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Systematic Review

Efficacy and Safety of Transcranial Direct Current Stimulation on Multiple Health Outcomes in Neurological Disorders: An Umbrella Review of Meta-Analyses of Randomized Controlled Trials

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Abstract

Background: Neurological disorders are a leading cause of disability worldwide. Transcranial direct current stimulation (tDCS) is a promising therapeutic tool for neurological disorders. However, a consensus on clinical recommendations for using tDCS in patients with neurological disorders is lacking. In this umbrella review, we aimed to establish evidence-based guidance for using tDCS to treat neurological disorders. **Methods**: This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines 2020. PubMed/MEDLINE, Embase, the Cochrane Library, the Web of Science, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) were systematically searched to identify and evaluate existing systematic reviews and meta-analyses on the use of tDCS for neurological disorders. Quality was assessed using the Measurement Tool to Assess Systematic Reviews 2 (AMSTAR 2) and the Grades of Recommendations, Assessment, Development, and Evaluation (GRADE) tool. The Hartung-Knapp-Sidik-Jonkman random effects model was employed for reanalysis. **Results**: A total of 17 systematic reviews and meta-analyses encompassing 358 randomized controlled trials and 7160 participants were analyzed. tDCS demonstrated efficacy across seven distinct health conditions, including stroke, Parkinson's disease, Alzheimer's disease, cerebellar ataxia, fibromyalgia, disorders of consciousness, and migraine. Adverse effects were rarely reported, with the exception of mood changes associated with fibromyalgia. Our results indicated that tDCS significantly improved 34 distinct health outcomes related to these conditions. **Conclusions**: We found that tDCS may be a promising treatment for neurological disorders, with mild and infrequent adverse effects. Further studies are warranted to validate the therapeutic potential of tDCS in the reported neurological conditions, investigate additional neurological health outcomes, and explore the underlying mechanisms of tDCS effects. **The PROSPERO Registration**: CRD42024589432, https://www.crd.york.ac.uk/PROSPERO/view/CRD42024589432.

Keywords: transcranial direct current stimulation; tDCS; neurological disorders; efficacy; adverse effect; umbrella review

1. Introduction

Neurological disorders are an important cause of disability and death worldwide, including cerebrovascular and neurodegenerative diseases, neurological-immunological disorders, neuromuscular or peripheral nervous system disorders, traumatic injuries, and a broad range of other neurological disorders [1]. Neurological disorders and the dysfunctions associated with them impose an overwhelming burden on patients. For example, stroke accounts for the largest proportion of disability-adjusted life-years (47.3%) among all nervous system conditions [2]. Approximately 80% of patients develop motor function, 29–81% of individuals in the acute phase experience post-stroke dysphagia [3], 30–50% develop varying degrees of cognitive deficits [4], and 18–33% of individuals experience post-stroke depression [5]. What cannot be disregarded is that the incidence rates of Parkinson's disease and Alzheimer's disease are increasing. Based on the Global Burden of Disease (GBD) 2021, over 11.77 million people worldwide have Parkinson's disease [6]. By 2050, 25.2 million people are projected to be living with Parkinson's disease worldwide, representing a 112% increase from 2021 [7]. Meanwhile, 7.75 million individuals are thought to experience dementia, and the population is predicted to increase significantly, reaching 152.80 million by 2050 [8,9]. Disability from these two degenerative diseases increases with time. Motor symptoms, such as bradykinesia, stiffness, postural instability, and tremors, are prominent in Parkinson's disease, whereas Alzheimer's disease impacts older adults' cognitive and memory abilities. Neurorehabilitation is a key component of regaining neurological function. The most crucial aspect is that neurorehabilitation begins following the diagnosis and continues throughout any further treatment procedures [10]. Although neurorehabilitation is actively pursued, treatment effectiveness varies considerably.

Effective and safe neurorehabilitation techniques are desperately needed due to the major impact of the dysfunction associated with these conditions on patients' daily lives and their social reintegration.

Over the past 20 years, transcranial direct current stimulation (tDCS) has emerged as a promising therapeutic tool for neurorehabilitation. As a non-invasive brain stimulation technique, it is characterized by effectiveness, safety, and cost-effectiveness [11]. In tDCS, mild electrical currents (usually 1 to 2 mA) are applied through scalp electrodes. The process enables polarity-dependent cortical excitability control [12], induces neuroplasticity [13], and activates brain network regions and so on [14,15]. tDCS has prompted extensive research in various neurological conditions, yet a comprehensive review focusing on the effectiveness and safety of tDCS in neurological disorders is lacking. Currently, the use of tDCS in neurological diseases is controversial. First, its therapeutic efficacy and safety have not been consistently reported. Second, previous studies are highly heterogeneous and use relatively few outcome indicators.

We conducted an umbrella review incorporating the latest studies in neurological health-related studies to enhance evidence-based clinical decision-making about tDCS. The main objective was to verify tDCS's efficacy and safety by a thorough analysis of neurological disorders. Heterogeneity practices and risk of bias were evaluated as secondary objectives.

2. Materials and Methods

2.1 Literature Search Strategy

This umbrella review aimed to systematically analyze systematic reviews and meta-analyses of randomized controlled trials (RCTs) investigating the effect of tDCS on neurological health outcomes. This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines 2020 for overviews of reviews of healthcare interventions [16] and was registered in the Prospective Register of Systematic Reviews (PROSPERO) (CRD42024589432) [17]. The PRISMA 2020 checklist for overviews of reviews of healthcare interventions is shown in **Supplementary Material-A**. Two authors, Tianfeng Ye and Yuli Shuai, independently and methodically searched PubMed/MEDLINE (https://pubmed.ncbi.nlm.nih.gov/), Embase (https://www.embase.com), the Cochrane Library (https://www.cochranelibrary.com/), the Web of Science (https://www.webofscience.com), and Cumulative Index to Nursing and Allied Health Literature (CINAHL, https://www.ebsco.com/products/research-databases/cinahl-database) from each database's inception until October 16, 2024, and extracted data into a spreadsheet. The following search terms and their variations were used: "meta-analysis" OR "systematic review" AND "tDCS" OR "transcranial direct current stimulation" OR "HD-tDCS" OR "high-definition transcranial direct current stimulation" (**Supplemental Material-B**).

2.2 Inclusion and Exclusion Criteria

2.2.1 Inclusion Criteria

Participants: All participants were diagnosed with neurological disorders using standard diagnostic criteria. Interventions: Only tDCS was applied. Control: Any comparator could serve as the control, including sham stimulation, other active interventions, medicines, and treatment as usual. Outcomes: Neurological health outcomes. Study types: Systematic reviews and meta-analyses with adequate data (mean, standard deviation, and sample size) were included, which was essential to the Hartung-Knapp-Sidik-Jonkman (HKSJ) estimation.

2.2.2 Exclusion Criteria

The exclusion criteria included (1) patients with no neurological disorders, (2) interventions other than tDCS, and (3) neither safety nor efficacy data to extract.

Two researchers screened the titles, abstracts, and full texts independently. Any disagreements in the selection of papers between the two researchers were resolved by a third researcher (Yiwei Liu). When two or more original papers probed the same effect, only the latest published or more robust evidence-based paper was chosen [18,19].

2.3 Data Extraction

The data were extracted from all the studies, including health outcomes, the first author, publication year, type, tDCS parameters (electrode location, intensity, duration, and session), the number of participants, the number of included RCTs, effect measures, the model used for effect estimation (random or fixed effects), effect sizes, and 95% confidence intervals (95% CIs).

Neurological health outcomes were operationally defined as any quantifiable measure of signs, symptoms, functional status, or quality of life that directly results from dysfunction of the nervous system or constitutes a core clinical manifestation of the neurological disorders. Outcome domains were conceptualized based on the World Health Organization's International Classification of Functioning, Disability and Health (ICF) framework to ensure a systematic approach, encompassing body structures, body functions, activities and participation, and environmental factors [18]. Outcomes, such as pain from fibromyalgia or migraine and depression in post-stroke patients, were included only when they were explicitly recognized as core symptoms of the neurological disorder. A specific list of all searched outcomes is provided in the **Supplementary Material-C**.

2.4 Quality Assessment of Methods and Evidence

The two authors also independently performed methodological quality and evidence assessments to ensure accuracy.

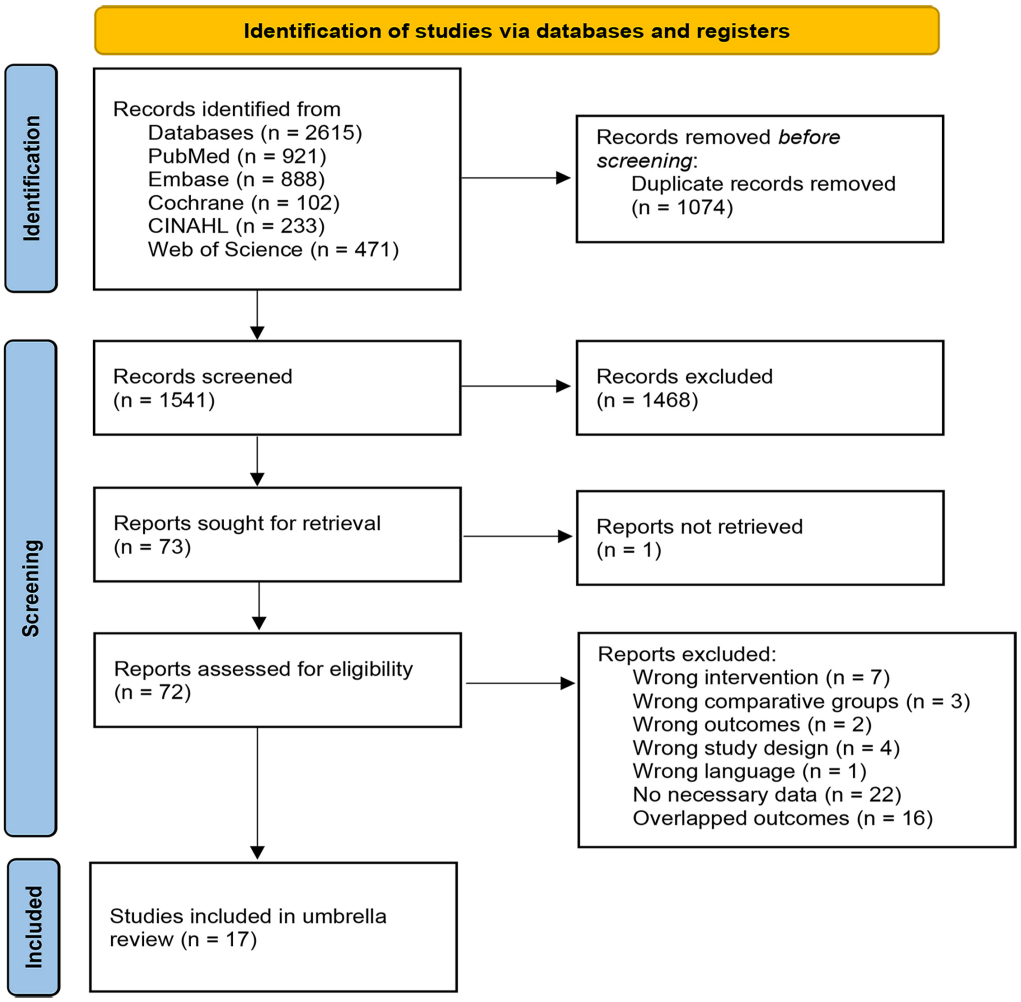

Fig. 1. PRISMA 2020 flow diagram. PRISMA, preferred reporting items for systematic reviews and meta-analyses.

Methodological quality was assessed in each study using the Measurement Tool to Assess Systematic Reviews 2 (AMSTAR 2) [20]. Seven of the 16 items in AMSTAR 2 were critical. The crucial items were items 2, 4, 7, 9, 11, 13 and 15. Four ratings were assigned to the methodological quality assessments: high, moderate, low, and critically low.

The quality of evidence for each study included in this umbrella review was evaluated using the Grades of Recommendations, Assessment, Development, and Evaluation (GRADE) [21]. The GRADE system encompasses five domains for downgrading and three domains for upgrading the quality of evidence. The downgrading domains comprise (1) risk of bias, (2) inconsistency, (3) indirectness, (4) imprecision, and (5) publication bias. The upgrading domains include (1) large effect, (2) plausible confounding, and (3) a dose-response gradient. Based on these criteria, the quality of evidence was classified into four levels: high, moderate, low, and very low.

Detailed rationales for each AMSTAR 2 and GRADE rating per health outcome are provided in a **Supplementary Material-D**.

2.5 Data Synthesis

The effect sizes expressed as mean difference (MD) or standardized mean difference (SMD) with associated 95% CI were recalculated independently using the DerSimonian and Laird fixed- or random-effects model [22]. This initial step was taken to maintain consistency with the methods commonly reported in the original publications, thereby facilitating direct comparisons. Subsequently, we prespecified the HKSJ random-effects model as the primary reanalysis for all outcomes to provide more robust estimates, particularly in the context of small study samples and substantial heterogeneity. The HKSJ method is recognized for providing more conservative and reliable confidence intervals when the number of included studies is small (e.g., <10) or when considerable heterogeneity is present (I^2 $>50\%$). It was applied by reporting the reanalyzed effect estimates, including 95% CI, I^2, Tau^2, and 95% prediction interval (95% PI) [23–25]. I^2 measures the proportion of total variation due to heterogeneity, with values above 75% indicating significant heterogeneity [26]. Tau^2 estimates the variance of the true effect sizes. Tau^2 values greater than zero signify the presence of heterogeneity across studies,

with higher Tau^2 values indicating more pronounced heterogeneity. The 95% PI was used to assess the uncertainty of the observed estimates and predict the range of true effects in future studies [27]. The updated effect estimates were visually presented using forest plots. Then, a sensitivity analysis was performed to systematically compare the effect estimates from the DerSimonian and Laird (DL) and HKSJ models. Results were considered robust if the estimates were consistent between both methods.

Small sample studies tend to overestimate the effects of tDCS compared to larger ones. Our primary assessment consisted of the visual inspection of funnel plots for asymmetry. For meta-analyses that included a sufficient number of studies (at least 10 RCTs), we additionally employed Egger's linear regression test to statistically evaluate funnel plot asymmetry [28]. This threshold was set because Egger's test is known to be underpowered and unreliable in syntheses with a smaller number of studies ($k < 10$). An Egger's test *p*-value below 0.05 indicated the potential overestimation of intervention effects. For the other syntheses in our study that included fewer than 10 RCTs, we applied the "trim-and-fill" method as an exploratory, secondary tool to gain a preliminary impression of the potential influence of missing studies [29]. We explicitly acknowledge that the performance of the trim-and-fill method is also unstable in such small-k meta-analyses, and its results should be interpreted with extreme caution. All analyses were conducted using the "meta" and "metafor" packages in R software (version 4.4.2; R Foundation, Vienna, Austria).

3. Results

3.1 Literature Selection

The study selection process is illustrated in Fig. 1. A total of 2615 references were retrieved through the database search. After removing 1074 duplicates, 1468 articles were excluded based on title and abstract screening. Then, full-text reviews excluded 55 articles, and finally, 17 eligible publications were identified [30–46].

3.2 Basic Characteristics of Included Studies

Details regarding patient demographics and tDCS protocols in the included studies are summarized in Table 1 (Ref. [30–46]). Most studies had sample sizes below 800, which were considered small sample studies. The majority of the systematic reviews and meta-analyses included fewer than 10 RCTs, limiting the application of Egger's test for publication bias. Parameters, such as polarity of the protocol, active electrode placement and the number of sessions, varied according to the disease being studied. However, the intensity and duration of tDCS predominantly ranged from 1–2 mA and 10–20 minutes, respectively. Furthermore, many included studies did not provide information on a stimulation site or a follow-up period, negatively impacting the AMSTAR 2 quality rating.

3.3 Quality Assessment

Using AMSTAR 2, the quality of the original study was high in six, moderate in two, low in eight, and critically low in one meta-analysis. Those studies rated high offered an accurate and comprehensive summary of the included health outcomes, containing Montreal Cognitive Assessment Test (MoCA), Mini-Mental State Examination (MMSE), Loewenstein Occupational Therapy Cognitive Assessment (LOTCA), Modified Barthel Index (MBI), Barthel Index (BI), P300 latency, and upper extremity motor function scores in stroke patients; global cognition, memory, and reaction time in Parkinson's disease; Scale for Assessment and Rating of Ataxia (SARA), International Cooperative Ataxia Rating Scale (ICARS), and 8-Meter Walk Time (8-MWT) scores in cerebellar ataxia; gait functionality in multiple sclerosis; and pain, depression, and Fibromyalgia Questionnaire (FIQ) scores in fibromyalgia.

The detailed classification of the methodological quality is shown in Fig. 2. All studies satisfied the criteria for items 1, 3, 9, 11, 12, and 14, with 9 and 11 identified as key items. However, the majority of the studies received a downgraded rating due to shortcomings in critical items 4, 7, and 15. Regarding item 4, most studies were rated as "Partially Yes" owing to the absence of complete reference lists in the studies found. In the assessment of item 7, a considerable proportion of the studies failed to provide a comprehensive list of potentially relevant research, along with justifications for excluding them. Concerning item 15, six studies were rated as "No" for the insufficient investigation of publication bias.

The evidence quality of the original study assessed using GRADE was rated as high in 2, moderate in 12, low in 19, and very low in 2 studies. High-certainty evidence demonstrated that tDCS significantly improved upper extremity motor function in patients with stroke and 8-MWT in cerebellar ataxia. The evidence classification details are comprehensively outlined in Fig. 3. All studies included were RCTs with direct evidence, thereby avoiding rating downgrades. No survey demonstrated plausible confounding or a dose-response gradient, maintaining the current evidence rating.

3.4 Reanalysis

This umbrella review offered valuable insight regarding whether tDCS could guide clinical practice and patient management. The analysis of evidence from 17 publications indicated that tDCS exerted partial beneficial effects in seven distinct health conditions: stroke, Parkinson's disease, Alzheimer's disease, cerebellar ataxia, fibromyalgia, disorders of consciousness, and migraine, with adverse effects related to mood change reported in fibromyalgia. Furthermore, tDCS was found to influence 34 unique health outcomes, with one adverse effect.

Table 1. Basic characteristics of included published studies.

Health outcomes	First author/year	Population	Session	Electrode location	Intensity/Duration	Sample
Stroke						
Score of MoCA	Lyu 2023 [30]	PSCI	10–40	DLPFC, frontal and temporal different brain regions	1.1–2.0 mA 20–30 min	403
Score of MMSE	Lyu 2023 [30]	PSCI	15–40	DLPFC, frontal and temporal different brain regions	1.1–2.0 mA 20–30 min	290
Score of LOTCA	Lyu 2023 [30]	PSCI	30	DLPFC, frontal and temporal different brain regions	0.5 mA, 1.2 mA 20 min	34
Score of MBI	Lyu 2023 [30]	PSCI	10–40	DLPFC,frontal and temporal different brain regions	1.2–2.0 mA 20, 30 min	264
P300 latency	Lyu 2023 [30]	PSCI	20, 24	DLPFC, frontal and temporal different brain regions	1.2 mA, 2.0 mA 20 min	72
PSD scale score (HAMD/BDI/SADQ-H/SDS)	Li 2022 [31]	PSD	10–20	L-DLPFC, M1 of lesioned side	1.0–2.0 mA 20, 30 min	206
Upper extremity motor function (FMA-UE/ARRT)	Tang 2024 [32]	Stroke	5–60	C3, C4, M1, F3, 2.5 cm anterior to M1, right cerebellum	0.5–3.0 mA 9–40 min	807
Score of BI	Tang 2024 [32]	Stroke	10–60	C3, C4, M1, F3	1.0–2.0 mA 10–30 min	283
Change of FMA-UE score	Chow 2022 [33]	Stroke	1–36	Ipsilesional M1 and supraorbital region, paretic M1, contralesional supraorbital region	1.2–3.0 mA 10–40 min	802
Lower extremity motor assessment (FMA-LE)	Chow 2022 [33]	Stroke	10–24	Ipsilesional M1, precentral gyrus and leg area	1.5–3.0 mA 10–30 min	179
Spasticity (MAS)	Huang 2022 [34]	Stroke	6–40	Anodal: M1, dual stimulation Cathodal: non-lesioned primary sensorimotor cortex	Anodal: 0.7–2.0 mA Cathodal: 0.5–2.0 mA 13–30 min	458
Rating about TUGT	Dong 2021 [35]	Stroke	1, 12	Ipsilesional motor cortex, SMA	1.0, 2.0 mA 15, 20 min	45
Rating about FAC	Dong 2021 [35]	Stroke	10–20	Ipsilesional leg motor area, ipsilesional leg and hand motor area	1.0–2.0 mA 7–20 min	49

Table 1. Continued.

Health outcomes	Author/year	Population	Session	Electrode location	Intensity/Duration	Sample
Dysphagia (DOSS/MMASA/FOIS/FDS/VFSS)	Zhao 2022 [36]	Stroke	4–48	Hemisphere about pharyngeal cortex, cerebellar hemisphere	1.0–2.0 mA 20, 30 min	334
Hemispatial neglect (LBT)	Salazar 2018 [37]	Stroke	15	Posterior parietal cortex, left posterior parietal cortex	1.0 mA, 2.0 mA 20, 30 min	26
Parkinson's disease						
Score of MoCA	Liu 2021 [46]	PD	20, 56	L-DLPFC, CZ	2.0 mA 20 min	63
Score of UPDRS-I	Liu 2021 [46]	PD	20, 30	DLPFC, Bi PFC, Fz	1.0 mA, 1.2 mA 20 min	97
Global cognition (SCOPA/UPDRS/PD-MCI)	De Souza Souto 2024 [38]	PD	2–10	L-DLPFC/DLFPC, M1, MFC	1.0–2.0 mA 5–20 min	317
Memory (DS-F/S-IT/the Go/No-Go Task)	De Souza Souto 2024 [38]	PD	2–10	L-DLPFC/DLFPC, M1	1.0 mA, 2.0 mA 5, 20 min	124
Reaction time (DS-F/S-IT/the Go/No-Go Task)	De Souza Souto 2024 [38]	PD	2, 10	L-DLPFC/DLFPC, MFC	1.5 mA, 2.0 mA 6–20 min	66
Alzheimer's disease						
Score of MMSE	Hou 2024 [39]	AD/MCI	10–224	L-DLPFC, L-FTL, L-TPL	1.0–5.0 mA 20–30 min	150
Score of MoCA	Hou 2024 [39]	MCI	5–36	L-DLPFC/R-DLPFC, L-TL	1.0–2.0 mA 20, 30 min	159
Score of MODA	Hou 2024 [39]	AD	14–244	L-DLPFC, L-FTL	2.0 mA 20 min	22
P300 latency	Hou 2024 [39]	AD/MCI	5–56	L-DLPFC, L-TL contralateral Supraorbital Region	2.0–5.0 mA 20, 25 min	103
Cerebellar ataxia						
Score of SARA	Chen 2021 [40]	CA	1–10	Cerebellum, spine, M1	2.0 mA 20 min, 40 min	58
Score of ICARS	Chen 2021 [40]	CA	1, 10	Cerebellum, spine	2.0 mA 20 min	51
8-MWT	Chen 2021 [40]	CA	1, 10	Cerebellum, spine	2.0 mA 20 min	51

Table 1. Continued.

Health outcomes	Author/year	Population	Session	Electrode location	Intensity/Duration	Sample
Fibromyalgia						
Pain intensity (VAS/NRS/FIQ-R/PCP:S)	Yang 2024 [41]	FM	1–60	DLPFC, M1, OIC, ON	1.0 mA, 2.0 mA 20, 30 min	440
Depression (HAM-D/BDI-II)	Yang 2024 [41]	FM	1–60	DLPFC, M1, OIC, ON	1.0 mA, 2.0 mA 20, 30 min	337
Score of FIQ	Yang 2024 [41]	FM	5–15	DLPFC, M1, OIC, ON	1.0 mA, 2.0 mA 20 min	294
Epilepsy						
The Frequency of seizures	Lima 2024 [42]	Drug-resistant epilepsy	1–28	Cathodal: epilepsy focus	1.0–2.0 mA 20, 30 min	127
Disorders of consciousness						
Score of CRS-R	Fan 2023 [43]	DoC	1–20	L-DLPFC/DLFPC, PFC, posterior parietal cortex, bilateral frontoparietal areas, bilateral fronto-temporo-parietal cortices	2.0 mA, 4.0 mA 20 min	140
Multiple sclerosis						
Gait functionality (TUG, 2MWT, 25FWT)	Nombela-Cabrera 2023 [44]	MS	1–12	M1, right cerebellar hemi-sphere, cerebellum affected	1.5–2.5 mA 13–30 min	84
Migraine						
Pain intensity	Cai 2021 [45]	Migraine	4 w, 8 w	Anodal: LDLPFC, L-M1 Cathodal: CZ	1.0 mA, 2.0 mA 15, 20 min	104
Adverse effect						
Mood change	Yang 2024 [41]	FM	1–60	DLPFC, M1, OIC, ON	1.0 mA, 2.0 mA 20, 30 min	21

PSCI, post stroke cognitive impairment; PSD, post stroke depression; PD, Parkinson's Disease; AD, Alzheimer's Disease; MCI, mild cognitive impairment; CA, cerebellar ataxia; FM, fibromyalgia; DoC, disorders of consciousness; MS, multiple sclerosis; MoCA, Montreal Cognitive Assessment Test; MMSE, Mini-Mental State Examination; LOTCA, Loewenstein Occupational Therapy Cognitive Assessment; MBI, Modified Barthel Index; HAMD, Hamilton Depression Scale; BDI, Beck Depression Inventory; SADQ-H, Stroke Aphasic Depression Questionnaire Hospital Version; SDS, Self-Rating Depression Scale; FMA-UE, upper extremity Fugl–Meyer Assessment; ARRT, Action Research Arm Test; BI, Barthel Index; FMA-LE, Lower Extremity Fugl–Meyer Assessment; MAS, Modified Ashworth Scale; TUG/TUGT, Timed Up and Go Test; FAC, Functional Ambulation Category; DOSS, Dysphagia Outcome Severity Scale; MMASA, Modified Mann Assessment of Swallowing Ability; FOIS, Functional Oral Intake Scale; FDS, Functional Dysphagia Scale; VFSS, Video Fluoroscopic Swallowing Study; LBT, Line Bisection Test; UPDRS-I, Unified PD Rating Scale I; SCOPA, Scales for Outcomes in PD; PD-MCI, Parkinson's disease with mild cognitive impairment; DS-F, Digit Span-Forward; S-IT, Stroop Interference Test; MODA, Milan Overall Dementia assessment; SARA, Scale for Assessment and Rating of Ataxia; ICARS, International Cooperative Ataxia Rating Scale; 8-MWT, 8-Meter Walk Time; VAS, Visual Analog Scale; NRS, Numeric Rating Scale; FIQ-R, Modified Fibromyalgia Questionnaire; PCP:S, Profile of Chronic Pain: Screen; HAM-D, Hamilton Depression Rating Scale; BDI-II, Beck Depression Inventory-II; FIQ, Fibromyalgia Questionnaire; CRS-R, Coma Recovery Scale-Revised; 2MWT, 2-Minute Walk Test; 25FWT, 25-Foot Walk Test; L-/R-, left/right; DLPFC, Dorsolateral Prefrontal Cortex; M1, Primary Motor Cortex; C3/C4/F3/CZ/FZ, according to the 10–20 International Electroencephalography System; SMA, Supplementary Motor Area; PFC, Prefrontal Cortex; MFC, Medial Frontal Cortex; FTL, Frontotemporal Lobe; TPL, Temporo-Parietal Lobe; TL, Temporal Cortex; OIC, Opercular-Insular Cortex; ON, Occipital Nerve Regions.

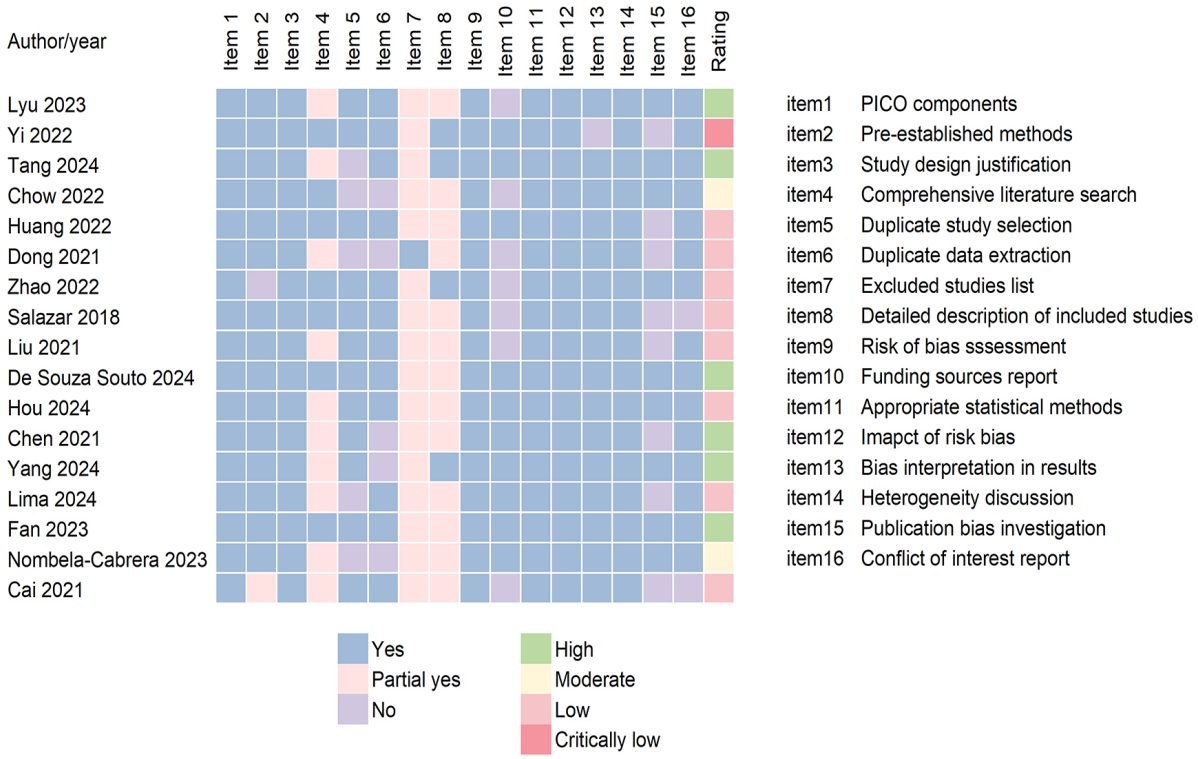

Fig. 2. AMSTAR 2 quality assessment of each study. AMSTAR 2 contains 16 items. Each item has two or three ratings and the final rating is assigned to four assessments: high, moderate, low, critically low. AMSTAR 2, measurement tool to assess systematic reviews 2; PICO, Population, Intervention, Comparison, Outcome.

The original effect estimates with 95% CI, alongside reanalyzed effect estimates with 95% CI, I^2, Tau^2, and 95% PI, and the quality assessments were all listed (Tables 1,2,3). Effect estimates with original and new 95% CIs are shown in Table 2. MDs are presented in the most commonly used original scale units, while SMDs are interpreted using Cohen's conventions (small: 0.2–0.5, medium: 0.5–0.8, and large: >0.8). Heterogeneity, publication bias, and significant associations are shown in Table 3. Among the 34 health outcomes evaluated, 76.47% (26/34) of the reanalyzed 95% CIs indicated the potential therapeutic utility of tDCS across a diverse range of neurological conditions. The significant findings spanned multiple neurological conditions, including stroke-related outcomes (such as MoCA scores, MMSE scores, LOTCA scores, MBI scores, post-stroke depression (PSD) scale scores, BI scores, change in upper extremity Fugl–Meyer Assessment (FMA-UE) scores, upper extremity motor function, P300 latency, spasticity and dysphagia), Parkinson's disease cognitive parameters (global cognition, memory, and reaction time), Alzheimer's disease cognitive measures (MMSE score, Milan Overall Dementia assessment (MODA) scores, and P300 latency), cerebellar ataxia functional improvements (ICARS score and 8-MWT), fibromyalgia-associated symptoms (pain, depression, and FIQ scores), and Coma Recovery Scale-Revised (CRS-R) scores in patients with disorders of consciousness and pain intensity in individuals with migraines. The adverse effect of mood change was reported in patients with fibromyalgia.

The reanalysis of the 34 outcomes using the HKSJ random-effects model in this umbrella review showed that 18 out of 34 (38.24%) outcomes exhibited low heterogeneity (I^2 <25%), with 13 studies showing no heterogeneity. Sensitivity analysis comparing the DL and HKSJ methods demonstrated a discrepancy in Timed Up and Go Test (TUGT) scores in stroke, primarily with a very small number of contributing studies or exceptionally high heterogeneity. All health outcomes were mapped on forest plots. Publication bias was assessed using our prespecified tiered approach. For analyses with at least 10 RCTs (k ≥10), Egger's test served as the primary statistical measure. Consequently, Egger's test was performed in 13 analyses, of which 10 (76.92%) indicated no evidence of publication bias. For analyses with fewer studies (k <10), for which Egger's test was not feasible, we employed the trim-and-fill method as an exploratory alternative. The results of this exploratory analysis should be interpreted with caution due to the known instability of the method with a small k. The forest plot, funnel plot with contours and funnel plot with contours from the trim-and-fill method are provided in the **Supplementary Material-E**.

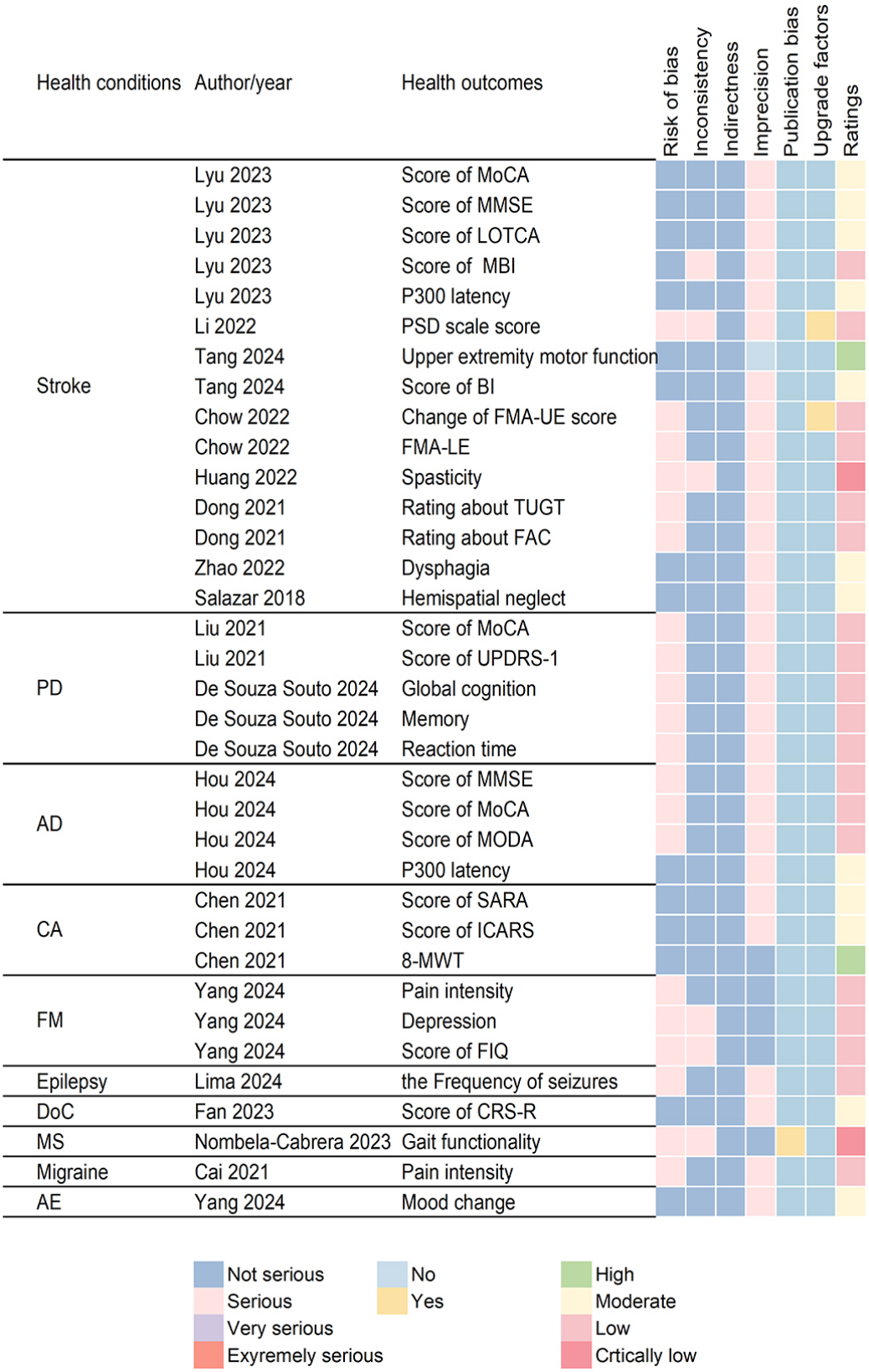

Fig. 3. GRADE evidence assessment of the association between tDCS and each health outcome. The GRADE system encompassed five downgrade domains and three upgrade domains. Each downgrade domain has four ratings and the upgrade domains are totally assessed as "Yes" or "NO". The final rating is assigned to four assessments: high, moderate, low, and critically low. GRADE, Grades of Recommendations, Assessment, Development, and Evaluation; tDCS, transcranial direct current stimulation; AE, adverse effect.

Table 2. 95% CI of included published studies.

Health outcomes	Included studies	Effect measure	Reported models	Reported 95% CI	Reanalysis		HKSJ	HKSJ *p*-value
					Fixed	Random		
Stroke								
Score of MoCA	16	MD	fixed	2.53 [2.15 to 2.91]	2.53 [2.15 to 2.91]	2.51 [2.05 to 2.98]	2.46 [1.82 to 3.09]	<0.001***
Score of MMSE	10	MD	fixed	1.94 [1.48 to 2.40]	1.94 [1.48 to 2.40]	2.26 [1.51 to 3.00]	2.25 [1.52 to 2.98]	<0.001***
Score of LOTCA	2	MD	fixed	2.27 [1.42 to 3.11]	2.27 [1.42 to 3.11]	2.27 [1.42 to 3.11]	2.27 [1.76 to 2.78]	<0.001***
Score of MBI	12	MD	random	5.47 [3.76 to 7.18]	5.47 [3.76 to 7.18]	5.47 [3.76 to 7.18]	5.56 [2.87 to 8.25]	<0.001***
P300 latency	3	MD	fixed	–14.53 [–20.41 to 8.66]	–14.53 [–20.41 to 8.66]	–14.54 [–20.69 to 8.38]	–14.57 [–28.60 to –0.54]	<0.05*
PSD scale score	8	SMD	random	1.61 [1.02 to 2.19]	1.39 [1.16 to 1.61]	1.60 [1.02 to 2.19]	1.64 [0.73 to 2.54]	0.004**
Upper extremity motor function	48	SMD	fixed	0.22 [0.12 to 0.32]	0.22 [0.12 to 0.32]	0.22 [0.07 to 0.37]	0.22 [0.07 to 0.37]	0.006**
Score of BI	15	MD	fixed	4.65 [2.82 to 6.49]	4.65 [2.82 to 6.49]	4.42 [1.84 to 7.00]	4.50 [1.63 to 7.37]	0.005**
Change of FMA-UE score	28	MD	fixed	1.68 [0.25 to 3.11]	1.68 [0.25 to 3.11]	1.68 [0.25 to 3.11]	1.77 [0.70 to 2.86]	0.003**
Lower extremity motor assessment	5	MD	fixed	2.19 [1.07 to 3.30]	2.19 [1.07 to 3.30]	2.19 [1.07 to 3.30]	2.62 [–0.34 to 5.57]	0.070
Spasticity	12	SMD	random	–0.83 [–1.25 to 0.40]	–0.77 [–0.92 to –0.62]	–0.83 [–1.25 to –0.40]	–0.83 [–1.33 to –0.33]	0.004**
Rating about TUGT	5	MD	fixed	–2.61 [–4.00 to –1.22]	–1.08 [–1.96 to –0.22]	–2.18 [–4.51 to 0.15]	–4.57 [–15.17 to 6.03]	0.300
Rating about FAC	5	MD	fixed	0.35 [0.11 to 0.58]	0.15 [0.01 to 0.28]	0.34 [–0.14 to 0.82]	0.34 [–0.22 to 0.90]	0.170
Dysphagia	18	SMD	random	0.80 [0.45 to 1.14]	0.74 [0.58 to 0.90]	0.80 [0.45 to 1.15]	0.81 [0.35 to 1.26]	0.002**
Hemispatial neglect	3	SMD	random	–1.07 [–1.76 to –0.37]	–1.07 [–1.76 to –0.37]	–1.07 [–1.76 to –0.37]	–1.08 [–2.26 to 0.10]	0.060
Parkinson's disease								
Score of MoCA	2	SMD	random	0.87 [0.50 to 1.24]	0.87 [0.50 to 1.24]	0.87 [0.50 to 1.24]	0.87 [–0.61 to 2.35]	0.080
Score of UPDRS-I	2	SMD	random	–1.29 [–1.60 to –0.98]	–1.29 [–1.61 to –0.98]	–1.29 [–1.60 to –0.98]	–1.30 [–3.17 to 0.58]	0.070
Global cognition	27	SMD	random	0.24 [0.09 to 0.40]	0.24 [0.09 to 0.40]	0.24 [0.09 to 0.40]	0.25 [0.10 to 0.40]	0.002**
Memory	11	SMD	random	0.34 [0.07 to 0.61]	0.34 [0.08 to 0.59]	0.34 [0.07 to 0.61]	0.35 [0.04 to 0.66]	0.030*
Reaction time	6	SMD	random	0.42 [0.07 to 0.76]	0.42 [0.07 to 0.76]	0.42 [0.07 to 0.76]	0.41 [0.14 to 0.69]	0.010*
Alzheimer's disease								
Score of MMSE	7	MD	fixed	1.76 [1.29 to 2.23]	1.76 [1.29 to 2.23]	1.97 [1.24 to 2.71]	2.11 [0.99 to 3.23]	0.004**
Score of MoCA	7	MD	fixed	0.56 [0.11 to 1.11]	0.56 [0.11 to 1.01]	0.56 [0.04 to 1.07]	0.54 [–0.08 to 1.16]	0.080
Score of MODA	2	MD	fixed	6.52 [3.73 to 9.31]	6.52 [3.73 to 9.31]	6.52 [3.73 to 9.31]	6.52 [3.55 to 9.49]	0.020*
P300 latency	4	MD	fixed	–39.73 [–51.78 to 27.68]	–39.73 [–51.78 to 27.68]	–38.35 [–56.19 to 20.50]	–38.15 [–65.51 to 10.79]	0.020*
Cerebellar ataxia								
Score of SARA	4	SMD	random	–0.71 [–1.18 to –0.23]	–0.68 [–1.07 to –0.29]	–0.71 [–1.18 to –0.23]	–0.74 [–1.56 to –0.09]	0.070
Score of ICARS	3	SMD	random	–0.62 [–1.03 to –0.21]	–0.62 [–1.03 to –0.21]	–0.62 [–1.03 to –0.21]	–0.62 [–1.10 to –0.15]	0.030*
8-MWT	3	SMD	random	–0.42 [–0.82 to –0.02]	–0.42 [–0.82 to –0.02]	–0.42 [–0.82 to –0.02]	–0.42 [–0.60 to –0.24]	<0.01**

Table 2. Continued.

Health outcomes	Included studies	Effect measure	Reported models	Reported 95% CI	Reanalysis		HKSJ	HKSJ *p*-value
					Fixed	Random		
Fibromyalgia								
Pain intensity	20	SMD	random	–1.04 [–1.38 to –0.69]	–0.82 [–0.98 to –0.67]	–1.04 [–1.38 to –0.69]	–1.08 [–1.53 to –0.64]	<0.001***
Depression	20	SMD	random	–0.73 [–1.09 to –0.36]	–0.56 [–0.75 to –0.37]	–0.73 [–1.09 to –0.36]	–0.75 [–1.18 to –0.31]	0.003**
Score of FIQ	20	SMD	fixed	–0.46 [–0.64 to –0.29]	–0.46 [–0.64 to –0.29]	–0.57 [–0.92 to –0.21]	–0.57 [–0.96 to –0.18]	0.007**
Epilepsy								
The Frequency of seizures	7	MD	random	–3.15 [–5.11 to –1.18]	–3.15 [–5.11 to –1.18]	–3.15 [–5.11 to –1.18]	–4.31 [–11.86 to 3.25]	0.210
Disorders of consciousness								
Score of CRS-R	9	MD	random	2.07 [1.58 to 2.57]	0.90 [0.61 to 1.18]	1.34 [0.57 to 2.10]	1.39 [0.34 to 2.44]	0.020*
Multiple sclerosis								
Gait functionality	11	SMD	fixed	–0.71 [–1.05 to –0.37]	–0.71 [–1.05 to –0.37]	–0.67 [–1.29 to –0.05]	–0.67 [–1.41 to 0.07]	0.070
Migraine								
Pain intensity	5	MD	random	–1.44 [–2.13 to –0.76]	–1.47 [–1.95 to –0.99]	–1.46 [–1.99 to –0.92]	–1.46 [–2.29 to –0.62]	0.008**
Adverse effect								
Mood change	2	RD	fixed	–0.06 [–0.11 to –0.01]	–0.06 [–0.11 to –0.01]	–0.06 [–0.11 to –0.01]	–0.06 [–0.07 to –0.05]	0.006**

95% CI, 95% confidence interval; HKSJ, hartung-knapp-sidik-jonkman; SMD, standardized mean difference. HKSJ *p*-values: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

3.4.1 Stroke

tDCS was significantly associated with 11 health outcomes among post-stroke patients, including improvements in MoCA scores (MD = 2.46 points, 95% CI: 1.82–3.09), MMSE scores (MD = 2.25 points, 95% CI: 1.52–2.98), LOTCA scores (MD = 2.27 points, 95% CI: 1.76–2.78), MBI scores (MD = 5.56 points, 95% CI: 2.87–8.25) with large magnitude, BI scores (MD = 4.50 points, 95% CI: 1.63–7.37) with large magnitude, upper extremity motor function (SMD = 0.22, 95% CI: 0.07–0.37), and dysphagia (SMD = 0.81, 95% CI: 0.35–1.26), decreases in PSD scale scores (SMD = 1.64, 95% CI: 0.73–2.54) with a significant large effect, P300 latency (SMD = –14.57, 95% CI: –28.60 to –0.54) with a significant large effect, spasticity (SMD = –0.83, 95% CI: –1.33 to –0.33), and changes in FMA-UE scores (MD = 1.77 points, 95% CI: 0.70–2.86). Among the associated health outcomes, 7 out of 11 studies exhibited low heterogeneity (<25%). Egger's test applied to eight analyses and indicated no evidence of publication bias. The methodology evidence in 7/15 (46.67%) of the analyses was rated high by AMSTAR 2. Only one health outcome (upper extremity motor function) received a high rating according to GRADE criteria.

3.4.2 Parkinson's Disease

Three out of five (60%) analyses supported the association of tDCS with improvements in global cognition (SMD = 0.25, 95% CI: 0.10–0.40), memory (SMD = 0.35, 95% CI: 0.04–0.66), and reaction time (SMD = 0.41, 95% CI: 0.14–0.69), with low heterogeneity. Egger's test was conducted in two studies, with publication bias detected in one study assessing global cognition in Parkinson's disease. Furthermore, 60% (3/5) of the health outcomes were rated as having high methodological quality, while all analyses achieved a low-grade rating.

3.4.3 Alzheimer's Disease

Three out of four (75%) analyses indicated that tDCS was associated with improvements in MMSE scores (SMD = 2.11, 95% CI: 0.99–3.23), MODA scores (SMD = 6.52, 95% CI: 3.55–9.49), and reductions in P300 latency (SMD = –38.15, 95% CI: –65.51 to –10.79). Fifty percent (2/4) of the studies exhibited low heterogeneity. All included studies were separately assessed as low quality according to AMSTAR 2. Only one outcome received a moderate GRADE rating, while the others were low.

3.4.4 Cerebellar Ataxia

Two-thirds (66.67%) of the analyses indicated that tDCS improved ICARS scores (SMD = –0.62, 95% CI: –1.10 to –0.15) and decreased 8-MWT (SMD = –0.42, 95% CI: –0.60 to –0.24), without heterogeneity. Compared with other associated health outcomes, these two outcomes both received high methodological quality and moderate to high evidential ratings.

3.4.5 Fibromyalgia

Our study demonstrated that tDCS was effective for three health outcomes related to fibromyalgia, including pain, depression, and FIQ scores (SMD = –1.08, 95% CI: –1.53 to –0.64; SMD = –0.75, 95% CI: –1.18 to –0.31; SMD = –0.57, 95% CI: –0.96 to –0.18, respectively). The heterogeneity across these outcomes ranged from 69.30% to 77.40%. Although the AMSTAR 2 ratings scored highly, the GRADE ratings were low.

3.4.6 Epilepsy

The new estimated 95% CI was insignificant (MD = –4.31 times, 95% CI: –11.86 to 3.25, $p > 0.05$), indicating that whether tDCS decreases seizure frequency is still unclear. It is critical to note that this result exhibited extreme heterogeneity (Tau^2 = 1026.65) and an implausibly wide 95% PI of –91.36 to 82.74. This indicates that the true effect of tDCS on seizure frequency varied enormously across the included studies, and the pooled estimate was highly unstable. Furthermore, the methodological and evidence ratings were both low. Therefore, evidence that tDCS reduces seizure frequency remains inconclusive and must be interpreted with extreme caution.

3.4.7 Disorders of Consciousness

Because only one analysis was included and it had a reanalyzed *p*-value of less than 0.05, we found that tDCS significantly increased CRS-R scores (MD/RD = 1.39, 95% CI: 0.34 to 2.44), with high heterogeneity. The AMSTAR 2 rating was high, and the GRADE rating was moderate.

3.4.8 Multiple Sclerosis

One analysis found that tDCS was not helpful for enhancing gait functionality in patients with multiple sclerosis (SMD = –0.67, 95% CI: –1.41 to 0.07). The heterogeneity was 69.20%. Its AMSTAR 2 rating was moderate, but the very low GRADE rating did not support the evidence.

3.4.9 Migraine

The reanalyzed estimated 95% CI showed that tDCS alleviated pain intensity in migraine patients (MD/RD = –1.46, 95% CI: –2.29 to –0.62). Moreover, the quality assessments of this health condition were both low.

3.4.10 Adverse Effects

Most studies included reported mild adverse effects, including skin itching, skin tingling, skin burning, headache, dizziness, sleepiness, postural hypotension, and constipation. Mood change was experienced by patients with tDCS (MD/RD = –0.06, 95% CI: –0.07 to –0.05). The AMSTAR 2 rating was high, while the GRADE rating was moderate. No serious adverse events were reported by the authors.

Table 3. Other effect sizes of the included published studies.

Health outcomes	I^2	Tau^2	95% PI	Egger's *p*-value	Trim-and-fill method	Association
Stroke						
Score of MoCA	23.30%	1.05	[0.15 to 4.77]	0.33	2.73 [2.06 to 3.40]	association
Score of MMSE	49.40%	0.53	[0.41 to 4.09]	0.15	1.39 [0.50 to 2.29]	association
Score of LOTCA	0.00%	0.01	[0.84 to 3.70]	NA	2.14 [1.70 to 2.57]	association
Score of MBI	0.00%	9.47	[–2.32 to 13.44]	0.85	5.56 [2.87 to 8.25]	association
P300 latency	8.20%	15.10	[–37.88 to 8.74]	NA	–14.57 [–28.60 to –0.54]	association
PSD scale score	83.90%	1.05	[–0.95 to 4.22]	NA	1.19 [0.15 to 2.23]	association
Upper extremity motor function	48.80%	0.19	[–0.68 to 1.12]	0.82	0.22 [0.07 to 0.37]	association
Score of BI	37.20%	16.48	[–4.82 to 13.81]	0.92	3.71 [0.76 to 6.66]	association
Change of FMA-UE score	0.00%	2.45	[–1.87 to 5.41]	0.24	0.96 [–0.22 to 2.15]	association
Lower extremity motor assessment	0.00%	4.23	[–4.23 to 9.46]	NA	1.92 [–1.36 to 5.21]	NA
Spasticity	86.60%	0.54	[–2.53 to 0.87]	0.50	–0.83 [–1.33 to –0.33]	association
Rating about TUGT	69.80%	80.47	[–32.34 to 23.20]	NA	–0.93 [–11.12 to 9.26]	NA
Rating about FAC	90.20%	0.16	[–0.92 to 1.59]	NA	–0.14 [–0.77 to 0.50]	NA
Dysphagia	76.70%	0.73	[–1.06 to 2.67]	0.47	0.80 [0.35 to 1.26]	association
Hemispatial neglect	0.00%	0.07	[–3.11 to 0.95]	NA	–1.08 [–2.26 to 0.10]	NA
Parkinson's disease						
Score of MoCA	0.00%	0.00	[–1.72 to 3.47]	NA	NA	NA
Score of UPDRS-I	0.00%	0.01	[–3.99 to 1.40]	NA	NA	NA
Global cognition	0.00%	0.07	[–0.31 to 0.81]	0.02*	0.09 [–0.08 to 0.26]	association
Memory	13.20%	0.10	[–0.45 to 1.15]	0.08	0.15 [–0.19 to 0.49]	association
Reaction time	0.00%	0.01	[–0.15 to 0.98]	NA	0.47 [0.21 to 0.72]	association
Alzheimer's disease						
Score of MMSE	35.00%	1.01	[–0.66 to 4.88]	NA	2.11 [0.99 to 3.23]	association
Score of MoCA	18.00%	0.21	[–0.80 to 1.89]	NA	0.67 [0.13 to 1.22]	NA
Score of MODA	0.00%	0.00	[–11.57 to 24.61]	NA	NA	association
P300 latency	42.80%	159.02	[–88.37 to 12.08]	NA	–41.67 [–66.33 to –17.02]	association
Cerebellar ataxia						
Score of SARA	27.40%	0.16	[–2.32 to 0.85]	NA	–0.39 [–1.22 to 0.43]	NA
Score of ICARS	0.00%	0.00	[–1.59 to 0.34]	NA	–0.62 [–1.10 to –0.15]	association
8-MWT	0.00%	0.00	[–1.30 to 0.47]	NA	–0.42 [–0.60 to –0.24]	association
Fibromyalgia						
Pain intensity	77.40%	1.14	[–3.33 to 1.16]	0.01	–0.64 [–1.21 to –0.07]	association
Depression	69.30%	0.48	[–2.30 to 0.80]	0.01	–0.39 [–0.92 to 0.15]	association
Score of FIQ	73.60%	0.41	[–1.99 to 0.86]	0.10	–0.40 [–0.83 to 0.04]	association
Epilepsy						
The Frequency of seizures	0.00%	1026.65	[–91.36 to 82.74]	NA	–2.96 [–15.00 to 9.07]	NA
Disorders of consciousness						
Score of CRS-R	82.80%	1.33	[–1.55 to 4.33]	NA	0.70 [–0.55 to 1.96]	association
Multiple sclerosis						
Gait functionality	69.20%	0.57	[–2.61 to 1.27]	NA	–0.67 [–1.40 to 0.07]	NA
Migraine						
Pain intensity	21.90%	0.03	[–2.35 to –0.56]	NA	–1.40 [–2.30 to –0.50]	association
Adverse effect						
Mood change	0.00%	<0.00	[–0.36 to 0.24]	NA	NA	association

NA, not available; 95% PI, 95% prediction interval. Egger's *p*-values: *$p < 0.05$.

4. Discussion

4.1 Findings

This umbrella review focused on neurological disorders, offering robust evidence on the efficacy and safety of tDCS in a broad range of neurological disorders. A total of 17 systematic reviews and meta-analyses encompassing 358 RCTs and 7160 participants were analyzed. tDCS demonstrated efficacy in seven distinct health conditions, including stroke, Parkinson's disease, Alzheimer's disease, cerebellar ataxia, fibromyalgia, disorders of consciousness,

and migraine, with adverse effects related to mood changes reported in patients with fibromyalgia. Our results indicated that tDCS significantly influenced 34 neurological health outcomes. Literature on upper extremity motor function in stroke and 8-MWT in cerebellar ataxia showed high methodological and evidential quality based on AMSTAR 2 and GRADE assessments.

4.1.1 Stroke

tDCS was associated with improvements in cognition, depression, and swallowing in stroke patients, consistent with current research. A previous study showed that tDCS improved global cognitive function in stroke patients more than other non-invasive stimulation methods [47]. Notably, tDCS could also reduce anxiety symptoms [48]. The predominant mechanisms of tDCS treatment in patients with cognitive and psychiatric dysfunction are the modulation of cortical excitability and the plasticity of cortical neurons. Thereby, it can regulate the dynamic imbalance between the default mode network and the frontal-parietal control network, harmonizing cognitive control and emotion regulation [49]. Furthermore, the majority of studies on swallowing function recovery in stroke patients support the positive impact of tDCS in decreasing the rate of complications [50]. Anodal tDCS, specifically targeting the left inferior frontal gyrus, represents a therapeutic way to enhance swallowing function [51]. However, our analysis did not demonstrate that tDCS significantly elevated hemispatial neglect, potentially owing to inadequate evidence. One review reported very low evidence supporting the effect of tDCS on hemispatial neglect [51]. Additionally, tDCS showed efficacy in the management of post-stroke depression, alleviating depressive symptoms by multiple assessment scales in stroke survivors [52]. However, the methodological evidence supporting the association was rated as critically low quality. Therefore, the findings must be interpreted with considerable caution due to the underlying limitations in the primary evidence.

Regarding the effect of tDCS on motor function in stroke patients, our umbrella review, based on the synthesis of existing meta-analyses, demonstrated a significant improvement in upper extremity motor function (as measured by FMA-UE/Action Research Arm Test [ARRT]), with high-quality evidence assessed by AMSTAR 2 and GRADE. This supports the overall efficacy of tDCS for this specific outcome. Maybe because tDCS increases cerebral blood flow or balances the symmetry between the cerebral hemi-spheres [53,54]. However, the ongoing controversy and heterogeneity in the field must be acknowledged. For instance, some primary studies and systematic reviews have reported limited or inconclusive effects, potentially attributable to variations in study quality, small sample sizes, or differences in outcome measures focusing on muscle strength alone [55,56]. Notably, a recent large-scale multicenter trial found that adding tDCS to constraint-induced movement therapy did not result in additional benefits in reducing motor impairment in a specific subacute stroke cohort [57]. This apparent inconsistency underscores that the therapeutic efficacy of tDCS is likely significantly modulated by key parameters, such as intensity, target, duration, sessions and patient characteristics (e.g., time since stroke). Therefore, while the aggregated high-quality evidence from meta-analyses supports its potential, the optimal application of tDCS for post-stroke motor recovery requires further refinement. Future research should focus on defining precise stimulation protocols and identifying the patient subgroups most likely to benefit, which is crucial for translating this promising intervention into consistent and effective clinical practice. Although certain effects remain to be clarified, improvements in various functional impairments by tDCS treatment were confirmed and can be broadly applied in the field of stroke rehabilitation.

4.1.2 Parkinson's Disease

The study suggested tDCS significantly increased cognition in patients with Parkinson's disease, with low heterogeneity. Likewise, insight from related fields aligns with what we found. tDCS combined with cognitive training was suggested to enhance attention and working memory in Parkinson's disease [58–60]. tDCS over the dorsolateral prefrontal cortex (DLPFC) improved several cognitive performances with large effect sizes [61]. Both of the included studies [38,46] mentioned that tDCS-induced cognitive gains may stem from enhanced neural connectivity between cortical and subcortical networks, neuroplasticity [51,62], and increased dopamine release [63] due to cortical stimulation. However, we did not investigate the impact of motor function in Parkinson's disease patients owing to a lack of substantial evidence. Thus, the effect of tDCS on this condition is unclear. Some insight from this field suggests a slight benefit on the motor ability of patients with Parkinson's disease [64,65]. However, the latest secondary study argued that tDCS combined with motor training improves motor function, particularly in gait-related parameters [66]. tDCS that was designed to simultaneously target motor and cognitive regions effectively improved motor and cognitive performance during tasks [67,68]. Therefore, research efforts are proposed to further confirm the effect of tDCS on motor areas.

4.1.3 Alzheimer's Disease

Regarding patients with Alzheimer's disease, we reported the effects of tDCS on distinct cognitive domains, including MMSE, MODA, and p300 latency scores. Many studies have been conducted recently on tDCS as a potentially beneficial intervention for Alzheimer's disease patients. Our findings are consistent with these investigations [69,70]. Despite the significant efficacy, meta-analytic evidence on specific cognitive functions is inconsistent. An up-to-date umbrella review indicated that tDCS could sig-

nificantly boost cognitive abilities like global cognition, language, executive functions, and memory in patients with Alzheimer's disease and mild cognitive impairment [71]. Another meta-analysis provided insight that tDCS effectively enhanced global cognition in older adults with mild cognitive impairment but no specific memory or executive functions [72]. However, the etiology and pathogenesis of AD remain inadequately explored. The potential mechanisms are as follows. On the one hand, tDCS could facilitate alterations in synaptic efficacy to enhance cortical function [73]. On the other hand, tDCS could increase the permeability of the blood-brain barrier, promote cerebral perfusion, and elevate blood flow velocity [74]. tDCS probably impacts amyloid-beta (Aβ) production and degradation to recover cognition among patients with Alzheimer's disease [75]. Given the contrasting conclusions and variety of mechanisms involved, studies concentrating on the effect of tDCS on Alzheimer's disease are urgently needed.

4.1.4 Cerebellar Ataxia

Our research provides evidence that tDCS mitigates ataxia symptoms in patients with cerebellar ataxia with lasting results. The involved meta-analysis [40] reported that tDCS modulates cortical excitability to promote neuroplasticity in the cerebellar cortex [51]. Given that cerebellar ataxia can lead to slow and irregular patterns in Purkinje cells [76], the predominant neuronal type in this region, the application of tDCS could enhance Purkinje cell functionality and restore the normal functions of the cerebellar network. tDCS proved to be better than other non-invasive stimuli in treating cerebellar ataxia [77]. A previous study showed that tDCS reduced disease severity and enhanced finger dexterity and quality of life in patients with cerebellar ataxia [78]. A meta-analysis and systematic review further substantiated the superior efficacy of tDCS in improving gait ataxia compared to finger dexterity [40]. While there is some evidence regarding the effects of tDCS on cerebellar ataxia, the scarcity of literature underscores the necessity for further research to gain a comprehensive understanding of the subject.

4.1.5 Fibromyalgia

Our study found that tDCS was useful for three key health outcomes of fibromyalgia: pain, depression, and FIQ scores. Regarding pain alleviation, prior systematic reviews and meta-analyses have consolidated existing evidence for the clinical effectiveness of tDCS in managing fibromyalgia-related pain [79,80]. They confirmed that applying tDCS at 2 mA to the left primary motor cortex was the most effective approach. It is presently unclear whether depression can be alleviated by tDCS. While one systematic review questioned the effects on anxiety and depression, another study argued that tDCS is a safe approach to reducing depression [41]. The potential mechanism underlying fibromyalgia is believed to be linked to central sensitization [81,82]. The primary meta-analysis [41] indicated that tDCS mitigated abnormal central nervous system function by promoting structural plasticity and neuronal reorganization [83]. As the debate regarding this concern is ongoing, further evidence is necessary.

4.1.6 Epilepsy

Our study demonstrated that tDCS did not significantly reduce the frequency of seizures. The newly estimated 95% CI calculated using the HKSJ method differed from the original 95% CI. In contrast, some previous evidence has indicated the potential effect of tDCS on epilepsy patients. Several studies suggested that tDCS reduces seizure frequency in patients with epilepsy and refractory epilepsy [84–86]. Nevertheless, a meta-analysis found that tDCS did not appear to affect epileptiform discharges, although it could lower seizure frequency [87]. The fundamental mechanism of tDCS in epilepsy remains unclear, but it is probably due to the decreased excitability of the cerebral cortex resulting from cathodal hyperpolarization or modulation of N-methyl-D-aspartate (NMDA) receptors and the Gamma-aminobutyric acid (GABA) system [88,89]. Considering the differences and vagueness, we hypothesize that the inconsistency might be attributed to remarkable heterogeneity. Whether tDCS produces adverse effects in patients with epilepsy has been controversial for many years. Consequently, we recommend that future studies prioritize minimizing heterogeneity and providing more credible evidence to substantiate the effectiveness and safety of tDCS in treating epilepsy.

4.1.7 Disorders of Consciousness

This umbrella review proposed that tDCS was efficient for disorders of consciousness, consistent with the results of other studies. Professor Aurore Thibaut, whose research focuses on the efficacy of tDCS in disorders of consciousness, has consistently demonstrated [90–93] that tDCS can enhance consciousness levels in patients with disorders of consciousness. Meanwhile, a guideline provided class II evidence supporting the efficacy of tDCS for disorders of consciousness [94]. Earlier meta-analyses reported that multiple tDCS sessions on the left-dorsolateral prefrontal cortex (L-DLPFC) were the most effective [95,96] in patients with disorders of consciousness. Moreover, several studies reported that tDCS demonstrated notable efficacy for patients diagnosed with a minimally conscious state [97,98]. The following are some potential explanations mentioned for why tDCS may enhance consciousness. One reason is that tDCS may alter the cortex's excitability in response to anodal stimulation [99]. According to the mesocircuit model [16,100], tDCS stimulation targeting the L-DLPFC induces increased cortical activity, which subsequently robustly stimulates the striatum. This increased striatal output inhibits the internal globus pallidus (GPi), thereby reducing GPi-mediated suppression of the thala-

mus. Consequently, the disinhibited thalamus effectively excites cortical regions, particularly the prefrontal cortex, establishing a self-reinforcing positive feedback loop. This sustained neurocircuitry activity maintains high-level, organized cortical processing, potentially promoting the recovery of wakeful consciousness. Another reason is that it can enhance synaptic plasticity by altering the NMDA acid receptor's mediation [12]. Patients with disorders of consciousness have a long and difficult recovery process. Thus, it is essential to identify the therapeutic mechanism of tDCS for this patient population.

4.1.8 Multiple Sclerosis

We discovered the potential of tDCS to improve gait functionality for patients with multiple sclerosis, along with very low-quality evidence. Despite low certainty, some findings support the effect of tDCS in patients with multiple sclerosis [101,102]. tDCS had favorable effects on cognitive processing speed, mood, pain, and fatigue in multiple sclerosis [103]. Fatigue, recognized as the most common disabling symptom in multiple sclerosis, was effectively treated with tDCS and benefited the most [104], while motor performance benefited the least [105]. The mechanism of tDCS in treating multiple sclerosis remains unclear. Uncertain mechanisms and considerable heterogeneity across studies persist, underscoring the need for further large-scale, long-term investigations.

4.1.9 Migraine

This study demonstrated the efficacy of tDCS in reducing pain intensity among migraine patients, corroborating earlier findings [106]. tDCS exhibited a superior effect on pain relief compared to other non-invasive stimulation techniques [107]. One significant pathophysiological mechanism of migraine is central sensitization [108]. The original study [45] explained that multiple tDCS sessions may induce cumulative and long-term neuroplastic changes within the cerebral cortex of individuals experiencing migraine [109].

4.1.10 Adverse Effects

Our reanalysis reported that tDCS led to mood changes in patients with fibromyalgia. Future studies should use large sample sizes to confirm this negative effect. Considering other studies, we can conclude that the mild and transient adverse effects support tDCS as a low-risk treatment for neurological disorders. This idea is in accordance with the preliminary evidence [110–112]. Effects were categorized into three groups: mostly skin harms, effects on neurological or psychological problems and other potential effects. No serious adverse events were reported from our reanalysis, suggesting it is a safe therapeutic tool for short-term use. However, the long-term safety profile remains inadequately characterized because of the lack of systematic long-term monitoring. Therefore, the safety of long-term tDCS application is unknown.

This umbrella review synthesized evidence regarding the clinical efficacy and safety of using tDCS in patients with neurological disorders, while also providing a framework for mechanistic investigations. tDCS delivers a subthreshold direct current, typically between 1 and 2 mA, through electrodes placed on the scalp. First, this technique induces polarity-dependent modulation of cortical excitability. Specifically, anodal stimulation normally enhances neuronal firing, while cathodal stimulation generally decreases it. Then, these transient excitability shifts can subsequently facilitate synaptic plasticity. During the transformation, tDCS is thought to modulate NMDA receptor-dependent processes, inducing long-term potentiation-like or long-term depression. Synaptic plasticity is integral to the reconstruction of neural networks. This process applies to the majority of neurological disorders, typically stroke. tDCS may affect neurotransmitter systems for therapeutic purposes, including modulating dopamine levels in Parkinson's disease and GABA levels in epilepsy. Additionally, emerging evidence suggests that tDCS could potentially modulate cerebral blood flow, particularly affecting motor function in stroke and treating Alzheimer's disease. Also, there are certain mechanisms based on the pathogenesis. For example, tDCS may impact the production and degradation of Aβ, thereby aiding cognitive recovery in patients with Alzheimer's disease. Collectively, these mechanisms of excitability modulation, synaptic plasticity induction, network connectivity regulation, and potential neurochemical or vascular changes interact to mediate the clinical improvements observed with tDCS in various neurological conditions. Therefore, this study could provide mechanistic priorities for future research: (1) listing clinically validated tDCS protocols for reproducible experimentation (electrode placement/intensity/duration/session), (2) identifying responsive phenotypes to guide personalized treatment and targeted mechanistic investigation (e.g., arousal-responsive subgroups in disorders of consciousness), and (3) prioritizing cross-disease mechanistic questions (e.g., shared synaptic plasticity in cognitive dysfunction).

4.2 Heterogeneity and Its Implication

We identified significant heterogeneity (I^2 >75%) in several analyses in our study, a common issue in meta-analyses of tDCS interventions, which indicates substantial variation in effect sizes among the included primary studies. This variability may stem from multiple factors. First, stimulation parameters diverged widely: intensity (0.5–5.0 mA), target (M1 vs. DLPFC vs. cerebellar), duration (5–40 min), and session number (1–60) all influence neuroplastic efficacy. Second, heterogeneity exists in participant characteristics. Even within a specific disorder, such as stroke, factors such as lesion location, disease stage (acute, subacute, or chronic), and baseline impairment severity can profoundly affect responsiveness to tDCS. Third, small sample studies (<800) and publication bias inflate apparent

between-trial variance by selectively inserting exaggerated effect sizes. Finally, different assessment tools, each with distinct properties and responsiveness, may introduce measurement variability.

Thus, we recommend that future studies conduct subgroup analyses based on predefined factors (e.g., etiology or tDCS protocol) or meta-regressions to examine the influence of continuous variables (e.g., mean age and baseline scores) on effect size to explore the sources of heterogeneity. We urge the field to develop and adopt consensus-based tDCS protocols for specific neurological disorders. Concurrently, primary studies must rigorously adhere to reporting guidelines, such as the template for intervention description and replication (TIDieR) checklist [113] to ensure the complete and transparent documentation of all intervention details. In conclusion, the high heterogeneity observed in this study does not necessarily challenge the potential efficacy of tDCS but rather highlights that its effects are significantly modulated by protocol choices and patient factors. Acknowledging and systematically investigating these sources of variation are critical next steps toward refining tDCS into a reliable and precise therapeutic tool.

4.3 Limitations

The quality of the methodology and supporting evidence was crucial for our conclusion. Compared to other health endpoints, literature on upper extremity motor function in stroke and on the 8-MWT in cerebellar ataxia demonstrated high methodological and evidential quality according to AMSTAR 2 and GRADE assessments. In contrast, certain studies focusing on stroke, Alzheimer's disease, Parkinson's disease, epilepsy, and migraine had notable methodological shortcomings. These findings underscore the need for cautious interpretation and highlight areas where future research should aim to reduce variability and strengthen evidence quality.

The volume of literature and the availability of sufficient demographic and clinical data were critical. The health endpoints for Alzheimer's disease, cerebellar ataxia, fibromyalgia, epilepsy, disorders of consciousness, multiple sclerosis, and migraine each included just one systematic review and meta-analysis, which could reduce the credibility of the results. Additionally, reanalysis showed no association between tDCS and epilepsy or multiple sclerosis. Due to insufficient data (mean, standard deviation, and sample size) for reanalysis by HKSJ, some health endpoints, such as spinal cord injury, traumatic brain injury, headache, and central neuralgia, were excluded.

In the reanalysis, the new estimated 95% CI was generally narrower than the 95% PI, likely because the 95% PI accounts for variability in individual observations. Moreover, the 95% PI range included zero, indicating that tDCS efficacy was highly variable. This meant that the effectiveness of tDCS was unpredictable and could be negative in certain medical circumstances. Most included studies involved small sample sizes below 800, leading to potential publication bias, except for two meta-analyses [32,33]. Thus, we conducted Egger's test to address this limitation. Nevertheless, most meta-analyses incorporated fewer than 10 RCTs, preventing their application. Although some studies were not eligible for review using Egger's test, publication bias could be tested by funnel plot with contours and correction using the trim-and-fill method. This indicated that while selective reporting or unpublished small-sample studies may exist, they did not significantly impact the overall conclusions.

4.4 Future Work

This umbrella review suggests that future research should focus on the efficacy of tDCS on motor function in stroke, Parkinson's disease, epilepsy, and multiple sclerosis patients. It also calls for more RCTs testing the efficacy of tDCS in patients with Alzheimer's disease, cerebellar ataxia, fibromyalgia, epilepsy, disorders of consciousness, multiple sclerosis, and migraine. We encourage studies to offer more detailed information for performing secondary research. For example, future primary meta-analyses on tDCS should prioritize sensitivity analyses to identify the sources of the observed heterogeneity. Investigating moderators, such as stimulation parameters (intensity, target, duration, and sessions) and patient demographics, will be essential for developing personalized and optimized tDCS protocols. Secondary research is also recommended to analyze multiple effect sizes, assess heterogeneity, and thoroughly report publication bias.

5. Conclusions

In conclusion, this umbrella review systematically summarized a vast amount of existing evidence from published systematic reviews and meta-analyses. We found that tDCS was associated with improvements in a majority of the health outcomes evaluated in multiple neurological disorders, and it exhibited a favorable safety profile. However, the strength of this evidence was often limited, necessitating further high-quality research to confirm the efficacy of tDCS for specific conditions. Further studies should validate the therapeutic potential of tDCS in the reported neurological conditions, investigate additional neurological health outcomes, and explore the underlying mechanisms of tDCS effects.

Abbreviations

GBD, global burden of disease; tDCS, transcranial direct current stimulation; PRISMA, preferred reporting items for systematic reviews and meta-analyses; PROSPERO, prospective register of systematic reviews; CINAHL, cumulative index to nursing and allied health literature; HD-tDCS, high-definition transcranial direct current stimulation; HKSJ, hartung-knapp-sidik-jonkman; AMSTAR 2, measurement tool to assess systematic reviews

2; GRADE, grades of recommendations, assessment, development, and evaluation; MD, mean difference; SMD, standardized mean difference; 95% CI, 95% confidence interval; 95% PI, 95% prediction interval; MoCA, montreal cognitive assessment test; MMSE, mini-mental state examination; LOTCA, loewenstein occupational therapy cognitive assessment; MBI, modified barthel index; HAMD, hamilton depression Scale; BDI, beck depression inventory; SADQ-H, stroke aphasic depression questionnaire hospital Version; SDS, self-Rating depression scale; FMA-UE, upper extremity fugl–meyer assessment; ARRT, action research arm test; BI, barthel index; FMA-LE, lower extremity fugl–meyer assessment; MAS, modified ashworth scale; TUG/TUGT, timed up and go test; FAC, functional ambulation category; DOSS, dysphagia outcome severity scale; MMASA, modified mann assessment of swallowing ability; FOIS, functional oral intake scale; FDS, functional dysphagia scale; VFSS, video fluoroscopic swallowing study; LBT, line bisection test; UPDRS-I, unified PD rating scale I; SCOPA, scales for outcomes in Parkinson's Disease; PD-MCI, Parkinson's disease with mild cognitive impairment; DS-F, Digit Span-Forward; S-IT, stroop interference test; MODA, milan overall dementia assessment; SARA, Scale for Assessment and Rating of Ataxia; FIQ-R, modified fibromyalgia questionnaire; PCP:S, profile of chronic pain:screen; HAM-D, Hamilton Depression Rating Scale; BDI-II, Beck Depression Inventory-II; FIQ, fibromyalgia questionnaire; CRS-R, coma recovery scale–revised; 2MWT, 2-minute walk Test; 25FWT, 25-foot walk test.

Availability of Data and Materials

The original contributions presented in this study are included in the article and **supplementary material**. Further inquiries can be directed to the corresponding author.

Author Contributions

TY, YS, YL, SL, XT, WT, YZ and YK were involved in the original conceptualization. TY, YS, YL and SL were responsible for developing the study methodology. TY, YS and YL did the literature search. SL, XT, WT and YZ were responsible for data curation. TY and YS did the formal statistical analysis. TY wrote the original draft. YS and YK edited and reviewed the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

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