The Effect of Transcranial Direct Current Stimulation and Inhibitory Control Training on Working Memory in Post-stroke Rehabilitation

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Aim: The impairment of working memory is a common phenomenon after stroke and critically affects daily functioning. Transcranial direct current stimulation and computer-based cognitive training are widely used in neurorehabilitation to enhance cognitive functions. This study examined the single vs combined effect of anodal stimulation and computer-based inhibitory control training on working memory function among post-stroke patients. **Methods:** Thirty-five participants were randomly allocated to receiving either active stimulation, sham stimulation with training, or active stimulation with training. Forward/Backward Digit Span Task, Listening Span Task, Corsi Block Tapping Task, and Trail Making Test were used to assess working memory functions at baseline and after the ten-session experimental program. For statistical analysis, we performed a Linear Mixed-effects Model. **Results:** A significant group-by-time interaction showed in favour of the combined group over the active stimulation group in the case of forward digit span (p=.028). **Conclusion:** Results indicate that cognitive training and stimulation solely did not lead to significant improvements in working memory related functions among post-stroke patients. However, the combined application may be favourable. The effectiveness of cognitive training and transcranial direct current stimulation needs further examination.

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Keywords: rehabilitation, stroke, transcranial direct current stimulation, cognitive training, working memory

INTODUCTION

Stroke is one of the most common medical causes of cognitive deficit and deterioration in quality of life (Carod-Artal & Egido, 2009). Impairment in language, executive, and memory functions is highly prevalent and presumably associated with working memory (WM) deficits in stroke (Kalaria & Ballard, 2001; Shaker et al., 2018). WM is a multiregional system crucial for everyday activities, as it plays a pivotal role in goal-directed behavior by storing and manipulating information (Baddeley, 1974). The main domain of WM, also known as the central executive (CE), modulates the following subdomains: phonological loop (short-term recall), visuospatial sketchpad (visuospatial WM), and episodic buffer (Baddeley, 2000). Given the integrative role of WM, its functional rehabilitation is of utmost importance in post-stroke recovery (Elliott & Parente, 2014).

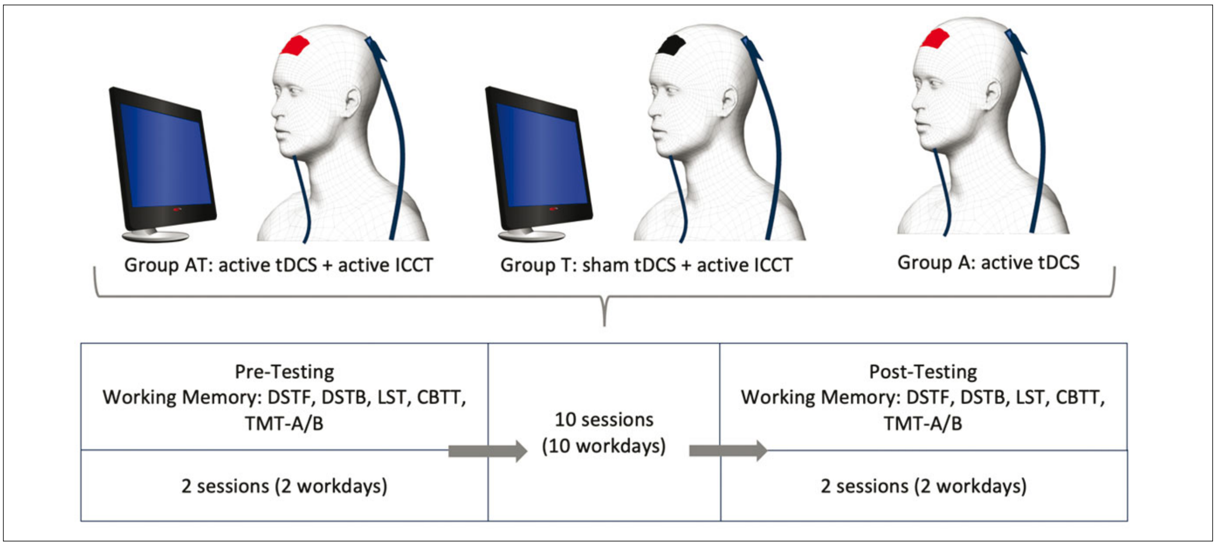
In post-stroke cognitive rehabilitation, a wide range of tools are available, including traditional rehabilitation techniques (e.g., fine motor development), non-invasive neuromodulation (e.g., transcranial magnetic stimulation or transcranial direct current stimulation), and computer-based cognitive training (CCT) (Draaisma et al., 2020). Among these, transcranial direct current stimulation (tDCS) is gaining interest in clinical neuroscience and neurorehabilitation (Zaehle et al., 2011; Zhao et al., 2017). Modulating the synaptic connections between neurons via direct current affects the pre- and postsynaptic membrane potential, resulting in inhibitory or excitatory effects (Draaisma et al., 2020). The effect mechanism of tDCS on cognitive functioning is not yet fully understood; nevertheless, positive results in WM-related skills have been obtained in both neurotypical individuals and stroke patients by stimulating the Dorsolateral Prefrontal Cortex (DLPFC) (Berryhill & Jones, 2012; Gomez Palacio Schjetnan et al., 2013). However, it is not yet clear how stimulation parameters (e.g., localization or intensity) relate to the induced behavioral changes (Esmaeilpour et al., 2018). The most effective tDCS parameters remain to be determined in post-stroke cognitive rehabilitation, especially when combined with a specific CCT.

Cognitive training with domain-specific tasks at an individualized level of difficulty appears to facilitate particular skills. The choice of CCT depends on the functions that need to be rehabilitated (Nisha & Kumar, 2013). As a part of WM, the CE manipulates phonological and visuospatial information through executive functions (EFs), such as updating, inhibition, and shifting (Soveri et al., 2017). WM training tasks impact the EFs, and the most common experimental WM training is the 'N-back task,' which achieves beneficial effects by loading updating functions (Lindeløv et al., 2016). However, the EFs are not independent of each other (St Clair-Thompson & Gathercole, 2006). As shown in the experiment of Scharinger and colleagues (2015) and Kim and colleagues (2017), there is a close interplay between updating and inhibition, a phenomenon confirmed by other neurophysiological findings in recent years (Figueroa-Vargas et al., 2020; Kim et al., 2017; Scharinger et al., 2015). Scharinger and colleagues showed that a simultaneous demand for WM updating and inhibition enhanced inhibitory processes instead of resulting in a depletion effect. They used Flanker task elements to load inhibitory functions and measured behavioral factors, such as electroencephalography (EEG) and pupil dilation. With similar outcomes, Kim and colleagues (2017) also claim a possibility of a fronto-parietal neurocognitive network (including prefrontal and parietal cortices) associated with updating and inhibition.

Although the 'N-back task' is also successfully used in stroke rehabilitation to improve WM performance (Oguh et al., 2014; Zakariás et al., 2018); it needs further investigation whether an advantageous effect can also be induced by other training tasks, such as inhibition training (e.g., Flanker Task Training). Furthermore, patients may be unable to perform the 'N-back task', despite its successful use in improving WM performance. Therefore, finding alternative WM training tasks would be pivotal in clinical practice. Inhibition training is a good candidate, but no conclusive information is available about its transfer effect on WM subsystems (van Geest & Engelbregt, 2022).

This study aims to determine the effects of anodal tDCS stimulation of the (left) DLPFC and CCT on WM among post-stroke patients. Based on previous research, we applied Martin and colleagues' (2013) experimental design, investigating effects in three conditions: tDCS therapy alone (A), sham tDCS with ICCT (T), and active tDCS combined with ICCT (AT) (Martin et al., 2013). Following Scharinger and colleagues (2015) and Geest and Engelbregt (2022), we administered a modified version of a single Flanker Task as inhibitory control training (ICCT). Here, we used word stimuli, based on Kanske and Kotz (2010), to enhance the performance of EFs via inhibitory control functions (Kanske & Kotz, 2010a). We did not

Figure 1. Experimental design. During the first testing phase (2 sessions) baseline assessment was conducted using the following test batteries: Digit Span Task, Backward Digit Span Task, Listening Span Task, Corsi Block Tapping Task, associated with working memory functions. This was followed by the experimental intervention (10 sessions) with participants divided into three groups (A – Active tDCS, T - Sham tDCS with Interference Control Training, AT - Active tDCS with Interference Control Training). Lastly, the retesting phase involved 2 follow-up testing sessions using similar batteries as during baseline.



only stimulate the DLPFC, but a fronto-parietal area corresponding to the multiregional structure of WM based on the findings of Kim and colleagues (2017). We hypothesized a positive training effect in the WM assessments of patients in the combined condition, as measured by the Listening Span Task (LST), the Forward/Backwards Digit Span Task (DSTF, DSTB), and the Trail Making Test (TMT).

METHODS

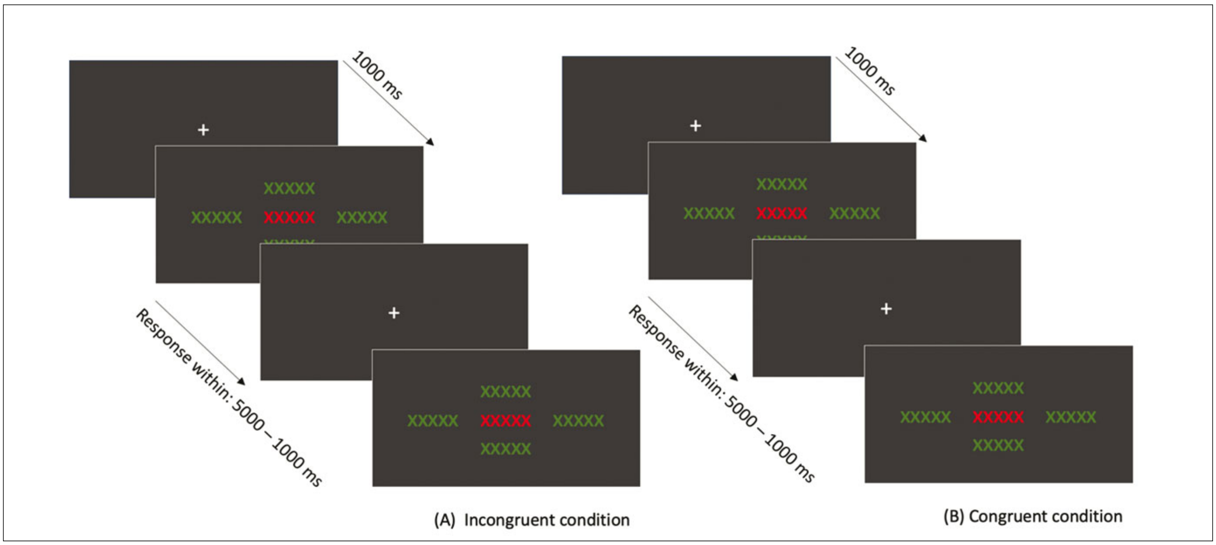
Participants

Thirty-five post-stroke patients (aged M=59.6; SD=10.9) were recruited from the Neurorehabilitation Unit of the Department of Neurology, Albert Szent-Gyorgyi Health Centre, University of Szeged. All participants were native Hungarian speakers hospitalized for an average of two weeks. They received additional physiotherapy, speech therapy, and fine motor therapy. We selected patients with a detectable, measurable cognitive deficit but intact reading comprehension abilities (inclusion criteria). The exclusion criteria were the following: the presence of stroke-independent dementia, cerebral atrophy, alcohol use disorder, significant psychiatric disorder, hemorrhagic stroke, ferromagnetic metal in the body (e.g., pacemaker or deep brain stimulator), severe language impairment (e.g., aphasia), or epilepsy. Patients had a mean score of 76.3 (SD=9.89) on the Addenbrooke's Cognitive Examination. Regarding lesion location, 12 patients with definite right-sided lesions, 12 patients with definite left-sided lesions, and 11 patients with bilateral or subcortical lesions participated in the rehabilitation program. Nineteen patients received experimental therapy (see Experimental design) within 3 months of the lesion (M=1.29, SD =0.87), and 16 patients received experimental therapy 3 months after the first lesion (M = 41.81, SD = 46.21) (see Table 1 for baseline characteristics). Participants were excluded from the study if there were deliberate cancellations or if they experienced severe adverse effects during the program. The Regional Ethics Committee of the University of Szeged approved the study (165/2014), and all patients signed an informed consent form, in accordance with the principles of the Declaration of Helsinki.

Experimental Design

We randomly assigned the participants into one of three experimental groups (Active tDCS without ICCT (A), Sham tDCS with ICCT (T), and Active tDCS with ICCT (AT)). The participants were unaware of the experimental group they had been placed in during the selection process. We administered data on general characteristics (e.g., age, gender, education, type of stroke, time after stroke) and cognitive functions at the beginning and end

Figure 2. Inhibitory Control Training (ICCT). Inhibitory Control Training was used to train inhibitory control functions. The program consisted of two conditions: incongruent (A) and congruent (B). In both conditions, the same word is displayed at the top, bottom, right and left of the screen around the middle word presented in green in the congruent condition (B) and red in the incongruent (A). Patients indicated the different conditions (A or B) by button press.



of the 10-session experimental program. Baseline testing was performed in two sessions on consecutive workdays to ensure optimal workload (Figure 1).

The experimental groups received a ten-session intervention on ten consecutive working days. Follow-up measurements were performed on two separate days. Participants were unaware of the expected benefits of targeted cognitive training or tDCS stimulation on cognitive function but were informed them in detail about the possible side effects. Those receiving sham tDCS stimulation were prepared identically to those in the active tDCS group (e.g. electrode placement and postitioning), but unaware that no actual stimulation was taking place. The neuropsychological tests, participant documentation, cognitive training program, tDCS apparatus, and research materials were stored in a lockable cabinet. Data collection and testing were carried out by experienced psychologists from the Neurorehabilitation Unit of the Department of Neurology, Albert Szent-Gyorgyi Health Centre.

Clinical Neuropsychological Testing

Primary Outcome Measures

Participants completed a complex test battery assessing neurocognitive and WM functions to determine the transfer effect of ICCT and the consequence of tDCS stimulation. Short-term verbal recall was measured with the Digit Span Forward Test (DSTF), a subtest of the Wechsler Adult Intelligence Scale (WAIS) (Wechsler, 1944). Complex WM functions were assessed by the Hungarian version of the Listening Span Task (LST) and Digit Span Backward Test (DSTB) (Janacsek et al., 2009; Wechsler, 1944). The processing speed of EFs was measured with the Trail Making Test (TMT-A/B) (Reitan, 1958). We examined visuospatial functions using the Corsi Block Tapping Task (CBTT) (Corsi, 1973).

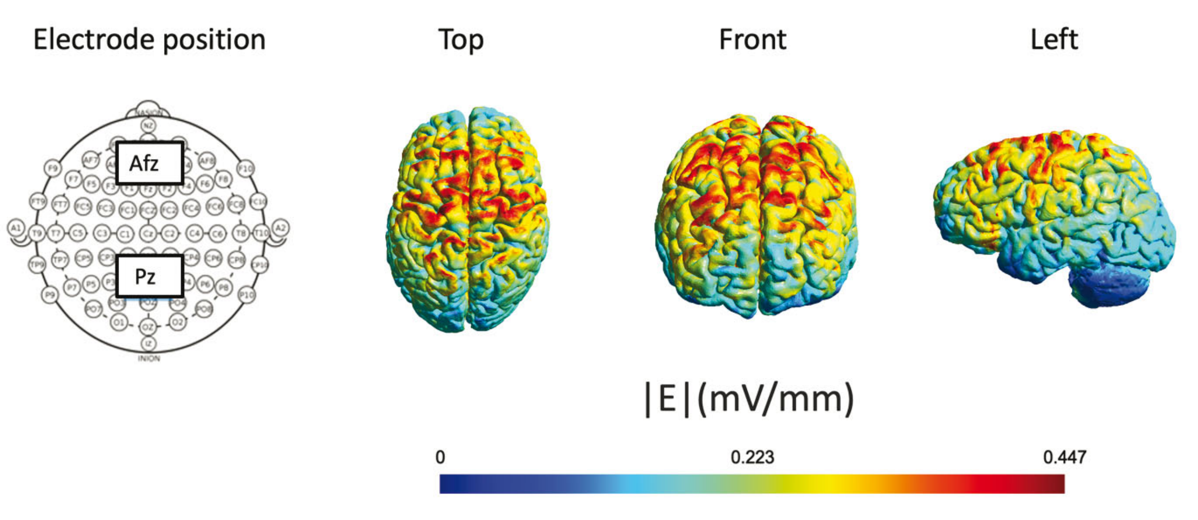
Additional Cognitive Measurements

We also administered the following neuropsychological assessments: Addenbrooke's Cognitive Examination (ACE), which includes six components assessing various cognitive abilities, including orientation, attention, memory, verbal fluency, language, and visuospatial abilities (Mathuranath et al., 2000); the Wisconsin Card Sorting Test (Grant & Berg, 1948), assessing flexibility and task switching; and the National Adult Reading Test (NART) to assess premorbid intellectual abilities (Nelson & Willison, 1982).

Inhibitory Cognitive Training Task (ICCT)

The cognitive training task was presented using E-prime 2.0 software (Psychology Software Tools,

Figure 3. Stimulation Parameters of Transcranial Direct Current Stimulation (tDCS). During active tDCS stimulation, areas of the cortex highlighted in red were stimulated, the electrode current was set at 2 mA. The anode electrode is placed over the frontal areas (AFz), and the cathode over the parietal areas (Pz).

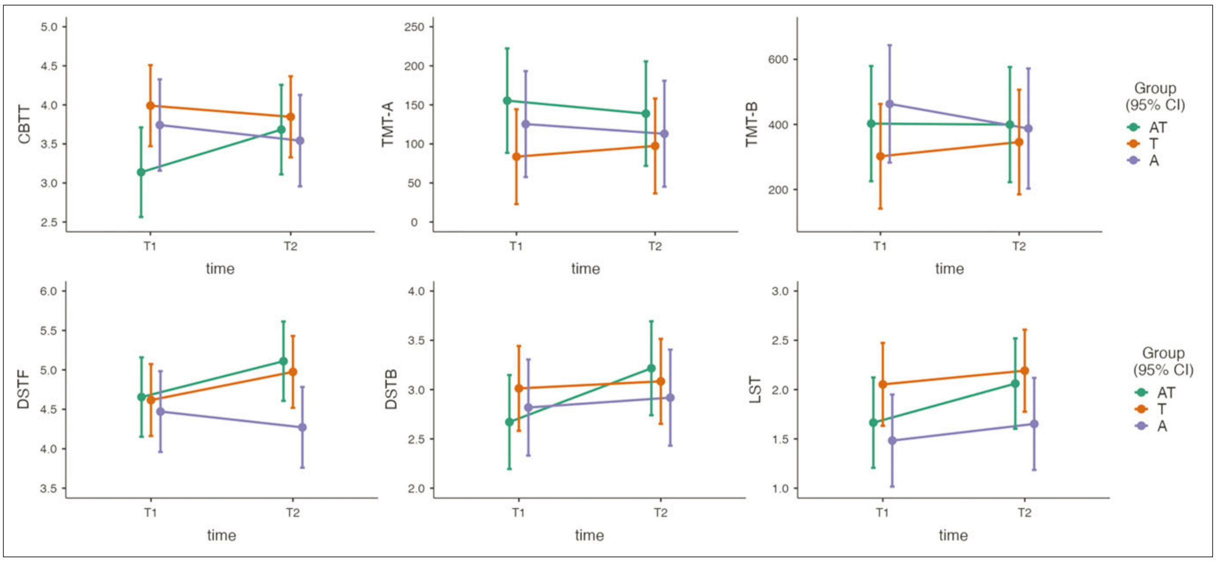


Pittsburgh, PA). Subjects were asked to respond on a black computer screen placed at a 75 cm distance. During the task, a fixation cross (1000 ms) followed by the target stimulus (word) appeared in the middle of the screen in font size 48. The same word appeared simultaneously around the target word on the left, right, below, and above in font size 48 and color green. The color of the target word was either green or red. Participants were asked to indicate by pressing the corresponding key whether the target word was presented in red (incongruent condition; red target - green surrounding words, key A to be pressed) or green (congruent condition; green target - green surrounding words, key L to be pressed). The interference/inhibitory effect was indicated by switching between congruent and incongruent conditions. During the first session, subjects were allowed five seconds (5000 ms) to respond to each stimulus. If a patient could complete the preceding block with an 80% success, the task's difficulty was adjusted by reducing reaction time (based on each subject's previous performance, to 4000, 3000, 2000, or 1000 ms). Before every session, subjects had unlimited practice time while also receiving feedback on their answers (correct/wrong). The training session consisted of 4 blocks containing 4x45 sets of words. Stimuli were pulled from three types of word lists (3x15) containing an equal proportion of words with positive, negative, or neutral emotional valence (Figure 2).

Stimulation Parameters

The NeuroConn DC Stimulator Plus device was used for transcranial direct current stimulation (neuroConn GmbH, Germany). The current was conducted through a pair of surface sponge electrodes (5,5 cm x 7,5 cm) with a strength of 2 mA. We positioned the anode ovver the 'AFz' and the cathode electrode over the 'Pz' areas (according to the international 10-20 EEG system). When positioning the electrodes, the primary goal was to stimulate the cortex bilaterally in as large an area as possible from the frontal to occipital regions, corresponding to the multiregional WM structure theory (Chai et al., 2018; Kim et al., 2017). We also modeled the direction and strength of current flow using the 'SimNIBS 3.2' (www.simnibs.org) modeling program. The model showed that the main stimulation fields were the frontal (including DLPFC), parietal and parietal-occipital areas of the cortex. Parietal-temporal areas also received stimulation at a lower intensity, which may further enhance WM performance (Spitoni et al., 2013). In both active tDCS groups (A, AT), a 12-minute stimulation phase was introduced per session. The AT group's cognitive training program ran parallel to the stimulation. Experienced neuropsychologists carried out the stimulations under the supervision of a psychiatrist and a neurologist from the Neurorehabilitation Unit of the Department of Neurology, Albert Szent-Gyorgyi Health Centre (Figure 3).

Figure 4-5. The results between the three experimental groups (AT, T, A) at T1 and T2 for the neuropsychological tests: DSTF=Digit Span Task; DSTB=Backward Digit Span Task; LST=Listening, Span Task; CBTT=Corsi Block Tapping Task; TMT = Trail Making Test.



Statistical Analyses

We performed statistical analyses with IBM SPSS for Windows, v25.0 (IBM SPSS Statistics for Windows, version 25.0) and Jamovi 2.3.28 (Jamovi Project, 2023), and the significance level was set at α (p) = 0.05. For demographic data, frequency, means, and standard deviations were determined. We used the Shapiro-Wilk normality test to examine whether the data were normally distributed within the experimental groups. For continuous variables, baseline characteristics of experimental groups were compared either with One-way Analysis of Variance (ANOVA) (parametric data) or the Kruskal-Wallis Test (non-parametric data); contingency tables were calculated for categorical data ($\chi 2$ test).

The effects of tDCS and ICCT treatment on neuropsychological parameters related to WM were investigated and measured at baseline (T1) and post-intervention (T2). The effects of the interventions were estimated using a Linear Mixed-effects Model (LMEM), which may be more beneficial than mixed ANOVA models in repeated measures studies where multiple observations per experimental unit are not necessarily independent of each other, where there is a relatively low number of items per group, or where data series are non-normally distributed. In the models, we treated group type („Group": AT, T, A), measurement occasion („Time": T1 and T2) and their interaction („Group x Time") as predictors, using a fixed intercept. The time main effect is the pre-post change in neuropsychological scores independent of group membership. The group main effect reflects the average differences between group scores, regardless of the measurement time. The Group-by-Time interaction effect, a key variable in this study, indicates differences between groups in the extent of pre-post score changes. In the analysis, Satterthwaite's approximation was used to determine the p-values. A posthoc test was performed to examine possible group differences, with Bonferroni correction, to test a significant main effect of the interaction.

Given the heterogeneity of the descriptive data, we included the following covariates in all models: „age," „time since stroke (months)," „location of lesion," and „gender." In the results, intercepts represent average baseline scores, while slopes indicate changes from baseline to post-measurement, plotted as mean differences (MD). Estimated parameters (b) capture main effects, interactions, and covariates (e.g., age, gender). Within-class correlation coefficients (ICC) represent variance due to subject differences, while R^2 values (marginal and conditional), SE, t- and p-values, and residual variances (σ^2) assess model fit. Effect sizes for Group x Time interactions were calculated as follows:

$$f_b^2 = \frac{R_{ab}^2 - R_a^2}{1 - R_{ab}^2}$$

where R^2_{ab} represents the full model variance and R^2_a the reduced model without the interaction term. The f^2 value corresponds to moderate ($f^2 \geq 0.15$) to

Table 1. Baseline characteristics of the sample

	Sample	**Group AT**	**Group A**	**Group T**	
	Mean SD (±)	Mean SD (±)	Mean SD (±)	Mean SD (±)	Between Group Significance *(p)*
Age	59.68 11.10	54.27 12.97	63.20 9.63	61.54 9.36	.135
Education (years)	12.03 3.40	11.36 3.10	11.60 3.13	12.92 3.88	.493
NART (Error Score)	27.21 14.50	23.60 9.31	31.44 5.38	27.07 16.57	.514
ACE	76.31 9.89	75.45 9.88	71.50 8.37	79.92 10.00	.084
Gender (male/female)	22/13	6/5	5/5	11/3	.341
Stroke localization (left/right/both or subcortical)	12/12/11	5/2/4	3/5/2	4/5/5	.626
Elapsed time after stroke (within 3 months/after 3 months)	19/16	6/5	7/3	6/8	.435

The results show no significant baseline difference between the groups. Abbreviations: NART= National Adult Reading Test; ACE=Addenbrooke's Cognitive Examination; DSTF=Digit Span Task; DSTB=Backward Digit Span Task; LST=Listening Span Task; CBTT=Corsi Block Tapping Task; TMT = Trail Making Test. A=Active tDCS without ICCT; T=Sham tDCS with ICCT; AT=Active tDCS with ICCT.

large ($f^2 \geq 0.35$) effect sizes, as outlined in Cohen's (1988) guidelines (Cohen, 1988). This approach is in line with established guidelines for evaluating the contribution of predictors in LMEM (Selya et al., 2012). Furthermore, Cohen's d was used to assess within-group pre-post change effect sizes:

$$d = \frac{M_{post} - M_{pre}}{SD_{pooled}}\ ;\ SD_{pooled} = \sqrt{\frac{SD_{pre}^2 + SD_{post}^2}{2}}; SD = SE\ x\ \sqrt{n}$$

Cohen's d values of 0.2–0.5, 0.5–0.8, and ≥0.8 indicate small, medium, and large effect sizes, respectively (Cohen, 1988). Using $f = 0.35$, we conducted an a priori analysis ($\alpha = 0.05$, $1\text{-}\beta = 0.90$) with G*Power (Faul, Erdfelder, Lang, & Buchner, 2007), determining a minimum sample size of 30 patients altogether for sufficient power (0.91).

RESULTS

Sample and Baseline Characteristics

Participants in the study had a mean age of 59.68 years (SD ± 11.10), with no significant age differences between the experimental groups (Table 1). Education levels were comparable across groups, with a mean of 12.03 school years (SD ± 3.40). Cognitive baselines, as assessed by the NART and ACE, showed no significant differences either. Gender distribution was balanced across groups, with 22 males and 13 females overall. Stroke localization and time elapsed since the stroke (within or after 3 months) were similarly distributed across groups.

Furthermore, no baseline differences in primary outcome measures (DSTF, DSTB, LST, CBTT, TMT-A/B) were observed between the experimental groups. The Shapiro-Wilk test showed that the averages of DSTF, DSTB, LST, TMT-A/B, and CBTT were not normally distributed at baseline.

Linear Mixed-effects Models

Digit Span Forward Test (DSTF)

The results of the LMEM showed that, among the factors influencing the DSTF as a dependent variable, time, group, sex, lesion site, age, and stroke time alone did not show significant effects. The difference between time-by-group interaction was

Table 2.1. Linear Mixed-effects Model statistics for neuropsychological tests related to working memory in the experimental groups - Intercepts and slopes

			DSTF	DSTB	CBTT	LST	TMT-A (sec)	TMT-B (sec)
Intercepts	AT	T1 scores	4.66	2.67	3.14	1.66	155.43	402.39
		SE	0.25	0.24	0.28	0.23	32.75	87.12
		95% CI	[4.15, 5.16]	[2.19, 3.15]	[2.56, 3.71]	[1.21, 2.12]	[88.49, 222.36]	[225.25, 579.53]
	A	T1 scores	4.47	2.82	3.74	1.48	125.40	463.05
		SE	0.25	0.24	0.29	0.23	33.22	88.79
		95% CI	[3.96, 4.98]	[2.33, 3.31]	[3.16, 4.33]	[1.02, 1,95]	[57.51, 193.29]	[282.60, 643.50]
	T	T1 scores	4.62	3.01	3.99	2.05	88.67	302.00
		SE	0.22	0.21	0.26	0.21	29.74	79.10
		95% CI	[4.15, 5.16]	[2.58, 3.44]	[3.47, 4.51]	[1.63, 2.47]	[22.87, 144.48]	[141.12, 462.88]
Slopes	AT	T2 scores	5.11	3.22	3.68	2.06	138.79	399.39
		95% CI	[4.61, 5.61]	[2.74, 3.69]	[3.11, 4.26]	[1.60, 2.52]	[71.85, 205.73]	[222.25, 576.53]
		SE	0.25	0.24	0.28	0.23	32.75	87.12
		MD	0.45	0.55	0.54	0.40	-16.64	-3.00
	Cohen's d (Pre-post)		0.54	0.69	0.58	0.52	0.15	0.01
	A	T2 scores	4.27	2.92	3.54	1.65	113.00	387.31
		95% CI	[3.76, 4.78]	[2.43, 3.41]	[2.96, 4.13]	[1.18, 2.12]	[45.11, 180.89]	[202.74, 571.87]
		SE	0.25	0.24	0.29	0.23	33.22	91.06
		MD	-0.20	0.10	-0.20	0.16	-12,40	-75.74
	Cohen's d (Pre-post)		0.25	0.13	0.21	0.23	0.12	0.26
	T	T2 scores	4.97	3.08	3.85	2.19	97.39	345.72
		95% CI	[4.52, 5.43]	[2.65, 3.51]	[3.33, 4.37]	[1.78, 2.61]	[36.58, 158.19]	[184.83, 506.60]
		SE	0.25	0.21	0.26	0.20	29.74	79.10
		MD	0.35	0.07	-0.14	0.14	8.72	43.72
	Cohen's d (Pre-post)		0.39	0.08	0.14	0.18	0.07	0.14

The table presents the intercept (baseline (T1) scores) and slope values (indicating the rate of change over time (T2)) across the groups. Mean differences (MD) reflect the average difference between baseline and post measurements. Cohen's d (Pre-post): represents the effect size for the change within each group from pre- to post-intervention. Abbreviations: DSTF=Forward Digit Span Task; DSTB=Backward Digit Span Task; LST=Listening Span Task; CBTT=Corsi Block Tapping Task; TMT = Trail Making Test; T1=Pre-measurement (Baseline); T2=Post-measurement; SE=Standard Error; CI=Condifence Interval; A=Active tDCS without ICCT; T=Sham tDCS with ICCT; AT=Active tDCS with ICCT.

significant when groups A and AT were compared (b=-0.65, SE=0.28, p=0.028). Analysis of the random effects showed that within-subject variance (σ^2=0.39) contributed significantly to the results, and the intraclass correlation coefficient (ICC=0.65) confirmed the relevance of including random effects in the model. In the analysis, the model fit was characterized by a conditional R^2 of 0.72 and a marginal R^2 of 0.21, indicating that fixed effects alone explain a small proportion of the variance. In contrast, the full model has significant explanatory power.

Digit Span Backward Test (DSTB)

The results of the LMEM showed that none of the fixed effects on the dependent variable DSTB were

Table 2.2. Linear Mixed-effects Model statistics for neuropsychological tests related to working memory in the experimental groups – Main effects and interactions

			DSTF	**DSTB**	**CBTT**	**LST**	**TMT-A (sec)**	**TMT-B (sec)**
Main effects and Interactions	**Time**							
		b	0.20	0.24	0.07	0.23	-5.11	-11.68
	T1/T2	*SE*	0.12	0.14	0.15	0.08	7.68	33.28
		t-value	1.84	1.67	0.46	2.96	-0.67	-0.35
		p	0.076	0.105	0.651	0.006*	0.511	0.728
	Group							
	T/AT	*b*	-0.09	0.10	0.51	0.26	-56.58	-77.03
		SE	0.31	0.27	0.34	0.29	43.39	111.53
		t-value	-0.28	0.38	1.49	0.89	-1.30	-0.69
		p	0.781	0.704	0.149	0.381	0.203	0.496
	A/AT	*b*	-0.51	-0.08	0.23	-0.30	-27.91	24.29
		SE	0.34	0.30	0.37	0.32	47.49	122.53
		t-value	-1.51	-0.25	0.62	-0.93	-0.59	0.20
		p	0.142	0.801	0.541	0.362	0.562	0.844
	Group x Time							
	T/AT	*b*	-0.10	-0.47	-0.69	-0.26	30.35	46.71
		SE	0.26	0.34	0.35	0.19	18.12	77.09
		t-value	-0.37	-1.40	-1.97	-1.37	1.67	0.61
		p	0.713	0.171	0.057	0.182	0.104	0.549
	A/AT	*b*	-0.65	-0.45	-0.75	-0.23	4.24	-72.74
		SE	0.28	0.37	0.38	0.20	19.65	85.74
		t-value	-2.30	-1.21	-1.97	-1.13	0.22	0.85
		p	**0.028***	0.234	0.058	0.267	0.831	0.403
	Effect size of interaction	f^2	0.143	0.018	0.000	0.086	0.000	0.000

The table summarizes main effects and interactions for WM tests across groups, showing time effects (T1 vs. T2), group comparisons (A vs. T vs. AT), and effect sizes, with significant results ($p < 0.05$) marked by *. Estimate (b) values represent the predicted changes in test scores, reflecting how factors influence the measured scores across conditions.
T-values, and p-values represent model parameters, while f^2 represent the effect size of interaction. Abbreviations: SE = Standard Error, DSTF = Forward Digit Span Task; DSTB = Backward Digit Span Task; LST = Listening Span Task; CBTT = Corsi Block Tapping Task; TMT = Trail Making Test; T1=Pre-measurement (Baseline); T2 = Post-measurement; A = Active tDCS without ICCT; T = Sham tDCS with ICCT; AT = Active tDCS with ICCT.

significant. Time, group, sex, lesion site, age, and stroke duration did not show significant effects independently. Time-by-group interaction was also insignificant. In the random effects analysis, within-subject variance (σ2= 0.21) indicates that individual variation moderately affects the dependent variable. The intraclass correlation coefficient (ICC=0.37) suggests that between-subject differences can explain 37% of the total variance. A marginal R^2 of 0.14 indicates that fixed effects explain 14% of the total variance of the outcome variable. At the same time, a conditional R^2 of 0.45 suggests that fixed and random effects combined explain 45% of the variance. This result indicates that the random effects contribute significantly to explaining the results, while the fixed effects have relatively weak explanatory power.

Table 2.3. Linear Mixed-effects Model statistics for neuropsychological tests related to working memory in the experimental groups - Demographic and clinical factors

		DSTF	DSTB	CBTT	LST	TMT-A (sec)	TMT-B (sec)
Age	b	0.01	-0.00	-0.02	-0.01	2.12	6.74
	SE	0.01	0.01	0.01	0.01	1.85	4.75
	t-value	0.76	-0.26	-1.33	-1.20	1.14	1.42
	p			0.195	0.242	0.262	0.168
Time Wsince stroke (m)	b	-0.01	-0.00	-0.00	-0.00	-0.36	-0.16
	SE	0.00	0.00	0.00	0.00	0.59	1.51
	t-value	-1.56	-1.13	-0.64	-0.62	-0.51	-0.11
	p	0.129	0.269	0.528	0.543	0.544	0.916
Location of lesion							
Right/Left	b	-0.18	-0.28	-0.03	-0.25	4.21	60.19
	SE	0.32	0.28	0.35	0.30	44.54	114.46
	t-value	-0.55	-0.99	-0.09	-0.83	0.09	0.53
	p	0.585	0.332	0.931	0.414	0.925	0.603
Both sides or subcortical/Left	b	-0.20	-0.31	-0.26	-0.30	37.31	87.75
	SE	0.31	0.27	0.34	0.29	43.44	112.17
	t-value	-0.64	-1.15	-0.76	-1.03	0.86	0.78
	p	0.528	0.262	0.451	0.310	0.398	0.441
Gender (F/M)	b	-0.08	-0.03	-0.68	-0.21	-27.64	-19.96
	SE	0.30	0.26	0.33	0.28	41.86	107.80
	t-value	-0.27	-0.13	-2.05	-0.75	-0.66	-0.19
	p	0.789	0.897	0.050	0.458	0.515	0.854

The table presents the model statistics for WM-related neuropsychological tests, assessing the impact of demographic and clinical factors, including age, time since stroke, lesion location, and gender. Estimate values show how each factor affects the test scores. T-values, and p-values represent model parameters. Abbreviations: SE = Standard Error, DSTF = Forward Digit Span Task; DSTB = Backward Digit Span Task; LST = Listening Span Task; CBTT = Corsi Block Tapping Task; TMT = Trail Making Test.

Listening Span Task (LST)

The results of the LMEM showed that the time variable had a significant effect on LST as a dependent variable (F(1, 31.30)=8.76, p=0.006). Estimates of the changes over time (b=0.23, SE=0.08) indicate that LST values increased significantly. Group, gender, lesion site, age, and stroke time alone did not show significant effects. The interaction between time and group was not found significant either. Analysis of the random effects showed that within-subject variance (σ2=0.39) was significant, with the intraclass correlation coefficient (ICC = 0.78) indicating that between-subject differences explained 78% of the total variance. In comparison, the remaining 22% was attributable to random noise and other factors. A marginal R^2 of 0.25 indicates that fixed effects explain 25% of the variance. A conditional R^2 of 0.84 indicates that fixed and random effects account for 84% of the variance.

Corsi Block Tapping Task (CBTT)

The results of the LMEM showed that time, group, gender, lesion site, age, stroke time, and the interaction between time and group did not show significant effects. Analysis of the random effects revealed that within-subject variance (σ2=0.42) was significant, with the intraclass correlation coefficient (ICC = 0.53) indicating that between-subject differences explained 53% of the total variance. A marginal R^2 of 0.26 indicates that fixed effects accounted for 26% of the total variance, while a conditional R^2 of 0.65 demonstrates that fixed and random effects together explained 65% of the variance.

Trail-Making Test – A (TMT-A)

The results of the LMEM model for TMT-A showed that no fixed effects, including time, group, gender, lesion site, age, stroke time, or their interaction, were statistically significant. Within-subject variance (σ2= 9265.32) together with the intraclass correlation coefficient (ICC=0.90) indicated that between-subject differences explained 90% of the total variance. The remaining 10% was attributable to within-subject variability and random noise. A marginal R^2 of 0.10 indicates that fixed effects contributed minimally to the explained variance, while a conditional R^2 of 0.91 demonstrates that the variance explained was driven primarily by random effects.

Trail-Making Test – B (TMT-B)

The results of the LMEM for TMT-B showed that no fixed effects, including time, group, gender, lesion site, age, stroke time, or their interaction, were statistically significant. Analysis of the random effects showed that within-subject variance (σ2=55375.74) was significant, with the intraclass correlation coefficient (ICC=0.75) indicating that between-subject differences explained 75% of the total variance. A marginal R^2 of 0.09 suggests a negligible contribution of fixed effects, while a conditional R^2 of 0.75 indicates substantial variance explained by random effects.

For detailed information on LMEM intercepts (baseline mean scores), slopes (post-measurement changes), main effects, interactions, and parameter estimates, see Tables 2.1 and 2.2. and 2.3.

DISCUSSION

This study aimed to investigate the potential rehabilitation effect of fronto-parietal stimulation with tDCS and the transfer effect of inhibitory control training on WM-related functions among stroke patients. The experiment was based on the neurophysiological and neuropsychological framework, which claims that there is a significant association between domains of Efs (Kim et al., 2017; Scharinger et al., 2015); and this system involves fronto-parietal cortical structures, targeted during tDCS stimulation. With the cognitive task used in this study, we aimed to improve EF functions by training inhibition and examining its transfer effect to WM. As shown by the results, we did not obtain significant changes in WM functions measured by various neuropsychological assessment tools. We found a significant group difference (A-AT) in short-term phonological skills (DSTF). However, this result does not indicate broader changes in cognitive functions. Neither the application of tDCS nor that of ICCT demonstrated statistically significant effects. Several potential interpretations exist for the effects observed in our experiment.

Fronto-parietal tDCS and Working Memory

Multiregional stimulation did not show evidence of tDCS enhancing WM-related cognitive functions in our study. Effect sizes calculated for within-group changes indicated that active tDCS without the training task had the smallest effect sizes across all neurocognitive assessments compared to other groups. No between-group differences were statistically significant. This may be due to the lack of appropriate localization or intensity of direct current. Indeed, Utz and colleagues (2010) proposed placing tDCS electrodes over the brain region associated with the cognitive function under investigation. However, other studies suggest that a specific localization of current flow can not be guaranteed despite accurate electrode placement (Datta et al., 2011; Utz et al., 2010). WM researchers mostly agree that anodal electrode placement over DLPFC and surrounding areas (e.g., F3, F4, AFz) appears to be an adequate choice; however, cathodal electrode placement varies quite a bit, depending on study goals (Thair et al., 2017). As the theoretical framework claims, WM is a multiregional system, and EFs are mainly associated with the DLPFC. However, other cortical structures, such as the parietal-occipital areas, also play a pivotal role, linked to visuospatial skills and the episodic buffer. In contrast, the inferior parietal lobe (Broca's area) is associated with (short-term) phonological functions (Müller & Knight, 2006). The DLPFC is the most common primary target of stimulation in EF studies. However, it has been suggested that stimulation over a larger cortical area could also affect WM. The model used here involved the DLPFC, extending the stimulation area to a broad cortical stimulation. Based on the current literature, it is likely that a more targeted montage may result in more robust effects on working memory (Martin et al., 2023). For example, a Broad-frontal montage in which the anodal electrode is located over the left DLPFC (e.g., F3 in the 10-20 EEG system) and the cathodal electrode is located extracephally (e.g., supraorbital area) has been shown to improve reaction time in WM tasks. This montage allows for a broader range of stimulation effects adapted to the distributed network needs of WM. Alternatively, a Bi-frontal montage, where the anodal electrode is located over F3 and the cathodal electrode over F4, should also be considered for a more focused stimulation approach (Martin et al., 2023). In addition, using 2 mA current intensity with smaller electrode sizes (e.g., 25 cm^2) may increase focalization and current density, potentially leading to a more efficient modulation of cortical excitability.

Methodological Considerations of tDCS Stimulation

The methodological variability of studies may also explain inconsistent results of tDCS use, including variance of samples, frequency of treatment, duration, current intensity, electrode size, and localization (Holczer et al., 2020; Nikolin et al., 2023). Most research in this area works with stimulation time between 5 and 30 minutes, which is usually delivered with an intensity ranging between 1 and 3 mA. The safety recommendation of 2 mA and electrodes with a size between 25 cm^2 and 35 cm^2 seem to be an appropriate choice for cognitive rehabilitation (Bikson et al., 2009, 2016; Horvath et al., 2014). Here, we followed literature recommendations for stimulation parameters, but the placement of the cathodal electrode was adjusted to ensure a larger stimulation area, which may have influenced the outcomes. Therefore, it may now be presumed that the position of the cathode used in this experiment is less favorable for beneficial changes in EFs. It should still be noted that the model we generated revealed that the peak current flow intensity/electric field (~.39 V/m) was nearly equal to an anodal stimulation of 1 mA (~.49 V/m), according to the calculation of Esmaeilpour and colleagues (2018) and the larger stimulation area can explain this. Our results indicate that the stimulation parameters used in this study may have limited the potential for significant behavioral changes, highlighting the need for further research into more targeted or higher-intensity tDCS protocols. On the other hand, several previous studies reported instrumentally measurable electrophysiological changes related to WM function (Kanske & Kotz, 2010b; Scharinger et al., 2015). Further research incorporating electrophysiological measures, such as EEG, may provide additional insights into the effects of tDCS. Above that, Nikolin and colleagues (2018) demonstrated significant changes in an event-related EEG component (P3) as a result of tDCS, while behavioral markers (e.g., response time, d-prime) remained unchanged, regardless of current intensity.

Another aspect that influences tDCS effects is whether stimulation is delivered during cognitive training (online) or before/after task solving (offline) (Thair et al., 2017). Martin and colleagues (2014) demonstrated that online anodal tDCS is significantly beneficial compared to offline stimulation and enhances skill acquisition on WM tasks (e.g., dual N-back tasks) among healthy participants (Martin et al., 2014). In one of our groups (AT) we applied online tDCS but did not find significant differences compared to the ICCT combined with sham tDCS (T). Since a clear effect of tDCS treatment is yet to be found, it is not possible to determine whether online tDCS stimulation was more beneficial than offline stimulation in the current experimental design. However, this does not mean that no effect can be expected from offline stimulation, as Hill and colleagues (2016) found a benefit of offline anodal tDCS stimulation on WM among healthy individuals (Hill et al., 2016). Also, literature is limited regarding the less beneficial effects of tDCS, as negative or no effects are much less likely to be published in this field. This aspect could also influence our assumptions about non-invasive brain stimulation techniques and their effect on cognitive functions (Kekic et al., 2016).

Transfer Effect of ICCT on Working Memory

In our study, we found a significant improvement in complex WM when investigating the main effect of time measured by LST, but no group-by-time interaction. In contrast, we found no significant change in another measure of complex WM (measured by DSTB). It is, therefore, questionable whether we experienced an actual transfer effect of ICCT to WM. Further explanation is needed as to why no significant transfer effect was found on tasks requiring complex executive functions. The primary explanation, reflecting on the work of Miyake and colleagues (2000), may be that ICCT does not affect EFs as a whole, as we measured with the complex working memory test (Miyake et al., 2000). Another aspect may be that there is no reciprocal relationship between updating and inhibition or updating has a different impact on EFs compared to inhibition. Besides, we still need to consider the possibility that long-term training of IC functions may be depleting the CE processes (Hedden & Park, 2001), which could also explain why no advantageous effect was found on the complex WM measures.

The question also arises whether, in clinical practice, we should accept instrumental electrophysiological measurements or neuropsychological tests as markers of a successful rehabilitation method. There is a large body of research on cognitive training tasks that reveals no development in the trained functions (Melby-Lervåg et al., 2016); thus, we might not expect beneficial neuropsychological changes when inhibitory and attentional processes are demanded in a parallel manner. However, some studies also report changes in non-trained domains and trained cognitive skills (Payne & Stine-Morrow, 2017). It is regularly cited that various implicit processes interact with each other, possibly explanaining the above phenomenon (Dunning & Holmes, 2014). Several research studies also claim that attention and EFs are jointly associated and induce a top-down mechanism in connection with the WM system (Gazzaley & Nobre, 2012). In this context, our cognitive training may have imposed a more significant cognitive load on complex WM and attention than short-term recall. However, further evidence is needed to substantiate this interpretation.

The question arises why visual short-term recall did not develop in this case. However, we should still consider that the tDCS cathode electrode was placed right above this area, which could cause an inhibition effect on the visuospatial functions. We developed our cognitive training on the design of Kanske and Kotz (2010). Their work suggests a similar outcome with different explanations. Corresponding to their assumption, the reaction during conflicting tasks supports goal-oriented and cohesive behavior (top-down mechanism). According to their results, a form of early attentional processing was facilitated (a bottom-up mechanism), experienced when projecting incongruent word stimuli with various emotional valence, similar to our experiment. However, this process contradicts the previously mentioned top-down processes, making the EF less subject to our cognitive training. Lastly, some studies emphasize the unpredictability of cognitive training tasks, suggesting that this makes them inadvisable for clinical application (Melby-Lervåg & Hulme, 2013).

Short-term Phonological Recall

The tDCS and ICCT combined had the most accentuated effect on short-term recall. It is to be noted, however, that this study featured non-neurotypical patients as a sample. In early research into Alzheimer's disease (AD), Collette and colleagues (1999) investigated the behavior of the EFs and the phonological loop in AD and found similar mechanisms and trends of change (Collette et al., 1999). They found that a general CE impairment was prevalent in AD, and the classification of the executive functions by impairment showed a further interaction with phonological memory. They associated lower executive performance with reduced short-term phonological functions, whereas subjects with higher scores did not show dysfunctions. It is crucial to emphasize that AD and stroke have different courses, so we cannot necessarily draw parallels in cognitive decline in the two conditions. However, we might assume that the CE may have been dysfunctional in our sample but not to the extent that phonological memory functions were adversely involved. This may also be related to the lack of significant transfer effects for complex WM functions. This could be an essential aspect worth considering in the future, not simply for studying alternative WM tasks for rehabilitation, but for more precisely identifying the level of impairment and deciding on adequate rehabilitation techniques.

Finally, the question may be raised regarding which exact features were practically valuable outcomes for stroke rehabilitation in our experimental model. The observed changes in short-term phonological memory and complex WM are likely unrelated to our experimental intervention, as no statistically significant effects were detected. The work of Fisk and Peter (1996) indicates that complex WM functions are more diminished in the elderly (aged 60-80), whereas no difference in phonological loop functions occur as compared to a younger cohort (aged 20-33) (Fisk & Warr, 1996). This may also mean that these functions are relatively intact and more responsive to therapeutic intervention. Knoflach and colleagues (2012) reached a similar conclusion in the field of neurorehabilitation. They found that patients younger than 55 years have an advantage in recovery from cognitive impairment. Under 55 years, the most significant improvement is expected between the ages of 18 and 35, with a steady decline of 3.1% and 4.2% in later age groups with every decade (Knoflach et al., 2012). The explanations involve neuroplasticity and vascular compensation, as this phenomenon appears independent of stroke type and may be interpreted as a general factor in stroke recovery. Thus, it is also worthwhile to consider how certain age groups are enrolled cognitive rehabilitation, as this may influence outcomes. However, this does not mean that targeted rehabilitation in older age groups is not worthwhile. Patients generally respond to treatment, as highlighted by Payne and Stine-Morrow (2017), who found that, on average, WM training can induce positive changes in EFs and related language functions at 68 years of age.

Clinical Implications

The results of this study may be relevant for developing neurorehabilitation protocols targeting WM and EFs in post-stroke patients. While no statistically significant effects on complex WM functions were observed with the combined use of tDCS and ICCT, the significant group difference in short-term phonological memory (Digit Span Forward Test) suggests that cognitive functions may respond favorably to combined treatment compared to tDCS alone.

Optimizing tDCS parameters, such as targeting the DLPFC with smaller electrodes and higher current intensities, could enhance stimulation effects. Integrating tDCS with concurrent cognitive training, rather than applying these interventions in isolation, appears more promising for cognitive improvement. Clinicians should also consider individual variability in response to treatment and baseline cognitive performance assessments to personalize rehabilitation. Even minor, targeted improvements in working memory and executive functions can lead to meaningful functional gains, emphasizing the potential value of these interventions in stroke rehabilitation programs.

LIMITATIONS

This study has several limitations. The relatively small sample size may have reduced the statistical power and generalisability of the findings, highlighting the need for larger samples in future research. Although the tDCS protocol was designed to stimulate the multiregional structure of WM, the stimulation area and cathodal electrode placement may have limited the focus of the intervention. Targeting more specific regions, such as the DLPFC, with optimized parameters (e.g., smaller electrode size, adjusted intensity) could improve efficacy. In addition, the tasks used to measure WM may only partially match the mechanisms targeted by inhibitory control training. The incorporation of electrophysiological measures such as EEG into future studies could provide deeper insights into the neural effects of these interventions.

CONCLUSION

In the present study, we investigated the effect of the combined use of tDCS and ICCT on WM-related functions in post-stroke patients. No statistically significant main effect was obtained on the cognitive functions investigated. Among the tasks tested, the Digit Span Forward Test showed the most prominent change. Furthermore, we observed a statistically significant difference between the AT and A groups in this task. Using tDCS or ICCT alone did not result in a statistically significant effect. Translating these results into everyday practice in neurorehabilitation requires further investigation. Nevertheless, the current results broaden our view on cognitive rehabilitation after stroke and provide essential considerations for further experimental designs.

ABBREVIATIONS

tDCS = Transcranial Direct Current Stimulation
CCT = Computer-based Cognitive Training
ICCT = Inhibitory Control Cognitive Training
WM = Working Memory
DSTF = Digit Span Forward Test
DSTB = Digit Span Backward Test
LST = Listening Span Task
CBTT = Corsi Block Tapping Task
TMT = Trail Making Test
CE = Central Executive
EFs = Executive Functions
DLPFC = Dorsolateral Prefrontal Cortex
ACE = Addenbrooke's Cognitive Examination
NART = National Adult Reading Test
LMEM = Linear Mixed-Effects Model

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Data availability statement

The data supporting this study are available from the authors upon reasonable request.

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Transzkraniális egyenáramú stimuláció és gátló kontroll tréning hatása a munkamemóriára stroke utáni rehabilitàció során

Célkitűzés: A munkamemória károsodása gyakori jelenség a stroke után, és jelentősen befolyásolja az érintettek mindennapjait. A transzkraniális egyenáramú stimulációt és a számítógépes kognitív tréninget széles körben alkalmazzák a neurorehabilitációban a kognitív funkciók javítása érdekében. Ez a tanulmány az anódos transzkraniális egyenáramú stimuláció és a gátló funkció tréning hatását vizsgálta a munkamemória működése szempontjából stroke betegek körében. **Módszerek:** Harmincöt résztvevő véletlenszerűen került alábbi három csoport egyikébe: csak aktív ingerlés, sham ingerlés tréninggel kombinálva vagy aktív ingerlés tréninggel kombinálva. A munkamemóriával kapcsolatos funkciók értékelésére a következő tesztek kerültek felvételre: Előre- és fordított Számterjedelem, Hallási Terjedelem Teszt, Corsi Kocka Teszt és Trail Making teszt. Az eredmények a tízalkalmas program előtt és után kerültek rögzítésre. A statisztikai elemzést Lineáris Mixed-effects Modellel végeztük. **Eredmények:** Jelentős csoport- és időinterakciós hatás mutatkozott a kombinált kezelést kapó csoport javára a csak aktív ingerlést kapó csoporttal szemben az előre számterjedelem esetében (p=0,028). **Következtetés:** Az eredmények arra utalnak, hogy az tréning és az ingerlés önmagában nem vezet szignifikáns javuláshoz a munkamemóriával kapcsolatos funkciók terén, míg a kombinált alkalmazás előnyös lehet. A számítógépes kognitív tréning és az transzkraniális ingerlés hatékonyságának további vizsgálata szükséges.

Kulcsszavak: rehabilitáció, stroke, transzkraniális egyenáramú stimuláció, kognitív tréning, munkamemória