Non-invasive Brain Stimulation Can Reduce Unilateral Spatial Neglect after Stroke: ELETRON Trial

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Objective: Rehabilitation top-down techniques based on brain stimulation present variable outcomes in unilateral spatial neglect (USN) after stroke. This study aimed to examine the effects of physical therapy after anodal and cathodal transcranial direct current stimulation (A-tDCS and C-tDCS, respectively) to improve visuospatial and functional impairments in individuals with USN after stroke.

Methods: This double-blinded, pilot randomized clinical trial enrolled patients with USN after ischemic stroke. Randomization was stratified according to the Behavior Inattention Test–Conventional (BIT-C) and Catherine Bergego Scale (CBS). Outpatient physical therapy was conducted for 7.5 weeks after 20 minutes of tDCS. The primary outcome was the USN degree evaluated by the BIT-C. Secondary outcomes were the difference in CBS score, stroke severity (National Institutes of Health Stroke Scale [NIHSS]), disability (modified Rankin Scale), autonomy (Barthel Index, Functional Independence Measure), and quality of life (EuroQol Group 5-Dimension Self-Report Questionnaire). Outcomes were analyzed using an analysis of covariance model corrected by age, baseline NIHSS, and baseline BIT-C. Pairwise post hoc comparisons were performed using Bonferroni correction.

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Results: In the primary outcomes, A-tDCS led to greater improvement in BIT-C after intervention (mean difference [MD] = 18.4, 95% confidence interval [CI] = 3.9–32.8, $p = 0.008$) compared to sham. However, no significant differences were observed between A-tDCS and C-tDCS (MD = 13.9, 95% CI = −0.3 to 28.1, $p = 0.057$), or C-tDCS and sham (MD = 4.5, 95% CI = −9.7 to 18.8, $p = 0.99$). There were no significant differences between groups in terms of secondary outcomes.

Interpretation: A-tDCS associated with physical therapy can decrease the severity of USN after stroke. However, these preliminary findings must be confirmed by collecting additional evidence in a larger phase 3 trial.

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Unilateral spatial neglect (USN) consists of an exaggerated spatial asymmetry in processing information in bodily and/or extrabodily space due to a cerebral lesion, which cannot be explained by primary motor or sensory deficits.[1] USN occurs in approximately 50% of individuals after right hemisphere stroke, and may persist in 75% of cases in the chronic phase,[2] leading to poor functional outcome[3] and low quality of life.[4] Some evidence suggests that top-down and bottom-up USN treatment can help effectively improve spatial attention and alleviate right-hemisphere bias after stroke.[5] However, even with therapy, studies on functional outcomes have often revealed contradictory results.[5,6]

The predominance of USN after right-hemisphere stroke is in accordance with the "attention hypothesis," which postulates an asymmetrical distribution of brain activity when orienting attention.[7] Kinsbourne proposed that allocation of spatial attention is balanced by mutual transcallosal inhibition, resulting in a competition of the hemispheres to direct attention to the contralateral side.[8] A lesion-induced imbalance within this competitive attentional network accordingly leads to hypoactivity of the lesioned hemisphere and hyperactivity of the intact hemisphere. Converging evidence points to the potential of noninvasive brain stimulation to restore interhemispheric balance and ameliorate USN symptoms.[9]

The American Heart Association guidelines suggest that the use of adjunctive transcranial direct current stimulation (tDCS) with rehabilitation techniques can improve USN symptoms; however, this has only been supported by low-quality evidence.[10] tDCS is a noninvasive method that involves sending an electrical current to induce polarity-specific excitability changes in the human brain.[11] Although the specific neural mechanism underlying tDCS modulation is only partly understood, anodal tDCS (A-tDCS) has been shown to generally increase cortical activity, and cathodal tDCS (C-tDCS) usually has the opposite effect.[12,13]

Most neglect studies conducted so far have been small, single-center trials.[10] In a recent meta-analysis, using the results of one study, the authors concluded that A-tDCS and C-tDCS were not superior to sham when treating USN after stroke.[14] However, their clinical trial used a single session of tDCS, and there was no add-on rehabilitation intervention.[11,14] In contrast, other studies showed improvement in neglect symptoms following A-tDCS and C-tDCS, indicating that both techniques could induce neuronal changes in the parietal cortex and add rehabilitation benefits.[12,15] In addition, there are no reports of head-to-head clinical trials comparing A-tDCS and C-tDCS with sham combined with physical therapy in patients with USN after stroke.

We conducted a double-blind, pilot randomized clinical trial to test the effect of physical therapy after A-tDCS or C-tDCS on USN degree and functionality in patients with USN in the subacute phase of stroke. The alternative hypothesis was that A-tDCS was beneficial compared to C-tDCS and sham tDCS (S-tDCS), and the null hypothesis was that A-tDCS was not beneficial compared to C-tDCS and S-tDCS.

Patients and Methods

Trial Design and Oversight

This was a pilot, multicenter, prospective, randomized, double-blind, controlled trial conducted in Brazil, with a blinded central evaluation of outcomes in patients with stroke. Patients were assigned in a 1:1:1 ratio to be treated with A-tDCS, C-tDCS, or sham tDCS in subacute stroke phase (>7 days to <6 months after stroke onset). The trial protocol was approved by the National Regulatory Agency in Research and the institutional review board of each participating site (Botucatu Medical School, 41171315.8.0000.5411; Ribeirao Preto Medical School, 41171315.8.2001.5440;, University of São Paulo, 41171315.8.2002.0068; Toronto Western Hospital, 41171315.8.1001.5411). The enrolled patients or their surrogates provided written informed consent.

The trial was designed and conducted by a steering committee composed of independent academic investigators and statisticians. An independent data and safety monitoring board monitored the trial. An independent clinical events committee adjudicated safety outcomes, procedure-related complications, and serious adverse events.

The trial was registered in the Brazilian Registry of Clinical Trials (ReBEC; RBR-78jvzx) and funded by the Brazilian National Council for Scientific and Technological Development and the São Paulo Research Foundation. The trial sponsor and commercial entities were not involved in the design or conduct of the trial or writing of the manuscript. Information on the inclusion and exclusion criteria, interventions, and assessments has been published previously.[16]

Trial Sites

The patients were enrolled at 3 sites and randomly assigned to 1 of the 3 groups, namely, A-tDCS, C-tDCS, and S-tDCS. The trial sites were certified stroke centers within the Brazilian universal public health care system. Safety was monitored by an investigator from Toronto Western Hospital. Participating sites with no previous experience of tDCS treatments were also required to perform at least an additional 3 to 5 procedures in the roll-in phase of the trial. Data from patients who had undergone tDCS during the open-label roll-in phase trial were not included in the primary analyses of the trial results.

Sample Size

During the study design, there were no published estimates of the magnitude of differences between A-tDCS, C-tDCS, and S-tDCS in the target trial population. Thus, a sample size of 15 patients per group was estimated assuming type I and II error probabilities of 0.05 and 0.20, respectively, normal distribution for the outcomes. No studies have reported the responsiveness of the Behavior Inattention Test–Conventional (BIT-C) in patients with stroke. Therefore, the sample size calculation was based on an estimated reduction of 15% in the line cancelation tasks (subtest of BIT-C) after A-tDCS,[12] and a variation coefficient of 20% based on implemented computer simulations.

Patients

Patients were eligible for inclusion in the trial if they were aged at least 18 years and had suffered USN after ischemic stroke diagnosis within 6 months of the onset of stroke symptoms (subacute phase). Ischemic stroke was confirmed using computed tomography or magnetic resonance imaging, and USN was objectively diagnosed using BIT-C with a cutoff value of <129. The BIT-C is the gold standard scale that helps identify USN by assessing the tasks of drawing and copying figures and tests of line bisection. The BIT-C scale contains 6 conventional subtests (line cancelation, letter cancelation, star cancelation, line bisection, copying figures and forms, and figure representation tasks). The maximum score was set at 146, and a score of 129 was considered the cutoff point for USN. There was no time limit for completing the tests.[17] The USN diagnosis was performed during the screening period.

Individuals were excluded if they had suffered a hemorrhagic stroke, metal-in-cranium injuries near the electrode placement area, intracerebral vascular clips or any other electrically sensitive support system, clinical instability, epilepsy, severe cognitive impairment, bilateral lesions, global aphasia, previous visual disturbances, pregnancy, or other neurological diseases.

Assignment of Interventions: Allocation

Randomization was performed using a real-time, dynamic, Internet-based, randomized minimization procedure to balance the numbers of patients across the 3 groups (block of 3) with respect to age, baseline National Institutes of Health Stroke Scale (NIHSS) score, use or nonuse of intravenous alteplase, baseline BIT-C score, and participating center. After the baseline assessment, a second research assistant opened consecutively numbered, randomly ordered, opaque envelopes containing the group allocation results.

Assignment of Interventions: Blinding

Outcomes were assessed by a therapist blinded to the treatment allocation results and study hypothesis, who conducted a detailed assessment of the participants' conditions for the training program.

Treatments

The individuals were instructed to refrain from vigorous activities, ingestion of beverages containing caffeine or alcohol, and tobacco usage for 24 hours prior to each session. They were then seated in a room with minimal external influences (such as noise, lamps, or electromagnetic waves).

A direct current was delivered by a battery-powered device (DC-Stimulator Plus model, NeuroConn, neuroCare Group, Munich, Germany) using 2 pairs of surface saline-soaked sponge electrodes (5cm × 5cm). Each side of the sponge was soaked in saline solution. For a 25cm^2 sponge, approximately 6ml of solution per side was used (12ml per sponge). The study mode was designed to encode the sham and active stimulation attempts using 5-digit codes. Only the study manager could change the parameters as long as the study mode was enabled.

The participants had 2 electrodes placed in all 3 stimulation modes. The location was determined using the International 10/20 Electroencephalogram System.[18] The locations of the electrodes in each mode are shown in Figure 1. For A-tDCS, the anode was placed over P4, and the cathode was placed over the left supraorbital area (Fp1). For C-tDCS, the cathode was placed over P3, and

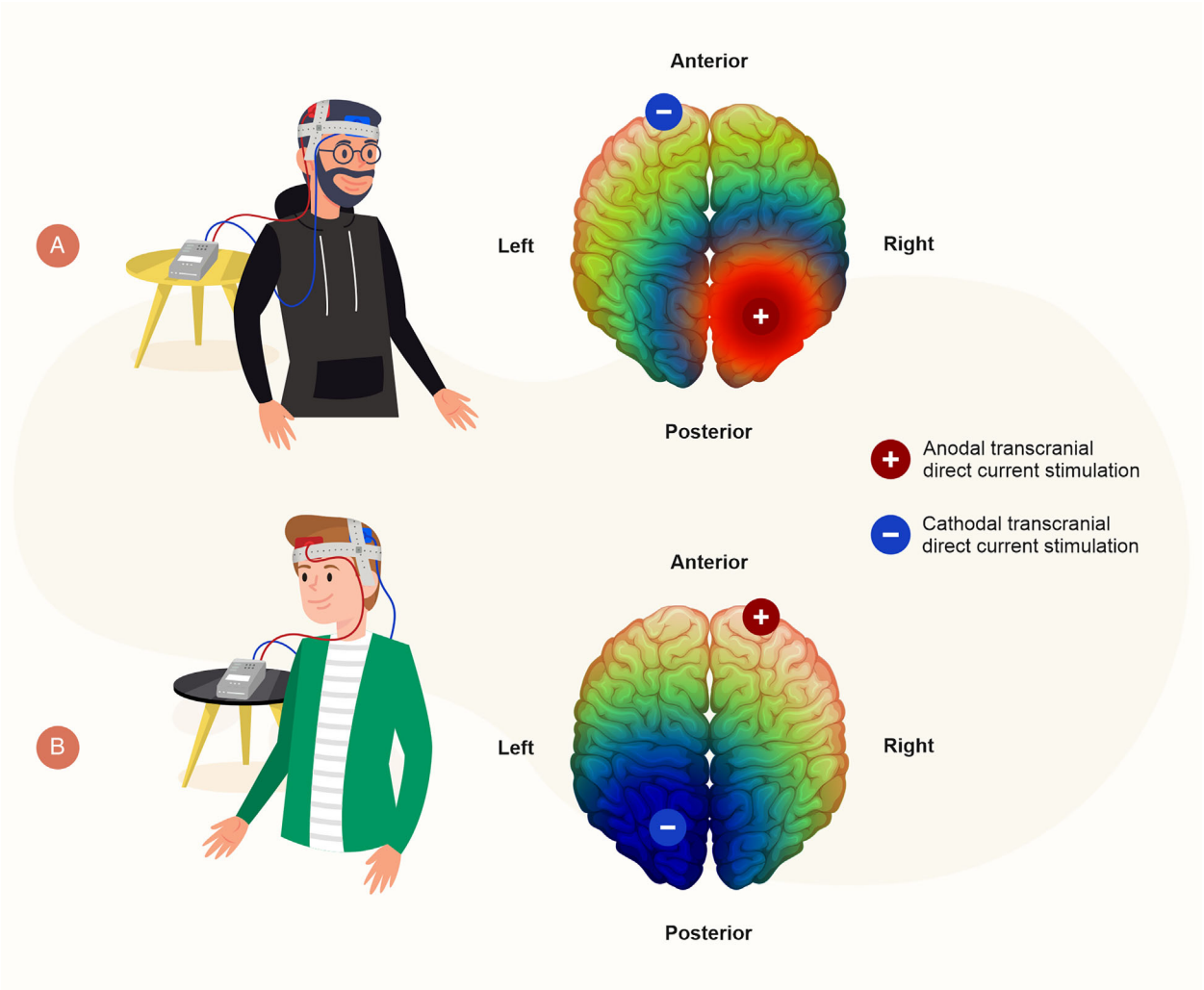

FIGURE 1: Brain stimulation using transcranial direct current stimulation (tDCS) protocol. The red scale represents an increase in cortical excitability, and the blue color represents a decrease in cortical excitability. (A) Anodal tDCS; the anode (+) was placed over P4, and the cathode (−) was placed over the left supraorbital area. (B) Cathodal tDCS; the cathode (−) was placed over P3, and the anode (+) was placed over the right supraorbital area. [Color figure can be viewed at www.annalsofneurology.org]

the anode was placed over the right supraorbital area (Fp2). A constant current of 1mA was delivered for real stimulation for 20 minutes. Sparing et al showed that 1mA applied over parietal posterior cortex (PPC) can be used to bidirectionally modulate visuospatial task performance in healthy individuals and patients with neglect according to the concept of hemispheric rivalry.[13] This was maintained for 20 minutes before being ramped down linearly for 30 seconds, maintaining a resistance of <10kΩ. For the sham condition, the stimulator was turned on, and the current intensity was gradually increased for 30 seconds and tapered off over 30 seconds. The researcher who applied tDCS did not participate in the other steps of the study.

Brain stimulation was applied for 15 sessions, 2 times per week, for 7.5 weeks. All participants received 1 hour of physical therapy immediately after tDCS protocol. The physical therapy intervention consisted of visual scanning exercises and trunk rotation integrated with task-specific activities, including mobility, strength, and body perception exercises adjusted by the functional status (Appendix 1). None of the participants was exposed to other interventions during the trial. In the last session, all participants gave their opinion about whether they received real or placebo (sham) stimulation.

Variables

All patients' information and potential confounding variables are shown in Appendix 2.

Outcomes

The primary outcome was the USN degree evaluated by the difference between baseline (D1) and postintervention session (D15) values of the BIT-C.

Secondary outcomes were the impact of USN in activities of daily life measures by Catherine Bergego Scale (CBS). The objective of this scale is to measure the extent to which USN interferes with day-to-day tasks. The scale assesses performance in terms of 10 activities, each scored from 0 to 3. The maximum score on the scale is 30, which indicates a severe degree of USN impact on functionality.[19] Stroke severity was evaluated by NIHSS (score range from 0 to 42, with higher values indicating worse stroke severity).[20] Dependency level was based on the modified Rankin Scale (mRS; score range from 0 to 6, with higher values indicating worse dependency level).[20] Autonomy level was based on the Barthel Index (BI; score range from 0 to 100, with higher values indicating better autonomy)[20] and Functional Independence Measure (FIM, on which scores range from 0 to 42, with higher values indicating better functional independence).[21] Quality of life was measured by the EuroQol Group 5-Dimension Self-Report Questionnaire, on which scores range from 0 to 15, with higher values indicating a better quality of life.[22] All secondary outcomes were also measured from the difference between baseline (D1) and postintervention (D15) values.

Safety outcomes included the percentage of any adverse effects reported during the study period using the safety questionnaire proposed by Brunoni et al.[23]

Study Protocol and the Statistical Analysis Plan

The study protocol and statistical analysis plan have been published previously.[16] The study protocol was published in 2016 and required adjustments due to local barriers. The protocol had to undergo methodological changes and required the inclusion of new research centers (multicenter trial). The statistical analysis was updated and aligned with the clinical trial registry.

Statistical Analysis

Statistical analysis was performed using complete case analysis, also known as listwise deletion. Only the datasets with no missing values on any variables were included in the analysis. Analysis of variance with fixed effects or Kruskal–Wallis test was used for numerical variables, and chi-squared or Fisher exact test were used for categorical variables to identify statistical differences in baseline values between groups. Outcomes were analyzed using analysis of covariance (ANCOVA). The covariates age, baseline NIHSS, and baseline BIT-C were included in the ANCOVA model. The goodness of fit was evaluated through the normality of ordinary residuals and homoscedasticity using Levene test. Pairwise post hoc comparisons were performed using Bonferroni correction. Statistical significance was set at $p < 0.05$. All statistical analyses were performed using SPSS Statistics for Windows/Macintosh, version 24.0 (IBM, Armonk, NY).

Results

Characteristics of the Patients

Figure 2 shows the flow of the participants throughout the study period. Enrollment of individuals began in April 2017 and was completed in June 2020. Analyses began in July 2020. A total of 3 sites enrolled 63 patients, including 12 who had undergone tDCS during the open-label roll-in phase (not included in outcome analyses) and 51 who had undergone randomization to 1 of the 3 treatment groups (16 in the A-tDCS group, 18 in the C-tDCS group, and 17 in the sham group). A total of 46 patients completed all sessions of stimulation. All participants believed that they received stimulation during all sessions. The frequency per person (time) and total amount per person (minutes) of physical therapy intervention were the same in the 3 groups.

Participants had a median (range) age of 64.5 (35.0–84.0) years. There were 26 women (56.5%) and 20 non-Hispanic white individuals (43.5%). The median NIHSS score at hospital discharge was 5 in both intervention groups (A-tDCS and C-tDCS), and 2 patients in each group received intravenous alteplase. The baseline characteristics were similar among the 3 groups (File S3). BIT-C and CBS at baseline were included in the statistical analysis to calculate the evolution rate.

Outcomes

The analysis of the primary and secondary outcomes between the groups is shown in Table 1.

Primary Outcome

There was a significant difference between groups on the BIT-C ($F_{2,46} = 5.48$, $p = 0.007$) before and after intervention. Post hoc analyses showed significant differences in scores in the A-tDCS group when compared to the sham group (mean difference [MD] = 18.4, 95% CI = 3.9–32.8, $p = 0.008$); however, no significant differences were observed when A-tDCS and C-tDCS were compared (MD = 13.9, 95% CI = −0.3 to 28.1, $p = 0.057$), or when C-tDCS and sham were compared (MD = 4.5, 95% CI = −9.7 to 18.8, $p = 0.99$; Fig 3).

Secondary Outcomes

There was no significant difference between groups on the CBS ($F_{2,46} = 0.28$, $p = 0.756$). Post hoc analyses showed no significant differences in CBS scores in the A-tDCS group compared to the sham group (MD = 0.06, 95% CI = −4.5 to 4.6, $p = 0.99$), in the A-tDCS compared to the C-tDCS group (MD = 0.7, 95% CI = −3.8 to 5.2, $p = 0.91$), or in the C-tDCS

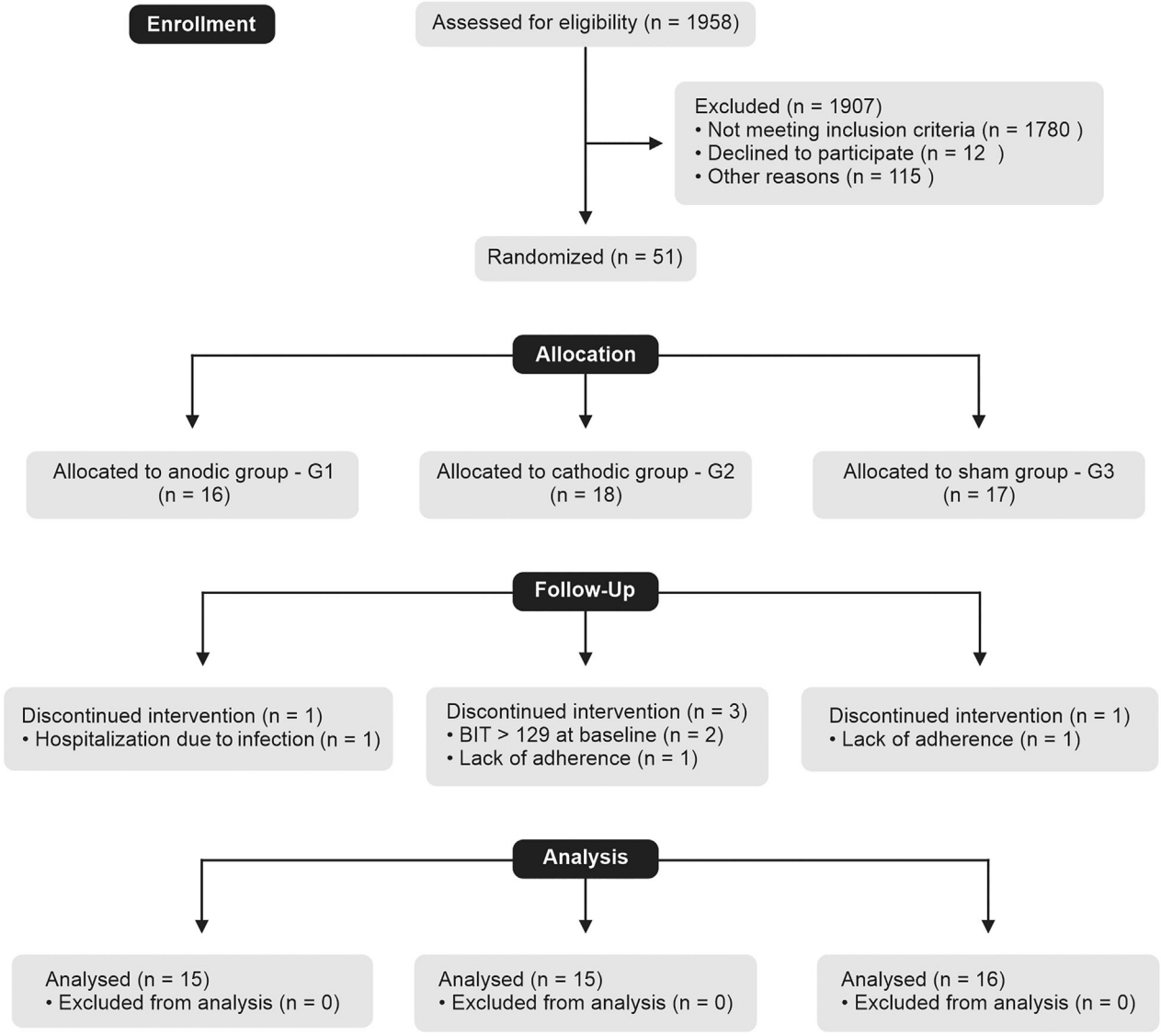

FIGURE 2: CONSORT (Consolidated Standards of Reporting Trials) flow diagram. BIT = Behavior Inattention Test.

compared to the sham group (MD = 0.6, 95% CI = −3.8 to 5.2, $p = 0.93$).

There was no significant difference between groups on the NIHSS ($F_{2,46} = 0.18$, $p = 0.302$). Post hoc analyses showed no significant differences in NIHSS scores in the A-tDCS group when compared to the sham group (MD = 0.7, 95% CI = −0.8 to 2.2, $p = 0.54$), in the A-tDCS compared to the C-tDCS group (MD = 0.7, 95% CI = −0.8 to 2.2, $p = 0.54$), or in the C-tDCS compared to the sham group (MD = 0.0, 95% CI = −1.5 to 1.5, $p = 0.99$).

There was no significant difference between groups on the mRS ($F_{2,46} = 0.12$, $p = 0.663$). Post hoc analyses showed no significant differences in mRS scores in the A-tDCS group when compared to the sham group (MD = 0.1, 95% CI = −0.5 to 0.8, $p = 0.86$), in the A-tDCS compared to the C-tDCS group (MD = 0.07, 95% CI = −0.6 to 0.7, $p = 0.96$), or in the C-tDCS compared to the sham group (MD = −0.7, 95% CI = −0.7 to 0.6, $p = 0.96$).

There was no significant difference between groups on the BI ($F_{2,46} = 0.20$, $p = 0.617$). Post hoc analyses showed no significant differences in BI scores in the A-tDCS group when compared to the sham group (MD = −5.3, 95% CI = −20.8 to 10.2, $p = 0.68$), in the A-tDCS compared to the C-tDCS group (MD = −4.3, 95% CI = −19.8 to 11.2, $p = 0.77$), or in the C-tDCS compared to the sham group (MD = 1.0, 95% CI = −14.5 to 16.5, $p = 0.98$).

There was no significant difference between groups on the FIM ($F_{2,46} = 0.14$, $p = 0.866$). Post hoc analyses showed no significant differences in FIM scores in the A-

TABLE 1. Outcomes between Different Groups

Outcomes (comparison)	MD	95% CI	*p*
BIT-C			
A-tDCS × sham	18.4	3.9 to 32.8	0.008
C-tDCS × sham	13.9	−0.3 to 28.1	0.057
A-tDCS × C-tDCS	4.5	−9.7 to 18.8	0.99
CBS			
A-tDCS × sham	0.06	−4.5 to 4.6	0.99
C-tDCS × sham	0.7	−3.8 to 5.2	0.91
A-tDCS × C-tDCS	0.6	−3.8 to 5.2	0.93
NIHSS			
A-tDCS × sham	0.7	−0.8 to 2.2	0.54
C-tDCS × sham	0.7	−0.8 to 2.2	0.54
A-tDCS × C-tDCS	0.0	−1.5 to 1.5	0.99
mRS			
A-tDCS × sham	0.1	−0.5 to 0.8	0.86
C-tDCS × sham	0.07	−0.6 to 0.7	0.96
A-tDCS × C-tDCS	−0.7	−0.7 to 0.6	0.96
BI			
A-tDCS × sham	−5.3	−20.8 to 10.2	0.68
C-tDCS × sham	−4.3	−19.8 to 11.2	0.77
A-tDCS × C-tDCS	1.0	−14.5 to 16.5	0.98
FIM			
A-tDCS × sham	−4.0	−16.7 to 8.7	0.90
C-tDCS × sham	−2.2	−14.9 to 10.5	0.73
A-tDCS × C-tDCS	−1.8	−14.5 to 10.9	0.93
EuroQol			
A-tDCS × sham	0.7	−1.2 to 2.7	0.56
C-tDCS × sham	0.8	−1.1 to 5.2	0.91
A-tDCS × C-tDCS	0.07	−1.8 to 1.9	0.99

A-tDCS = anodal transcranial direct current stimulation; BI = Barthel Index; BIT-C = Behavioral Inattention Test–Conventional; CBS = Catherine Bergego Scale; CI = confidence interval; C-tDCS = cathodal transcranial direct current stimulation; EUROQOL = EuroQol Group 5-Dimension Self-Report Questionnaire; FIM = Functional Independence Measure; MD = mean difference; mRS = modified Rankin scale; NIHSS = National Institutes of Health Stroke Scale.

tDCS group when compared to the sham group (MD = −4.0, 95% CI = −16.7 to 8.7, $p = 0.90$), in the A-tDCS compared to the C-tDCS group (MD = −2.2, 95% CI = −14.9 to 10.5, $p = 0.73$), or in the C-tDCS compared to the sham group (MD = −1.8, 95% CI = −14.5 to 10.9, $p = 0.93$).

There was no significant difference between groups in terms of quality of life ($F_{2,46} = 0.46$, $p = 0.635$). Post

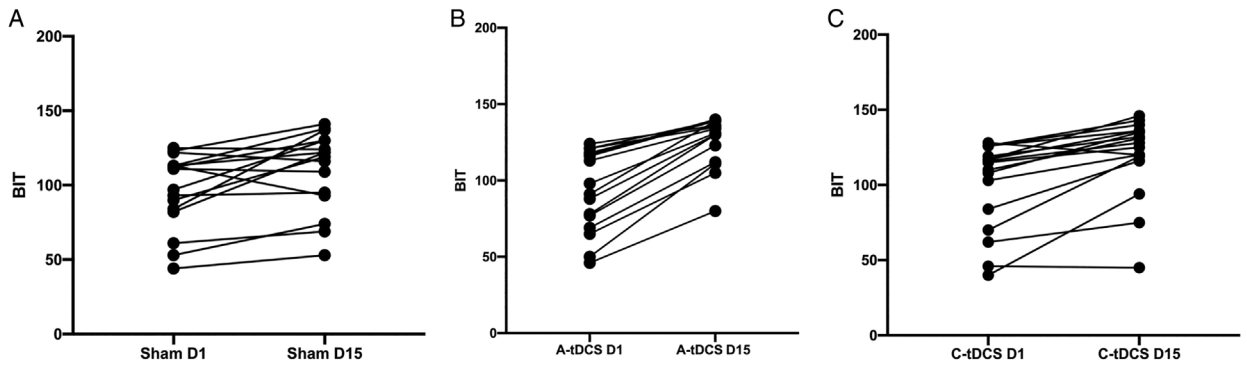

FIGURE 3: Individual values of Behavior Inattention Test–Conventional (BIT) for each group before and after brain stimulation. A-tDCS = anodal transcranial direct current stimulation; C-tDCS = cathodal transcranial direct current stimulation; D1 = before stimulation; D15 = after 15 sessions of brain stimulation. (A) Sham group. (B) A-tDCS group. (C) C-tDCS group. Significant difference occurred only between A-tDCS and sham treatment ($p = 0.008$).

TABLE 2. Safety: Main Related and Nonrelated Side Effects

Event	A-tDCS, n = 15	C-tDCS, n = 15	Sham, n = 16	*p*
Related events, n (%)				
Headache[a]	3 (20.0)	2 (13.3)	2 (12.5)	0.819
Redness at the electrode site[a]	0 (0.0)	1 (6.7)	0 (0.0)	0.347
Itch[a]	0 (0.0)	1 (6.7)	1 (6.2)	0.602
Nonrelated events, n (%)				
Lower limb pain[a]	0 (0.0)	0 (0.0)	1 (6.2)	0.383
Tremor[a]	0 (0.0)	1 (6.7)	0 (0.0)	0.347
Hypoglycemia[a]	1 (6.7)	0 (0.0)	0 (0.0)	0.347
Dizziness[a]	0 (0.0)	0 (0.0)	1 (6.2)	0.383

[a]Chi-squared test.
A-tDCS = anodal transcranial direct current stimulation; C-tDCS = cathodal transcranial direct current stimulation.

hoc analyses showed no significant differences in quality-of-life scores in the A-tDCS group when compared to the sham group (MD = 0.7, 95% CI = −1.2 to 2.7, $p = 0.56$), in the A-tDCS compared to the C-tDCS group (MD = 0.8, 95% CI = −1.1 to 5.2, $p = 0.91$), or in the C-tDCS compared to the sham group (MD = 0.07, 95% CI = −1.8 to 1.9, $p = 0.99$).

Safety

The main related and nonrelated adverse events are listed in Table 2. tDCS was considered a safe procedure for this trial. There was a low frequency of related side effects, and there was no difference between the groups in terms of the main side effects reported.

Discussion

This pilot trial compared the effects of A-tDCS over the right PPC and C-tDCS over the left PPC on the USN in stroke patients with sham stimulation. A-tDCS over the right parietal cortex applied before physical therapy can decrease the severity of USN assessed with the BIT-C. However, we observed no improvements in activities of daily life, stroke severity, dependency level, autonomy, functional independence, and quality of life. Both stimulation methods were found to be safe. Neuromodulation intervention add-on therapies for rehabilitation might increase the recovery speed or lead to greater recovery gains than sham treatment.

USN might be caused by a disturbance in the balance between the activities of both hemispheres following

stroke. It is, therefore, reasonable to suggest that visuospatial attention can be improved by rebalancing hemispheric activity using noninvasive transcranial brain stimulation. According to the hypothesis of imbalance in the interhemispheric inhibition, inhibition of the contralesional hemisphere or excitation of the ipsilesional hemisphere might ameliorate USN after stroke.[24–26] In our pilot study, A-tDCS over the right parietal cortex before physical therapy improved USN in patients who suffered a stroke. Recent pharmacological studies have suggested that the effects of A-tDCS are probably a result of polarity-specific shifts of the cell's resting membrane potential and an increase in N-methyl-D-aspartate receptor efficacy.[27,28] This type of change in the polarity of the membrane before a specific physiotherapeutic intervention is called the priming effect.[29]

The priming effect is the phenomenon by which the exposure of intervention strategy before or concomitant with another strategy improves neural activity before or during an intervention, and the neuromodulation techniques can influence the response of an intervention and the magnitude of its effect.[30] Some studies applied tDCS in patients with USN after stroke as an add-on treatment, during or before physical or occupational therapy.[26,31] Làvadas et al observed that tDCS combined with prism adaptation (specific USN treatment) induced greater neglect improvement in the A-tDCS group than the sham group.[26] Bang and Bong suggested that tDCS combined with feedback training (visual treatment) positively affects USN in patients with subacute stroke.[31] In our study, we observed an improvement in USN after A-tDCS combined with physical therapy intervention (an increase of 29% in the magnitude of the effect compared to the sham group). In this scenario, enhancing cortical excitability before physical therapy may translate into greater clinical benefits than those achieved with traditional therapies alone.

In this pilot trial, no significant effects on secondary measures were observed after A-tDCS or C-tDCS compared to sham. A recent systematic review shows that A-tDCS and C-tDCS might improve activities of daily living when applied in the subacute phase of the ischemic stroke.[32] Koo et al[33] showed that A-tDCS over the primary somatosensory cortex might be a useful adjuvant therapy for recovery after stroke. In contrast, Yi et al[15] observed that A-tDCS and C-tDCS could be a successful adjuvant therapeutic modality to recover neglect symptoms, but this recovery may not lead to improvements in functional independence. We believe that to observe changes in stroke severity (NIHSS), dependency level (mRS), autonomy (BI), functional independence (FIM), and quality of life, it is necessary to have specific training, as well as adequate intensity, repetition, and frequency. In addition, the selection of patients who best respond to tDCS therapy should be incorporated in a future trial through imaging or neurophysiological tests. Our study included more severe cases, and those with milder USN would be better candidates for brain stimulation.

There are some differences between the published study protocol and the clinical trial. In the published protocol, the plan was to deliver 3 sessions per week for 5 weeks.[16] However, in the trial, 2 sessions were delivered per week over 7.5 weeks. This adaptation was necessary because we observed a lack of adherence in some patients during treatment due to transportation difficulties and a lack of caregivers to take patients to sessions. In addition, a single-center trial was initially planned[16]; however, we need to include more centers to achieve the desired sample size.

This study had some limitations, including the small study population size. First, we could not compare the effects between patients with cortical, subcortical, or cortical–subcortical lesions due to the small number of subjects in these subgroups. Second, the exercise intensity was not controlled by specific scales. Third, we did not evaluate the long-term effects and self-efficacy of tDCS treatment. Fourth, the sham group consisted of only the right anodal sham group. Finally, there was no per-protocol or intent-to-treat analysis (sensitive analysis). Thus, further studies that address these limitations, including crossover design to overcome small sample sizes, online (during physical therapy) tDCS stimulation, location of the anode in the parietal cortex (or if it could be placed anywhere over the right hemisphere), and testing other tDCS dose groups (high doses should be better to improve functional outcomes). Moreover, biomarkers and neuroimaging tests are needed to understand the plasticity mechanisms in USN patients to help select the best candidates for neuromodulation interventions. Some authors reported that lesions in the superior longitudinal fasciculus might cause persistent USN, and the evaluation by diffusion tensor imaging studies can provide direct evidence of anatomical localization of brain function for a better response after brain stimulation.[34–36] However, no biomarkers have been validated in stroke patients with USN. Therefore, future efforts should compare optimal intervention strategies according to individual characteristics before larger and more comprehensive trials can be planned.

USN is associated with a longer length of hospital stay and decreased function after stroke.[37,38] Improvements in the USN facilitate recovery. As depicted by the results from the sham group, USN often improves spontaneously. It has been pointed out previously that most

rehabilitation trials to enhance neglect have been limited by small sample sizes and insufficient methodological quality. Anodal stimulation is a type of tDCS stimulation that can influence synaptic plasticity of the affected hemisphere, facilitating neural excitability and thereby enhancing the acquisition and consolidation of motor skills.[39]

In conclusion, our findings suggest that A-tDCS produced significant priming effects for physical therapy protocol, reducing USN in the subacute phase of stroke. The small sample size of this study should not be interpreted as clear evidence of efficacy for A-tDCS but as additional evidence that must be confirmed in a larger, adequately powered phase 3 trial.

Author Contributions

G.J.L., R.B., A.B.C., and H.R.d.C.N. contributed to the conception and design of the study; T.R.d.S., L.G.M., R.D.M.d.C., J.T.d.S., F.C.W., L.C.A.S., G.P.M., N.C.F., J.C.d.S.R., R.K., M.O.F., G.F.B., G.R.S.R., P.W.R., D.B.F., L.A., S.G.Z.B., L.E.G.B., L.C.d.O.A., V.M.P., T.E.G.S., and O.P.-N. contributed to the data acquisition and analysis of data; G.J.L., A.B.C., R.B., and T.R.d.S. contributed to drafting the text or preparing the figures.

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Potential Conflicts of Interest

Nothing to report.

Registration

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