)^2 \quad (2)$$

$$+ \sum_{j=1}^{m} (\mathrm{vi}) + \sum_{\mathrm{j} \neq \mathrm{k}}^{\infty} (\mathrm{rjk} \sqrt{\mathrm{Vj}} \sqrt{\mathrm{Vk}})$$

$$V_{\bar{Y}} = \left(\frac{1}{m}\right)^2 \left(\sum_{j=1}^{m} v_j + \sum_{j \neq k} r_{jk} \sqrt{v_j} \sqrt{v_k} \right) \quad (2)$$

where "V" is variance, and "m" is the number of variances in the formula.[34] $p < 0.05$ was considered statistically significant in all analyses.

Results

Literature search

After sifting through the databases electronically, a total of 5241 articles were found; however, 2186 papers were removed from consideration since they were duplicates. Another 2,880 articles were excluded from the remaining 3,055 publications after they were subjected to title, abstract, and keyword screening.. Following title and abstract screening, 175 full-text studies were screened for eligibility, and 158 studies were excluded for various reasons as indicated in Figure 1. Accordingly, only 17 studies met our inclusion criteria and were included in this systematic review. A meta-analysis could not be performed on five of these studies, as one[35] had inadequate data for analysis, and the other four[36-39] were case reports (Figure 1). Twelve studies, with 7 on aphasia, 3 on neglect, and 3 on attention (one study was the same in neglect, and attention domains) were included in the meta-analysis.

Study characteristics

The main characteristics of the 17 studies are presented in Tables 1 and 2. These 17 studies included 9 randomized clinical trials, 4 case series, and 4 case reports. Of the 296 participants, 149 were in the dual-site tDCS group, and 147 were in the control group. The mean age of the patients ranged from 53.05 to 67.33 years. Among included studies, 177 (59.79%) patients were male, and 172 (77.47%) had an ischemic stroke. Six studies included both stroke types, ten studies focused only on ischemic stroke, and in two studies, the stroke type was not specified. In almost all of the studies, bilateral or dual-site tDCS was directed between an anode applied over the lesioned hemisphere and a cathode over the contralateral hemisphere, with a current intensity of 1 to 2 mA. The mean ± SD of sessions was 11.11 ± 5.81; two studies tested the effect of a single session. The mean ± SD session duration was 21.94 ± 3.88 minutes.

It is worth noting that while dual- site tDCS has been used alone in four trials, the majority of studies have included various other therapies in addition to tDCS, such as speech and language therapy, cognitive neglect therapy, conventional rehabilitation, and (computer-assisted) cognitive rehabilitation.

All studies provided information on the duration following stroke onset, with 12 studies focusing on chronic stroke subjects and 5 studies involving subacute subjects. Of the 17 studies, 15 were conducted in Europe (n = 10) and Asia (n = 5), while 1 study took place in South America and another in Africa. The data of case report studies are presented in Table 2.

Results of individual studies

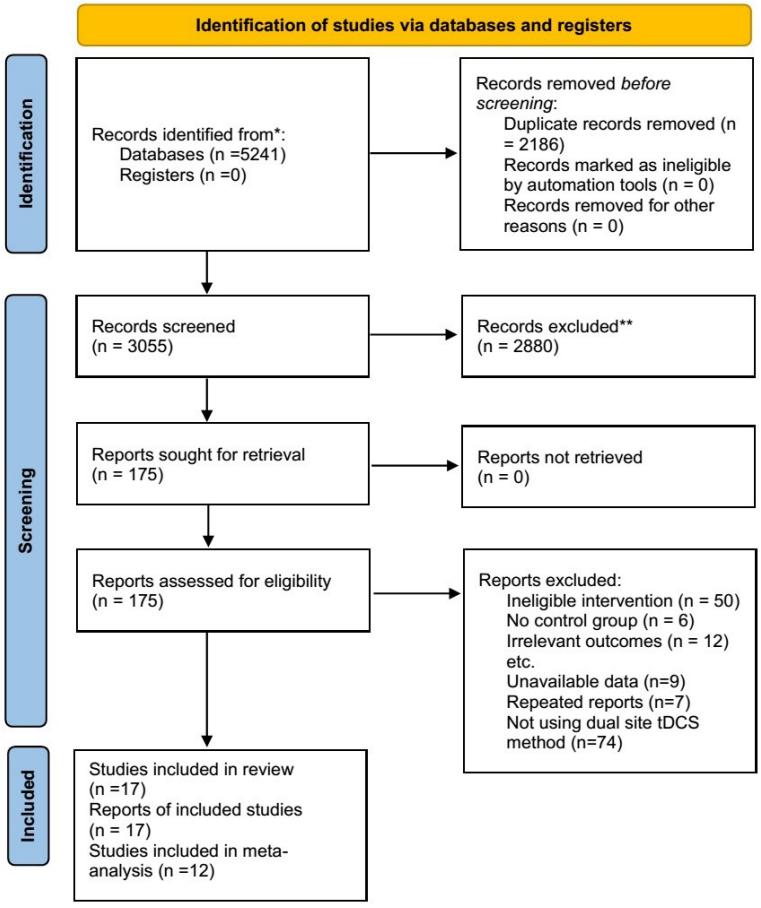

Figure 1. PRISMA flow diagram. Literature selection summary based on the PRISMA guidelines depicting the number of inclusions and exclusions from the initial search

The effects of dual-site tDCS on attention in stroke patients

The effects of dual-site tDCS on attention were evaluated in three studies. Out of them, two studies by Park et al.[17] and Shaker et al.[16] investigated how dual-site tDCS and cognitive training tools together affected stroke patients' attention. tDCS was used to target both prefrontal cortical regions. Both groups showed a considerable improvement in the attention test scores, with the tDCS group showing a significantly larger improvement than the sham group. Guillouët et al.[40] looked at the impact of speech-language therapy and bihemispheric tDCS (bilateral F7 and F8 areas) on post-stroke aphasic patients. There was no significant changes in outcome measures between the active and sham tDCS.

The effects of dual-site tDCS on working memory in stroke patients

The impact of dual-site tDCS on working memory was evaluated in two comparisons. Dual-site tDCS effects on the DLPFC regions (F3 & F4) were investigated by Shaker et al.[16], where a noticeable improvement in figural memory performance was reported (78.08% in the tDCS group vs 27.63% in the sham group). The synergistic effects of dual-site tDCS and computer-assisted cognitive rehabilitation (CACR) on patients' working memory performance were examined by Park et al.[17]. The non-dominant arm and the bilateral prefrontal cortex, respectively, served as the anode and cathode attachment sites. The four items of the SCNT were used to assess each patient. The findings showed no improvement in the four SCNT working memory tests.[17]

The effects of dual-site tDCS on neglect in stroke patients

The impact of dual-site tDCS on neglect was evaluated in three comparisons. The combined effects of cognitive training tools and dual-site tDCS or solely dual-site tDCS on neglect performance were investigated by Bang and Bong[41] and Sunwoo et al.[23], respectively. tDCS was used to target the bilateral parietal cortex. The tDCS group's improvements in neglect test scores were considerably greater than those of the sham group. On the other hand, Smit et al.[18] used a dual-site tDCS on the posterior parietal cortex with no discernible treatment-related effects.

The effects of dual-site tDCS on aphasia in stroke patients

The impact of dual-site tDCS on aphasia was evaluated in seven comparisons. Marangolo et al.[15,42,43] showed significant effects of dual-site tDCS of bilateral Broca's and intense language therapy on language skills in stroke patients. Pisano et al.[14] showed a higher improvement in writing following dual-site tDCS on bilateral temporoparietal regions compared to the sham. The bihemispheric tDCS over frontal cortex by Yekta et al.[44] resulted in a significant increase in the aphasic score in the active tDCS group which persisted for three months following treatment. Feil et al.[45] investigated the effects of bilateral inferior frontal gyrus (IFG) tDCS. They found a substantial improvement

Table 1. Characteristics of the included RCTs and case series in the systematic review and meta-analysis

Follow-up (days)	Adverse effects	Effect of tDCS	Outcomes measured	Cognitive domains	Cathode location	Anode location	Number of sessions	Stimulation Intensity and duration	Stroke phase (Ischemic/ Hemorrhagic)	Education level (year)	Age	Sex M/F	Subjects N Sham/Exp	Design	Study [author (year)]
21	NM	dual↑	P-WAB-1	Broca's aphasia	Right frontal cortex (F4)	Left frontal cortex (F3)	7	2mA/ 20min	Subacute (30/0)	NM	Exp: 63 ± 11.5 sham: 65.3 ± 10.1	Exp: 6/9 Sham: 7/8	15/15	RCT Parallel	Yekta et al. (2022)
7	Not reported	dual↑	Oral NN &VN, Written NN & VN, WR, NWR, W Read & Dict, NW Read & Dict	Aphasia	Right Tempo parietal cortex (CP4)	Left Tempo parietal cortex (CP5)	10	2mA/ 20min	Chronic (13/1)	12.7 ± 3	59.5 ± 4.3	7/7	14/14	RCT Crossover	Pisano et al. (2021)
-	4 person in real and 2 person in sham group experienced headache or skin redness	dual↑ > sham↑	WCST, SCWT, DST, MMSE, MOCA, ADLs	Global cognition, Executive function	Right DLPFC	Left DLPFC	20	2mA/ 20min	Chronic (21/29)	Exp: 8 Sham: 9	Exp: 65 [60.5-70.5] Sham: 64 [55-70]	Exp: 15/10 Sham: 12/13	25/25	RCT Parallel	Yuan-Wen et al. (2021)
-	Not reported	No significant difference	HDAE job test, Paraphasias, verbal working memory, Bells test, verbal fluency tests	Aphasia, Attention, Executive function	Right IFG (F8)	Left IFG (F7)	2-5/ week, during 6 weeks	2mA/ 20min	18 months [1-60] (12/2)	10 patients > 12 years; 4 patients 9-12 years	53.8 ± 13.1	9/5	14/14	RCT Crossover	Guillouët et al. (2020)
28	NM	dual↑ > sham↑	PN, AAT, ANELT, Alertness	Aphasia	Right IFG	Left IFG	10	2mA/ 20min	Subacute (12/0)	Exp: 13 ± 1.7 Sham: 13.8 ± 3.1	Exp: 59.1 ± 11.6 Sham: 67.3 ± 13	10/2	6/6	RCT Parallel	Feil et al. (2019)
-	NM	dual↑ in all tests	RehaCom Subsets: ACL, FML, LRL, RBL, FIM	Attention, Memory	Contralateral supraorbital region	Bilateral prefrontal cortex (F3&F4)	12	2mA/ 30min	Chronic (40/0)	at least 10 years	Exp: 54.4 ± 4.6 Sham: 53 ± 6.3	40/0	20/20	RCT Parallel	Shaker et al. (2018)
-	NM	dual & FT↑ > FT↑	MVPT, LBT, MBI	Visuospatial neglect	Left & right supraorbital area	Left & right PPC (P3&P4)	15	1mA/ 20min	Subacute (NM)	NM	Exp: 66.0 ± 4.2 Sham: 65.6 ± 4.7	4/8	6/6	RCT Parallel	Bang et al. (2015)
-	NM	dual↑ for attention test	SCNT Test, K-MMSE	Global cognition, Attention, Memory	Non- dominant arm	Bilateral prefrontal cortex (F3&F4)	5/ week, mean period of 18.5 days	2mA/ 30min	Subacute (7/4)	Exp: 5.0 ± 4.5 Sham: 6.0 ± 4.2	Exp: 65.3 ± 14.3 Sham: 66 ± 10.8	5/6	5/6	RCT Parallel	Park et al. (2013)
-	In dual stimulation 3 person reported mailed headache	dual↑ in line bisection test	Line bisection test, star cancelation test	Visuospatial neglect	Left PPC	Right PPC	1	1mA/ 20min	Chronic (7/3)	NM	62.6 ± 13.3	4/6	10/10	RCT Crossover	Sunwoo et al. (2013)
-	Not reported	dual↑	PD, NN, VN, WR, NWR, W & NW Read	Aphasia	Right Broca's area	Left Broca's area	15	2mA/ 20min	Chronic (9/0)	13.8 ± 3.9	58.2 ± 7.1	5/4	9/9	Case series	Marangolo et al. (2016)
-	Most of patients reported slight tingling under anodal electrode	No differences	BIT Subsets: SC, LC, Lic, LB, FSC-A&B, RD	Hemispatial neglect	Left PPC	Right PPC	5	2mA/ 20min	Chronic (2/3)	NM	64.8 ± 8.8	3/2	5/5	Case series	Smit et al. (2015)
7	Not reported	dual↑ in first three outcome	PD, VN, NN, word & Sentence comprehension	Aphasia	Contralesional Broca's area	Ipsilesional Broca's area	10	2mA/ 20min	Chronic (7/0)	11.1 ± 4.3	57.5 ± 6.8	5/2	7/7	Case series	Marangolo et al. (2014)

Table 1. Continued.

Follow-up (days)	Adverse effects	Effect of tDCS	Outcomes measured	Cognitive domains	Cathode location	Anode location	Number of sessions	Stimulation Intensity and duration	Stroke phase (Ischemic/ Hemorrhagic)	Education level (year)	Age	Sex M/F	Subjects N Sham/Exp	Design	Study [author (year)]
7	Not reported	dual↑	Accuracy & speed in articulating the treated stimuli, PD, VN, NN, WR, W Read	Aphasia	Right Broca's area	Left Broca's area	10	2mA/ 20min	Chronic (8/0)	4.7 ± 12	6.2 ± 55.9	4/4	8/8	Case series	Marangolo et al. (2013)

AAT, Aachen aphasia test; ACL, attention concentration level; ADLS, Activities of Daily Living Scale; ANELT, Amsterdam Nijmegen Everyday Language Test; ASHA-FACS, Functional Assessment of Communication skills for Adults; BADA, Battery for the Analysis of the Aphasic Deficit; BIT, Behavioral Inattention Test; CACR, computer-assisted cognitive rehabilitation; SC, Star Cancellation; DLPFC, dorsolateral prefrontal cortex; DST, Digital Symbol Test; FIM, functional independent measure; FML, figural memory level; FSC-A&B; Figure and Shape Copying; FT, feedback training; HDAE, Boston Diagnostic Aphasia Examination; IFG, inferior frontal gyrus; K-MMSE, Korean Mini-Mental State Examination; LB, Line Bisection; LBT, line bisection test; LC, Letter Cancellation; LiC, Line Crossing; LRL, logical reasoning level; MBI, modified Barthel index; MMSE, Mini-mental State Examination; MoCA, Montreal Cognitive Assessment; MVPT, Motor-Free Visual Perception Test; NET, Neglect-Test; NM, not mentioned; NWD, Nonword under Dictation; NWR, Nonword Reading; NWR, Nonword Repetition; Oral NN, Oral Noun Naming; Oral VN, Oral Verb Naming; PD, Picture Descriptions; PN, Picture Naming; PPC, posterior parietal cortex; P-WAB-1, Persian version of the Western Battery-1; RBL, reaction behavior level; RCT, randomized controlled trial; RD, Representational Drawing; SCNT, Seoul Computerized Neuropsychological Test; SCWT, Stroop Color-Word Test; TAP, Test for Attentional Performance; Tdcs, transcranial direct current stimulation; WCST, Wisconsin Card Sorting Test; W Dict, Word under Dictation; W Read, Word Reading; WR, Word Repetition; Written NN, Written Noun Naming; Written VN, Written Verb Naming

Table 2. Characteristics of the case report studies included in the systematic review

Study [author (year)]	Sex (M/F)	Age	Education level	Stroke phase (Ischemic/ Hemorrhagic)	Stimulation Intensity and duration	Number of sessions	Anode location	Cathode location	Cognitive domains	Outcomes measured	Effect of tDCS	Follow-up (Days)
Manenti et al. (2015)	F	49	8	Chronic (Ischemic)	2mA /25min	20	Left DLPFC	Right DLPFC	Aphasia	Verb anomia	dual↑	84, 168 and 336
Tommaso et al. (2015)	M	58	8	6 months (Ischemic)	1.5mA/ 20min	12	Left parietal (P3)	Right parietal (P4)	Aphasia	AAT, ASHA-FACS, Modified BADA, Neuropsychological tests	dual↑	28
Costa et al. (2014)	F	57	13	Chronic (Ischemic)	1mA/ 20min	Exp1: 10 Exp2: 10	Exp1: Left BA (44/45) Exp2: Left BA (39/40)	Exp1: Right BA (44/45) Exp2: Right BA (39/40)	Aphasia	PN, BADA, visuospatial abilities tests, Bell's test, Benton's Judgment of Line Orientation	Exp1: dual↑ Exp2: No differences	3
Brem et al. (2014)	M	72	NM	Subacute (Ischemic)	1mA/ 20min	6	Right parietal cortex (P4)	Left parietal cortex (P3)	Visuospatial neglect	TAP subsets: covert attention, alertness, NET Subsets: Line bisection, cancelation, copying figures and ADL	dual↑	84

AAT, Aachen aphasia test; ADLS, Activities of Daily Living Scale; ASHA-FACS, Functional Assessment of Communication skills for Adults; BA, Brodman areas; BADA, Battery for the Analysis of the Aphasic Deficit; DLPFC, dorsolateral prefrontal cortex; NET, Neglect-Test; NM, not mentioned; PN, Picture Naming; TAP, Test for Attentional Performance

in the picture naming task and communication task of the Aachen aphasia test one month following treatment in the active tDCS group. However, Guillouët et al.[40] used speech-language therapy in conjunction with dual-site tDCS on bilateral IFG. The number of distinct nouns and other outcome measures did not significantly change in the HDAE subset.[40]

The effects of dual-site tDCS on global cognition in stroke patients

The impact of dual-site tDCS on global cognition was evaluated in two comparisons. Park et al.[17] conducted one of the first trials to combine CACR and tDCS. The findings indicated no difference in Korean Mini-Mental State Examination (K-MMSE) scores between the experimental and sham groups. Yuan-Wen et al.[35] found that the dual-site DLPFC tDCS group experienced greater improvements in MMSE and MoCA than the sham group.

The effects of dual-site tDCS on executive function in stroke patients

The impact of dual-site tDCS on executive function was evaluated in two comparisons. Yuan-Wen et al.[35] used bilateral DLPFC tDCS to examine the effects of this treatment on stroke patients. Following therapy in the tDCS group, test indices were found to be noticeably greater than those in the sham group. Guillouët et al.[40] investigated the effects of bihemispheric tDCS on left and right IFG (F7& F8) areas in post-stroke aphasic patients. Ten out of the fourteen patients finished every phase of the trail. However, the outcome measures did not demonstrate statistically significant changes between the active- and sham tDCS situations.[40]

Meta-analysis findings

GRADE Certainty of Evidence

Using the GRADE framework, the certainty of evidence was

assessed for each cognitive domain. For aphasia, certainty was rated as VERY LOW due to serious risk of bias, serious inconsistency ($I^2 = 82.42\%$), and imprecision from small sample sizes. For attention, certainty was rated as VERY LOW due to very serious inconsistency ($I^2 = 88.51\%$) and serious imprecision. For neglect, certainty was rated as VERY LOW due to risk of bias and imprecision. No GRADE assessment was performed for global cognition, executive function, or working memory due to insufficient studies (Table 3).

The effects of dual-site tDCS on attention

Table 3. GRADE Assessment and Summary of Findings Table for Dual-site transcranial direct-current stimulation (tDCS) compared to sham/control for post-stroke cognitive impairment and dementia (PSCID)

Outcome	№ of participants (studies)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Effect estimate (SMD, 95% CI)	Interpretation
Aphasia	114 (7 RCTs)	Randomized trials	Serious[1]	Very serious[2]	Not serious	Serious[3]	Undetected[4]	⊕◯◯◯ VERY LOW	**Random-effects:** 1.965 (0.950 to 2.979)**HKSJ:** 1.266 (0.560 to 1.972)	Dual-site tDCS may improve aphasia outcomes, but the evidence is very uncertain. Substantial heterogeneity limits confidence.
Attention	61 (3 RCTs)	Randomized trials	Serious[1]	Very serious[5]	Not serious	Serious[3]	Undetected[4]	⊕◯◯◯ VERY LOW	**Random-effects:** 1.702 (-0.070 to 3.474)**HKSJ:** 1.355 (-0.087 to 2.798)	The evidence is insufficient to determine whether dual-site tDCS improves attention. Confidence intervals cross the null.
Neglect	42 (3 RCTs)	Randomized trials	Serious[1]	Serious[6]	Not serious	Very serious[7]	Undetected[4]	⊕◯◯◯ VERY LOW	**Random-effects:** -1.041 (-2.209 to -0.126)**HKSJ:** -0.658 (-2.165 to 0.849)	The evidence is insufficient to determine whether dual-site tDCS improves neglect. Wide confidence intervals and direction inconsistency limit confidence.
Global cognition	50 (2 RCTs)	Randomized trials	Serious[1]	N/A[8]	Not serious	Very serious[9]	N/A	Not rated	Qualitative synthesis only	Insufficient studies for meta-analysis. Results conflicting: one study showed improvement, one showed no difference.
Executive function	50 (2 RCTs)	Randomized trials	Serious[1]	N/A[8]	Not serious	Very serious[9]	N/A	Not rated	Qualitative synthesis only	Insufficient studies for meta-analysis. Results inconsistent.
Working memory	56 (2 RCTs)	Randomized trials	Serious[1]	N/A[8]	Not serious	Very serious[9]	N/A	Not rated	Qualitative synthesis only	Insufficient studies for meta-analysis. Results conflicting.

Footnotes:

[1] **Risk of Bias (Serious)**
- Most studies had unclear or high risk of bias for allocation concealment and selective reporting
- Several= studies lacked preregistered protocols
- Blinding of outcome assessment was inconsistently reported
- Downgraded by one level

[2] **Inconsistency (Very Serious)**
- $I^2 = 82.42\%$ for aphasia (substantial heterogeneity)
- Wide prediction interval: -0.15 to 4.08
- Heterogeneity remained high across all sensitivity analyses
- Downgraded by two levels

[3] **Imprecision (Serious)**
- Total sample size across studies is small (n = 114 for aphasia, n = 61 for attention, n = 42 for neglect)
- Wide confidence intervals
- Downgraded by one level

[4] **Publication Bias (Undetected)**
- Funnel plot asymmetry observed but trim-and-fill analysis unreliable with few studies
- Not downgraded, but limitation acknowledged

[5] **Inconsistency (Very Serious)**
- $I^2 = 88.51\%$ for attention
- Heterogeneity extremely high
- Only 3 studies available
- Downgraded by two levels

[6] **Inconsistency (Serious)**
- $I^2 = 64.73\%$ for neglect
- Direction inconsistency between random-effects and HKSJ estimates
- Downgraded by one level

[7] **Imprecision (Very Serious)**
- Very small sample size (n = 42, 3 studies)
- Very wide confidence intervals
- HKSJ confidence interval crosses the null widely
- Downgraded by two levels

[8] **N/A** = Not applicable (insufficient studies for quantitative assessment of inconsistency)

[9] **Imprecision (Very Serious)**
- Only 2 studies available per domain
- Cannot perform meaningful meta-analysis

Downgraded by two levels

In the attention domain, the stimulation sites in the meta-analysis included studies were frontal area. Also, the intensity and duration for all included studies were 2 mA and 20-30 min stimulation/session.

A random effects meta-analysis using 3 studies yielded a SMD of 1.702 (95% CI: -0.07 to 3.474, $p = 0.06$, I^2: 88.51), also HKSJ method results showed SMD of 1.355 (95% CI: -0.087 to 2.798, $p = 0.065$, I^2: 93.71), suggesting no effects of dual-site tDCS on attention in stroke patients (Figure 2).

Due to the small number of studies (k = 3) and substantial heterogeneity, the pooled estimates are highly uncertain. Prediction intervals were wide and crossed the null, indicating that the true effect in a future study could range from beneficial to harmful. Consequently, we interpret these findings as 'insufficient evidence to detect a significant effect' rather than 'no effect exists,' and emphasize that the current evidence does not support definitive conclusions about the clinical efficacy of dual-site tDCS for attention.

The effects of dual-site tDCS on aphasia

In aphasia domain the stimulation sites in meta-analysis included studies were broca's area. Also, the intensity and duration for all included studies was 2 mA and 20 min stimulation/session.

A random effects meta-analysis using 7 studies yielded the pooled estimate of SMD: 1.965 (95% CI: 0.95 to 2.979, $p < 0.001$, I^2: 82.42), also HKSJ method results showed SMD of 1.266 (95% CI: 0.56 to 1.972, $p = 0.000$, I^2: 93.27), indicating possible effects of dual-site tDCS on aphasia in stroke patients (Figure 3). The prediction interval (-0.15 to 4.08) indicates that the true effect in a future study could range from negligible to large, underscoring the uncertainty. Moreover, pooling across different aphasia subtypes (Broca's aphasia, global aphasia) and language domains (naming, repetition, writing, comprehension) may not be clinically meaningful. These results should be interpreted as hypothesis-generating rather than practice-changing. Although statistics showed that dual-site intervention significantly improved performance in aphasia tests, I^2 value suggests substantial heterogeneity across the included trials, which increases the uncertainty of outcome.

The effects of dual-site tDCS on neglect

In the neglect domain, the stimulation sites in the meta-analysis included studies were posterior parietal cortex. Also, the intensity and duration for all included studies was 1-2 mA and 20 min stimulation/session

A random effects meta-analysis using 3 studies yielded a pooled estimate of SMD: -1.041 (95% CI: -2.209 to -0.126, $p = 0.08$, I^2: 64.73), also HKSJ method results showed SMD of 0.658 (95% CI: -2.165 to 0.849, $p = 0.391$, I^2: 91.046), suggesting no effects of dual-site tDCS on neglect in stroke patients (Figure 4). The direction of the HKSJ estimate (favoring sham) should be interpreted with caution due to the wide confidence interval. Using the more conservative HKSJ method (which is recommended for meta-analyses with few studies), the pooled estimate indicated no significant effect of dual-site tDCS on neglect.

Adverse events and dropouts

Adverse events were not prespecified as a primary or secondary outcome in this review. Harms data were extracted from included studies where reported. Mild symptoms such as itching, tingling, and slight burning were frequently reported in several tDCS studies. A small proportion of studies reported mild symptoms, such as skin redness or flushing and headache, during the tDCS sessions. For studies that did not report adverse events, we categorized this as 'not reported' rather than 'no events

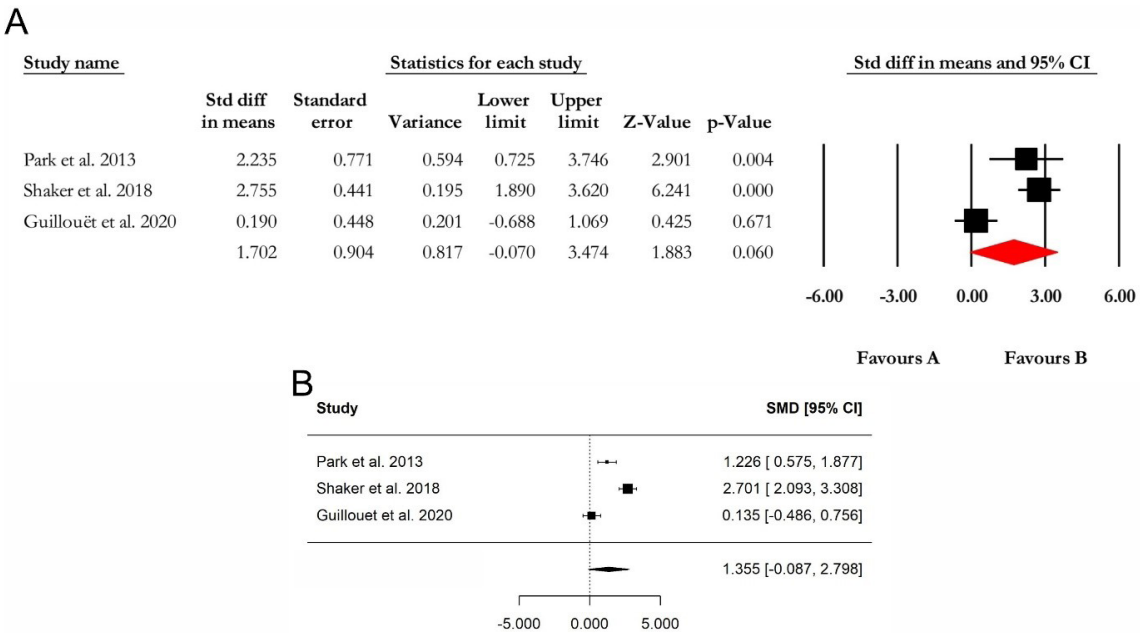

Figure 2. Forest plot of standardized mean difference (SMD) for attention after dual-site transcranial direct-current stimulation (tDCS) in patients with stroke. The lozenges shows the overall pooled effect. Squares indicate the SMD in each study. Horizontal lines represent a 95% confidence interval (CI). A) Random-effects models; B) Hartung, Knapp, Sidik, and Jonkman (HKSJ) method, which provides more conservative estimates for meta-analyses with few studies

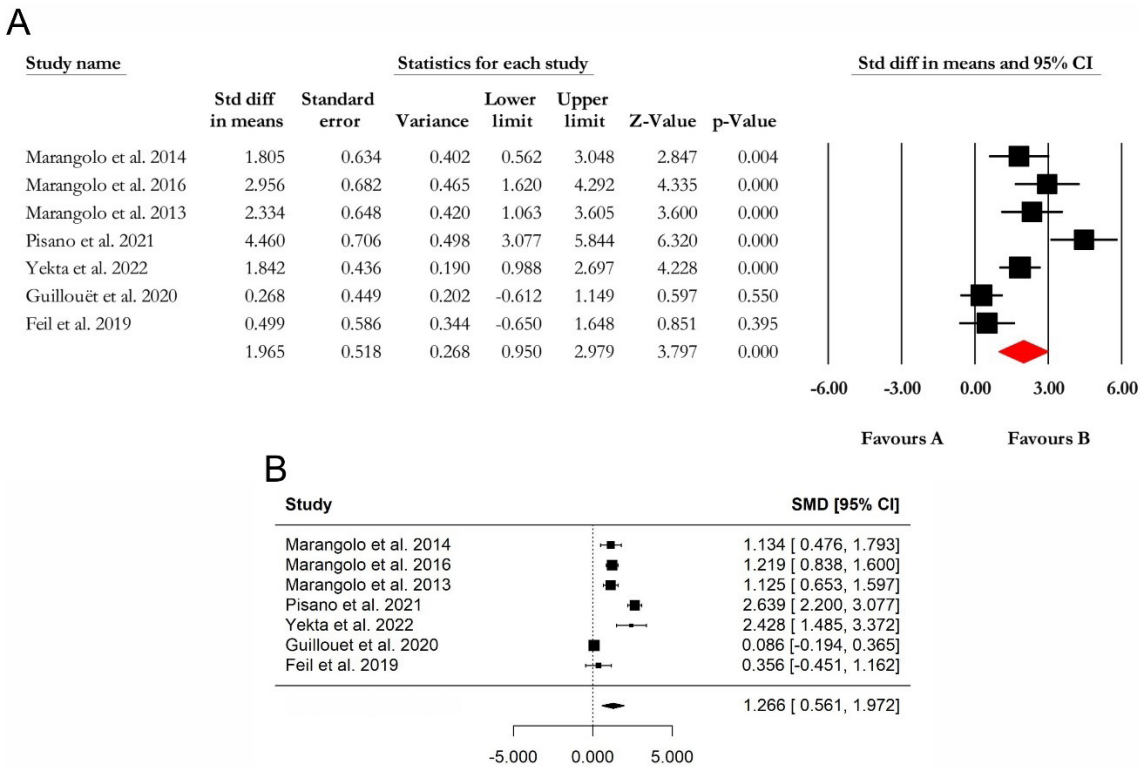

Figure 3. Forest plot of standardized mean difference (SMD) for aphasia after dual-site transcranial direct-current stimulation (tDCS) in patients with stroke. The lozenges shows the overall pooled effect. Squares indicate the SMD in each study. Horizontal lines represent a 95% confidence interval (CI). A) Random-effects models; B) Hartung, Knapp, Sidik, and Jonkman (HKSJ) method, which provides more conservative estimates for meta-analyses with few studies

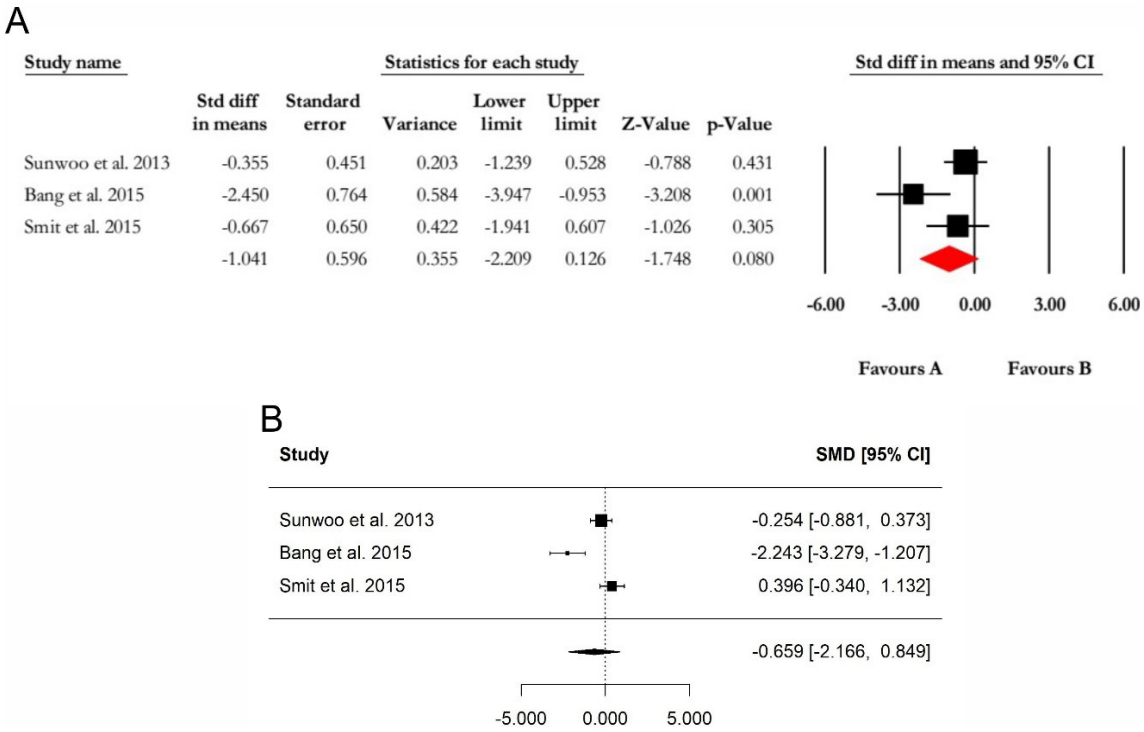

Figure 4. Forest plot of standardized mean difference (SMD) for neglect after dual-site transcranial direct-current stimulation (tDCS) in patients with stroke. The lozenges shows the overall pooled effect. Squares indicate the SMD in each study. Horizontal lines represent a 95% confidence interval (CI). A) Random-effects models; B) Hartung, Knapp, Sidik, and Jonkman (HKSJ) method, which provides more conservative estimates for meta-analyses with few studies

occurred. Group-specific event counts where available are now provided: in Yuan-Wen et al, 4 participants in the active tDCS group and 2 in the sham group reported headache or skin redness[35]; in Sunwoo et al, 3 participants in the dual-stimulation group reported mild headache[23]; in Smit et al, most participants reported slight tingling under the anodal electrode.[18] No serious adverse events (e.g., seizures, hospitalization) were reported in any study.

In the meta-analysis included studies, 5 studies didn't mention the adverse effects[16,17,41,44,45], while no significant

adverse events were reported in 5 other studies.[14,15,40,42,43]

Publication bias

The asymmetry observed in the funnel plot, which is a bivariate scatter plot of standard error versus intervention effect, suggests the potential for publication bias. The funnel plot exhibited a degree of asymmetry (Figure S1). Trim and fill analysis showed two missing studies to the left of the mean; additionally, the observed values effect was 1.7 and the adjusted values effect was calculated at 1.2. However, these methods have limited power and reliability with such small numbers of studies; therefore, conclusions regarding publication bias should be interpreted with caution.

Risk of bias assessment

The ROB of the included randomized controlled trials was assessed using the Cochrane ROB tool and is summarized in Figure S2. Overall, the methodological quality of the included studies was variable, with several domains judged as having unclear or high ROB.

For random sequence generation, only a minority of studies were judged to be at low ROB, while most provided insufficient details regarding the randomization procedure and were therefore rated as unclear. Allocation concealment represented a major methodological limitation, with several studies judged to be at high ROB due to inadequate or unreported concealment methods.

In contrast, blinding of participants and personnel was generally well addressed, with most studies rated as low risk of performance bias, reflecting the use of sham stimulation protocols. However, blinding of outcome assessment was inconsistently reported, and several studies were judged to be at high or unclear risk of detection bias, particularly for outcomes relying on subjective or assessor-dependent neuropsychological measures.

All included studies were judged to be at low ROB for incomplete outcome data, as attrition rates were low and adequately explained. Selective reporting bias was predominantly rated as unclear across studies, largely due to the absence of preregistered protocols or publicly available statistical analysis plans. No major concerns were identified regarding other sources of bias.

Taken together, the ROB assessment indicates that although some methodological domains were adequately addressed, limitations related to allocation concealment, outcome assessment blinding, and selective reporting were common.

The methodological quality of non-randomized studies, including case series and case reports, was assessed using the JBI Critical Appraisal Checklists. The results are summarized in Table S3.

Four case series were evaluated using the JBI checklist for case series. Overall, the methodological quality ranged from moderate to high. Three studies were rated as having moderate quality (60–80%), while one study achieved a high-quality rating (> 80%).

Most case series clearly defined inclusion criteria, used valid and reliable methods for outcome assessment, and adequately reported participant demographics, clinical characteristics, and follow-up outcomes. However, several methodological limitations were identified. Consecutive and complete inclusion of participants was frequently unclear, and statistical analysis was either limited or absent in some studies, contributing to uncertainty in internal validity. In addition, reporting of study setting and recruitment processes was occasionally insufficient.

Five case reports were assessed using the JBI checklist for case reports, and the majority were judged to be of high methodological quality (> 80%), with one study rated as moderate quality.

In general, case reports provided clear descriptions of patient demographics, clinical history, diagnostic procedures, interventions, and post-intervention outcomes. However, reporting of adverse events was inconsistent, and in some reports harms or unanticipated events were not explicitly addressed. This limitation restricts the interpretability of safety outcomes derived from these studies.

Sensitivity analysis

Stepwise study removed analysis showed that the p value did not change substantially in the aphasia data following the removal of Guillouët et al,[40] or Feil et al.[45] or both of the studies. However, heterogeneity remained high ($I^2 > 80\%$) across all sensitivity analyses (Figure S3, Table 4), underscoring the robustness of heterogeneity and the need for cautious interpretation of pooled estimates. One-study removed test shows stability of results for attention and neglect outcome. Additionally, removal of low-quality studies or case series did not show significantly affect the outcomes.

Discussion

This systematic review and meta-analysis evaluated how dual-site tDCS may affect some cognitive domains, including executive function, global cognition, aphasia, and working memory, in PSCID patients. Seventeen studies met the criteria for inclusion, with a total of 296 patients. Accordingly, twelve studies were included in the quantitative analysis, and only data from three cognitive domains, namely, aphasia, neglect, and attention, were examined. The effect of tDCS on cognitive functions following stroke has been assessed in a limited number of systematic reviews without any qualitative analysis.[8,46] To the best of our knowledge, only one meta-analysis has looked into the impact of tDCS on different cognitive functions in PSCID patients.[47] Our meta-analysis revealed that dual-site tDCS attenuated aphasia (with substantial heterogeneity), but not neglect and attention after PSCID. According to the existing evidence on post-stroke aphasia patients, a favorable recovery is easier to achieve when patients downregulate the opposite hemisphere using cathodal stimulation[48,49] and predominantly activate specific regions in the ipsilateral hemisphere, such as the left temporoparietal areas and the left IFG.[50-55] The quantitative analysis results of aphasia treatment studies

Table 4. Summary of sensitivity analysis on aphasia outcome

Stepwise removed studies	SMD	Confidence interval	*P* value	Heterogeneity (I^2)
All studies (without removing any study)	1.26	0.56 - 1.97	0.0001	93.27%
Guillouët et al	1.48	0.79 - 2.17	0.0001	89.11%
Feil et al.	1.40	0.64 - 2.16	0.0001	93.95%
Guillouët et al & Feil et al.	1.68	1.02 - 2.34	0.0001	87.26%

in this review indicate that tDCS at these regions reliably improves performance in various language tasks in stroke subjects.[14,15,42-45] Different electrode montages of tDCS in post-stroke aphasia patients, has shown that in comparison to single-site montage, dual-site stimulation has better resolution and outcomes and more focally distributed over the perilesional region.[14] In another study, mild cognitive impairment (MCI) patients were treated with High-definition-tDCS. MCI patients with apolipoprotein E (APOE) allele 4 in the treatment group, showed a significant improvement in language function compared to sham group. This study, showed that high-definition and focal electrical stimulation has an advantages in these patients.[56]

In line with these findings, some meta-analyses have also demonstrated the benefits of tDCS for post-stroke neglect and aphasia.[25,46,57] In another systematic review by Galletta et al, it was found that tDCS can be combined with other behavioral interventions to support language recovery after aphasia.[8]

Besides, the effectiveness of tDCS for post-stroke aphasia was assessed in a network meta-analysis.[58] Another meta-analysis found that anodal tDCS was more effective for spontaneous speech while dual- and anodal tDCS outperformed in naming and repetition.[59] However, another systematic review showed that the effect of tDCS was comparable to that of the sham in aphasia cases.[60] Accordingly, since the evidence was insufficient to guarantee tDCS efficacy, no recommendations for aphasia were included in the evidence-based tDCS guidelines in 2021.[61]

This controversy of the results may stem from several possible explanations: First, studies on tDCS have utilized various protocols, including differences in electrode placement, stimulation duration, intensity, and polarity (anodal vs. cathodal).[62] Second, the patient populations often vary significantly in terms of stroke severity, time post-stroke, and specific language deficits in different studies.[62,63] Third, some meta-analyses suggest that tDCS may be more effective when combined with behavioral therapies. However, the extent and nature of these combinations are not standardized across studies, leading to controversial findings.[58]

This meta-analysis couldn't find the effect of dual-site tDCS on neglect in PSCID. The interhemispheric dual stimulation method included anodal tDCS over the lesioned hemisphere (usually P4) and cathodal tDCS over the undamaged hemisphere (usually P3) in all the studies on neglect to stimulate the posterior parietal cortex.[46] When combined with other therapies, dual-site tDCS might attenuate neglect by reducing visuospatial impairments. However, these results were not replicated after receiving biparietal tDCS.[18]

DLPFC stimulation was used as the target in nearly all studies evaluating attention. While two trials reported significant improvements in attention test scores, Guillouët et al.[40] found no significant improvement by the treatment, compared to control. However, in a meta-analysis, Yun et al.[64] found a connection between improved attention and anodal tDCS. Similarly, Begemann et al.[65] conducted a meta-analysis and found that tDCS has a small trans-diagnostic effect on attention/vigilance across diagnoses.

Several mechanisms justify the ameliorating effects of dual-site tDCS on PSCID. First, according to the theory of interhemispheric competition, the damaged cerebral hemisphere's inability to develop a normal inhibitory impact causes pathological excitation in the healthy hemisphere.[66] In that regard, excitation of the damaged hemisphere and inhibition of the healthy hemisphere are the two potential therapeutic options[67] that could be used in PSCID, helping these patients regain their cognitive function.

Based on studies conducted in various cognitive domains in stroke patients, it has been determined that anodic stimulation on the affected hemisphere and cathodic stimulation on the contralateral hemisphere can have a better effect than single-mode anodic stimulation on the affected area. The mechanism underlying this hypothesis is that both hemispheres interact via the transcallosal pathway. Therefore, the modulatory effect of tDCS on the unilateral cortical area is enhanced by these interhemispheric interactions and produces a greater effect than single-mode tDCS. In a 2013 study on patients with unilateral visuospatial neglect, dual-mode tDCS was found to be more effective than single-mode tDCS for treating patients.[23]

Second, synaptic architecture and signal transmission are distorted in stroke.[68] Thus, enhancing synaptic plasticity represents a possible therapeutic approach for recovering impaired cognitive function[69] in PSCID. tDCS has been shown to improve synaptic plasticity possibly resulting from long-term potentiation.[70-72] Third, Cognitive deficits arise from diminished local blood flow to brain tissue in the ischemic core and penumbra.[73] The beneficial effect of tDCS on cerebral blood flow augments cognitive function. Lastly, there is evidence to suggest a significant link between LC activity changes after stroke and the potential benefits of LC stimulation in addressing motor deficits and PSCID.[74] After a stroke, the activity of the LC may change, affecting cognitive recovery and overall brain plasticity.[74] As discussed in the introduction, evidence suggests that tDCS activates cranial nerves located on the skull such as the trigeminal nerve, increasing neuronal activity in the brain stem's main and mesencephalic trigeminal nuclei.[11,75] These nuclei may in turn activate LC and RNs[12] and affect PSCID in stroke patients.

Of note, tDCS was primarily utilized with conventional

physical or cognitive therapy, producing a notably higher degree of improvement than either type of the therapy alone. Therefore, it appears that applying tDCS in combination with other therapy modalities creates a synergistic impact that amplifies the advantages of more traditional procedures used alone.

Limitations

The main shortcomings of this systematic review and meta-analysis on the effects of dual-site tDCS on PSCID are:

1. Heterogeneity in patient populations: The included studies likely had significant variability in factors such as stroke severity, time post-stroke, and specific cognitive deficits (aphasia, neglect, attention). Subgroup analyses were not performed due to the limited number of studies within each cognitive domain, precluding meaningful stratification.
2. Diverse tDCS protocols: The included studies used diverse tDCS protocols, including differences in electrode placement, stimulation duration, intensity, and polarity.
3. Non-standardized combination therapies: Some studies combined tDCS with other cognitive rehabilitation therapies in a non-standardized manner.
4. Risk of bias concerns: Most included studies were of medium or low quality based on the ROB assessment, with critical concerns regarding allocation concealment and selective reporting. This undermines confidence in the pooled effect for aphasia, which was derived from studies with moderate-to-high ROB.
5. Limited statistical power: The meta-analysis included only 12 studies, with small numbers per domain limiting statistical power.
6. Lack of long-term follow-up: The review did not assess the long-term effects of dual-site tDCS on cognitive recovery after stroke. Understanding the durability of the effects is important for evaluating the clinical utility of this intervention.
7. Insufficient parameter-specific data: There was insufficient data detailing specific tDCS parameters most effective for each cognitive domain. This limits the ability to make recommendations for clinical practice.
8. Language and grey literature exclusion: Non-English articles and grey literature were excluded, which may introduce language and publication bias. The generalizability of findings may be limited as positive results may be overrepresented in English-language publications.
9. Unreliable publication bias assessment: Funnel plots and trim-and-fill analyses have limited power and reliability with small numbers of studies; therefore, conclusions regarding publication bias should be interpreted with caution.
10. Lack of prospective registration: The absence of protocol registration introduces a potential risk of selective outcome reporting and post-hoc methodological decisions.

Future research should prioritize: (1) standardization of tDCS protocols (electrode placement, intensity, duration, number of sessions); (2) longer follow-up periods to assess durability of effects; (3) stratification by stroke subtype (ischemic vs. hemorrhagic), stroke phase (acute, subacute, chronic), and specific cognitive domain; and (4) adequately powered, multicenter randomized controlled trials with preregistered protocols.

Conclusion

This systematic review and meta-analysis found limited and heterogeneous evidence regarding the effects of dual-site tDCS on post-stroke cognitive impairment. While a pooled improvement was observed for aphasia, substantial heterogeneity, small sample sizes, and moderate-to-high ROB limit the robustness and generalizability of this finding. No significant effects were identified for attention or neglect. The GRADE certainty of evidence was rated as VERY LOW for all cognitive domains assessed. Overall, current evidence is insufficient to support definitive clinical effectiveness of dual-site tDCS, highlighting the need for high-quality, adequately powered randomized trials with standardized protocols and long-term follow-up before clinical implementation.

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Competing Interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethical Approval

This article does not contain any studies with human participants or animals performed by any of the authors.

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Supplementary Files

Supplementary file 1 contains Tables S1-S4.
Supplementary file 2 contains Figures S1-S3.

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