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TOPICS IN STROKE REHABILITATION
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Role of tDCS plus virtual reality in enhancing cognitive function in patients with chronic stroke: a quasi-randomized clinical trial

R. De Luca[a], A. Gangemi[a], R. A. Fabio[b], M. G. Maggio[a], M. Bonanno[a], C. Rifici[a], D. Di Ciuccio[a], F. Corallo[a], C. Mento[b], M. R. A. Muscatello[b], A. Quartarone[a], and R. S. Calabro'[a]

[a]IRCCS Centro Neurolesi "Bonino-Pulejo", Messina, Italy; [b]Department of Biomedical, Dental and Morphological and Functional Imaging Sciences, University of Messina, Messina, Italy

ABSTRACT

Background: Alone or combined with other advanced rehabilitative treatments , non-invasive transcranial direct current stimulation (tDCS) is a promising tool to augment neuroplasticity as well as improve cognitive function post stroke.

Objective: To investigate the psychological and neurophysiological effects of tDCS application combined with cognitive virtual reality training (VRT) in patients with chronic ischemic stroke.

Material and methods: Twenty subjects were enrolled in this quasi-randomized pilot study and assigned to the experimental (EG) or control groups (CG). The EG received VRT combined with tDCS, while the CG received the VRT with sham-tDCS, five times a week for 4 weeks. Each patient was evaluated using a psychometric battery, including Mini Mental State Examination (MMSE), Hamilton Rating Scale (HRS-D), and Frontal Assessment Battery (FAB), at the beginning (T0) and the end (T1) of the study. Additionally, a neurophysiology technician measured the brain electrical activity through event-related potential P300.

Results: A significant improvement in MMSE scores from T0 to T1 was observed in the EG. A significant improvement in FAB scores was observed over time (i.e. at the intragroup analysis), with greater gains in the group receiving active tDCS. On the contrary, both groups showed a significant reduction in depressive symptoms scores over time. A key finding of the study was the enhancement of cognitive processing speed, as indicated by reduced P300 latency, in the EG.

Conclusions: This study suggests that tDCS may potentiate the effects of VR by promoting neuroplasticity and improving the efficiency of cognitive networks, ultimately contributing to better recovery outcomes in patients with stroke.

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Stroke; cognitive alterations; neurorehabilitation: tDCS; VRT; synergic approach

Introduction

Global epidemiological data indicate that approximately 16.9 million people suffer from stroke each year.[1,2] Stroke is the second most frequent cause of death worldwide, and is the most frequent cause of permanent disability, encompassing debilitating cognitive, language, motor, and psychological impairments, as well as behavioral changes, often including symptoms of anxiety and depression.[3] Post-stroke cognitive impairment (PSCI) is a common and potentially disabling consequence of stroke, with an incidence ranging from 20% to 80%.[4–6] The high prevalence of PSCI makes cognitive rehabilitation essential. Multimodal assessment of stroke impairments is fundamental to predict prognosis and functional recovery.[7] To this aim, the NIH stroke scale[7,8], Barthel index[9], FIM[10] and Rankin Scale[11] are commonly used in the current clinical practice, although they lack a specific assessment of cognitive function. Indeed, multidisciplinary and coordinated rehabilitation has a fundamental role in stimulating motor and cognitive recovery after stroke.[12] The conventional stroke rehabilitation principally includes physical therapy, occupational therapy, speech and cognitive treatments. Cognitive rehabilitation (CR) addresses skills in the cognitive domains of attention, memory, and executive functioning and how they impact functionality and safety.[13] However, only with standard methods in CR, using paper and pencil approach, in a standard setting, face to face with the therapist[14] many stroke survivors still have a residual disability

CONTACT R. De Luca rosaria.deluca@irccsme.it IRCCS Centro Neurolesi "Bonino-Pulejo", S.S. 113, Cda Casazza, Messina 98124, Italy

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which impairs their ability to perform activities of daily living, for an insufficient therapy dose, low engagement and motivation of the patient, or lack of objective feedback to achieve significant improvements in function. In fact, even with standard rehabilitation after stroke, the majority of stroke patients are disabled when they enter the chronic phase.[14] Many technology-based stroke cognitive rehabilitation treatments have been developed in the last few decades which have shown promising results in improving stroke patient's recovery, also in chronic phase.[15,16] The most important technological advances in stroke cognitive rehabilitation, including virtual and augmented reality, suggesting the potential effectiveness of a VR-based rehabilitation approach in promoting neuroplastic changes even in the chronic phase of stroke.[17–19] Moreover, several studies have demonstrated that noninvasive brain stimulation (NIBS) techniques such as transcranial direct current stimulation (tDCS) can induce brain plasticity and have beneficial effects in post-stroke cognitive recovery[20] to modulate synaptic plasticity in stroke.[21] Neuroimaging has demonstrated that the right and left dorsolateral prefrontal cortex (DLPFC) are involved in cognitive function. Then, stimulation of this area can improve cognition in patients with cognitive impairment.[22,23] Limited research has shown that simultaneous intervention of virtual reality (VRT) and tDCS could be a promising treatment for upper limb function, cognitive function, and executive function in stroke patients[24,25], producing a synergistic outcome, ultimately enhancing prognoses for stroke patients.[26–29] This emerging approach looks promising but still rather lacking in the cognitive rehabilitation field. In fact, today there is no robust consolidated evidence in current literature. We hypothesized that it is possible that by combining these two advanced approaches (VR and tDCS) a therapeutic effect could be achieved. As both therapeutic techniques activate the DLPFC, we believed that tDCS along with simultaneous cognitive VRT might specifically and better improve cognitive functioning in the ischemic stroke population in chronic phase. Our purpose is to investigate the psychometric and neurophysiological effects of tDCS combined to VRT in a cohort of patients with chronic ischemic stroke. 10] and Rankin Scale[11] are commonly used in the current clinical practice, although they lack a specific assessment of cognitive function. Indeed, multidisciplinary and coordinated rehabilitation, including physical and occupational therapy as well as speech and cognitive training, has a fundamental role in stimulating functional recovery after stroke.[12] Cognitive rehabilitation (CR) targets skills in the cognitive domains of attention, memory, and executive functioning, focusing on their impact on daily functionality and safety.[13] However, by using only standard CR methods, such as paper and pencil approach,[14] many stroke survivors still have a residual disability which impairs their ability to perform activities of daily living. This could be due to an insufficient therapy dose, low engagement and motivation of the patient, or lack of objective feedback to achieve significant improvements in function.

In the last few decades, many technology-based stroke CR treatments have been developed showing promising results in improving stroke patient's recovery, also in chronic phase.[15,16] The most important technological advances in stroke CR include virtual (VR) and augmented reality, given their potential effectiveness in promoting neuroplastic changes.[17–19] On the other hand, several studies have demonstrated that noninvasive brain stimulation (NIBS) techniques, such as transcranial direct current stimulation (tDCS), can boost brain plasticity and have beneficial effects in post-stroke cognitive recovery.[20,21] Neuroimaging has demonstrated that the right and left dorsolateral prefrontal cortex (DLPFC) are involved in cognitive function. Then, the stimulation of this area can improve cognition in patients with cognitive impairment.[22,23] Preliminary studies suggest that the simultaneous application of virtual reality training (VRT) and transcranial direct current stimulation (tDCS) may be a promising approach to improving motor and cognitive function in stroke patients[24,25], producing synergistic effects that could ultimately enhance patient outcomes.[26–29] This emerging approach appears promising but remains underexplored in the field of cognitive rehabilitation. Currently, no robust or consolidated evidence is available in the literature. The aim of this study is to evaluate whether the combination of tDCS and VRT, both applied over the DLPFC, can produce additive or synergistic benefits in patients with chronic ischemic stroke. Specifically, we seek to investigate whether this combined intervention improves cognitive functioning (with regard to

executive abilities), psychological outcomes (such as mood), and neurophysiological markers of cortical plasticity, beyond what could be achieved with either technique alone.

Material and methods

Study setting and participants

Twenty patients (mean ± SD age: 50.35 ± 9.59) affected by chronic-stage ischemic stroke and attending the Neurorehabilitation Unit of the IRCCS Centro Neurolesi "Bonino-Pulejo" (Messina, Italy) between March 2023 and April 2024 were enrolled in the study. They were divided into either experimental (EG: $n = 10$) or control (CG: $n = 10$) groups, with similar demographic and medical characteristics. Stroke patients were provided with adequate information about the study and offered the opportunity to participate with written consent.

The study adhered to the principles set forth in the Declaration of Helsinki on Human Rights, and the local Ethics Committee approved the study (ID: IRCCS-ME-23/2022). In detail, this pilot study is part of an umbrella registered protocol (NCT07066137) on the use of combined approaches to improve recovery and potentiate motor/cognitive function. This manuscript conforms to the CONSORT Guidelines, according to a completed checklist (see CONSORT 2010).

Eligibility criteria included diagnosis of first right ischemic stroke in the chronic phase, ≥6 months after the event, age range 18–65 years, absence of disabling sensory impairment (i.e. hearing and visual impairment), and moderate to severe disability (Rankin Scale score between 3 and 4). Exclusion criteria were intake of psychoactive drugs potentially interfering with the training, presence of neurological disorders other than the first ever ischemic stroke, inability to understand verbal delivery of a simple order (Token Test ≤ 4), presence of severe psychiatric symptoms such as psychotic disorders, schizophrenia or personality disorders or recurrent/active epilepsy.

Although a formal a priori power analysis was not conducted due to the pilot nature of the study, a post hoc estimate indicates that detecting a medium effect size ($f = 0.25$) in a 2 × 2 repeated-measures design (group × time) would require approximately 28 participants (14 per group) for 80% power at $\alpha = 0.05$. With the current sample ($n = 10$ per group), the estimated power is only ~5%, indicating that the study is underpowered for formal hypothesis testing. This pilot study focused on feasibility and preliminary effects, providing data to inform future larger trials.

Procedures

Twenty subjects were enrolled in this quasi-randomized double-blinded controlled study and assigned to the experimental (EG: $n = 10$) or control (CG: $n = 10$) groups. The assignment was based on the enrollment order, where the assessor remained unaware of the study group to which each participant had been assigned. The sample size was selected based on resource availability, and feasibility considerations within our clinical setting. Preliminary statistical power calculations were not necessary because of the pilot nature of the study.

In this pilot study, the EG received VRT combined with tDCS, referred to as VRT-Plus. The CG received the VRT with sham-tDCS, referred to as VRT alone. Then, also the patients were blinded to the experimental treatment.

Both groups received an intensive VRT in a dedicated setting, five times a week for 4 weeks (i.e. a total of 20 sessions), each VRT session lasting 40 min, whereas tDCS (lasting 20 min) was applied to both groups before the VRT. Then, the amount of the EG intervention was identical to the duration of the CG intervention. Each patient was evaluated by a psychiatric rehabilitation technician using an ad hoc multimodal assessment, employing psychometric battery at the beginning (T0) and the end (T1) of the study. Evaluations were performed by a clinician not involved in the study (i.e. the assessor was blinded to the patient's training type). Additionally, a neurophysiology technician measured brain electrical activity through event-related potential P300.

Psychometric evaluation

The Psychometric battery included the Mini Mental State Examination (MMSE), the Hamilton

Rating Scale for depression (HRS-D), and the Frontal Assessment Battery (FAB).

MMSE is a neuropsychological test used to examine global cognitive functioning by assessing seven domains: orientation in time and space, attention and computation, verbal registration, language, memory, and constructive application, according to specific scoring. Scores below 18 indicate significant cognitive impairment, scores between 18 and 24 indicate moderate to mild impairment, 25 is a borderline score, in fact scores between 26 and 30 indicate a nearly normal cognitive functioning.[30]

The HRS-D is a clinical instrument used to assess the presence or absence of depressive symptoms. It includes 21 items, 4 of which are specifically intended to subtype depression. The score ranges from 0 to 7 to indicate the absence of depression, up to a score above 23 indicating a very severe depressive condition.[31]

FAB is a brief executive function (EF) screening tool that takes approximately 5–10 min to administer and comprises six tasks evaluating different facets of EF: (1) concept formation and abstract reasoning (similarities); (2) mental flexibility (phonemic verbal fluency); (3) motor programming (Luria motor sequences); (4) sensitivity to interference (conflicting instructions); (5) inhibitory control (go-no-go); (6) environmental autonomy (prehension behavior). The total score ranges from 0 to 18, with higher scores indicating better executive functions.[32] Of the two normative available calibrations of the FAB, we used the version by Appollonio et al. (2005), which was standardized on a broader sample (ages 20–95 years, 1–13 + years of education) and proposed a cutoff score of 13.5/18.[33]

Neurophysiological measures of brain activity

P300 latency was measured using electroencephalogram (EEG) techniques. P300 latency refers to the time required for the P300 component of the event-related potential (ERP) to emerge after the presentation of a stimulus. This measurement is crucial for evaluating cognitive processes, such as attention and stimulus evaluation. The assessment was conducted before and after each treatment to determine the impact of the interventions on cognitive processing speed. In the context of the study, P300 latency was used to monitor and compare the effects of active tDCS versus sham-tDCS, integrated with VRT. During the EEG sessions, participants were exposed to a series of visual or auditory stimuli, depending on the study design. EEG analysis allowed for the identification of the P300 component through the observation of positive deflections in the EEG trace, which typically occur around 300 ms after stimulus presentation. P300 latency was compared between the pre-treatment (T0) and post-treatment (T1) periods to assess whether the addition of active tDCS to VRT resulted in a reduction in P300 latency, indicating increased cognitive processing speed. A decrease in P300 latency would suggest an improvement in the efficiency of cognitive processes, such as stimulus processing and response, potentially facilitated by brain stimulation.

Conversely, a lack of significant change or an increase in P300 latency might indicate that the intervention did not positively impact cognitive processing speed or that observed effects could be influenced by other factors.

VRT

The VRT was carried out using the Virtual Reality Rehabilitation System (VRRS). This is a simple and flexible device providing different modules to support and improve motor (postural, upper and lower limbs activity, facial expressions and respiratory exercises), logopedic and cognitive (i.e. executive functions, attention, praxis, memory abilities and so on …) function in different neurological disorders. Indeed, this advanced, comprehensive, and clinically tested VR system can support both rehabilitation and tele-rehabilitation.[23] The VR cognitive training program was tailored to enhance specific cognitive domain, such as orientation (personal, topographic and temporal), attention abilities (selective, alternative, substituted, split) and executive processes (verbal fluency, categorization, reasoning, coping strategies, problem solving) (Figure 1). In particular, the VRRS consists of a large set of interactive activities for cognitive rehabilitation, using virtual touch modality, with more than 50 exercises already available and many others under development to stimulate different



Figure 1. Shows the VRT: cognitive therapist guided the stroke patient in carrying out goal-oriented, verbal executive functions while he is seated in a wheelchair in front of the VRRS station.

neuropsychological domains. Each type of virtual exercise provided through the VRRS can be organized in two main criteria, differing in the way of interaction with the virtual reality tool. The first category includes 2D exercises where the patient interacts with objects and scenarios through the touch screen or through a particular magnetic tracking sensor coupled with a squeezable object, thus emulating mouse-like interaction capabilities. The second category consists of 3D exercises, where the patients interact with 3D on virtual scenarios and objects through magnetic wearable sensors generally placed over the hand (that permits a 3D position tracking of the end effector). This means that, although non-immersive VR is in both cases represented in the same flat screen, using such a "3D" modality, upper and lower limbs can move in the 3-dimensions of the space while interacting with the virtual environment. Furthermore, neuropsychological tasks consisted of pick and place activities, ordering activities, selection tasks, and sequential selection, properly stimulating each attention sub item, such as selective attention, alternating, sustained, and split. Notably, the level of the exercise performed can be simple, moderate, personalized and advanced in relation to satisfaction of specific criteria: execution' time, number of repetition and errors in each set, and indicators of the accuracy task performed. In fact, the psychiatric therapist planned and organized all virtual exercises (after consultation with the neurologist), increasing the difficulty in relation to the time of execution and the category of activity.

VRT-Plus: VRT + tDCS

Before starting the treatment, all participants underwent a careful and detailed preliminary neurophysiological evaluation. This process included the use of the P300 Event-Related Potential, an essential measure to assess cognitive processing speed and brain activity in response to specific stimuli. In addition to the neurophysiological assessment, a thorough clinical evaluation was conducted, involving various scales and tests to measure cognitive functioning, executive functioning, and depressive symptoms, thereby establishing a solid baseline for each participant. In the pre-treatment phase, participants in the EG received tDCS targeted at the DLPFC before each session of VRT, a combination referred to as VRT-Plus (see Figure 2).



Figure 2. Shows a patient receiving tDCS treatment by neurophysiopathology technician.

In this context, tDCS aimed to modulate brain activity to enhance the effects of cognitive therapy, thereby improving learning processes and cognitive recovery. On the other hand, participants in the CG received a placebo stimulation (sham tDCS), which replicated the treatment experience without delivering any active current, thus allowing for the isolation of the specific effects of active tDCS compared to VRT alone. During and after each tDCS treatment session, participants were continuously monitored to promptly identify any adverse effects or undesirable symptoms. Any negative reactions were recorded and managed, ensuring a high standard of safety and comfort for the participants. At the end of the treatment protocol, all participants were reassessed. The P300 ERP was recorded again to detect any neurophysiological changes that occurred during the therapy. Additionally, the same clinical scales used in the pretest phase were reapplied to evaluate progress in various cognitive and affective domains. This post-treatment evaluation allowed for a rigorous comparison of the initial and final data, providing a clear view of the treatment effects. To ensure the objectivity and reliability of the results, the evaluators conducting the post-treatment assessments were unaware of the type of treatment (active or placebo tDCS) received by the participants, thus ensuring a blind and unbiased evaluation.

In this research, the BrainSTIM transcranial electrical stimulator, produced by EMS S.r.l. in Bologna, Italy, was used.[34] This advanced device is known for its precision and reliability. The stimulation was performed using sponge electrodes with a diameter of 25 mm, carefully coated with saline gel to improve conductivity and minimize skin impedance. A constant current was delivered by the battery-powered stimulator, ensuring stable and safe stimulation. To specifically activate the left DLPFC, the anode electrode was placed on the F7 region of the scalp, according to the EEG 10–20 electrode positioning system, while the cathode reference electrode was placed in the right supraorbital region. The stimulation was administered with an intensity of 2 mA, with a current density of 2.5 mA/cm^2, for a total duration of 20 min per session, parameters selected to optimize the effectiveness of the stimulation without compromising safety.

Statistical analysis

Data analysis was conducted using IBM SPSS Statistics, Version 24 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were calculated and analyzed for the parameters of interest in both the experimental and control groups. A repeated measures MANOVA was used with a between-subjects factor (EG: VRT-Plus, VRT combined with tDCS, and CG: VRT combined with placebo tDCS) and a within-subjects factor (Phase: T0 – baseline pre-intervention, T1 – posttest) for each outcome measure (MMSE, HRS-D, and FAB), as well as for P300 latency. We employed a repeated-measures MANOVA because multiple outcome variables were considered, and these variables were expected to be intercorrelated. A multivariate approach reduces the risk of inflated Type I error associated with multiple univariate tests and allows assessing whether the intervention exerted an overall effect on the combined set of outcomes. When the MANOVA yielded significant multivariate effects, univariate follow-ups were conducted to identify which specific outcomes contributed to the multivariate results. Bonferroni correction was applied to account for multiple comparisons, with the significance level set at $p < .05$ for all statistical tests. In case of significant effects, effect sizes were reported. Effect sizes were calculated and categorized using eta squared (η^2) for MANOVA and Cohen's d for effect size calculations when t-tests were applied.

Results

Table 1 presents the sociodemographic characteristics of the experimental and control groups at baseline. No significant differences emerged between groups in age, years of education, or gender distribution.

Table 2 shows the means and standard deviations for each score considered in the pre-intervention phase (T0) and the posttest phase (T1) for both the EG (cVRT-Plus) and the CG (cVRT).

To examine the effects of the intervention across the multiple outcome variables, we conducted a repeated-measures MANOVA with time (T0 vs. T1) as the within-subjects factor and group (experimental vs. control) as the between-subjects factor. This omnibus test allowed us to assess overall

Table 1. Sociodemographic characteristics of participants at baseline.

	Experimental		Control				
Measures	*M*	*SD*	*M*	*SD*	*t(18)*	*p*	*Cohen's d*
Age	51.90	8.18	48.80	11.01	0.713	.48	0.22
Years of Education	10.60	2.63	10.70	3.57	0.07	.94	0.34
Gender (female and male)	4	6	4	6		1	

Table 2. Means and standard deviations of MMSE, HRS-D, FAB and P300 latency.

	Experimental		Control	
Measures	*M*	*SD*	*M*	*SD*
MMSE baseline	17.5	1.51	18.2	1.48
post-test	23.3	1.34	18.8	1.23
HRS-D baseline	11.98	3.02	12.05	3.03
post-test	10.87	2.44	10.90	3.11
FAB baseline	12.51	1.04	12.94	1.79
post-test	14.91	1.25	12.99	2.08
P300 latency baseline	398.54	37.93	403.60	35.84
post-test	345.03	33.85	400.08	29.88

multivariate differences across the set of outcomes while controlling the familywise error rate. Follow-up univariate analyses were then conducted to clarify the pattern of effects on each outcome (see Table 2).

A significant effect of time (T0 vs T1) within subjects was observed ($F(1, 18) = 45.27$, $p < .001$, $\eta^2 = 0.19$), indicating a notable improvement in MMSE scores from the pre-intervention baseline (T0) to the posttest phase (T1) across the sample. The interaction time by group was also significant ($F(1, 18) = 37.28$, $p < .001$, $\eta^2 = 0.298$), indicating that improvements observed in the EG were significantly greater than those in the control group (Figure 3).

The repeated measures MANOVA revealed a significant effect of the Phase factor, indicating a notable reduction in HRS-D scores from T0 to T1 across the sample ($F(1, 18) = 49.88$, $p < .001$, $\eta^2 = 0.30$). This suggests that depressive symptoms decreased significantly over time, regardless of the group. However, no significant differences emerged between the experimental and control groups regarding overall HRS-D scores (main effect of Group: $F(1, 18) = 0.61$, $p = .80$, $\eta^2 = 0.11$) or in the change in scores from T0 to T1 (Group by

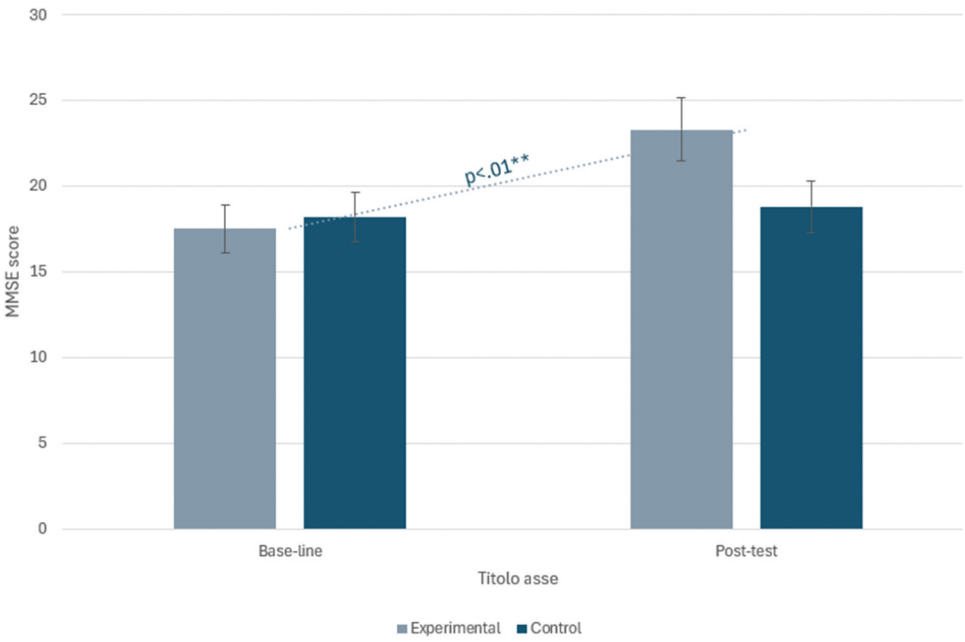


Figure 3. Means and standard deviation of MMSE score.

Phase interaction: $F(1, 89) = 2.11$, $p = .09$, $\eta^2 = 0.15$). This indicates that while both VRT-Plus and VRT led to a reduction in depressive symptoms, the addition of active tDCS did not produce a significantly greater reduction compared to placebo tDCS.

The repeated measures ANOVA examined the effectiveness of VRT combined with tDCS compared to placebo, focusing on improving executive functioning measured by the Frontal Assessment Battery (FAB). Results indicated a significant improvement in FAB scores over time ($F(1, 18) = 59.34$, $p < 0.001$, $\eta^2 = 0.30$) suggesting participants significantly improved their executive functioning from T0 to T1. Additionally, the interaction between time and groups was significant ($F(1, 18) = 14.9$, $p = 0.001$, $\eta^2 = 0.11$), indicating that improvement in FAB scores was greater in the active tDCS group compared to the placebo group. However, no significant difference between the groups overall was found ($F(1, 18) = 0.456$, $p =$ $\eta^2 = 0.04$). This suggests that while active tDCS contributed to a more pronounced improvement over time, the overall differences between groups were not strong enough to be statistically significant (Figure 4).

The repeated measures MANOVA revealed a significant effect of the Phase factor, indicating a substantial reduction in P300 latency from T0 to T1 across the sample ($F(1, 18) = 16.37$, $p < .001$, $\eta^2 = 0.19$). This suggests that cognitive processing speed improved significantly over time. The Group by Phase interaction was also significant ($F(1, 18) = 12.45$, $p < .001$, $\eta^2 = 0.18$), indicating that the reduction in P300 latency was greater in the experimental group (VRT-Plus) compared to the control group (VRT). This result suggests that active tDCS significantly improved cognitive processing speed more than placebo tDCS (see Figure 5).

Discussion

The aim of this study was to investigate the effects of VRT plus tDCS over the DLPFC compared to VRT alone in patients with chronic ischemic stroke. We enrolled individuals with right-hemisphere stroke to investigate a specific cognitive dysfunction associated with right-sided lesions and its relationship with disabling depressive symptoms. We believe that recognizing the key clinical signs of right-hemisphere stroke is essential

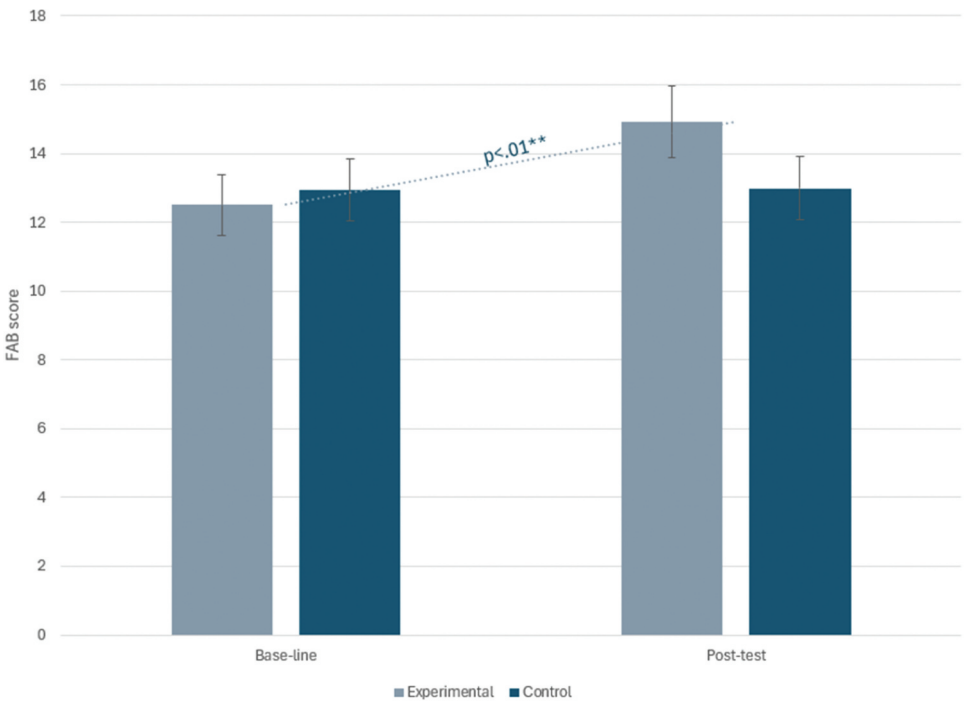


Figure 4. Means and standard deviation of FAB score.

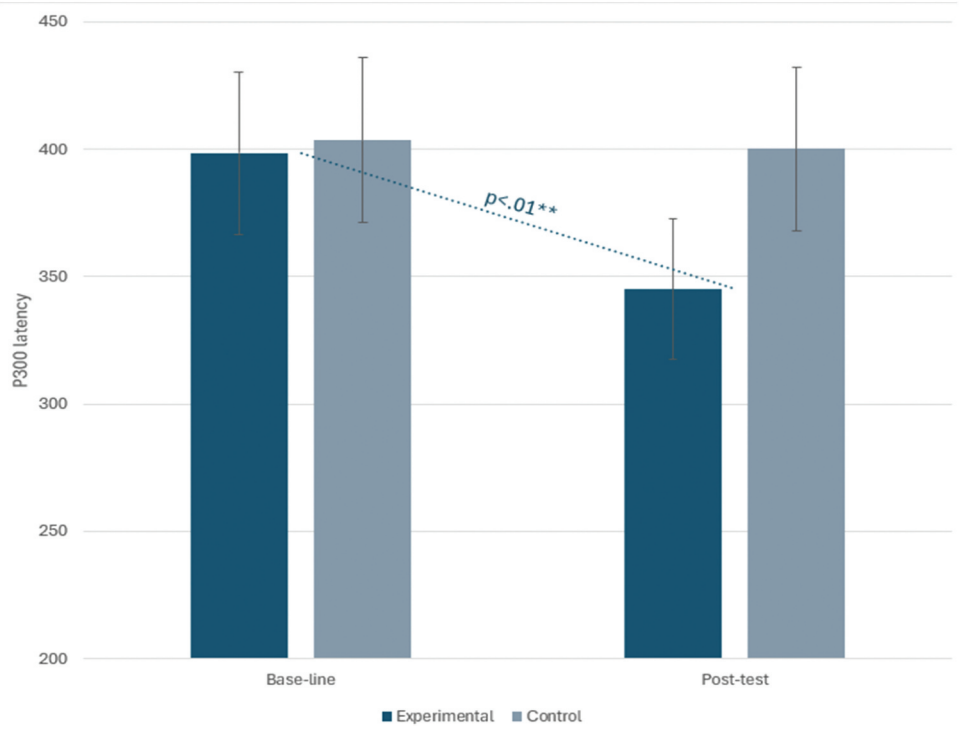


Figure 5. Means and standard deviation of P300 latency.

for timely intervention and management, for instance, through combined approaches such as transcranial direct current stimulation (tDCS) and virtual reality (VR), which remain underexplored to date.

The results of our study highlighted significant effects of neuromodulation in specific cognitive domains (such as cognitive processing speed and frontal abilities) without any additional effects in others behavioral aspects (such as depressive symptoms). This suggests a different impact of tDCS depending on the specific outcomes considered.

Different studies have suggested that the combination of these technologies (VR and tDCS) could be more effective than stand-alone treatments in relation to the specific therapeutic use or setting of application. For instance, it has been employed to induce embodiment for an artificial hand[35], to treat spider phobia[36] and in interventions in different populations, such as children with cerebral palsy, post-stroke patients, and healthy people.[37] In rehabilitation settings, different studies have investigated the potential of joining VR and noninvasive neuromodulation (tDCS/TMS) for the rehabilitation of the upper limb, one of the most common issues following a stroke.[38–42] Evidence in the field of cognitive rehabilitation remains instead limited. In this pilot study, we found a marked improvement in cognitive functioning, especially in executive/frontal abilities, supporting the hypothesis that adding active tDCS significantly enhances cognitive domains, as compared to placebo. This synergic stimulation could also enhance the efficiency of resources to deploy for conflict resolution during multiple stages of cognitive control processing. In our opinion, a plausible hypothesis is that high frequency tDCS over the left DLPFC might recruit more neural resources from the prefrontal cortex by inducing an electrophysiological excitatory effect.

As expected, participants in the CG showed negligible changes across all outcome measures. This stability suggests that the observed improvements in the EG cannot be attributed to practice or retest effects, but rather to the specific features of the VRT-Plus intervention. The control condition, based on the standard VRT, did not include the additional targeted components designed to enhance cognitive flexibility and executive engagement. This likely explains the absence of measurable gains in the CG and strengthens the conclusion that the added intervention elements were effective in producing the observed benefits.

In fact, according to Funahashi et al. (2013), neuromodulation techniques could induce a greater activation and efficacy of the prefrontal cortex[43], an area that is involved in accomplishing the VR tasks. In fact, an eclectic approach to cognitive rehabilitation achieves greater improvements based on the assumption that cognitive deficits are also determined and influenced by physical (e.g. illness, blood pressure, pain, sleep), emotional (e.g. anxiety, annoyances, arousal, mood), social (e.g. relationships, status, social pressure) and motivational (e.g. distractibility, goals, incentives) aspects.[44] tDCS was delivered over the left DLPFC, a region known to be involved in executive functions and in long-term memory due to its interaction with the medial-temporal network, including the hippocampus, as reported in different studies.[45–47] Moreover, we have shown that **V**RT is effective in reducing depressive symptoms, as previously demonstated by van 't Wout-Frank et al.[48] Nevertheless, the addition of tDCS did not yield a significantly greater effect. As suggested by Hao et al.[49], post-stroke depressive symptoms are likely influenced by multiple complex factors that may not have been adequately modulated by tDCS in this study.

A key finding of the study was the improvement in cognitive processing speed, measured by P300 latency, in the group receiving active tDCS. The significant reduction in P300 latency observed in the EG compared to the control group CG suggests that tDCS exerts a specific and relevant effect on cognitive processing speed, as demonstrated by Gangemi et al.[50] Elicitation of the P300 cognitive ERP is a relatively simple procedure that provides valuable insights into cognitive processes, both in healthy individuals and in those with psychopathological conditions.[51] The association between P300 and PSCI has been reported in previous studies[52,53]. The P300 waveform of the auditory or visual ERPs is a positive deflection peaking around 300 ms from stimulus onset in response to rare, novel, or deviant stimuli in an oddball paradigm. Its amplitude is proportional to the amount of cognitive resources.[54] Regarding the P300 responses, it is believed that the latency reflects the time spent for cognitive processing of the stimulus and the amplitude is related to the quantity of attentional resources allocated during the task.[55]

Our study has some limitations to acknowledge. First, the sample size is too small to extend the results to the general stroke population; however, the study was conceived as a pilot study with preliminary considerations and the number of subjects enrolled is in line with the study design. Another limitation was the lack of follow-up and the use of overly general scales to assess cognitive domains, such as the MMSE, which is generally considered more suitable as a screening tool than as a measure of intervention effectiveness. To address this, in addition to the MMSE, we included the FAB and the HRS-D to evaluate the effects of tDCS combined with VR on cognition and mood.

More studies with larger samples, higher-quality methodology, and long -term follow-up are needed to confirm the therapeutic effect of VR combined to tDCS on cognitive and behavior outcomes.

Conclusions

Our research has shown that Tdcs over the DLPFC, in addition to VRT, could be a strategic and valuable tool for enhancing cognitive functioning, especially in cognitive processing speed and to excite frontal abilities, and improve neurophysiological outcomes (P300). Moreover, VRT (independently from tDCS) can help reduce depressive symptoms in the same way. Our findings represent preliminary evidence that should encourage larger randomized controlled trials with long-term follow-up to more thoroughly evaluate the benefits of this promising combined approach.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Author contributions

Conceptualization, R.D.L. and R.S.C.; methodology, R.D.L., F. C. and R.S.C.; software, R.A.F. and A.G.; validation, M.G.M., M.B., and R.A.F. formal analysis, R.A.F. and A. G. investigation, A.G. and R.D.L.; resources, D.D.C., A.Q., F. C. and R.S.C.; data curation, M.R.A. M., and C.M.; writing-original draft preparation, R.S.C., R.D.L., and M.G.M; writing-review and editing, R.D.L., and R.S.C.

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ORCID

R. De Luca http://orcid.org/0000-0002-3905-9486
M. G. Maggio http://orcid.org/0000-0003-0757-2389
M. Bonanno http://orcid.org/0000-0002-3284-9741
A. Quartarone http://orcid.org/0000-0003-1485-6590
R. S. Calabro' http://orcid.org/0000-0002-8566-3166

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