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CLINICAL AND EXPERIMENTAL NEUROSCIENCE

THE USE OF TRANSCRANIAL DIRECT CURRENT STIMULATION AND COMPUTER-ASSISTED TRAINING PROGRAMS IN COGNITIVE AND AFFECTIVE REHABILITATION IN POST-STROKE PATIENTS

SUMMARY OF PH.D. THESIS

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2025

The publications relevant to the applicant's thesis:

Kazinczi, C., Kocsis, K., Boross, K., Racsmány, M., Klivényi, P., Vécsei, L., & Must, A. (2024). The effect of computerized cognitive training and transcranial direct current stimulation on working memory among post-stroke individuals: A systematic review with meta-analysis and meta-regression. *BMC Neurology, 24*(1), 314. *(Review Article, Q2, IF 2025: 2.2, DOI: https://doi.org/10.1186/s12883-024-03813-x (2024))*

Kazinczi, C., Szépfalusi, N., Németh, V. L., Holczer, A., Jakab, K., Vécsei, L., & Racsmány, M. (2025). The effect of transcranial direct current stimulation and inhibitory control training on depression and anxiety among post-stroke individuals. *BMC Neurology, 25*(1), 38. *(Original Research Article, Q2, IF 2025: 2.2, DOI: https://doi.org/10.1186/s12883-025-04042-6 (2025))*

Kazinczi, C., Szépfalusi, N., Németh, V. L., Holczer, A., Jakab, K., Vécsei, L., & Racsmány, M. (2025). The effect of transcranial direct current stimulation and inhibitory control training on working memory in post-stroke rehabilitation. *Neuropsychopharmacologia Hungarica, 27*(2), 88-10. *(Original Research Article, Q2, IF 2025: 0.86, (2025)*

INTRODUCTION

Stroke is one of the leading causes of disability and cognitive decline, often accompanied by executive function (EF) impairment and affective disorders. Among EFs, working memory (WM) and inhibitory control impairments are common, and post-stroke depression (PSD) and anxiety (PSA) also significantly affect functional recovery and the effectiveness of participation in rehabilitation. These cognitive and emotional deficits frequently occur together, suggesting shared underlying neural mechanisms that are often not adequately addressed in clinical practice.

Cognitive neuroscience increasingly views EFs and emotion regulation not as isolated functions linked to specific brain regions, but as elements belonging to large and dynamic brain networks. A central component of these networks is the frontoparietal network (FPN), which includes the dorsolateral prefrontal cortex (DLPFC) and the posterior parietal cortex (PPC). The FPN plays a pivotal role in cognitive control and goal-directed behaviour, while also interacting with the limbic system and the Salience Network, involved in emotion regulation. After stroke, the integrity of the FPN can be impaired, which may cause abnormalities in emotion regulation and EFs. Within the EFs, WM enables the temporary maintenance and manipulation of task-relevant information via updating, while inhibition helps suppress irrelevant responses.

In post-stroke rehabilitation, computerised cognitive training (CCT) offers an accessible method for addressing EF deficits. WM is commonly trained through tasks that emphasise updating, such as the "N-back task", which requires continuous monitoring and manipulation of incoming information. This close alignment with updating processes has made N-back protocols standard tools in WM-focused interventions. However, there is growing evidence that targeted CCT can also result in far transfer effects, meaning that training a specific function can also alter other, related functions. This raises the possibility that improving WM may also be achieved by training other executive functions, such as inhibition. In this context, Flanker-based inhibitory control training (ICCT) may provide a promising approach for investigating whether WM subcomponents can be trained in an interdependent manner, potentially producing transferable benefits for both cognitive and emotional functioning. The advantage of this is that WM can also be modulated using alternative CCTs other than N-back tasks.

In addition to CCT, other rehabilitation techniques are also available. Researchers explore transcranial direct current stimulation (tDCS), a non-invasive neuromodulation technique that modulates cortical excitability and promotes neuroplasticity through low-intensity electrical stimulation. Based on previous research, the stimulation of the DLPFC has been linked to improvements in WM and reductions in depressive symptoms. However, changes in network connections after stroke may limit the effectiveness of isolated regional stimulation.

Therefore, recent studies also support network-oriented stimulation protocols that involve the FPN more broadly and aim to influence both EFs and emotional regulatory processes.

Despite the growing interest in both CCT and tDCS interventions, their combined application remains underexplored in WM, inhibition and emotion regulation, especially in stroke populations. While CCT enables structured behavioural training of EF domains, tDCS may enhance these effects by modulating the underlying neural circuits. Given the shared neurocognitive substrates of cognitive and emotional dysfunctions, an integrated and alternative intervention that targets both domains simultaneously may offer improved therapeutic efficacy.

SCOPE AND AIM OF THIS WORK

Current research highlights the common influence of cognitive and affective factors in post-stroke rehabilitation. The reviewed studies raise key questions and offer insights that may guide alternative strategies for managing cognitive and emotional impairments after stroke. Based on this, our hypotheses were the following:

- **H1:** Based on the current literature, among the post-stroke rehabilitation tools, CCT is expected to show a more convincing rehabilitation potential compared to tDCS on WM-related measures.

- **H2:** Development of WM functions can be done by training inhibitory functions with Flanker-based inhibitory control training (ICCT).
- **H3:** Stimulation of a more extensive brain network (FPN) will show efficacy for WM and affective regulation.
- **H4:** The combined application of CCT and tDCS improves WM-related functions more effectively than the application of CCT or tDCS alone.
- **H5:** The combined application of CCT and tDCS significantly reduces post-stroke depression and anxiety symptoms compared to the application of CCT or tDCS alone.

This work addresses the issues identified in the literature through three first-authored studies: a two-part empirical investigation on the effects of tDCS and CCT on working memory and mood, and a meta-analysis comparing their rehabilitation efficacy, with results presented concerning WM.

METHODS AND MATERIALS

Methods and Materials of Systematic Review, Meta-analysis and Meta-regression

The meta-analysis aimed to examine randomised controlled studies (RCTs) on the rehabilitative effects of CCT and tDCS on WM subdomains in post-stroke rehabilitation, conducted according to PRISMA standards with a registered PROSPERO protocol. Eligibility

criteria were defined using the PICOS framework, including post-stroke adults aged 40–70, interventions of CCT or tDCS combined with standard rehabilitation, and control conditions involving conventional therapy or sham stimulation. WM outcomes were assessed with the Digit Span Forward and Backwards Tests and the Visual Span/Corsi Block Tapping Task.

A systematic search was performed in PubMed, Scopus, Cochrane Library, and Embase, supplemented by manual searches. Two independent reviewers screened titles, abstracts, and full texts, resolving disagreements by consensus. Methodological quality was assessed using the Cochrane Risk of Bias Tool 2.0, with high-risk studies excluded. Data extraction included demographic, clinical, and intervention characteristics, as well as detailed stimulation parameters for tDCS studies.

Statistical analyses were conducted in RevMan 5.4. For each study, post-intervention means and standard deviations were extracted or, if necessary, estimated from medians and interquartile ranges. Standardised mean differences (SMD) and 95% confidence intervals (CI) were calculated using a random-effects model to account for between-study heterogeneity. Heterogeneity was assessed with the I^2 statistic, with values of 25%, 50%, and 75% indicating low, moderate, and high heterogeneity, respectively. Statistical significance was set at $P < 0.05$, and heterogeneity was considered significant at $P < 0.10$ or $I^2 > 50\%$. Sensitivity analyses were performed by removing individual studies to

evaluate their influence on the pooled effect. Effect sizes were interpreted as small (0.2), medium (0.5), or large (0.8).

Methods and Materials of Empirical Study

The empirical research was published in two parts. The first part (I/I) focused on WM functions closely related to the theoretical background, while the second part (I/II) examined mood-related factors, specifically depression and anxiety. A total of 35 post-stroke patients (Mage = 59.6, SD = 10.9) were recruited from the Neurorehabilitation Unit at the Department of Neurology, University of Szeged. All participants were native Hungarian speakers, hospitalised for approximately two weeks, and received physiotherapy, speech therapy, and fine motor training. Inclusion criteria required measurable cognitive deficits with preserved reading comprehension. In contrast, exclusion criteria covered dementia unrelated to stroke, cerebral atrophy, alcohol use disorder, major psychiatric illness, extensive haemorrhage, metal implants, severe aphasia, or epilepsy. The mean Addenbrooke's Cognitive Examination score was 76.3 (SD = 9.89). Lesion sites included 12 right-hemispheric, 12 left-hemispheric, and 11 bilateral or subcortical locations. Nineteen participants began the intervention within three months after stroke (M = 1.29 months, SD = 0.87), while 16 began later (M = 41.81 months, SD = 46.21). Participants were blinded to their group allocation and informed only of potential side effects.

The experimental design consisted of three groups: Active tDCS only (Group A), sham tDCS combined with ICCT (Group T), and active

tDCS with ICCT (Group AT). The intervention phase comprised ten sessions, followed by post-testing using the same battery. tDCS was delivered using a NeuroConn DC Stimulator Plus device with a 2 mA current via two 5.5 × 7.5 cm sponge electrodes. The anode was placed over AFz and the cathode over Pz according to the 10–20 EEG system, with electrode placement verified using individual head measurements. SimNIBS 3.2 modelling confirmed peak stimulation in the dorsolateral prefrontal, parietal, and parieto-occipital cortices. Stimulation lasted 12 minutes per session, with the AT group receiving concurrent ICCT and the T group receiving ICCT without stimulation. The ICCT programme was a Flanker Task implemented in E-prime 2.0 to improve inhibitory control. Participants responded to congruent (green target and flankers) and incongruent (red target with green flankers) conditions, with reaction times reduced progressively from 5000 ms to 1000 ms depending on accuracy. Each session included four blocks of 180 trials.

In I/I, WM outcomes were assessed using the Digit Span Forward and Backwards Tests, Listening Span Task, Corsi Block-Tapping Task, and Trail Making Test A/B. In I/II, mood outcomes were measured using BDI, HAM-D, STAI-S, and STAI-T. Additional assessments included the Addenbrooke's Cognitive Examination, Wisconsin Card Sorting Test, and National Adult Reading Test. While in I/II, pre-testing included Beck's Depression Inventory (BDI), Hamilton Depression Scale (HAM-D), and the State-Trait Anxiety Inventory (STAI-S and STAI-T). The

testing process took place on two consecutive working days prior to the intervention.

For I/I, statistical analysis (SPSS v25.0, $\alpha = 0.05$) examined baseline group differences with one-way ANOVA or Kruskal–Wallis tests for continuous variables and χ^2 tests for categorical data. Intervention effects were tested using Linear Mixed Effects Models (LMEMs) with factors Group, Time, and Group × Time, adjusting for demographic and clinical covariates. Significant interactions were followed by Bonferroni-corrected post hoc tests, and effect sizes were reported as f^2 and Cohen's d. Power analysis indicated that N = 30 ensured adequate statistical power (0.91). For I/II, analyses (JAMOVI v2.3) applied 2 × 2 mixed ANOVA with Tukey post hoc tests, Pearson correlations, and Bayesian mixed-model ANOVA (BF_{10}, BFIncl) to account for baseline differences. The minimum clinically important difference (MCID) for BDI was defined as a positive change, ≥5-point reduction, and ≥29.64% relative decrease, with group differences assessed using χ^2 tests.

RESULTS

Results of Systematic Review, Meta-analysis, and Meta-regression

The database search identified 4,142 records (PubMed: 609, Scopus: 1,036, Embase: 929, Cochrane Library: 1,544) and an additional 24 from manual searches. After duplicate removal and eligibility screening, 53 studies were reviewed in full, of which 44 were excluded

for reasons including language, population, design, missing outcomes, or combined interventions. Ultimately, nine studies using CCT alone were included. Inter-rater agreement for study selection was substantial, with Cohen's Kappa ranging from 0.71 to 0.77, and PABAK values between 0.79 and 0.82, indicating good reliability. The nine studies, published between 2007 and 2022, included 461 participants (234 intervention, 227 control) from six countries, with mean ages between 43.9 and 67.5 years and an average post-stroke interval of 13.8 months. Control conditions varied across studies, and most interventions involved structured CCT programmes such as RehaCom, Lumosity, Cogpack, Erica, RoboMemo, or BrainGymmer, delivered over 10–58 sessions lasting 20–60 minutes. Risk of bias assessment classified four studies as 'low risk' and five as 'some concern', with no studies rated 'high risk'. Most methodological issues were related to incomplete reporting of randomisation or measurement rationale; however, no significant bias was identified for the WM-specific outcomes.

Meta-analysis of short-term phonological recall (Digit Span Forward, DSTF) across eight studies (n = 384) showed moderate heterogeneity (I^2 = 50%) and no significant improvement over controls (SMD = 0.30, 95% CI = 0.06–0.46; Z = 1.95; P = 0.05). Sensitivity analysis identified two outlier studies; their removal reduced heterogeneity (I^2 = 0%) but did not yield statistical significance. WM capacity (Digit Span Backwards, DSTB) was assessed in four studies (n = 193) and showed a significant improvement in favour of CCT (SMD =

0.39, 95% CI = 0.10–0.67; Z = 2.65; P = 0.008), with negligible heterogeneity (I^2 = 0%). Visuospatial WM (Visual Span Task, VSTF) analysis from seven studies (n = 323) showed a non-significant trend towards improvement (SMD = 0.22, 95% CI = –0.01–0.44; Z = 1.90; P = 0.06), with moderate heterogeneity (I^2 = 40%). Removal of one outlier study eliminated heterogeneity (I^2 = 0%) and revealed a significant effect (SMD = 0.43, 95% CI = 0.16–0.69; Z = 3.14; P = 0.002). Meta-regression tested participant age, session duration, and number of sessions as potential moderators of intervention effectiveness. None of these variables significantly influenced the WM outcomes.

Results of Empirical Study I/I and I/II

Participants had a mean age of 59.68 years (SD = 11.10) and an average of 12.03 years of education (SD = 3.40). Groups did not differ significantly in demographic variables (age, education, gender distribution, lesion location, or time since stroke), nor baseline cognitive performance measured by NART and ACE. According to LMEM, no significant baseline differences were found in primary WM outcomes (DSTF, DSTB, LST, CBTT, TMT-A/B) or affective measures (BDI, STAI-S, STAI-T), except for HAM-D, where the active tDCS group scored lower. Baseline BDI and HAM-D values were above clinical thresholds, while STAI scores were within normal limits. Strong correlations were observed between pre- and post-treatment affective

measures, the strongest between post-treatment STAI-T and BDI scores ($r = .79$, $p < .001$).

In **Empirical Study I/I,** DSTF performance showed a significant time × group interaction ($p = 0.028$) the AT group (active tDCS + CCT). No significant effects were found for DSTB, CBTT, TMT-A, or TMT-B. LST scores showed a significant main effect of time ($p = 0.006$), indicating post-intervention improvement across all groups. Variance components indicated high individual variability in most tasks (ICC = 0.37–0.90), with stronger model fits when random effects were included.

In **Empirical Study I/II,** BDI scores showed significant improvement over time ($p < .001$, $\eta p^2 = 0.30$) and a significant time × group interaction ($p < .001$, $\eta p^2 = 0.40$), with post hoc tests confirming that only the AT group improved significantly. Bayesian analysis supported both time and condition effects, with the AT group benefiting most. HAM-D scores showed significant main effects of time ($p = .004$, $\eta p^2 = 0.23$) and condition ($p = .012$, $\eta p^2 = 0.25$), indicating overall improvement and between-group differences, though without a significant interaction. STAI-S showed no significant changes, while STAI-T showed a significant time effect ($p = .015$, $\eta p^2 = 0.18$) reflecting a general reduction in trait anxiety. Analysis of MCID for BDI indicated that significantly more participants in the AT group achieved clinically relevant improvement compared to A and T groups ($\chi^2 = 10.14$, $p = .006$; $\chi^2 = 8.43$, $p = .015$), reinforcing the superior clinical effectiveness of the combined intervention.

DISCUSSION

In summary, these are the main findings of our investigations:

Empirical study: The short-term phonological recall (DSTF) showed a significant time × group interaction, with the AT group achieving the greatest improvement. The Listening Span Test demonstrated a significant main effect of time, indicating overall improvement across groups. For depressive symptoms, BDI scores showed significant time and time × group effects, with improvements limited to the AT group. HAM-D scores improved over time and differed between groups without a significant interaction. Trait anxiety (STAI-T) showed a significant time effect, indicating a general reduction across groups.

Meta-analysis: CCT significantly improved WM capacity (Digit Span Backwards Test) and visuospatial WM (Visual Span Forward Test) compared with control conditions.

Hypotheses: (H1) was partially supported: CCT improved specific WM domains (visuospatial and complex WM), while evidence for tDCS effects remained limited and inconsistent across WM measures. **(H2)** was unsupported: ICCT did not produce a significant transfer effect on WM. **(H3)** was unsupported: FPN stimulation via tDCS did not yield consistent benefits. **(H4)** was not supported; overall, no main WM effect

was observed, although a significant difference emerged between the A and AT groups in the DSTF. **(H5)** was partially supported, the combination of CCT and tDCS resulted in a significant reduction in depressive symptoms compared to the standalone applications; however, no clear effect was found in the anxiety measures.

The meta-analysis points to the value of CCT (particularly for complex and visuospatial WM) while the empirical results highlight the modest effects achievable when combining CCT with tDCS. A key implication is that the nature of the WM component being targeted matters. Tasks that engage EFs appear more responsive to training, while simpler storage-based functions (e.g., DSTF) show less improvement. This reinforces the importance of aligning intervention content with cognitive mechanisms most likely to benefit from rehabilitation. In the case of tDCS, our results highlight the difficulties also indicated in the literature: the inconsistency of the results is likely due to the heterogeneity of the montage, intensity, and individual neurobiological profiles. Although the AFz–Pz montage is theoretically promising in terms of involving the FPN, it may not have the specificity required for post-stroke effects. The lack of consistent transfer effects from ICCT to broader WM measures raises questions about the generalisability of transfer effects observed in healthy samples. Stroke-related alterations in neural connectivity, cognitive load constraints, and possible interference from stimulation parameters may all play a role. These findings suggest

that ICCT, while conceptually valuable, may need adaptation or supplementation with other WM-relevant exercises for this population.

In terms of affective outcomes, the pattern of improvement in depressive symptoms without improvement in anxiety symptoms is consistent with previous research findings that PSD and PSA have different neural bases and different modifiability. Although the combined tDCS + CCT approach showed the most promising direction of change, the variability and partial nature of these effects make them difficult to generalize.

Clinically, these findings advocate for targeted and individualised approach:

- CCT for WM is an easily accessible and adaptable tool for clinical rehabilitation, offering advantages over traditional cognitive rehabilitation tasks, yet requiring fewer resources than neuromodulation.
- tDCS protocols should be optimised and refined in terms of focus and intensity, determined individually for the current treatment
- Combined interventions should be integrated into multidisciplinary programmes, with careful monitoring of cognitive load and individual responsiveness

Finally, methodological heterogeneity in the literature, particularly in the design of interventions and measurement of outcomes, continues to

hamper the development of clear clinical applicability. Future research should prioritise standardisation, larger and more homogeneous samples, and long-term follow-up to assess the durability of effects. In addition to statistical significance, clinically significant changes should remain the guiding standard, ensuring that rehabilitation progress results in tangible improvements in patients' daily functioning and quality of life.

ACKNOWLEDGEMENT

I would like to thank my co-authors for their collaboration and contributions to the research included in this dissertation. I am also grateful to my supervisors, Dr. Mihály Racsmány and Dr. Anita Must, for their professional guidance and support throughout the preparation of this work. I also wish to thank the Department of Neurology at the University of Szeged for their collaboration and assistance in conducting this research.