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Transcranial electrical stimulation improves cognitive training effects in healthy elderly adults with low cognitive performance

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Abstract

Objective: To investigate the efficacy of transcranial direct (tDCS) or alternating current stimulation (tACS) in boosting cognitive training efficiency in healthy older adults. We further explored whether such improvements depend on general cognitive performance or age.

Methods: In this randomized, sham-controlled study, 59 healthy elderly participants (mean age 71.7) were assigned to receive computer-based cognitive training (10 sessions, 50 min, twice weekly) combined with tDCS (2 mA), tACS (5 Hz), or sham stimulation over the left dorsolateral prefrontal cortex (20 minutes). Cognitive performance was assessed with the Montreal Cognitive Assessment (MoCA), and a cognitive composite score derived from a broad neuropsychological test battery before and immediately after the intervention as well as at 6 and 12 months follow-ups.

Results: Performance in the cognitive composite score improved significantly in all groups but was not further modulated by neurostimulation. Additional analyses revealed that participants with a low initial MoCA score (< 1SD) improved significantly more in the tDCS than in the sham group.

Conclusion: TDCS increased the efficacy of cognitive training, but only in participants with initially low general cognitive performance.

Significance: Cognitive interventions including tDCS should address baseline performance as modulating factor of cognitive outcomes.

Highlights

- This study compared the effect of tDCS, tACS and sham stimulation on the efficacy of a cognitive training in healthy elderly adults.
- Cognitive performance improved significantly in all groups but was not further modulated by neurostimulation.
- TDCS boosted cognitive training efficiency in participants with low general cognitive performance, while age had no moderating effect.

Keywords: Cognitive training; Aging; tDCS; tACS; Motivation.

1. Introduction

Cognitive performance is known to decline during normal aging and has been associated with changes in brain structure and physiology (Ballesteros et al., 2009; Baudry, 2009). A range of interventions has been proposed to counteract this decline. One such intervention is computer-based cognitive training (CCT) (Shah et al., 2017; Willis and Belleville, 2016). Although it is difficult to draw firm conclusions from the existing literature due to its heterogeneity, group sessions up to thrice weekly appear optimal. Further, a multimodal training seems most beneficial to transfer improvements to tasks not directly trained (Lampit et al., 2014; Walton et al., 2019) and to achieve long term benefits (Cheng et al., 2012). An advantage of CCT is that it easily adapts to the individual level of performance. Adaptive training regimes promote motivation (Kueider et al., 2012), which is a particularly important factor for the outcome of a CCT leading to increased transfer effects and training gains (Carretti et al., 2011; Jaeggi et al., 2014; Peter et al., 2018; Zhao et al., 2018).

CCT is thought to elicit long-lasting cognitive effects what could delay functional decline and therefore help to maintain independence in daily life (Rebok et al., 2014). One possibility to enhance and prolong training effects is to combine CCT with transcranial electrical stimulation (tES), which may also increase the immediate training effects (Bartrés-Faz and Vidal-Piñeiro, 2016). The most frequently used type of tES in research is transcranial direct current stimulation (tDCS) (Santarnecchi et al., 2015). During tDCS, low electrical current increases the excitability of neurons close to the anode and the stimulation effects remain visible up to several hours after termination of the stimulation (Nitsche and Paulus, 2000; Reinhart et al., 2017).

Positive effects for single sessions of tDCS over the left dorsolateral prefrontal cortex (DLFPC) were found for several cognitive domains including attention (i.e., a Sternberg task; Gladwin et al. 2012) and speed of processing (Plewnia et al., 2015) in young adults. For working memory (WM) it seems like a training with repeated sessions in combination with tDCS is more effective than single sessions (Mancuso et al., 2016). Overall the results from studies investigating the combination of tDCS over the left DLPFC and different types of CCT are heterogeneous. While some studies reported increased cognitive performance after WM training in young adults (Au et al., 2016; Richmond et al., 2014; Ruf et al., 2017), others did not (Martin et al., 2013). In elderly adults, CCT targeting WM (Nilsson et al., 2017) or other executive functions (Horne et al., 2020; Yu et al., 2019) did not result in beneficial effects.

In other studies combining CCT and tDCS in older adults stimulation was applied over the right DLPFC (Jones et al., 2015; Stephens and Berryhill, 2016), left inferior frontal gyrus (Perceval et al., 2020), right temporoparietal cortex (Antonenko et al., 2018; Külzow et al., 2018) and bilateral frontal (Park et al., 2014).

Previous research showed that inter-individual differences, such as baseline cognitive performance or age, can moderate stimulation effects. For instance, participants with lower initial cognitive performance benefited more from tDCS (Habich et al., 2017; Katz et al., 2017; London and Slagter, 2015; Perceval et al., 2020). Cross-sectional studies indicated larger tDCS effects on behavioural outcomes in older than younger adults (Perceval et al., 2016). One study performed functional magnetic resonance imaging during a word generation task in elderly adults and reported more “youth like” brain activation through tDCS. Additionally, they found increased task performance (Meinzer et al., 2013). Transcranial alternating current stimulation (tACS), another form of tES, can be applied in sinusoidal curves of a certain frequency and has the ability to entrain the natural oscillation of brain networks (Antal and Paulus, 2013). Brain oscillations in the theta range during resting state have been associated with performance in tasks assessing verbal memory, attention and executive functions in healthy aging. Therefore, the authors interpret high theta power as a sign of optimal neurocognitive functioning (Finnigan and Robertson, 2011). Mitchell et al. (2008) reported correlations between WM as well as attention and theta activity also during task performance. A study by (Reinhart and Nguyen, 2019) investigated the effect of theta synchronizing across fronto-temporal brain areas on WM in older adults. The authors reported increased synchronisation after 25 minutes of High Definition (HD)-tACS which was accompanied by increased WM performance. The effects were visible for at least 50 minutes, which indicates tACS effects on neural plasticity.

Additionally, frontal theta was increased after cognitive training and seems relevant for observed long-term effects (Greenwood and Parasuraman, 2016). Studies using single session tACS in younger adults found positive effects in tasks for WM and other executive functions when applying tACS over frontal or parietal brain areas, especially in the theta frequency band. Like tDCS, tACS studies also frequently target the left DLPFC (Antonenko et al., 2016). To date, only two studies we are aware of combined tACS and CCT. In one study, multifocal tACS (40 Hz) over bilateral frontal and parietal regions was combined with CCT and did not find an effect of stimulation in healthy young participants (Brem et al., 2018). Another study combined bilateral prefrontal and parietal low gamma frequency tACS (35 Hz) with visuo-spatial WM training and found a negative effect of parietal tACS on training gains in young adults (Möller et al., 2017). Similar to tDCS, age also seems to be a modulating factor for tACS effects. One study reported that theta tACS supported memory performance only in the oldest participants in a sample of healthy elderly adults (Klink et al., 2020).

To our knowledge, the current study is the first to combine CCT with tACS in healthy elderly adults. Although the lack of preliminary data precludes assumptions about the extent or duration of possible effects from tACS, we hypothesized similar outcomes for both tDCS and tACS. Our primary aim was to test whether tDCS and/or tACS improve CCT outcome immediately after training and whether such an improvement depends on general cognitive performance or age. We moreover expected to observe online tES effects on CCT performance. At the follow-up assessments after 6 and 12 months, we expected possible beneficial effects of tES to decrease continuously. Furthermore, we investigated the effect of motivation on CCT outcome and hypothesized to find larger training gains in participants with higher achievement motivation.

2. Methods

We conducted this study in a double-blind, sham-controlled, parallel group design with a total of ten CCT sessions (twice weekly). Cognitive functions were assessed before and after the cognitive intervention, as well as 6 and 12 months after finishing the intervention. The study procedure is shown in Figure 1.

----Figure 1---

The study was approved by the local Ethics Committee and performed in accordance with the Declaration of Helsinki. We registered the study on ClinicalTrials.gov

(NCT03475446) and obtained written informed consent of all participants before study onset.

2.1. Participants

Four participants withdrew from study participation, and only data from the pre-assessment was available. Therefore, we excluded their data from all analyses.
Two participants discontinued before the cognitive intervention started because of time constraints and two after the first session (one because of acute health issues unrelated to the intervention and one was already participating in another study, which could have affected the results). Fifty-nine healthy elderly participants completed the cognitive intervention (mean age 71.7 ± 6.1, range: 61 – 85; 31 male; years of education median: 14, range: 9 – 25; see Figure 2 for a flow diagram of participants).

---Figure2---

Inclusion criteria were the ability to consent in study participation, age between 60 and 85 years, native or fluent German speaker, normal or corrected to normal vision and hearing and ability to visit the study location for 14 appointments.

Exclusion criteria were any history of seizure or stroke, traumatic brain injury, current psychiatric or neurological disorders, substance abuse, metal implants in the head, pacemaker, smoking, psychotropic medication, severe tinnitus and self-reported left-handedness.

We calculated the necessary sample size for a repeated measure analysis of variance with an interaction of the between-factor stimulation and the within-factor time (g*power) (Faul et al. 2007) where we assumed an effect size of .35 (Hsu et al. 2015; Mancuso et al. 2016). To achieve a sufficient power of .8 a minimum of 60 participants was needed. We took this as a rough estimate for the requested sample size for the linear mixed models.

2.2. Cognitive assessments and questionnaires

The cognitive assessments were performed before and after (i.e., within 6 weeks) the cognitive intervention, as well as 6 and 12 months after the end of the cognitive intervention. We assessed general cognitive performance with the pre-assessment scores in the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005). The MoCA is a frequently administered cognitive screening tool in studies in elderly participants (e.g., Horne et al., 2020; Klink et al., 2020; Yu et al., 2019) and provides an index of general cognitive performance (Nasreddine et al., 2005).

The cognitive assessment consisted of computer-based (Vienna Test System; Schuhfried GmbH, Mödling, Austria) and paper-pencil tests. The following computer-based tests from the Vienna Test System were administered: auditory word list learning task (learning sum, delayed recall, d prime (Pallier, 2002) word recognition), objective achievement motivation (baseline motivation) (Brandstätter, 2005), divided/selective attention (d prime), continuous figural recognition (d prime), inhibition (d prime Go/NoGo), semantic/lexical fluency (total number of words) and corsi blocks (block span backwards). Paper-pencil tests included: 5 point test (number of unique designs) (Regard et al., 1982), number connection test (average solving time) (Oswald and Roth, 1987). We used parallel versions of tests whenever available (i.e., for the MoCA, auditory wordlist learning, fluency and number connection tests).

As primary measure of cognitive outcome, we calculated a cognitive composite score running a principal component analysis on test scores from the pre-assessment. Based on the results we included all scores in the cognitive composite score except those of the inhibition test (see Supplementary Material for details and Table S1 for the single test scores aggregated in the composite score).

Furthermore, participants completed questionnaires to access cognitive reserve (Nucci et al., 2012), situational motivation (Guay et al., 2000), quality of life (Endicott et al., 1993), activities of daily living (Graf, 2008), depressive symptoms (Yesavage et al., 1983), and subjective memory performance. Subjective memory performance was also assessed in an informant rated version. The results of these questionnaires might be reported elsewhere.

We assessed potential side effects of stimulation after each cognitive intervention session (3 point Likert scale, 0 indicated no and 3 strongly perceived side effects) (Brunoni et al., 2011). Additionally, overall well-being and sleep quality during the previous night were assessed in each session.

2.3. Computer-based cognitive training (CCT)

Participants underwent ten sessions (twice weekly) of CCT for five weeks at the local memory clinic of Bern. CCT was administered on desktops (22-Inch screens) using special keyboards (Schuhfried GmbH, Mödling, Austria). The CCT sessions were scheduled at least two days apart (in two cases, participants had to reschedule a session and performed two sessions within two days). Each session included three different tasks, which were performed for 50 minutes in total (Figure 3). The sessions were conducted in groups of three to six participants. The participants trained in the same room, but individually and without interaction. We used five different tasks during the CCT ("CogniPlus" software, Schuhfried GmbH, Mödling, Austria), which are described in the Supplementary Material.

2.4. Study procedure

Participants were randomly assigned to one of the three stimulation conditions (tDCS, tACS, or sham) prior to their first on-site visit. The randomisation was conducted by REDCAP (Harris et al., 2009) and stratified for gender. Additionally, a code for either sham or real stimulation was provided. We operated the device in study mode and the investigator entering the code to start stimulation as well as participants remained blinded to the study group allocation (double-blind study design). We administered stimulation during the first 20 minutes of each session with a battery-driven current stimulator (DC-Stimulator PLUS, Neuro-Conn GmbH, Ilmenau, Germany). During stimulation participants alternately trained selective or divided attention, i.e., each attention domain was trained five times. We combined neurostimulation over the DLPFC with attention training as we hypothesized that this combination might drive overall stimulation effects and therefore induces most training benefits (Gladwin et al., 2012). The rationale of the electrode montage was based on previous research, which showed positive effects of tDCS over the left DLPFC for several cognitive domains, as reported in the introduction. Also, tACS stimulation over the left DLPFC led to beneficial effects in executive functions and memory (Antonenko et al., 2016). Electrodes were inserted in saline-soaked sponges prior to the stimulation. Sponges were fully soaked to ensure homogeneous stimulation of the underlying area. For tDCS, we placed the anode (5x7 cm) over the left DLPFC, and the cathode (10x10 cm) supraorbitally above the right eye. To target the left DLPFC we placed the anode centrally over F3 according to the 10-20 EEG system (Klem et al., 1999). The cathode was slightly larger in order to prevent unintended stimulation effects (Nitsche et al., 2008). For tDCS we applied 2mA, for theta tACS 1mA (0° initial phase shift, 5 Hz). Please see Figure S1 in the Supplementary Material for a model of current flow during tDCS calculated with the Soterix HD Explore modelling software (Soterix Medical, New York, NY). The application of tACS was performed with lower intensity to prevent the occurrence of phosphenes (Raco et al., 2014). We used a ramping up/down time of 15 seconds for all three conditions. During sham, tDCS was applied for 30 seconds between ramping up and down. The attention task was followed by a short break during which the stimulation electrodes were removed, and participants had the opportunity to leave the room and chat with each other. After the break, CCT continued with two out of three tasks that trained either WM, executive functions (inhibitory control) or speed of processing.

---Figure3---

After completing the last session of the cognitive intervention, participants, as well as the investigator, were asked to indicate whether the participants received real stimulation or not.

2.3. Statistical analyses

Data were analysed using R Studio (Team, 2015) and the following packages: *pcaMethods* (Stacklies et al., 2007), *lme4* (Bates et al., 2014), *lmerTest* (Kuznetsova et al., 2017) and *piecewiseSEM* (Lefcheck, 2016).

We performed Kruskal-Wallis (continuous variables) and Chi-Square (categorical variables) tests to investigate differences in demographic variables between stimulation groups.

Effect of cognitive intervention on composite score (Models 1.1-1.3)

Model 1.1: To test stimulation effects on CCT outcome, we conducted a linear mixed model (LMM) We included the factors *stimulation* and *time* as fixed effects and a random intercept for the factor *participant*. As outcome, we used *composite score difference*s (i.e., the difference between the post-/follow-up assessments and the pre-assessment composite scores). We used the difference score instead of raw values, as we were interested in improvement through the cognitive intervention.

The factors *time* (1.5, 7.5 and 13.5 months between baseline and follow- up assessments) and *stimulation* (tDCS, tACS or sham) each included three levels.

Model 1.2: The second LMM) investigated the interaction between general cognitive performance (centred and standardized *pre-assessment MoCA)* and the cognitive intervention. We included a fixed two-way interaction (*pre-assessment MoCA score***stimulation*) plus the factor *time* as a fixed effect and a random intercept for the factor *participant*. We further examined a significant two-way interaction between *pre-assessment MoCA score* and *stimulation* by analysing the conditional effect of *stimulation* for different MoCA scores (low MoCA scores: mean MoCA value - 1SD, average: mean MoCA value, high MoCA scores: mean MoCA value + 1SD).

Model 1.3: The third LMM assessed the modulating effects of *age* on the cognitive intervention. Therefore, we replaced the factor *pre-assessment MoCA score* from the previous Model 1.2 with the centred and standardized factor *age* (*age***stimulation*).

To estimate effect size, we calculated f^2, which is interpreted as the amount of variance explained by a fixed factor (Aiken et al., 1991; Lorah, 2018) and can be converted into Cohen's *d*.

We assessed goodness-of-fit of the LMM by conditional and marginal R^2 (Nakagawa and Schielzeth, 2013). Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) for this and the following LMMs and further details for model selection are reported in the Supplementary Material.

Task performance during stimulation (Models 2.1-2.3)

Model 2.1: Our second aim was to investigate whether tACS or tDCS were able to improve CCT performance during stimulation. Therefore, we tested the fixed interaction between *stimulation***session* on the outcome *last reached level in task* as outcome and a random intercept for the factor *participant.* This and the following LMM were performed for the selective and divided attention task separately. For details about the factor *session,* see the Supplementary Material.

Model 2.2: To assess the effect of general cognitive performance during the cognitive intervention, we conducted a LMM with a fixed three-way interaction (*pre-assessment MoCA score***stimulation***session*).

Model 2.3: We repeated Model 2.2 with the factor *age* instead of *pre-assessment MoCA score*, i.e., we tested the fixed interaction between *age***stimulation***session* on the outcome *last reached level in task*.

P - values and correction for repeated testing

Whenever investigating conditional interactions in any of the LMMs described above, we used one-sided p-values, assuming that real stimulation would lead to higher composite score differences than sham stimulation. These one-sided p-values were corrected for repeated testing with the Bonferroni-Holm-method (Holm, 1979).

Model 3: Effect of motivation on CCT outcome

To examine how well motivation predicted CCT outcome, we performed a multiple linear regression (MLR) analysis with the outcome *difference score one* and the fixed factors *achievement motivation* and *stimulation*.

In exploratory analyses, we repeated the MLR with the individual *pre-assessment test scores* included in the composite score instead of the factor *achievement motivation*. We performed these analyses to investigate, which single test score was the best predictor of CCT outcome.

The data of the follow-ups I and II were not used in these MLRs.

3. Results

3.1. Demographics

The stimulation groups did not significantly differ regarding age, gender, education, general cognitive performance (MoCA), GDS score and the cognitive composite score in the pre-assessment (Table 1). The results of the GDS did not indicate substantial depressive symptoms in any of the participants (cut-off 5<) (Herrmann et al., 1996).

---Table1---

3.2. Effect of cognitive intervention on composite score

<u>*Model 1.1:*</u> The LMM had an explanatory power of 62% (conditional R^2), in which the fixed effects explained 11% of the variance (marginal R^2). There was a significant effect of *time* ($F_{(2, 106.34)} = 13.66$, $p < .001$) but not *stimulation* ($F_{(2, 55.93)} = 2.43$, $p = .10$) on the *composite score differences*.

<u>*Model 1.2:*</u> *Effect of general cognitive performance and cognitive intervention on composite score:*
The LMM had an explanatory power of 64% (conditional R^2), in which the fixed effects explained 24% of the variance (marginal R^2). There was no significant effect of *pre-assessment MoCA score* on the *composite score differences* ($F_{(1,52.99)} = 0.01$, $p = .91$). Model 1.2 showed a significant interaction between *pre-assessment MoCA score* and *stimulation* ($F_{(2, 52.93)} = 7.48$, $p = .001$). Participants of the *tDCS* group with low MoCA scores improved more in the cognitive composite score than participants with low MoCA scores that underwent sham stimulation ($\beta = 0.34$, $t_{(56.40)} = 3.36$, $p < .001$, p adjusted = .004). This effect seems stable for up to 12 months (Figure 4). There was no significant effect for tACS when compared to sham stimulation or in the group with high MoCA scores, see Table S2 of conditional effects in the Supplementary Material.

---Figure4---

To explore possible differences between the two groups with real stimulation, we compared the tACS and tDCS groups separately. The results are reported in the Supplementary Material.

The effect size of *stimulation* in the group with the lowest *pre-assessment MoCA scores* (i.e., lowest tertile, MoCA < 26, $n = 21$) was small-moderate ($f^2 = 0.07$, Cohen's $d = 0.51$).

<u>*Model 1.3*</u>*: Effect of age and cognitive intervention on composite score:*
The LMM had an explanatory power of 64% (conditional R^2), in which the fixed effects explained 16% of the variance (marginal R^2). There was no significant effect of *age* on the *composite score differences* ($F_{(1,53.50)} = 0.07$, $p = .78$) and also no significant interaction between *age* and *stimulation* ($F_{(2, 53.41)} = 2.19$, $p = .12$).

3.3 Task performance during stimulation

<u>*Model 2.1:*</u> For the *divided attention task*, there was a significant interaction between *session* and *stimulation* ($F_{(2, 205.55)} = 3.06$, $p = .049$, Figure 5). Further analyses showed

significant differences in the conditional effects of the variable *session* between the *tACS* and sham group (β = 0.24, $t_{(205.88)}$= 2.47, *p* = .007, *p* adjusted = .03). The result indicated more improvement in the tACS than in the sham group during the training.

To explore possible differences between the two groups with real stimulation, we compared the tACS and tDCS groups separately. The results are reported in the Supplementary Material.

Model 2.1 for the *selective attention task* showed no significant interaction between *stimulation* and *session* ($F_{(2, 222.57)}$ = 0.14, *p* = .87).

---Figure5---

Regarding the close connection between attention and WM (Mitchell et al., 2008), we repeated the LMM for the *WM task* and found an effect of *tACS* across *sessions* when compared to the sham group ($F_{(2, 320.98)}$ = 5.34, *p* = .005, conditional effect of tACS across sessions: β = 0.32, $t_{(320.83)}$= 3.17, *p* = .002). As we did not hypothesize similar relationships between performance in the other CCT tasks, we did not perform further analyses of training performance.

Model 2.2: Effect of general cognitive performance on task performance during stimulation:
There was a significant effect of *session* (i.e. time) (divided attention: $F_{(1, 202.7)}$ = 1259.05, *p* < .001, selective attention: $F_{(1, 219.66)}$ = 543.95, *p* < .001) but not *pre-assessment MoCA score* (divided attention: $F_{(1, 86.06)}$ = 2.83, *p* = .10, selective attention: $F_{(1, 118.12)}$ = 0.13, *p* = .71) on the *last reached levels* for either attention task, which were performed during the stimulation. Model 2.2 showed no significant three-way interaction (*pre-assessment MoCA score***stimulation***session*) for the attention tasks (divided attention: $F_{(2, 202.28)}$ = 0.61, *p* = .54, selective attention: $F_{(2, 220.46)}$ = 0.81, *p* = .45).

Model 2.3: Effect of age on task performance during stimulation:
There was no significant effect of *age* (divided attention: $F_{(1, 82.11)}$ = 0.38, *p* = .54, selective attention: $F_{(1, 113.08)}$ = 0.26, *p* = .61) on the *last reached levels* for either attention task. Model 2.3 also showed no significant three-way interaction (*age***stimulation***session*) (divided attention: $F_{(2, 202.65)}$ = 1.54, *p* = .22, selective attention: $F_{(2, 219)}$ = 0.14, *p* = .87).

Model 3: Effect of motivation on CCT outcome:
The MLR showed no significant effect of *achievement motivation* on the *composite score difference* ($F_{(1, 54)}$ = 0.00, *p* = .95). The exploratory MLRs showed, that *d prime of word recognition* was the best predictor of the *composite score difference one* ($F_{(1, 55)}$ = 10.07, multiple R^2= .17, *p* = .002), followed by *delayed recall* ($F_{(1, 55)}$ = 6.01, multiple R^2= .12, *p* = .017). A table of beta values, multiple R^2, AIC and BIC for all tests can be found in the Supplementary Material (Table S3).

3.5. Side Effects
The two most commonly reported side effects were concentration problems (39.6 %), and tingling (18.1%), but these were not significantly more often reported in groups

with real stimulation (concentration problems: $\chi^2_{(1)}$= .01, *p* = .94, tingling: $\chi^2_{(1)}$= .80, *p* = .37).

3.6. Blinding

Guessing stimulation assignment was at chance level for both the examiners ($\chi^2_{(1)}$= .03, *p* = .86) and the participants ($\chi^2_{(1)}$= .74, *p* = .39), which indicates successful blinding.

4. Discussion

The aim of this study was to investigate, whether tACS or tDCS were able to boost the effect of a CCT and whether such an improvement depends on general cognitive performance or age. On average, participants in all three stimulation groups improved significantly in the composite score (offline effects) and the attention training tasks (selective and divided attention) that were performed during tES (online effects). There was no significant difference between tDCS and sham stimulation in the composite score after the intervention. But we demonstrated that tDCS improved performance in the composite score significantly more than sham stimulation in participants with a low level of general cognitive performance (as measured with the MoCA) at baseline. This effect remained stable up to 12 months after the end of the intervention. We did not find a significant online effect of tDCS when compared to sham stimulation.

For tACS there was no beneficial effect on the composite score, but participants improved faster in a CCT task performed during stimulation than those in the sham group.

Regarding the scarcity of data for trainings combined with tDCS in the healthy elderly, the comparison with previous results is difficult and, in the case of tACS, not possible. To our knowledge, two studies combined CCT and tDCS over the left DLFPC in healthy elderly adults. The first study combined tDCS with WM training and reported no additional benefit through tDCS (Nilsson et al., 2017), while studies with young participants did (Au et al., 2016; Richmond et al., 2014). The same holds true for other executive functions (EF). One study found no beneficial effects after EF training (decision making, Horne et al., 2020; reaction time, inhibition and multitasking, Yu et al., 2019) with tDCS in healthy elderly while in younger adults fluid intelligence improved after repeated tDCS combined with EF training (WM, inhibition and cognitive flexibility) (Brem et al., 2018). It remains unclear if the diverging results between old and young adults are caused by differences in brain physiology or in study design. In contrast to the present study, these participants trained only one cognitive domain and the authors did not address the potential moderating effect of baseline performance on tDCS, which might explain the different results.

The tDCS effect in this study was modulated by general cognitive performance in a way that only participants with lower MoCA scores benefitted from stimulation. The effect size of stimulation in the group with the lowest general cognitive performance was small to moderate (Cohen's *d* = 0.51). While we included only healthy elderly participants, it is still interesting to compare these effect sizes with those of medication in pathological aging. Cholinesterase inhibitors, for example, show similar effect sizes (i.e. small to moderate) in Alzheimer's disease (Cohen's *d*: 0.15 low doses, 0.28 high doses; standardised response mean: 0.26 low doses, 0.47 high doses) (Rockwood, 2004). Other tDCS studies reported similar results, indicating that tDCS is most effective when there is 'room for improvement'. This has been shown both after single tDCS sessions (Habich et al., 2017; London and Slagter, 2015) and when combining tDCS with WM training (Katz et al., 2017). This finding can possibly be explained by inter-individual differences in excitation-inhibition balance in the DLPFC, i.e., tDCS may promote the balance between excitation and inhibition in participants with sub-optimal excitability (London and Slagter, 2015). In this sample of elderly participants, low general cognitive performance might also indicate accelerated or abnormal age-related cognitive decline. The finding, that *age* per se had no modulating effect on stimulation further supports this assumption. Therefore, it is possible that in persons with increased cognitive decline, such as in mild cognitive impairment or dementia, the combination of CCT and tDCS could be particularly beneficial.

In the present study, tACS effects did not outlast the stimulation, but other studies applying tACS during a task reported such effects. For example, tACS increased retrieval performance in implicit language learning, which was assessed immediately after the stimulation (Antonenko et al., 2016). Also, in a WM task, performance was improved after tACS in comparison with sham stimulation, which indicates ongoing tACS effects after the stimulation (Röhner et al., 2018). There are some differences between these two and our study, which could have caused the diverging results. We used different tasks during stimulation and in the assessments, which was not the case in the studies mentioned above. Their post-assessments were conducted directly after the task, while in our study, the post-assessment was administered up to several days after the last stimulation session.

The group receiving tACS improved more rapidly in the divided attention task performed during tES. Its limitation to the attention task may be explained by the critical role of theta oscillations in attention but also WM processes (Mitchell et al., 2008). The finding of tACS effects also in the WM task supports this assumption. The WM task was not performed during stimulation but within 30 minutes afterwards. Therefore, it seems that tACS increased performance not only during stimulation but also for a short time window afterwards, however without resulting in beneficial effects in the post-assessment score. This is in line with other studies which reported positive online effects of theta tACS on WM performance in young adults (Alekseichuk et al., 2016; Jones et al., 2019; Meiron and Lavidor, 2014). In contrast to tDCS, tACS effects appeared to be independent of the pre-assessment MoCA score.

Based on previous research (Peter et al., 2018), we investigated if achievement motivation had an effect on CCT outcome. There was no effect on the composite score difference, but the composite score before the cognitive intervention was significantly correlated with achievement motivation. This finding indicates that participants with higher levels of motivation did not benefit more from the training but already reached higher composite scores before the training started. Best predictors of CCT outcome were low scores in measures of episodic memory (i.e., d prime of word recognition and delayed recall), indicating that an auditory verbal learning task could serve as a predictor of individual cognitive improvement.

4.1. Limitations

We did not vary the components of the CCT and had no control condition without the cognitive intervention (i.e., waitlist control group). This precludes conclusions on the efficiency of specific tasks of the CCT or retest effects.

It is possible that an age range of 25 years was too small to show stimulation effects depending on age, at least in a study setting combining CCT and tES in repeated sessions. The previously mentioned modulating effect of age on tACS in elderly participants has been reported in a study with a single session of stimulation in a task of associative memory in participants with a similar age range (Klink et al., 2020), which could explain the differing findings in our study. Furthermore, in order to systematically investigate age effects, future studies should include a larger age range of participants.

We did not find stimulation effects independently from general cognitive performance, which could possibly be explained by the chosen electrode montage. We used a larger cathode in order to limit unintended stimulation effects in tDCS. However, the size of the cathode also reduced the distance between the electrodes, which could have increased shunting effects (Faria et al. 2011). Possibly, the remaining current reaching the DLPFC was not sufficient to cause stimulation effects that would result in behavioural effects. In tACS other frequencies than 5 Hz might have induced offline effects. But, to our knowledge, no study combining CCT and tACS elicited offline effects, regardless of the applied tACS frequency.

Another possibility is that our electrode placement was not optimal for eliciting long-lasting tACS effects. It has been suggested, that strongest behavioural effects after tACS in WM or fluid intelligence can be expected when at least one electrode is located over parietal brain areas (Pahor and Jaušovec, 2018, 2014).

The tDCS group showed the lowest composite scores at baseline, although between-groups-differences were not statistically significant. Our study does not exclude the possibility that the improvements were regression-to-the-mean effects rather than specific effects of the intervention.

Our sample size of 59 participants is comparable to other studies (e.g.,Martin et al. 2013; Jones et al. 2015; Brem et al. 2018). Nevertheless, it is possible that the lack of stimulation effects independently of the MoCA score is due to insufficient power.

4.2. Conclusions

To our knowledge, this is the first study to compare the effects of tACS and tDCS in healthy elderly participants in combination with CCT. The larger improvement of divided attention during tACS compared to tDCS and sham stimulation is intriguing and warrants further investigation. Further, we were able to demonstrate a significant improvement in a composite score in the group receiving combined tDCS and CCT, but only in participants with a low MoCA score before the training. As there was no effect of age and stimulation on the composite score, we suggest that biological (as indexed by the MoCA score) rather than chronological age modulates stimulation effects. This finding indicates that baseline performance should be taken into account when evaluating the efficacy of tES.

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Declaration of interest

None.

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	sham (n = 22)		tDCS (n = 17)		tACS (n = 20)		p - value
	Mdn	Range	*Mdn*	Range	*Mdn*	Range	
Age (years)	70.5	62 - 82	75	63 - 85	71.5	61 - 85	.18[a]
Gender (m/f)	12/10		9/8		10/10		.96[b]
Pre-assessment MoCA score	27	21 - 30	27	21 - 30	27	22 - 30	.94[a]
Pre-assessment Cognitive Composite Score	0.15	-1.47 - 0.59	-0.22	-1.39 - 0.98	0.18	-1.24 - 1.14	.27[a]
Pre-assessment GDS	1	0 - 5	1	0 - 4	1.5	0 - 5	.37[a]
Education (years)	14	9 - 25	15	12 - 22	13	10 - 22	.28[a]

Note: Mdn = median, sham = sham stimulation, tDCS = transcranial direct current stimulation, tACS = transcranial alternating current stimulation, m = male, f = female, MoCA = Montreal Cognitive Assessment, GDS = Geriatric Depression Scale, n = number of participants, [a] Kruskal-Wallis test, [b] Chi-Square test. A p-value < .05 would indicate significant differences between the stimulation groups.

Table 1: Demographics of study sample.

Figure captions

Figure 1: ***Study procedure****. Participants underwent ten sessions (50 min) of* a computer-based cognitive training *(twice weekly for five weeks). Transcranial electrical stimulation was applied during the first 20 minutes of every session. Cognitive measures were assessed before the cognitive intervention (pre-assessment), directly after the cognitive intervention (post-assessment), as well as 6 and 12 months after the end of the combined intervention (follow-up I and II). The test for objective achievement motivation and the questionnaires for situational motivation and cognitive reserve were completed once before the start of the cognitive intervention, all other tests and questionnaires were repeated at the following assessments. Abbreviations: sham = sham stimulation, tDCS = transcranial direct current stimulation, tACS = transcranial alternating current stimulation.*

Figure 2: ***Consort flow diagram of participants.*** *In the post-assessment data of 50 participants were included, 52 in Follow-up I and 54 in Follow-up II. Abbreviations: sham = sham stimulation, tDCS = transcranial direct current stimulation, tACS = transcranial alternating current stimulation, n = number of participants, CCT = computer-based cognitive training.*

Figure 3: ***Training session.*** *During each session, participants were stimulated for the first 20 minutes. During this time, a task of divided or selective attention was performed in alternating order. After a break of ten minutes, two tasks targeting other functions (i.e., inhibitory control, working memory, or speed of processing) were performed for 15 minutes each.*

Figure 4: ***Estimates of the linear mixed model for the change in composite score differences stratified by initial scores in the Montreal Cognitive Assessment (MoCA).*** *Participants with low MoCA scores in the tDCS group improved more than those with low MoCA scores in the sham group (p = .004). Error bars reflect confidence intervals. Post = 'post-assessment composite score'- 'pre-assessment composite score', FU I = ''follow-up I composite score'- 'pre-assessment composite score', FU II = ''follow-up II composite score'- 'pre-assessment composite score'. Abbreviations: sham = sham stimulation, tDCS = transcranial direct current stimulation, tACS = transcranial alternating current stimulation.*

Figure 5: ***Estimates of the linear mixed model for stimulation effects for the last reached level in the divided attention task.*** *The group with transcranial alternating current stimulation improved more than the sham group during the cognitive intervention. Error bars reflect confidence intervals. The divided attention task was performed in every other session. Abbreviations: sham = sham stimulation, tDCS = transcranial direct current stimulation, tACS = transcranial alternating current stimulation.*