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RESEARCH ARTICLE

Randomized trial of cognitive training and brain stimulation in non-demented older adults

Daria Antonenko[1] | **Friederike Thams**[1] | **Ulrike Grittner**[2,3] | **Jessica Uhrich**[1] | **Franka Glöckner**[4] | **Shu-Chen Li**[4] | **Agnes Flöel**[1,5]

[1] Department of Neurology, Universitätsmedizin Greifswald, Greifswald, Germany

[2] Berlin Institute of Health (BIH), Berlin, Germany

[3] Charité – Universitätsmedizin Berlin, Humboldt-Universität zu Berlin, Berlin Institute of Health, Institute of Biometry and Clinical Epidemiology, Berlin, Germany

[4] Lifespan Developmental Neuroscience, Faculty of Psychology, TU Dresden, Dresden, Germany

[5] German Centre for Neurodegenerative Diseases (DZNE) Standort Greifswald, Greifswald, Germany

Correspondence
Agnes Flöel, Ferdinand-Sauerbruch-Straße, 17574 Greifswald, Germany.
E-mail: agnes.floeel@med.uni-greifswald.de

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Abstract

Introduction: Given rapid global population aging, developing interventions against age-associated cognitive decline is an important medical and societal goal. We evaluated a cognitive training protocol combined with transcranial direct current stimulation (tDCS) on trained and non-trained functions in non-demented older adults.

Methods: Fifty-six older adults (65–80 years) were randomly assigned to one of two interventional groups, using age and baseline performance as strata. Both groups performed a nine-session cognitive training over 3 weeks with either concurrent anodal tDCS (atDCS, 1 mA, 20 minutes) over the left dorsolateral prefrontal cortex (target intervention) or sham stimulation (control intervention). Primary outcome was performance on the trained letter updating task immediately after training. Secondary outcomes included performance on other executive and memory (near and far transfer) tasks. All tasks were administered at baseline, post-intervention, and at 1- and 7-month follow-up assessments. Prespecified analyses to investigate treatment effects were conducted using mixed-model analyses.

Results: No between-group differences emerged in the trained letter updating and Markov decision-making tasks at post-intervention and at follow-up timepoints. Secondary analyses revealed group differences in one near-transfer task: Superior n-back task performance was observed in the tDCS group at post-intervention and at follow-up. No such effects were observed for the other transfer tasks. Improvements in working memory were associated with individually induced electric field strengths.

Discussion: Cognitive training with atDCS did not lead to superior improvement in trained task performance compared to cognitive training with sham stimulation. Thus, our results do not support the immediate benefit of tDCS-assisted multi-session cognitive training on the trained function. As the intervention enhanced performance in a near-transfer working memory task, we provide exploratory evidence for effects on non-trained working memory functions in non-demented older adults that persist over a period of 1 month.

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KEYWORDS
cognitive intervention, computational modeling, electric fields, executive functions, healthy aging, memory, non-invasive brain stimulation, transcranial electrical stimulation

1 | INTRODUCTION

New strategies against age-associated cognitive decline are urgently needed, preferably operational early in the process of aging, that is, before mild cognitive impairment or dementia. At this stage, strategies with potentially severe side effects (e.g., anti-amyloid treatments) are not justifiable in terms of risk–benefit ratio, and non-drug behavioral strategies, such as cognitive training, are desirable.[1,2] Although promising, training programs are often exhausting and protracted, and evidence regarding sustainability and transfer of effects is inconclusive.[3]

Here, concurrent application of transcranial direct current stimulation (tDCS) during multiple sessions of task practice may boost training gains, and potentially lead to longer-lasting and more generalized cognitive improvement, that is, transfer to non-trained tasks.[4–7] Anodal tDCS (atDCS) over task-relevant brain regions facilitates cortical excitability by changing membrane potentials toward depolarization, thus supporting and tuning ongoing neural network processes[8] and thereby enhancing cognitive outcome.[5,9,10] Only a few prior studies have used atDCS over dorsolateral prefrontal regions during executive training over multiple practice sessions, which resulted in enhanced working memory in the atDCS compared to sham tDCS groups in the trained tasks or the so-called near-transfer tasks probing similar functional processes.[4,9,11,12] Thus, some studies have even observed transfer to non-trained cognitive tasks, with effects that could be maintained for up to 4 weeks.[11–13] Although these first empirical studies have provided encouraging results for beneficial effects of combined interventions, multiple tasks at multiple timepoints (e.g., effects on trained tasks as well as transfer tasks and long-term effects) were not systematically assessed; most studies were conducted in young adults; and three out of seven studies (targeting executive functions) in non-demented older adults did not show beneficial effects.[14–16] None of the studies adhered to CONSORT (Consolidated Standards of Reporting Trials) guidelines for clinical trials. Thus, firm conclusions about the efficacy of such combined interventions, particularly in older populations, and regarding transfer tasks and longer term effects, are not possible yet.

Given unmet medical needs in the increasing aging population, we aimed to assess the efficacy of a combined intervention strategy in a clinical trial. We performed a monocentric, randomized, placebo-controlled clinical trial in older adults without cognitive impairment to determine the effects of atDCS-accompanied cognitive training. Immediate and delayed effects on training and transfer tasks, as well as induced individual electric field as potential predictor of performance enhancement, were determined.

2 | METHODS

2.1 | Study design and participants

We performed a monocenter, single-blind randomized controlled trial comparing cognitive training to concurrent atDCS or sham. Both groups underwent nine sessions evenly distributed over 3 weeks, aiming for a feasible multi-session design, thus increasing feasibility and reducing the drop-out rate. The study was performed at University Medicine Greifswald. The full study protocol including eligibility criteria, detailed descriptions of the tasks, and statistical analysis plan has been published previously.[17] The study protocol was approved by the ethics committee of the University Medicine Greifswald and registered at ClinicalTrials.gov (Identifier NCT03838211). All participants gave written informed consent at the beginning of the baseline-visit (see Table S1 in supporting information for baseline characteristics).

2.2 | Randomization and masking

Fifty-six eligible participants were randomly allocated to target and control intervention group with a 1:1 ratio (see Antonenko et al.[17] for details). Participant blinding was ensured using sham stimulation in the control intervention group: Current was initially applied for 30 seconds to elicit the typical tingling sensation of active stimulation on the scalp and turned off subsequently. Previous research showed that sham tDCS is a valid and safe method for blinding participants.[18] After the last training session, participants were asked to state whether they believed they received anodal or sham tDCS. To minimize implicit investigator bias in our single-blind design, data were digitalized and were analyzed according to the statistical analysis plan by study personnel members blinded to the stimulation condition.

2.3 | Intervention

After randomization participants adhered to a pre-assessment, immediately followed by nine training visits with a consecutive post-assessment and follow-up assessments at 1 and 7 months after the post-assessment. In each of the nine training visits, participants performed two cognitive training tasks (letter updating task[1] and three-stage Markov decision-making task,[19] being vulnerable to the effects of aging and well suited to examine the effects of practice over multiple sessions in older adults[1,19–21]). Participants first performed a letter updating task[1] on a tablet computer, where they were presented with

RESEARCH IN CONTEXT

1. Systematic review: Searching the terms [cognitive training] AND [non-invasive brain stimulation OR transcranial direct current stimulation OR tDCS] AND [aging OR ageing OR older adults] yielded seven reports investigating multi-session cognitive training interventions targeting executive functions with transcranial direct current stimulation in non-demented older adults. The evidence reported in these studies is inconclusive regarding effects on the trained task, transfer effects, and long-term effects after the intervention.
2. Interpretation: Our study provides no evidence for the efficacy of this intervention in increasing performance on the trained task, but exploratory results suggest its potential to induce sustained near-transfer effects.
3. Future directions: It remains to be determined (a) under which circumstances transfer effects occur, (b) how a more prolonged effect (i.e., > 1 month after intervention) may be obtained, and (c) whether individually "tuned" stimulation parameters using computational modeling analyses may enhance its benefit.

lists of letters A to D in random order. After each list, participants were asked to recall the last four letters that were presented. Subsequently, in a three-stage Markov decision-making task,[19] presented on a laptop computer, participants had to learn to choose the optimal sequence of actions to maximize overall gains and minimize overall loss.

The cognitive training was administered while participants received either anodal or sham tDCS via a battery-operated stimulator (Neuroelectrics Starstim-Home Research Kit). At the beginning of each session, tDCS set-up was mounted with two round saline-soaked sponge electrodes (5 cm diameter; anode: F3, cathode: Fp2) in a neoprene head cap using the 10–20 EEG-system grid. Direct current was delivered with 1 mA intensity for 20 minutes in atDCS group (sham: 30 seconds, with the neoprene cap remaining on participants' heads for the duration of the training session). The stimulation was started simultaneously with the first task and finished after approximately the first half of the Markov task. Adverse events were assessed by questionnaire every third training session.

At pre-, post-, and follow-up assessments the two training tasks were followed by administration of four transfer tasks (near-transfer for letter updating task: n-back task, near-transfer for Markov decision-making task: Wiener matrices test,[22] far transfer: auditory verbal learning test,[23] virtual reality maze task[24]). First, a numerical n-back task, comprised of a 1-back and a 2-back condition, was performed on a laptop computer. Each condition consisted of nine trials and 10 items. Next, the German version of the Auditory Verbal Learning Test (AVLT) was administered.[23] In the 30-minute interval before the delayed recall, participants performed the Wiener Matrices Test (WMT-2).[22] The last task was a virtual reality (VR) maze task, in which participants had to encode a designated route and then recall the route by navigating to specific goals along it.[24]The recall trial consisted of four blocks (5 minutes duration each). During each block, participants could maximize the number of goals they could reach by correctly following the learned route as many times as possible within the 5 minutes. Parallel versions of the tasks were administered in randomized counterbalanced order for each session.

2.4 | Outcomes

Primary outcome measure was working memory performance at post-assessment as measured by number of correctly recalled lists in the letter updating task. Secondary outcomes were performance in decision-based learning at post-assessment as measured by the proportion of optimal actions in the Markov decision-making task as well as working memory and decision-based learning performance at follow-up assessments. Other secondary outcomes were performances on the transfer tasks at post and follow-up assessments: near-transfer was measured by percent correct working memory performance in an n-back task. Far-transfer tasks included: the German version of the AVLT[23] measuring episodic memory performance by number of words recalled at delayed recall, the WMT-2 Test[22] assessing reasoning ability, and a VR maze task[24] assessing spatial memory by number of goals reached.

2.5 | Computational modeling analysis

The software SimNIBS v3.1 was used to calculate the electric field induced by transcranial electrical stimulation, based on the finite element method and individualized tetrahedral head meshes generated from the structural T1- and T2-weighted images of the participant (see supporting information).[25] Total intracranial volume (ICV) and regional gray matter volume of the left rostral middle frontal gyrus (most probably corresponding to the target area) were extracted using FreeSurfer v6.0 (see supporting information).

2.6 | Statistical analysis

The predefined analyses were conducted using IBM SPSS software (v25) and R (v3.6.3),[26] described in the statistical analysis plan (SAP), uploaded before the analysis of primary outcome. All participants who received at least 1 day of intervention were included in the full dataset for intention-to-treat analysis. Separate linear mixed model analyses were conducted for post-assessment and follow-up timepoints, for each task (see supporting information, deviations from the SAP are specified in Table S2). We report model-based marginal means and group differences with 95% confidence intervals (CIs). Pearson correlation coefficients were computed as association measures between performance effects and modeling-based electric field strengths. A two-sided significance level of $\alpha = 0.05$ was used. All secondary hypotheses were tested exploratorily.

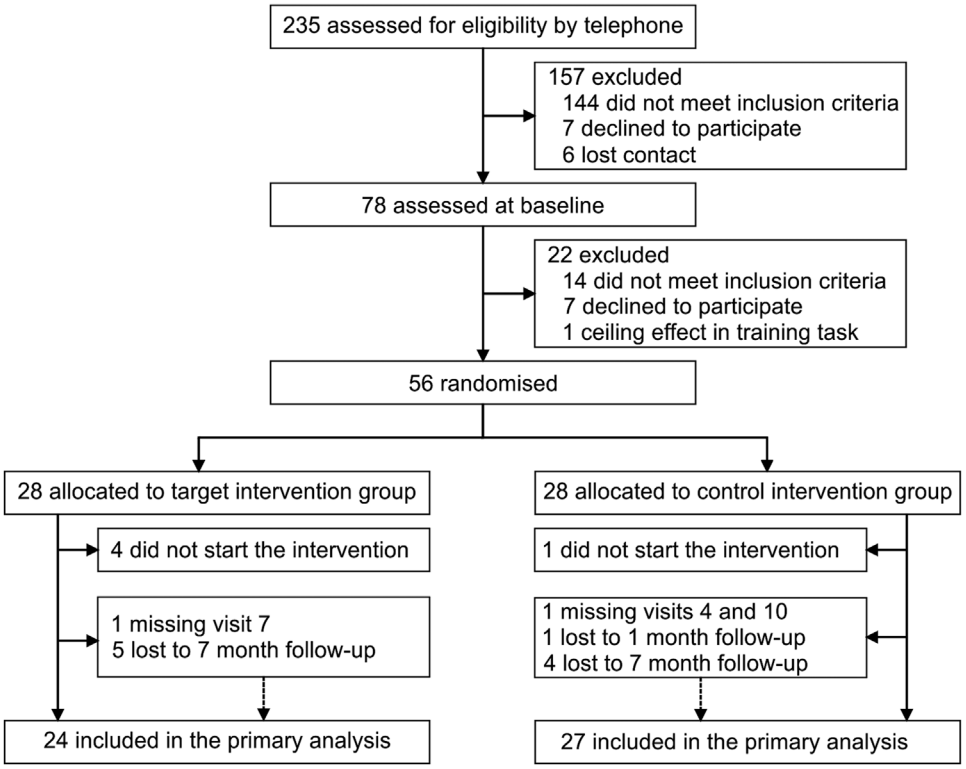


FIGURE 1 Consolidated Standards of Reporting Trials (CONSORT) diagram. Intention-to-treat analysis was performed for primary outcome at post-assessment. Five participants did not start the intervention and were therefore not included in analysis.

3 | RESULTS

From February 15, 2018 to August 02, 2018, we screened 235 potential participants by telephone; 78 were invited to the on-site screening and baseline assessment, 56 participants were included in the trial and randomly assigned to either atDCS-accompanied cognitive training (target intervention, n = 28) or sham-accompanied cognitive training (control intervention group, n = 28, Figure 1). Last post-assessment (primary outcome) was completed on November 11, 2019; last 7-month follow-up on March 25, 2020. Five participants did not commence the intervention, resulting in 51 participants (mean/standard deviation [SD] age 70/4 years, 36 women) in the intention-to-treat analysis.

3.1 | Treatment effects

3.1.1 | Training tasks

Figure 2 shows model-derived adjusted means in each group as well as adjusted treatment effects (group differences). For the primary outcome letter updating performance immediately after intervention, there were no substantial treatment effects. No differences were observed at follow-up timepoints (Figure 3A). For the Markov training task, there were no differences at post-assessment or follow-up (Figure 3B).

3.1.2 | Transfer tasks

For n-back task immediately after intervention, we observed a significant difference after intervention (post-assessment) and at follow-up (Figure 4A). Post hoc analysis to estimate effects at follow-up timepoints revealed a more pronounced group difference at 1-month follow-up. Further, treatment effect was larger for those participants with low initial performance levels (treatment effect over all follow-up timepoints at low baseline values, e.g., at 25th percentile of 86.7: 3.05, 95% CI 1.04 to 5.06, $P = .004$, in contrast to those with high baseline values, e.g., at 75th percentile of 96.7: 0.82, 95% CI −1.45 to 3.09, $P = .474$).

For all other transfer tasks (near-transfer WMT-2 task, Figure 4B, and far-transfer tasks: VLMT, Figure 5A and VR, Figure 5B), no difference was observed at post-assessment or follow-up.

3.2 | Individual electric fields

Computational modeling confirmed that electric fields were induced in the frontal cortices, showing a variability of field magnitudes up to 25% (Figure 6). Current distributions were similar in anodal and sham stimulation groups, as expected, as similar underlying anatomy is assumed (please note that in the sham group the fields were only induced for 30 seconds). Higher field strengths were associated with higher performance change through the intervention in the atDCS ($r = 0.49$, $P = .03$),

Outcome	Control group adj. mean (95% CI)	Target group adj. mean (95% CI)	Group differences (95% CI)	p−value
Post Training				
Letter Updating	8 (7 – 9)	8 (7 – 10)	−0.0 (−1.4 – 1.4)	0.994
Markov	68 (62 – 73)	70 (64 – 76)	2.7 (−5.3 – 10.6)	0.504
Post Transfer				
Nback*	91 (90 – 93)	94 (93 – 96)	3.1 (1.1 – 5.2)	**0.003**
WMT	50 (45 – 55)	53 (48 – 59)	3.1 (−4.6 – 10.8)	0.417
VLMT	12 (10 – 12)	11 (10 – 12)	−0.1 (−1.6 – 1.4)	0.859
VR*	14 (11 – 18)	14 (9 – 18)	−1.1 (−6.9 – 4.7)	0.706
Overall FU Training				
Letter Updating	8 (6 – 9)	8 (7 – 9)	0.6 (−1.0 – 2.4)	0.447
Markov	68 (62 – 74)	68 (61 – 74)	0.1 (−8.4 – 8.4)	0.998
Overall FU Transfer				
Nback	92 (91 – 93)	94 (93 – 96)	2.1 (0.3 – 3.9)	**0.021**
WMT	53 (49 – 57)	55 (51 – 60)	1.9 (−3.9 – 7.8)	0.512
VLMT	12 (11 – 13)	12 (11 – 13)	−0.1 (−1.2 – 0.9)	0.792
VR	16 (14 – 19)	16 (13 – 19)	0.0 (−3.8 – 3.8)	0.981
1m FU Training				
Letter Updating*	8 (6 – 9)	9 (8 – 11)	1.3 (−0.7 – 3.2)	0.198
Markov*	70 (63 – 76)	67 (59 – 74)	−3.0 (−12.8 – 6.8)	0.543
1m FU Transfer				
Nback*	92 (91 – 94)	96 (94 – 98)	3.2 (0.7 – 5.7)	**0.011**
WMT*	53 (48 – 58)	58 (53 – 63)	5.5 (−1.4 – 12.4)	0.120
VLMT*	12 (11 – 13)	12 (11 – 12)	−0.1 (−1.4 – 1.2)	0.869
VR†	17 (13 – 21)	19 (15 – 23)	1.4 (−3.9 – 6.7)	0.597
7m FU Training				
Letter Updating	7 (5 – 8)	7 (5 – 9)	0.4 (−1.7 – 2.5)	0.711
Markov‡	63 (56 – 70)	64 (57 – 72)	1.4 (−9.0 – 11.8)	0.793
7m FU Transfer				
Nback‡	93 (91 – 94)	93 (91 – 95)	0.4 (−2.2 – 3.0)	0.735
WMT‡	57 (52 – 62)	54 (48 – 60)	−3.3 (−10.6 – 4.0)	0.374
VLMT‡	13 (12 – 14)	12 (11 – 14)	−0.2 (−1.6 – 1.2)	0.765
VR§	17 (13 – 21)	17 (12 – 22)	−0.3 (−6.3 – 5.6)	0.911

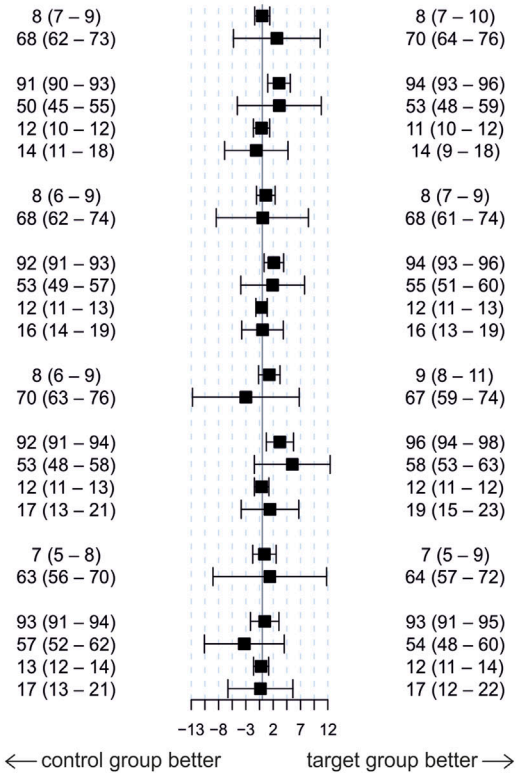


FIGURE 2 Analyses of training and transfer effects at post and follow-ups. Abbreviations and units: Letter Updating # correct. Markov % optimal actions. Nback % correct. WMT % correct. VLMT (German version of the AVLT) # words recalled. VR (virtual reality task) # goals reached. Separate linear mixed (except for "Post n-back": GEE) model analyses were conducted for post assessment and follow-up timepoints, for each task (ie, 1/7 m FU values are derived from the same models as for the corresponding overall FU scores). In case of missing data, results are based on multiple imputation. For separate timepoints: N = 51 if not indicated otherwise. *n = 50. †n = 49. ‡n = 42. Δn = 41. §n = 40. AVLT, Auditory Verbal Learning Test; CI, confidence interval; FU, follow-up; GEE, generalized estimating equation; WMT, Wiener Matrices Test.

but not in the sham group (r = −0.32, *P* = .12). Neither ICV nor regional volumes were not associated with performance change (see supporting information for correlation coefficients in intervention groups and Figure S1).

3.3 | Adverse events

Incidence of adverse events did not differ between groups (incidence rate ratio, 0.8, 95% CI 0.3–1.8, see supporting information and Table S3).

4 | DISCUSSION

In older adults without cognitive impairment, a 3-week intervention of cognitive training consisting of two executive function tasks (i.e., one working memory updating and one value-based decision-making task) combined with atDCS over left dorsolateral prefrontal cortex was not superior to cognitive training with sham stimulation based on the trained task performance at post-intervention. Thus, the combination of cognitive training with prefrontal atDCS did not lead to differences in training gain between target and control intervention groups. However, we found enhanced performance in a near-transfer working memory task. Improvement effect was observed post-intervention and at 1-month follow-up assessment. Together, the results of this trial do not support an immediate benefit of atDCS-assisted cognitive training on the trained function, but provide exploratory evidence for transfer effects on working memory in older adults that persist over a period of 4 weeks.

Our clinical trial did not provide evidence for our primary hypothesis that atDCS-assisted training will improve performance on a letter updating training task compared to sham in non-demented older adults. So far, only a few studies combining multi-session executive training and prefrontal atDCS have been conducted in older adults, providing mixed evidence,[11,12,14,15] with one study reporting a benefit in the trained task,[11] three which did not compare training task performance between interventional groups,[13,16,27] and three which were in line with our observation of no additional atDCS benefit in the trained task itself.[12,14,15]

Several "external" (related to training and stimulation protocols) and "internal" (related to participant characteristics) factors, and their

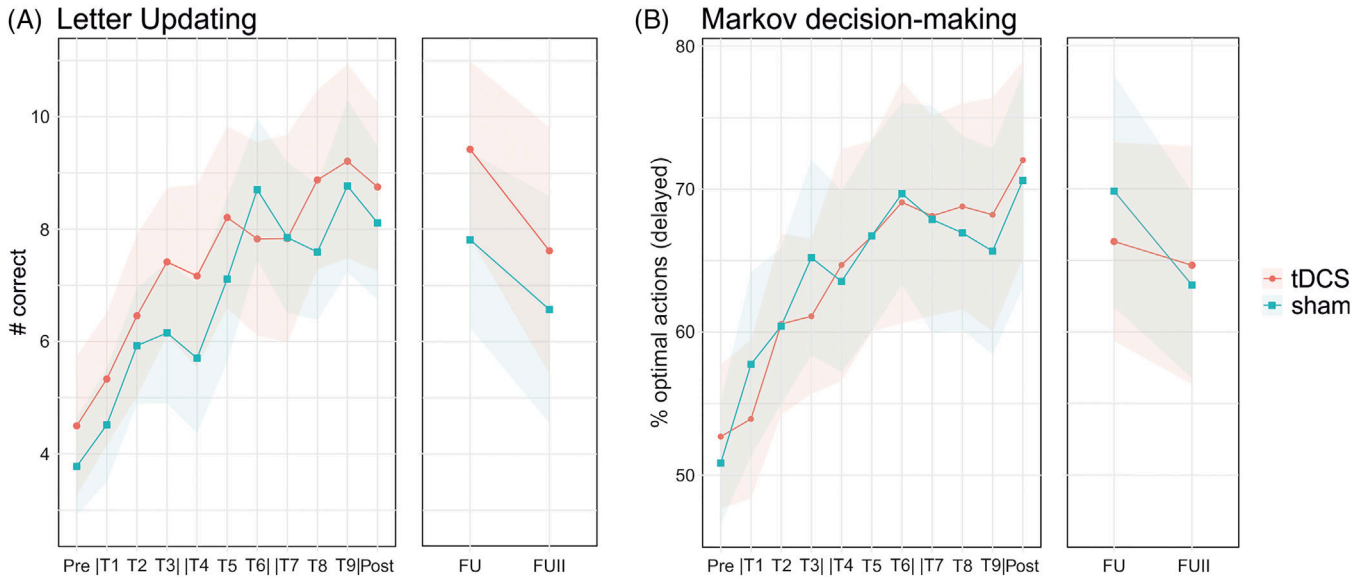


FIGURE 3 Performance on training tasks. Overall training improvement in the letter updating task (A) and the Markov decision-making task (B). atDCS did not additionally enhance training gains compared to sham. Pre, pre-assessment. T1-T9, training days 1 to 9. Dots represent mean values. Shaded areas indicate 95% confidence intervals. atDCS, anodal transcranial direct current stimulation; FU, 1-month follow-up; FUII, 7-month follow-up; Post, post-assessment.

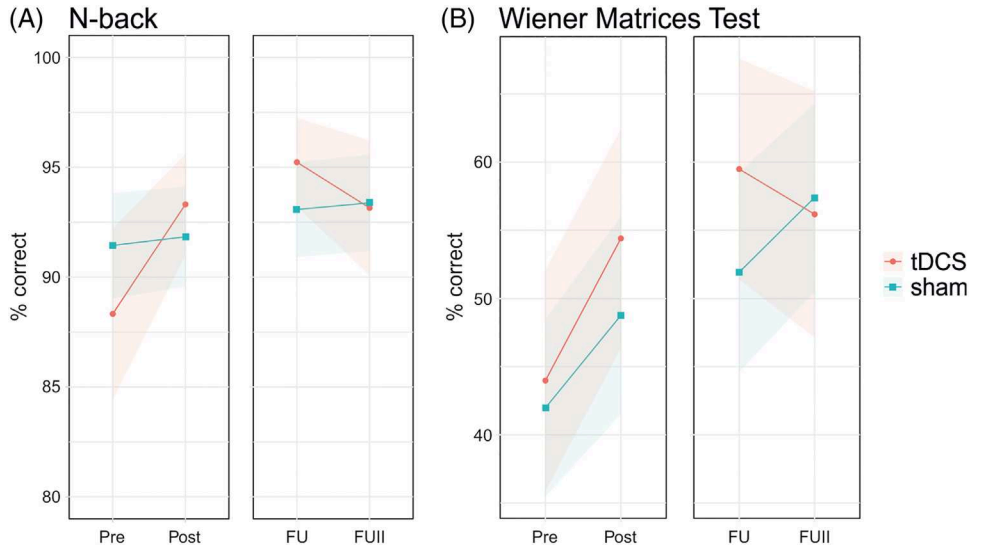


FIGURE 4 Performance on near-transfer tasks. Enhanced n-back performance after anodal transcranial direct current stimulation (atDCS) compared to sham at 1-month FU (A). No atDCS benefit over sham in Wiener Matrices Test (B). Pre, pre-assessment. Post, post-assessment. FU, 1-month follow-up. FUII, 7-month follow-up. Dots represent mean values. Shaded areas indicate 95%-confidence intervals.

interaction, may have precluded us from observing direct enhancement. Our training protocol was tailored to improve executive functions, consisting of a letter updating task and a decision-making task, and was administered for nine sessions over 3 weeks. In both groups, we observed a considerable improvement of the trained functions throughout the training sessions. Performance levels after the combined atDCS training on both tasks were not superior in the target compared to the control intervention, indicating that atDCS could not further enhance the trained functions. It is conceivable that longer combined interventions are required. However, evidence from two studies administering executive training with atDCS over more (i.e., 15–20) sessions is rather negative.[14,16] Recent research suggests that other cognitive tasks or domains, such as episodic memory, may be more amenable to atDCS-induced improvements during or immediately after intervention.[6,11,28] With regard to the stimulation protocol, there is no consent yet about the efficacy of specific parame-

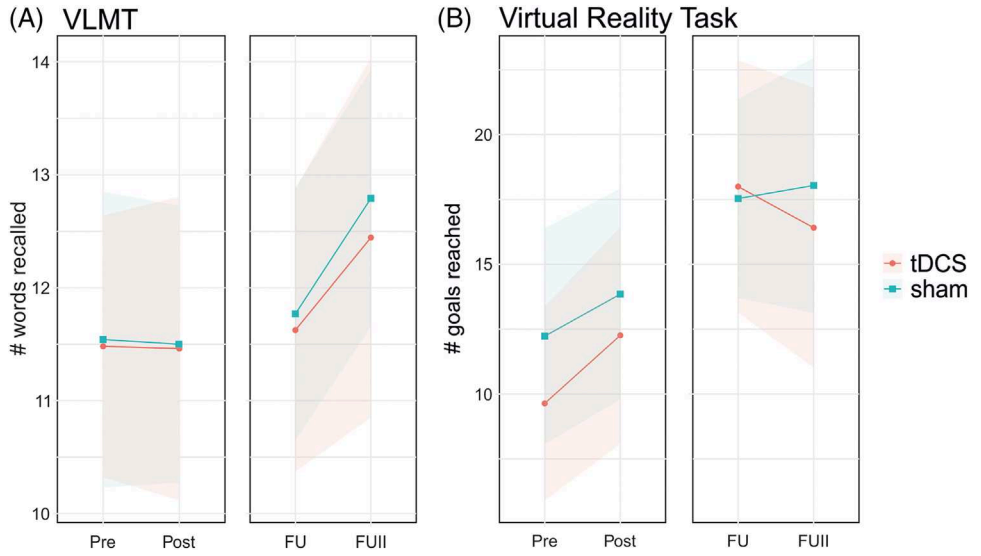


FIGURE 5 Performance on far-transfer tasks. No benefit of anodal transcranial direct current stimulation (atDCS) over sham in Verbal Learning and Memory Test (VLMT) (A) and Virtual Reality Task (B). Pre, pre-assessment. Post, post-assessment. FU, 1-month follow-up. FUII, 7-month follow-up. Dots represent mean values. Shaded areas indicate 95%-confidence intervals.

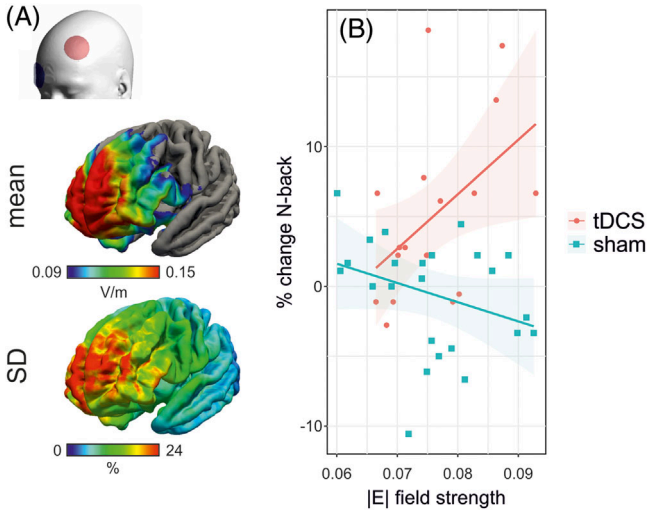


FIGURE 6 Electric fields induced by anodal transcranial direct current stimulation (atDCS). A, Electric field strength (|E|) averages transformed into "fsaverage" space (mean; in Volt per meter, V/m) and variability in field distribution (standard deviation, SD in %, scaled to the same values, here 99th percentile to illustrate the percentage of variation in relation to the "peak" field strength, thus how much individual brains differed from the mean distribution). B, Scatterplots showing the linear relationship of higher induced electric field strengths with higher performance change in the n-back task for atDCS.

ters over others, leaving the question of optimal stimulation intensity and electrode configuration unresolved. Previous studies have applied the same (1 mA) or higher intensities (1.5 or 2 mA) with the same (left prefrontal) or other electrode configurations (bilateral frontal, right prefrontal) with mixed evidence overall. With regard to participant characteristics, particularly in our older study cohort, age-related changes in brain volume that affect electric current flow induced by tDCS[29,30] may have compromised significant atDCS-induced improvements, for instance, due to less current reaching the brain. Further, brain regional variability within each individual may warrant adjusting stimulation intensities, or even placement of electrodes, to reach measurable effects.[29,31] Moreover, large variability among older adults not only with regard to baseline performance, but also in the degree of age-related brain atrophy and functional reorganization,[32] affect responsiveness to interventions.[31,33]

Note that most systematic evidence for the determinants of effects and their mechanisms stems from research conducted with young individuals.[33] Except for one study showing far transfer effects for 2 mA but not 1 mA,[12] systematic comparisons of different stimulation parameters and determinants for older cohorts are missing. Importantly, impact of varying stimulation intensity should be evaluated in combination with the respective simultaneously administered training task and protocol.[11,15] With regard to electrode configuration, a recent review suggests that simultaneous targeting of multiple nodes of the frontoparietal network with tDCS during cognitive training may be needed to produce benefits on the behavioral level in older adults.[28]

In sum, overall, variability between study designs regarding training and stimulation protocols (specific cognitive function to be trained, number of training sessions; intensity, duration, and location of concurrent tDCS application), as well as variability regarding the population of older participants recruited into each study (differences in age-related changes of brain volume, functional reorganization, and baseline performance) may produce inconsistent responses to atDCS.

Exploratory analyses showed small beneficial effects in the n-back task, lending support for the secondary hypothesis that executive training in combination with atDCS leads to working memory benefits as assessed by a near-transfer task. No effects on other transfer tasks were observed, suggesting domain-specific effects. This finding is con-

sistent with previous studies that included investigation on other than the trained function,[11,12] but contrasting evidence also exists.[14,15] Tentatively, tDCS may facilitate activity in domain-specific neural networks targeted with the intervention, such as the frontoparietal or default mode network,[34] thus allowing learning of new information. The effect persisted over a period of 4 weeks, but not 7 months, suggesting a temporally limited plasticity induction.

Using structural data from magnetic resonance imaging, we were able to simulate the electric field distribution induced by the tDCS protocol for each individual, and to relate the electric field strength to performance enhancement. We found higher working memory performance increases in the n-back task in participants in whom higher electric field strength was induced. No association of working memory performance was observed with neither whole-brain intracranial nor regional (left rostral middle frontal) volume, suggesting that age-associated gray matter atrophy does not account for the individual response to the intervention. Establishing a link between field strength and behavioral outcomes of brain stimulation interventions provides the opportunity to prospectively account for anatomical differences when individually tailoring brain stimulation experiments in the future.[35–40] Except one study reporting an association between prefrontal electric field density and verbal working memory in a group of young adults,[41] no prior clinical trial has assessed whether field strength determines behavioral outcomes of multi-session tDCS-assisted cognitive training interventions. By establishing this link, our data further confirm the impact of age-related brain atrophy on brain stimulation effects.[42,43] Whether increasing stimulation intensity would induce superior behavioral effects in a linear fashion, or whether this relationship is non-linear, remains to be examined in future trials.

In sum, we showed that while not exerting effects on the trained task, the target intervention may have the potential to improve similar functions with enhancement lasting up to at least 1 month. Analysis of electric field strength as potential determinant of performance enhancement suggests an impact of the amount of current reaching the targeted brain area on an individual level. However, this exploratory finding cannot be used for inferences on treatment effects.

The application of atDCS with 1 mA for 20 minutes on nine sessions over 3 weeks produced minimal adverse effects including itching and burning below the electrodes. Consistent with previous reports,[18] the occurrence and intensity of these effects did not differ between target and control intervention groups. Therefore, there are no safety concerns applying tDCS over multiple sessions concurrent to cognitive training.

We conducted a randomized controlled, single-center trial assessing the efficacy of a cognitive training combined with concurrent tDCS (compared to training with sham). Overall, we have designed a safe and well-tolerated intervention, as evidenced by excellent compliance and motivation of the older participants. While the broad assessment with multiple domains and multiple timepoints allowed a comprehensive evaluation of effects, several limitations must be considered. First, we tested a relatively small sample of older adults. A larger trial may be required to further evaluate the effects of atDCS-assisted cognitive training in aging. Second, despite random allocation, small performance differences before intervention were observed between groups, which might have affected the results. However, statistical models were appropriately adjusted for initial performance levels. Third, we did not include an additional "tDCS only" condition as we were specifically interested in learning- instead of stimulation-related plasticity and no beneficial effects on performance were expected through offline tDCS.[44–47] Moreover, we did not include additional control arms with alternative sites or stimulation parameters. This lack of additional controls may limit our understanding of determinants of the effects. Future studies might include different control conditions to conclude any specificity of the effects.[44]

4.1 | Clinical implications and future research

Taken together, our results do not provide evidence for the efficacy of an intervention consisting of a 3-week cognitive training with concurrent prefrontal tDCS. Further trials are needed to determine whether cognitive training improves measures of near-transfer at a clinically meaningful level, as suggested in our pre-specified, but secondary analyses. Future research also should evaluate additional approaches by varying stimulation and training parameters. Implementation of booster trainings (i.e., repeating the intervention after 1 month) may induce long-term effects,[2] a hypothesis to be explored in future studies. Variability among older adults regarding their amount of cognitive decline and age-associated regional atrophy emphasizes the need to develop individualized rather than uniform interventions, for example, adjusting stimulation intensity to reach a predefined electric field strength. If proven to be clinically effective, a combined atDCS-training approach that is well tolerated, carries no severe side effects,[18] and is of low cost, would present an auspicious tool to address one of the greatest medical needs of our generation.

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CONFLICTS OF INTEREST

The authors report no conflicts of interest.

AUTHOR CONTRIBUTIONS

DA, SCL, and AF designed the study. SCL and AF were responsible for funding acquisition. DA was responsible for investigation and project administration. FriT and JU acquired the data. DA, FriT, UG, and JU have accessed and verified the data. FriT, JU, and FraT were responsible for data aggregation and analysis of the paradigms. DA, FriT, and UG did the statistical analysis and were responsible for visualization and interpretation of data. AF supervised the study. DA, FriT, and AF wrote the original draft with input from UG and SCL. All authors critically revised the manuscript for important intellectual content and approved the final version of the manuscript. AF is the guarantor of the paper and

takes responsibility for the integrity of the work from inception to published article. The corresponding author confirms that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. The funders had no role in study design, data collection, data analysis, decision to publish, or preparation of the manuscript.

ORCID

Daria Antonenko https://orcid.org/0000-0002-2839-4609
Agnes Flöel https://orcid.org/0000-0002-1475-5872

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