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Linguistic effects of transcranial Direct Current Stimulation (tDCS) in patients with primary progressive aphasia: A systematic review and meta-analysis of randomised controlled trials

Diogo C. Godoi [a,1,*], Eduarda Pandiá [b,2], Maria Eduarda Rodrigues [c,3], Luísa Araújo [d,4], Marina Barbosa [e,5], Khaled Alhwaishel [f,6], Amanda Godoi [g,7], David J. McGonigle [h,i,8]

[a] Cardiff University School of Psychology, Cardiff, United Kingdom
[b] Faculdade Ciências Medicas de Minas Gerais, Belo Horizonte, Brazil
[c] Federal University of Tocantins, Palmas, Brazil
[d] Federal University of Pará, Belém, Brazil
[e] Barão de Mauá University, Ribeirão Preto, Brazil
[f] Mansoura University Faculty of Medicine, Mansoura, Egypt
[g] Cardiff University School of Medicine, Cardiff, United Kingdom
[h] CUBRIC, Cardiff University School of Psychology, United Kingdom
[i] Cardiff University School of Biosciences, Cardiff, United Kingdom

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ABSTRACT

Introduction: Transcranial Direct Current Stimulation (tDCS) has shown promising language improvements in patients with primary progressive aphasia (PPA). Yet, individual studies have not been sufficient to yield strong conclusions on its efficacy.

Methods: We performed a systematic review and meta-analysis of randomised controlled trials (RCTs) comparing tDCS against sham stimulation in patients with PPA. We searched PubMed, Embase, and Cochrane Central databases for eligible studies up to July 2024. Outcomes of interest included a performance in a range of language and cognitive tests. Summary data was extracted from published reports and pooled with a random-effects model using standardized mean differences (SMD) and 95 % confidence intervals (CI). The protocol was registered in PROSPERO, CRD42024499012.

Results: We included 10 parallel and cross-over RCTs with 178 patients and 218 observations. tDCS yielded significant improvements for general naming (SMD 0.37; 95 % CI 0.07–0.67; $p < 0.01$) and spelling ability (SMD 0.65; 95 % CI 0.10–1.20; $p = 0.02$) There were no differences between groups regarding naming performance for trained ($p = 0.76$) and untrained items ($p = 0.11$), global language ($p = 0.28$), working memory ($p = 0.15$), semantic fluency ($p = 0.38$), and comprehension ($p = 0.32$).

Abbreviations: PPA, Primary Progressive Aphasia; RCT, Randomised Controlled Trial; TDCS, transcranial Direct Current Stimulation; SMD, Standardized Mean Difference; CI, Confidence Intervals; NfvPPA, Non-Fluent Variant PPA; SvPPA, Semantic Variant PPA; LvPPA, Logopenic Variant PPA; FTDs, Frontotemporal Dementias; SLT, Speech and Language Therapy; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RTMS, Transcranial Magnetic Stimulation; REML, Restricted Maximum Likelihood; Rob-2, Cochrane Risk of Bias Assessment Tool.

* Correspondence to: Park Place, Cardiff CF10 3AT, United Kingdom.
E-mail address: carrazzonigodoid@cardiff.ac.uk (D.C. Godoi).
[1] ORCID 0009–0003-9326–8478
[2] ORCID 0009–0006-7439–6062
[3] 0009–0009-1999–2365
[4] 0009–0003-0218–8633
[5] 0009–0000-8804–1701
[6] 0000–0002-5532–9263
[7] ORCID 0000–0001-8666–7786
[8] 0000–0001-9595–6352

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Conclusion: In this systematic review and meta-analysis, tDCA showed benefits for performance in general naming ability and spelling in PPA patients. However, there was no significant evidence to supporting any effect of tDCS on other language functions.

1. Introduction

Primary progressive aphasia (PPA), a debilitating neurodegenerative condition, affects 3–7 inhabitants per 100,000. (Roytman et al., 2022) It is characterised by a gradual impairment in language capabilities appearing either in isolation, or in tandem with a decline in other cognitive functions. (Piguet, 2022; Kiymaz et al., 2024)

PPA can be divided into three distinct variants based on core symptoms: non-fluent variant PPA (nfvPPA) characterised by agrammatism (misuse of grammatical elements) (Babiak and Gorno-Tempini, 2014) and deficits in speech production; (2) semantic variant PPA (svPPA) characterised by anomia (word finding and naming difficulties) (Grossman, 2014), single-word comprehension difficulties, and a progressive loss of semantic organisational structure, (Piguet, 2022) and (3) logopenic variant PPA (lvPPA) characterised by impairments in single word retrieval, sentence repetition, and full sentence comprehension. (Kiymaz et al., 2024) The nfvPPA and svPPA variants of PPA are commonly labelled as Frontotemporal Dementias (FTDs), as they present with more pronounced atrophy in the frontal and temporal lobes respectively. In contrast, lvPPA is classified as an aphasic variant of Alzheimer's disease due to pathological similarity of the conditions. (Spinelli et al., 2017)

Currently, there is little evidence supporting one specific treatment for PPA. (Roheger et al., 2024) Research on pharmacological interventions is limited and has yielded mixed results. (Marshall et al., 2018) In contrast to specific interventions targeting the purported mechanisms of PPA, speech and language therapy (SLT) has yielded promising results and is generally the standard recommendation for PPA patients (Volkmer et al., 2020; Manouilidou and Nerantzini, 2020; Tippett et al., 2015) despite most research yielding only Level IIa and IIb evidence. (Wauters, 2023)

The relative failures of pharmacological and behavioural interventions to address PPA in a significant subset of patients are not unique: the treatment of many neurological and neuropsychiatric conditions such as epilepsy (Thijs et al., 2019), chronic pain (Hylands-White et al., 2017) and stroke (Shehjar et al., 2023) face similar issues. A potential way to address this therapeutic shortfall is to investigate the application of scalp electrical stimulation (transcranial Direct Current Stimulation; tDCS) to patients with PPA. In this treatment, an electrical current flows through two scalp electrodes, causing modulation of the resting potential of neurons and changing the action potential generation. While the current mechanistic principles underlying this technique are unclear, tDCS has been shown to aid treatment of neurological and psychiatric conditions such as depression, stroke impairments and neurodegeneration. (Sanches et al., 2020)

Recent studies using tDCS have demonstrated improvements in stroke-induced aphasia patients, (Ding et al., 2022) suggesting possible benefits to PPA patients. But despite recent systematic reviews indicating it might be an effective treatment for PPA (Roheger et al., 2024; Coemans et al., 2021; Perez-Martinez et al., 2023), randomized studies in this field have been scarce. (Roheger et al., 2024) 3 previous meta-analyses have demonstrated the effectiveness of tDCS for PPA patients—all published in 2020. (Cotelli et al., 2020; Byeon, 2020; Nissim et al., 2020) However, effect sizes varied between these analyses, and they included both observational and randomised studies under the same outcomes, increasing the risk of confounding. Additionally, the studies focused only on naming ability, (Cotelli et al., 2020; Byeon, 2020) or grouped distinct language modalities into the same statistical model, (Nissim et al., 2020) despite the established dissociation among different language functions. (Lorca-Puls et al., 2024; Hillis and Caramazza, 1991) Therefore, the additional sham-controlled randomised studies published in recent years prompt an updated, more stratified analysis to help clarify the possible clinical applications of tDCS on several language-relevant domains. In this updated systematic review and meta-analysis, we aim to test the effectiveness of tDCS in improving language and cognitive outcomes in patients with PPA using data restricted to RCTs.

2. Methodology

2.1. Study design and reporting guidelines

This systematic review and meta-analysis was performed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) and Cochrane Collaboration Handbook for Systematic Review of Interventions guidelines. (Higgins et al., 2023) The review's protocol was registered prospectively in PROSPERO (ID: CRD42024499012).

2.2. Search strategy and study selection

PubMed, Embase and Cochrane Central databases were systematically searched from January 1989 up to July 2024 with the strategy outlined in Appendix A. We also searched for additional eligible studies through a review of references cited in the included studies and previous meta-analyses.

Two authors (D.G. and M.R.) independently screened studies using Rayyan. (Ouzzani et al., 2016) Studies were included if they treated human patients with PPA; compared sham versus active tDCS treatments; patients were randomized to their respective treatment conditions; and reported language or cognitive outcomes. Studies were excluded if they were only published as a conference abstract; the articles were not published in the English language; had $N < 5$; or if the required data for PPA patients was not reported by study authors.

This study initially aimed to analyse the effectiveness of both repeated Transcranial Magnetic Stimulation (rTMS) and tDCS on PPA patients, however, not enough studies were found to conduct meaningful analyses with rTMS. Therefore, study triage criteria was updated to only include studies administering tDCS.

2.3. Endpoints and subgroup analyses

The primary outcomes of interest were the scores in tests for general naming ability, and naming for trained and untrained items. Secondary outcomes included global language; working memory; spelling; comprehension and semantic fluency. We categorised tests as "Global Language" if they summarised patient performance across multiple language domains under the same diagnostic scale (e.g. Boston Diagnostic Aphasia Examination, Western Aphasia Battery). (Spreen and Risser, 1998) Working Memory includes tests that measure patients' ability to hold information in their short-term store (e.g. Digit Span Task) (Baddeley, 1992), while semantic fluency included tests asked patients to belonging to a common category in a given amount of time. (Borrego-Écija et al., 2023; Wang et al., 2023) Finally, comprehension was defined as any test that measured the patient's ability to receive and process verbal information. (Borrego-Écija et al., 2023; Cotelli et al., 2014) A full description of assessment tools for each outcome can be found on Supplementary Table 1.

Performance in naming tests for trained and untrained conditions were analysed independently as separate outcomes, as provided by the

included studies. Naming for untrained items involved prompting stimuli (e.g. categories, first letters) that were unfamiliar to the patients, while prompts for trained items had been previously practised during SLT. When a study utilised the same scale for both outcomes, a weighted mean was calculated to generate another outcome (general naming) representing overall naming ability of patients. When a study made no distinction between trained and untrained conditions, the available data was included under the "untrained" and "general" naming analyses.

For crossover studies, an a priori strategy was used to analyse group means and standard deviations, assuming no correlation between groups (as parallel study designs) in accordance with suggestions by the Cochrane Collaboration. (Higgins et al., 2023) Outcome data was individually extracted and analysed by two authors (D.G. and E.P.), while data for baseline characteristics was extracted by two others (M.R. and L.A.). Disagreements over data collection and processing were resolved by a third author (A.G).

Participant-level data was not requested to study authors. Where data was only available in a graphical format, it was extracted using WebPlotDigitizer version 3.4 (beta), (Rohatgi) a widely-used and reliable data extraction tool. (Drevon et al., 2017; Aydin and Yassikaya, 2021) For outcomes which reported standard error as a measure of distribution, the statistic was converted to a standard deviation using the formula recommended by the Cochrane Collaboration. (Higgins et al., 2023)

2.4. Quality assessment

All included studies were individually analysed by two independent investigators (M.B. and K.A.). We used Cochrane Risk of Bias Assessment Tool (RoB-2) for parallel RCTs and the RoB-2 for Crossover Trials due to the high volume of crossover trials included in this meta-analysis. (Sterne et al., 2019) In instances where disagreements over the risk of bias assessment arose, they were solved by consensus. A funnel-plot analysis of point estimates according to study weights and an Egger's regression test were conducted to assess for small-study effects (publication bias) for naming outcomes.

2.5. Statistical analyses

Standard Mean Differences (SMDs) with 95 % Confidence Intervals (CI) were used as a measure of effect size for each outcome. A random effects model was chosen for all analyses, given the high variability in methodology and sample characteristics of the included studies. Outcome data was reported as either mean final values or mean change scores from baseline. Both were used in this meta-analyses, but when a study reported both, mean change scores from baseline were selected. (Higgins et al., 2023)

R studio (version 4.3.3) and was used for all statistical analyses. (R Core Team, 2024) The following packages were used: readxl; (Wickham and Bryan, 2023) meta; (Balduzzi et al., 2019) metafor; (Viechtbauer, 2010) and dmetar. (Harrer et al., 2019) Heterogeneity across outcomes was assessed using τ^2 and I^2 statistics, employing the Restricted Maximum Likelihood (REML) method. In cases of high heterogeneity in the model (defined by I^2>50 %) sources were sought using the leave-one-out strategy (Vehtari et al., 2017), as well as Baujat plots (Baujat et al., 2002).

Data belonging to the longest follow-up duration of each study was selected for all statistical models, in accordance with the Cochrane Collaboration recommendations when including studies measuring participants longitudinally. (Higgins et al., 2023) A generalised linear mixed-effects model meta-regression was used to understand the relationship between maximum follow-up durations and the results for naming outcomes across different studies. This was done to quantify the effect of the follow-up times on the improvements in general, untrained and trained naming ability.

3. Results

3.1. Study selection and characteristics

The search strategy yielded a total of 4843 records to be screened (Fig. 1). After duplicate removal and full-text screening, 11 RCTs fit the eligibility criteria. Among studies excluded for lack of available data, there were present clinical trial protocols with unreleased results and studies including patients with PPA in their sample but not providing specific outcome information for this subgroup. Other reasons for exclusions included overlapping populations with included studies, too few patients in the sample, among others. One study was excluded for administering a single-session tDCS treatment, which would too different from other studies' multi-session treatment.

Two of the included studies (Wang et al., 2023; de Aguiar et al., 2020) reported results from different outcomes of the same clinical trial. (Hopkins, 2023) These were be labelled as "Johns Hopkins 2023" for subsequent reporting and analyses. Two other studies (Sheppard, 2023; Coslett, 2021) were only published as clinical trial registers, but had published results. These were extracted and included in our analysis. In total, the included studies reported on data from 178 patients and used 218 patient observations. Of these, 107 (51.7 %) received tDCS and 111 (48.3 %) received sham stimulation. Follow up durations ranged from 0 to 6 months across studies. Mean age of patients varied from 60 to 70 years old and stimulation intensity from 1 to 2 mA. Participants were administered between 10 and 15 tDCS or sham sessions throughout different studies. The left inferior frontal gyrus was the targeted stimulation area in three studies, (Wang et al., 2023; de Aguiar et al., 2020; Sheppard, 2023; Harris et al., 2019) while the remaining studies targeted different regions, including the left prefrontal and occipital lobes (Coslett, 2021), the dorsolateral prefrontal cortex, (Cotelli et al., 2014) the left supramarginal gyrus, (Neophytou et al., 2024) the left inferior parieto-temporal region, (Roncero et al., 2017) the frontal lobe, (Roncero et al., 2019) and the. Six of the included RCTs had a crossover design. (Borrego-Écija et al., 2023; Wang et al., 2023; de Aguiar et al.,

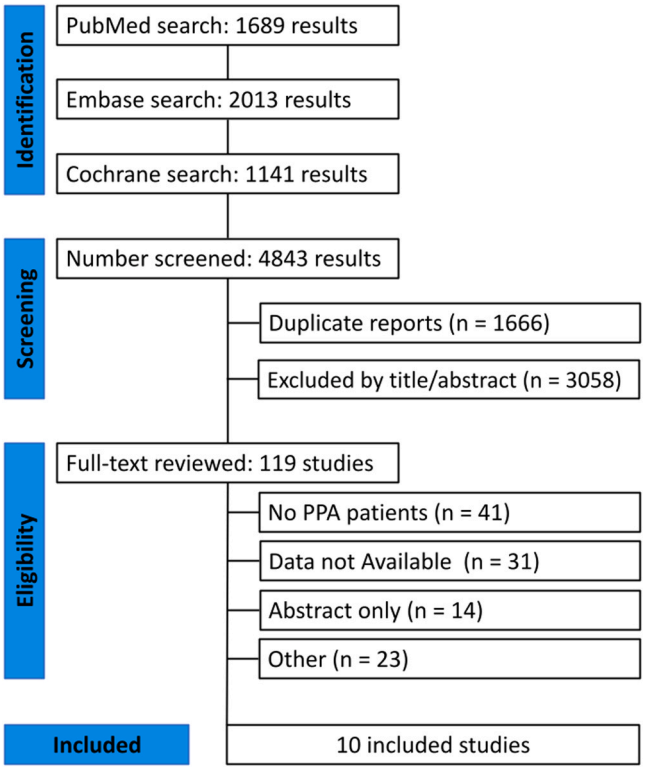

Fig. 1. PRISMA Flow diagram of study screening and selection.

2020; Sheppard, 2023; Coslett, 2021; Roncero et al., 2017; Roncero et al., 2019) Seven of the selected studies administered variations of SLT to patients in both the active and sham conditions. (Borrego-Écija et al., 2023; Wang et al., 2023; Cotelli et al., 2014; de Aguiar et al., 2020; Sheppard, 2023; Harris et al., 2019; Neophytou et al., 2024; Roncero et al., 2017; Roncero et al., 2019) Further study characteristics are reported in Table 1.

3.2. Effects on language

In pooled analyses of 7 and 5 RCTs respectively, no difference was found between active-tDCS and sham for naming performance for untrained (SMD 0.61; 95 % CI −0.13–1.35; $p = 0.11$; $I^2 = 83$ %; Fig. 2A), and trained stimuli (SMD −0.20; 95 % CI −1.53–1.12; $p = 0.76$; $I^2 = 77$ %; Fig. 2B).

In a combined analysis of the trained and untrained conditions of the seven available studies, tDCS had a significantly positive effect on general naming (SMD 0.37; 95 % CI 0.07–0.67; $p < 0.01$; $I^2 = 76$ %; Fig. 3), as well as spelling abilities (SMD 0.65; 95 % CI 0.10–1.20; $p = 0.02$; $I^2 = 32$ %; Supplementary Figure 1 A) in PPA patients. There were no significant differences between groups regarding performance in global language (SMD 8.71; 95 % CI −7.24–24.66; $p = 0.28$; $I^2 = 91$ %; Supplementary Figure 1B), working memory (SMD 0.41; 95 % CI −0.15–0.98; $p = 0.15$; $I^2 = 10$ %; Supplementary Figure 1 C), semantic fluency (SMD 0.25; 95 % CI −0.30–0.79; $p = 0.38$; $I^2 = 3$ %; Supplementary Figure 1D), or comprehension tests (SMD 0.51; 95 % CI −0.49–1.51; $p = 0.32$; $I^2 = 57$ %; Supplementary Figure 1E).

Meta-regression analyses according to follow-up durations of each study yielded no statistically significant findings for untrained stimuli ($\beta = 2.7935$; $p = 0.40$; $I^2 = 32.21$ %; Supplementary Figure 2 A), trained stimuli ($\beta = -0.1937$; $p = 0.794$; $I^2 = 17.90$ %; Supplementary Figure 2B), or general naming ability ($\beta = 0.1650$; $p = 0.182$; $I^2 = 23.39$ %; Supplementary Figure 2 C), suggesting a consistent effect of tDCS across time.

3.3. Sensitivity analyses

Sensitivity analyses were used to investigate sources of heterogeneity in models with $I^2 > 50$ %. Sheppard et al., 2023 (Sheppard, 2023) was identified as the main source in outcomes with high heterogeneity, as when omitting it from the analyses, the I^2 value decreases to 68 % for naming for untrained stimuli (Supplementary Figure 4), 0 % for trained stimuli (Supplementary Figure 6), 2 % for general naming (Supplementary Figure 8), and 60 % for global language (Supplementary Figure 10). After careful review of Sheppard et al., 2023's methodology, there was unfortunately little indication as to why such heterogeneous results were found. Analyses with Baujat plots indicate that in most outcomes, studies contributing to high heterogeneity did not greatly contribute to the overall result (Supplementary Figures 7, 9). However, Sheppard et al., 2023 and Roncero et al., 2019 highly contributed to heterogeneity and final results in the trained and untrained naming outcomes (Supplementary Figure 3, 5). However, removing these studies did not lead to significant changes in results in either analysis (Supplementary Figures 4, 6).

3.4. Quality assessment

Individual study appraisal can be found on Supplementary Table 2. Two studies had a different number of participants assigned to each condition, suggesting bias in the randomisation process. Two studies (Sheppard, 2023; Coslett, 2021) were rated as "some concerns" in deviations from the intended intervention due to high participant withdrawal in the sample. Another study (Wang et al., 2023; de Aguiar et al., 2020) was rated as "some concerns" regarding data availability as the "missing at random" assumption was applied for missing patient data, which might introduce bias in the statistical analysis.

Funnel plot analyses and Egger's regression tests in the naming outcomes did not reveal significant asymmetrical distribution of studies across measures of dispersion (Supplementary Figure 11).

4. Discussion

In this systematic review and meta-analysis of 11 RCTs and 178 patients, we tested the efficacy of tDCS on improving language outcomes for PPA patients. Our main findings include: Significant improvements in general naming and spelling performance, no significant differences in naming for trained and untrained items, global language, working memory, semantic fluency and comprehension, as well as consistent findings across different follow-up durations in naming outcomes.

Currently, treatment plans for PPA patients are generally reliant on SLT, which has still not shown high-certainty evidence for its efficacy. (Roheger et al., 2024; Wauters, 2023) The possible effectiveness of tDCS in randomised settings means that it could be an additional option for retaining and improving language capabilities in PPA patients, enhancing any potential benefits of SLT. Heterogeneric pathologies require a better, more targeted form of medicine: tDCS may potentially 'boost' the efficacy of currently used front-line tools.

Our pooled analysis represents a comprehensive synthesis of data on the topic, supporting the effectiveness of tDCS for improving general naming, and spelling abilities, while displaying how more data may be needed to confirm an effect in other language modalities.

These results slightly differ from previous meta-analyses on the topic. Cotelli et al. (Cotelli et al., 2020) found that tDCS caused significant improvement in written and oral naming abilities for both trained and untrained items in PPA patients. Meanwhile, Byeon (Byeon, 2020) and Nissim (Nissim et al., 2020) found that this treatment increases naming and global language abilities respectively. Our meta-analysis found less positive results. This was likely due to the more selective inclusion criteria restricted to RCTs, which minimises the risk of confounding and provide stronger support for the clinical use of tDCS.

While our study did not find a significant effect of tDCS on many important outcomes such as naming for trained, untrained items and global language, it is possible that the low number of participants pooled in the analyses of these and all outcomes could have contributed to a type I error. This is especially relevant given that the decision to treat different treatment arms as parallel study designs during statistical analysis: A decision that introduced a unit-of-analysis error (where number of observations exceeds the number of patients), which leads to more conservative analyses. (Higgins et al., 2023) Future research should focus on testing these language modalities in randomised settings to increase the power of the analysis. Furthermore, important clinical specifications for optimal treatment with tDCS such as target stimulation region, time of stimulation, optimal frequency, effect in different PPA variants and interactions with different SLTs could not be tested with the current available data. Future studies should focus on minimising variation between methodological approaches which may decrease heterogeneity and uncertainty in future updated analyses.

This study is not without limitations. Six of the included studies were crossover trials, which adds complexity to a meta-analysis because the effects of the intervention can carry-over from the first to the second arm of the study. (Higgins et al., 2023) Although all included crossover trials included a washout period to mitigate this, the risk of carry-over effects and the unit-of-analysis error could not be excluded. The progression of the condition may have caused the patients to deteriorate over time and the results of the second period to be different than those of the first period. (Higgins et al., 2023)

Heterogeneity was high for most outcomes. This finding was expected given the highly variable clinical and technical factors involved in studies performed in real-life conditions. Sensitivity analyses were performed to minimise and interpret such heterogeneities, yet we cannot exclude the possibility that such sub-analyses may be underpowered to detect significant differences. The high heterogeneity found

Table 1
Baseline characteristics of included studies.

Study	Study Design	Variants	Number of patients Active / Sham	Female, %, Active / Sham	Age, y	Intensity	Sessions	Stimulation Area	Anode Position	Cathode Position	Electrode Size	Auxiliary Therapy	Follow-up, months
Borrego-Écija 2023 (Borrego-Écija et al., 2023)	Crossover RCT	4 svPPA; 5 lvPPA; 6 nfvPPA.	13 / 13	66.6	63 ± 8.7	2 mA	10 sessions each condition (tDCS and sham)	Global Language Region	C1, F7, FC1, FC5, Fpz, P7, and PO8	N/A	1 cm radius	Speech Therapy	0
Coslett 2021 (Coslett, 2021)	Crossover RCT	13 PPA	13 / 13	38.5	66.3 ± 7.7 / 66.3 ± 6.2	1.5 mA	10 sessions each condition (tDCS and sham)	Left Prefrontal and Left Occipital Lobes	Forehead	Left and Right Temporal Regions	Anode: 5 cm× 5 cm Cathode: 5 cm× 7 cm	N/A	0
Cotelli 2014 (Cotelli et al., 2014)	Parallel RCT	16 nfvPPA	8 / 8	63 / 63	63.4 ± 6.8 / 70.4 ± 6.8	2 mA	10 sessions of either sham or tDCS	Left Dorsolateral Prefrontal Cortex	Left Dorsolateral Prefrontal Cortex 6 cm laterally and 8 cm frontally from vertex.	Right Arm	Anode: 5 cm× 5 cm Cathode: 6 cm x 10 cm	Speech Therapy	3
Harris 2019 (Harris et al., 2019)	Parallel RCT	8 nfvPPA 4 lvPPA 5 svPPA	7 / 10	41.2	66.6 ± 6.7	2 mA	10–15 sessions of either sham or tDCS	Left Inferior Frontal Gyrus	F7	Right Cheek	2 in x 2 in	Written Naming Task	2
Neophytou 2024 (Neophytou et al., 2024)	Parallel RCT	3 nfvPPA 4 lvPPA	4 / 3	75 / 33.3	69.25 ± 7.41 / 64.33 ± 2.08	2 mA	10 Sessions of either sham or tDCS (home-delivered)	Left Supramarginal Gyrus	CP3	Right Cheek	Not Specified	Verbal Short Term Memory / Working Memory Treatment	0
Roncero 2017 (Roncero et al., 2017)	Crossover RCT	6 nfvPPA; 2 lvPPA; 2 svPPA.	10 / 10	30	67.4	2 mA	10 sessions each condition (tDCS and sham)	Left Inferior Parieto-Temporal region	P3	Right Fronto Orbital Area	5 cm× 7 cm	Language Training	0.5
Roncero 2019 (Roncero et al., 2019)	Crossover RCT	4 nfvPPA; 4 lvPPA; 4 svPPA.	12 / 12	33.3	65.4	2 mA	10 sessions each condition (tDCS and sham)	Frontal Lobe	F3	Right Deltoid Muscle	5 cm× 7 cm	Language Training	2
Sheppard 2023 (Sheppard, 2023)	Crossover RCT	8 PPA	7 / 7	50	68.0 ± 5.9	1–2 mA	15 sessions each condition (tDCS and sham)	Left Inferior Frontal Gyrus	F5	Right Deltoid Muscle	5 cm× 5 cm	Verb Naming Therapy	2
Johns Hopkins 2023 (Wang et al., 2023; de Aguiar et al., 2020)	Crossover RCT	17 lvPPA; 15 nfvPPA; 8 svPPA.	15 / 18 For spelling 12 / 18 For other outcomes	45	66.1 ± 7.7 / 69.4 ± 5.1	2 mA	12 sessions each condition (tDCS and sham)	Left Inferior Frontal Gyrus	F7	Right Cheek	5 cm× 5 cm	Written naming/ spelling therapy or spelling therapy only	2

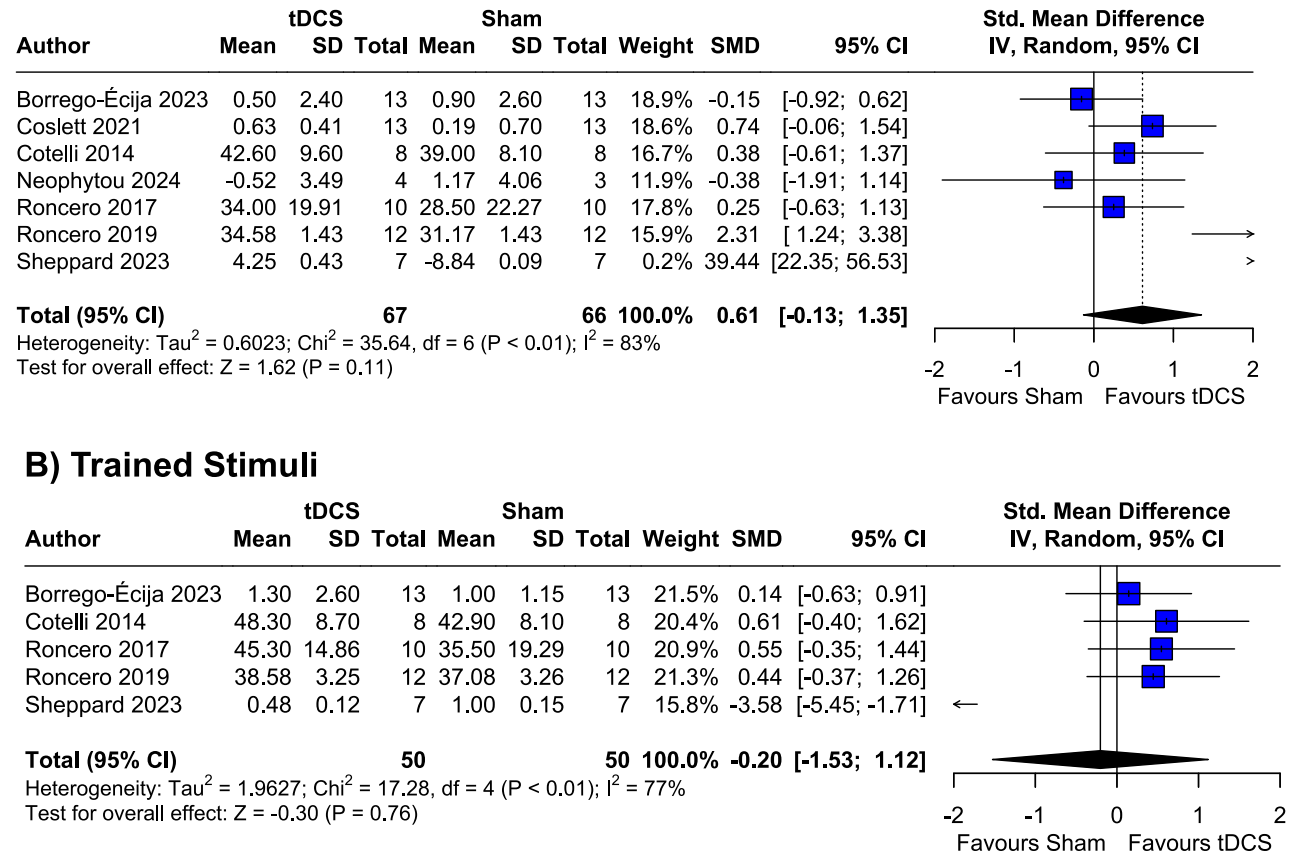

Fig. 2. tDCS did not significantly improve naming for (A) untrained items or (B) trained items compared to sham.

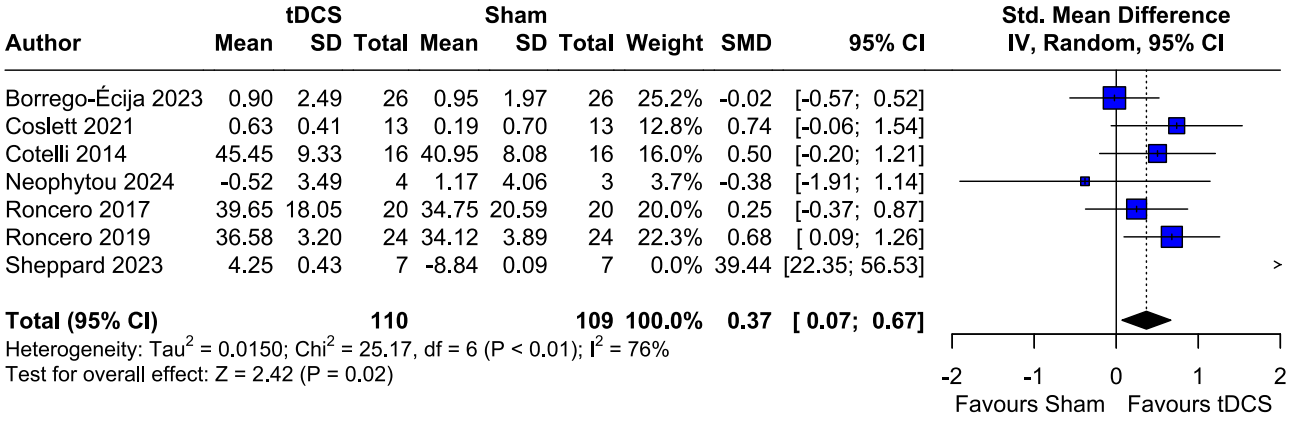

Fig. 3. tDCS significantly improved general naming ability.

in most analyses could have been caused by the varied assessment tools employed across studies. Under global language outcomes for example, some studies used questionnaire-based measures, (Roth, 2011) while others administered comprehensive testing batteries. (Miller et al., 2000; Kertesz, 2022) Each test also accounted for different subfunctions of language, sometimes weighted differently to generate the final tests score, introducing even more variability to our analysis. Higher consistency in measurement scales could lead to more accurate comparison between study findings, greater construct validity of meta-analytic outcomes, well as the ability to use unstandardised measures to pool results. Therefore, generating a quantifiable measure of benefit that can be directly applied to clinical practice. Future clinical trials could aim to use more standardised and valid measures of linguistic ability. These factors driving high heterogeneity and the concerns identified in the risk-of-bias analysis lend careful interpretation of our study results to prevent false interpretation of findings.

5. Conclusion

This systematic review and meta-analysis tested the efficacy of active tDCS vs. sham in 178 patients with PPA using data restricted to RCTs. There was a significant improvement in general naming ability and spelling, while naming of trained and untrained items, global language, working memory, and comprehension, significantly affected by the

intervention.

Compared to previous studies, the larger population and more selective criteria of our meta-analysis provides stronger evidence on the potentially beneficial use of tDCS in patients with PPA. While improvements in general naming and spelling abilities are more established, there is still some uncertainty regarding the optimal tDCS specifications for clinical practice, and whether other language modalities are improved by the use of tDCS.

Disclosures

During the preparation of this work the authors used ChatGPT-4 (OpenAI, 2025) in order to facilitate the use statistical analysis software and receive feedback on the writing, as well as Consensus AI (Consensus NLP, 2025) to find relevant papers on the topic of research. After using these tools/services, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

All authors report no relationships that could be construed as a conflict of interest. All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation. There were no external funding sources for this study.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2025.106264.

Data availability

Data will be made available on request.

References

de Aguiar, V., Zhao, Y., Ficek, B.N., Webster, K., Rofes, A., Wendt, H., Frangakis, C., Caffo, B., Hillis, A.E., Rapp, B., Tsapkini, K., 2020. Cognitive and language performance predicts effects of spelling intervention and tDCS in Primary Progressive Aphasia. Cortex J. Devoted Study Nerv. Syst. Behav. 124, 66–84.

Aydin, O., Yassikaya, M.Y., 2021. Validity and Reliability Analysis of the PlotDigitizer Software Program for Data Extraction from Single-Case Graphs. Perspect. Behav. Sci. 45, 239–257.

Babiak, M.C., Gorno-Tempini, M.L., 2014. Agrammatism. In: Aminoff, M.J., Daroff, R.B. (Eds.), in Encyclopedia of the Neurological Sciences (Second Edition). Academic Press, Oxford, pp. 84–85. https://doi.org/10.1016/B978-0-12-385157-4.00465-6.

Baddeley, A., 1992. Working Memory. Science 255, 556–559.

Balduzzi, S., Rücker, G., Schwarzer, G., 2019. How to perform a meta-analysis with R: a practical tutorial. Evid. Based Ment. Health 22, 153–160.

Baujat, B., Mahé, C., Pignon, J.-P., Hill, C., 2002. A graphical method for exploring heterogeneity in meta-analyses: application to a meta-analysis of 65 trials. Stat. Med. 21, 2641–2652.

Borrego-Écija, S., Montagut, N., Martín-Trias, P., Vaqué-Alcázar, L., Illán-Gala, I., Balasa, M., Lladó, A., Casanova-Mollà, J., Bargalló, N., Valls-Solé, J., Lleó, A., Bartrés-Faz, D., Sánchez-Valle, R., 2023. Multifocal transcranial Direct Current Stimulation in primary progressive aphasia does not provide a clinical benefit over speech therapy. J. Alzheimers Dis. 93, 1169–1180.

Byeon, H., 2020. Meta-Analysis on the Effects of Transcranial Direct Current Stimulation on Naming of Elderly with Primary Progressive Aphasia. Int. J. Environ. Res. Public. Health 17.

Coemans, S., Struys, E., Vandenborre, D., Wilssens, I., Engelborghs, S., Paquier, P., Tsapkini, K., Keulen, S., 2021. A Systematic Review of Transcranial Direct Current Stimulation in Primary Progressive Aphasia: Methodological Considerations. Front. Aging Neurosci. 13, 710818.

Consensus NLP (*2025*). *Consensus AI (March 16 Version)* [*Academic Search Engine*]. ⟨Https://Consensus.App/?Home=true⟩.

Coslett, H., 2021. ClinicalTrials.gov. Transcranial Magn. Stimul. constraint Induc. Lang. Ther. Chronic Aphasia. ⟨https://clinicaltrials.gov/study/NCT02928848⟩.

Cotelli, M., Manenti, R., Petesi, M., Brambilla, M., Cosseddu, M., Zanetti, O., Miniussi, C., Padovani, A., Borroni, B., 2014. Treatment of primary progressive aphasias by transcranial direct current stimulation combined with language training. J. Alzheimers Dis. JAD 39, 799–808.

Cotelli, M., Manenti, R., Ferrari, C., Gobbi, E., Macis, A., Cappa, S.F., 2020. Effectiveness of language training and non-invasive brain stimulation on oral and written naming performance in Primary Progressive Aphasia: A meta-analysis and systematic review. Neurosci. Biobehav. Rev. 108, 498–525.

Ding, X., Zhang, S., Huang, W., Zhang, S., Zhang, L., Hu, J., Li, J., Ge, Q., Wang, Y., Ye, X., Zhang, J., 2022. Comparative efficacy of non-invasive brain stimulation for post-stroke aphasia: A network meta-analysis and meta-regression of moderators. Neurosci. Biobehav. Rev. 140, 104804.

Drevon, D., Fursa, S.R., Malcolm, A.L., 2017. Intercoder Reliability and Validity of WebPlotDigitizer in Extracting Graphed Data. Behav. Modif. 41, 323–339.

Grossman, M., 2014. Anomia. In: Aminoff, M.J., Daroff, R.B. (Eds.), in Encyclopedia of the Neurological Sciences (Second Edition). Academic Press, Oxford, pp. 194–197. https://doi.org/10.1016/B978-0-12-385157-4.00468-1.

Harrer, M., Cuijpers, P., Furukawa, T., Ebert, D.D., 2019. dmetar: Companion R Package For The Guide 'Doing Meta-Analysis in R'. R. Package Version 0. 1. 0. ⟨http://dmetar.protectlab.org/⟩ (URL).

Harris, A.D., Wang, Z., Ficek, B., Webster, K., Edden, R.A., Tsapkini, K., 2019. Reductions in GABA following a tDCS-language intervention for primary progressive aphasia. Neurobiol. Aging 79, 75–82.

Higgins, J.P.T., Thomas, J., Chandler, J., Cumpston, M., Li, T., Page, M.J., Welch, V.A., 2023. editors). Cochrane Handbook for Systematic Reviews of Interventions. Cochrane.

Hillis, A.E., Caramazza, A., 1991. Category-specific naming and comprehension impairment: a double dissociation. Brain J. Neurol. 114 (Pt 5), 2081–2094.

Hopkins, Johns, 2023. tDCS Intervention in Primary Progressive Aphasia. Clin. Gov. ⟨https://clinicaltrials.gov/show/NCT02606422⟩.

Hylands-White, N., Duarte, R.V., Raphael, J.H., 2017. An overview of treatment approaches for chronic pain management. Rheumatol. Int. 37, 29–42.

Kertesz, A., 2022. The Western Aphasia Battery: a systematic review of research and clinical applications. Aphasiology 36, 21–50.

Kiymaz, T., Khan Suheb, M.Z., Lui, F., De Jesus, O., 2024. Treasure Island (FL). Primary Progressive Aphasia. in StatPearls. StatPearls Publishing.

Lorca-Puls, D.L., Gajardo-Vidal, A., Mandelli, M.L., Illán-Gala, I., Ezzes, Z., Wauters, L.D., Battistella, G., Bogley, R., Ratnasiri, B., Licata, A.E., Battista, P., García, A.M., Tee, B. L., Lukic, S., Boxer, A.L., Rosen, H.J., Seeley, W.W., Grinberg, L.T., Spina, S., Miller, B.L., Miller, Z.A., Henry, M.L., Dronkers, N.F., Gorno-Tempini, M.L., 2024. Neural basis of speech and grammar symptoms in non-fluent variant primary progressive aphasia spectrum. Brain 147, 607–626.

Manouilidou, C., Nerantzini, M., 2020. Treatment and Intervention Approaches for the Improvement of Language Abilities in Neurodegenerative Diseases. In: Argyropoulos, G.P.D. (Ed.), Translational Neuroscience of Speech and Language Disorders. Springer International Publishing, Cham, pp. 21–46. https://doi.org/10.1007/978-3-030-35687-3_3.

Marshall, C.R., Hardy, C., Volkmer, A., Russell, L.L., Bond, R.L., Fletcher, P.D., Clark, C. N., Mummery, C.J., Schott, J.M., Rossor, M.N., Fox, N.C., Crutch, S.J., Rohrer, J.D., Warren, J.D., 2018. Primary progressive aphasia: a clinical approach. J. Neurol. 265, 1474–1490.

Miller, N., Willmes, K., De Bleser, R., 2000. The psychometric properties of the English language version of the Aachen Aphasia Test (EAAT). Aphasiology 14, 683–722.

Neophytou, K., Williamson, K., Herrmann, O., Afthinos, A., Gallegos, J., Martin, N., Tippett, D.C., Tsapkini, K., 2024. Home-Based Transcranial Direct Current Stimulation in Primary Progressive Aphasia: A Pilot Study. Brain Sci. 14, 391.

Nissim, N.R., Moberg, P.J., Hamilton, R.H., 2020. Efficacy of Noninvasive Brain Stimulation (tDCS or TMS) Paired with Language Therapy in the Treatment of Primary Progressive Aphasia: An Exploratory Meta-Analysis. Brain Sci. 10.

Nissim, N.R., Moberg, P.J., Hamilton, R.H., 2020. Efficacy of Noninvasive Brain Stimulation (tDCS or TMS) Paired with Language Therapy in the Treatment of Primary Progressive Aphasia: An Exploratory Meta-Analysis. Brain Sci. 10.

OpenAI. (2025). ChatGPT (March 16 version) [Large language model]. ⟨https://chat.openai.com/chat⟩.

Ouzzani, M., Hammady, H., Fedorowicz, Z., Elmagarmid, A., 2016. Rayyan—a web and mobile app for systematic reviews. Syst. Rev. 5, 210.

Perez-Martinez, V., Zorzo, C., Mendez, M., 2023. Differential approach to stroke aphasia and primary progressive aphasia using transcranial magnetic stimulation: A systematic review. Acta Neurobiol. Exp. (Warsz.) 83, 280–298.

Piguet, O., 2022. Younger-Onset Dementias: Behavioral Neurology/Brain Diseases/Healthy & Pathological Aging. In: Sala, S.D. (Ed.), in Encyclopedia of Behavioral Neuroscience, 2nd edition (Second Edition). Elsevier, Oxford, pp. 88–96. https://doi.org/10.1016/B978-0-12-819641-0.00004-9.

R Core Team (2024). _R: A Language and Environment for Statistical Computing_. R Foundation for Statistical Computing, Vienna, Austria. <⟨https://www.R-project.org/⟩>.

Rohatgi, A.WebPlotDigitizer.

Roheger, M., Riemann, S., Brauer, A., McGowan, E., Grittner, U., Flöel, A., Meinzer, M., 2024. Non-pharmacological interventions for improving language and communication in people with primary progressive aphasia. Cochrane Database Syst. Rev. https://doi.org/10.1002/14651858.CD015067.pub2.

Roncero, C., Kniefel, H., Service, E., Thiel, A., Probst, S., Chertkow, H., 2017. Inferior parietal transcranial direct current stimulation with training improves cognition in anomic Alzheimer's disease and frontotemporal dementia. Alzheimers Dement. Transl. Res. Clin. Inter. 3, 247–253.

Roncero, C., Service, E., De Caro, M., Popov, A., Thiel, A., Probst, S., Chertkow, H., 2019. Maximizing the Treatment Benefit of tDCS in Neurodegenerative Anomia. Front. Neurosci. 13, 1231.

Roth, C., 2011. American Speech-Language-Hearing Association Functional Assessment of Communication Skills for Adults. In: Kreutzer, J.S., DeLuca, J., Caplan, B. (Eds.), in Encyclopedia of Clinical Neuropsychology. Springer, New York, NY, pp. 139–141. https://doi.org/10.1007/978-0-387-79948-3_854.

Roytman, M., Chiang, G.C., Gordon, M.L., Franceschi, A.M., 2022. Multimodality Imaging in Primary Progressive Aphasia. Am. J. Neuroradiol. 43, 1230–1243.

Sanches, C., Stengel, C., Godard, J., Mertz, J., Teichmann, M., Migliaccio, R., Valero-Cabré, A., 2020. Past, Present, and Future of Non-invasive Brain Stimulation Approaches to Treat Cognitive Impairment in Neurodegenerative Diseases: Time for a Comprehensive Critical Review. Front. Aging Neurosci. 12, 578339.

Shehjar, F., Maktabi, B., Rahman, Z.A., Bahader, G.A., James, A.W., Naqvi, A., Mahajan, R., Shah, Z.A., 2023. Stroke: Molecular mechanisms and therapies: Update on recent developments. Neurochem. Int. 162, 105458.

Sheppard, S.M., 2023. Rehabil. Decelerating Lang. Loss Prim. Progress. Aphasia tDCS Lang. Ther. ⟨https://clinicaltrials.gov/study/NCT03728582⟩.

Spinelli, E.G., Mandelli, M.L., Miller, Z.A., Santos-Santos, M.A., Wilson, S.M., Agosta, F., Grinberg, L.T., Huang, E.J., Trojanowski, J.Q., Meyer, M., Henry, M.L., Comi, G., Rabinovici, G., Rosen, H.J., Filippi, M., Miller, B.L., Seeley, W.W., Gorno-Tempini, M.L., 2017. Typical and atypical pathology in primary progressive aphasia variants. Ann. Neurol. 81, 430–443.

Spreen, O., Risser, A.H., 1998. Assessment of Aphasia. In: Taylor Sarno, M. (Ed.), in Acquired Aphasia (Third Edition), 4. Academic Press, San Diego, pp. 71–156. https://doi.org/10.1016/B978-012619322-0/50007-5.

Sterne, J.A.C., Savović, J., Page, M.J., Elbers, R.G., Blencowe, N.S., Boutron, I., Cates, C. J., Cheng, H.-Y., Corbett, M.S., Eldridge, S.M., Hernán, M.A., Hopewell, S., Hróbjartsson, A., Junqueira, D.R., Jüni, P., Kirkham, J.J., Lasserson, T., Li, T., McAleenan, A., Reeves, B.C., Shepperd, S., Shrier, I., Stewart, L.A., Tilling, K., White, I.R., Whiting, P.F., Higgins, J.P.T., 2019. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 366, l4898.

Thijs, R.D., Surges, R., O'Brien, T.J., Sander, J.W., 2019. Epilepsy in adults. Lancet 393, 689–701.

Tippett, D.C., Hillis, A.E., Tsapkini, K., 2015. Treatment of Primary Progressive Aphasia. Curr. Treat. Options Neurol. 17, 34.

Vehtari, A., Gelman, A., Gabry, J., 2017. Practical Bayesian model evaluation using leave-one-out cross-validation and WAIC. Stat. Comput. 27, 1413–1432.

Viechtbauer, W., 2010. Conducting Meta-Analyses in *R* with the **metafor** Package. J. Stat. Softw. 36.

Volkmer, A., Rogalski, E., Henry, M., Taylor-Rubin, C., Ruggero, L., Khayum, R., Kindell, J., Gorno-Tempini, M.L., Warren, J.D., Rohrer, J.D., 2020. Speech and language therapy approaches to managing primary progressive aphasia. Pract. Neurol. 20, 154–161.

Wang, Z., Ficek, B.N., Webster, K.T., Herrmann, O., Frangakis, C.E., Desmond, J.E., Onyike, C.U., Caffo, B., Hillis, A.E., Tsapkini, K., 2023. Specificity in Generalization Effects of Transcranial Direct Current Stimulation Over the Left Inferior Frontal Gyrus in Primary Progressive Aphasia. Neuromodulation J. Int. Neuromodulation Soc. 26, 850–860.

Wauters, L.D., et al., 2023. Behavioral Treatment for Speech and Language in Primary Progressive Aphasia and Primary Progressive Apraxia of Speech: A Systematic Review. Neuropsychol. Rev. https://doi.org/10.1007/s11065-023-09607-1.

Wickham H., Bryan J. (2023). readxl: Read Excel Files. https://readxl.tidyverse.org, ⟨https://github.com/tidyverse/readxl⟩.