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Combining electrical stimulation and cognitive control training to reduce concerns about subjective cognitive decline

Dear Editor:

Subjective cognitive decline (SCD) is characterized by a self-perceived deterioration of cognitive abilities in the absence of objective deficits or depression [1]. Concerns associated with SCD are increasingly acknowledged as risk factor for the development of Alzheimer's disease (AD) [1,2] and often affect psychological well-being [3].

The increased occupation with concerns about memory impairment is linked with deficient cognitive control (CC), negatively biased self-related cognitive processes, and reduced efficiency of executive functioning [4]. Consistently, a major hub of the CC network, the prefrontal cortex (PFC) shows compensatory activation in this condition [5]. It is therefore conceivable that a consolidation of CC may reduce the burden of concerns and potentially represent a perspective to support resilience against memory decline.

We have previously shown that the enhancement of PFC activity by transcranial direct current stimulation (tDCS) can support CC reflected in reduced distractibility by negative information and feedback [6]. Moreover, neuronal reorganization and learning can be facilitated by concurrent excitability enhancing tDCS [7]. Based on this evidence a targeted intervention combining the neuroplasticity-enhancing effects of tDCS and CC circuit retraining holds promise to reduce the negatively biased self-perception of cognitive performance in SCD.

We tested this notion in a randomized, single-blind, sham-controlled proof-of-principle study by applying 2mA active or sham tDCS with the anode over the left PFC and the cathode at the contralateral deltoid muscle during 12 sessions of CC training in participants with SCD. We hypothesized that this tDCS-enhanced CC training will reduce the amount of concerns regarding memory impairment.

Twenty-six subjects reporting SCD with concerns (M = 68.96 years, SD = 6.017; 14 females; 14 active tDCS, 12 sham) were enrolled (Sup. Tab. 1). The study was approved by the local Ethics Committee and followed the Declaration of Helsinki. Written informed consent was obtained from each subject. Exclusion criteria were age <60 years, left-handedness, objective cognitive impairment (CERAD-Plus neuropsychological battery >1.5 standard deviations below adjusted normal performance), current depression (Geriatric Depression Scale Score > 5) or other neurologic or psychiatric disorders (assessed by the Mini-International Neuropsychiatric Interview) [1]. Memory concerns (primary endpoint) were quantified with a 10-point self-rating Likert-Scale (1 = no concerns and 10 = maximal concerns) at the pre-, post- and follow-up sessions.

CC training was performed with the computerized adaptive Paced Auditory Serial Addition Task (PASAT) [8]. Subjects heard single digits and were instructed to add each new digit to the preceding one. Concurrent with the new digit, visual feedback was given on correct (green screen) and incorrect or missed (red screen) answers. The inter-stimulus-interval was decreased and increased by 0.1 second after four consecutive correct or incorrect answers, respectively. By adapting task difficulty to the individual maximum and distractive performance feedback, the PASAT is well-suited for a CC training [9].

A multichannel DC-Stimulator (NeuroConn GmbH, Germany) was used to apply 2mA tDCS via a pair of rubber electrodes (5 × 7 cm, 35cm^2) for 20 minutes (5 seconds fade-in/fade-out). The anode was placed over the left PFC (F3 according to the 10–20 system) and the cathode on the right deltoid muscle. In the sham condition, stimulation was applied for 40 seconds.

The experiment consisted of a pre-session, 12 training sessions (three per week for four weeks), a post-session four days, and follow-up three months after training (Sup. Fig. 1). The PASAT was performed completely parallel to sham or active tDCS. Computerized randomization of the subjects took place after screening, CERAD-plus testing and familiarization with the PASAT. Due to the use of multichannel tDCS, the operator was not blinded. During training and the self-rating of concerns, interaction with the experimenter was limited to a minimum. To test blinding efficacy after tDCS-enhanced training, the participants guessed if they received active or sham stimulation. Study design, sample size and primary endpoint were preregistered at Clinical-Trials.gov: NCT03236454.

A mixed two-way ANOVA (Fig. 1A) with between-subject factor 'stimulation condition' (active tDCS, sham) and within-subject factor 'time' (pre-training, post-training, follow-up) demonstrated a significant interaction between these factors with a large effect size ($F(1,24) = 10.088$, $p = 0.004$, $\eta p^2 = 0.296$). Post-hoc t-tests indicated a reduction of memory concerns after tDCS-enhanced CC training ($t(13) = 3.816$, $p = 0.002$, $d = 1.02$) and after three months follow-up ($t(13) = 2.662$, $p = 0.02$, $d = 0.7$). No change was found with sham stimulation. Between-group comparisons confirmed that at the pre-session, the amount of memory concerns was not different in both groups ($t(24) = -0.554$, $p = 0.585$, $d = 0.22$), but that tDCS-enhanced CC training resulted in less memory concerns than the similar training with sham stimulation ($t(24) = 2.543$, $p = 0.018$, $d = 1.0$). However, at follow-up this difference was no longer significant ($t(24) = 1.350$ $p = 0.190$, $d = 0.054$) (Sup. Tab. 2A).

To examine the effects of tDCS on across-session learning of the PASAT, a linear mixed-effect model was fitted with the number of

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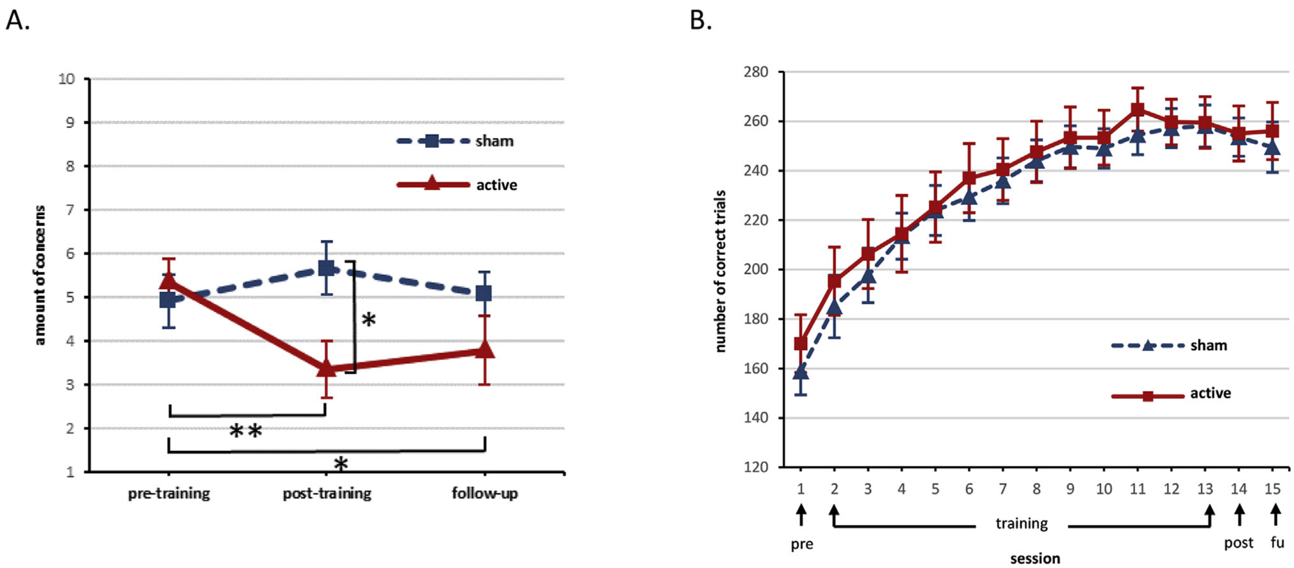

Fig. 1. Training effects. A.: Amount of memory concerns before and after tDCS-enhanced cognitive training. ** p < 0.01, * p < 0.05. B.: PASAT performance – the mean number of correct trials of each group is shown for each session; abbreviations: fu, follow-up.

correct responses as dependent variable, session, group, and baseline as fixed effects. Random-intercept and random-slope were entered to account for unsystematic individual differences. This model showed that PASAT performance was improved by training ($t(280) = 7.47$, $p < 0.0001$, $SE = 0.869$). However, active tDCS did not enhance performance increase compared to sham treatment ($t(280) = -0.57$, $p = 0.569$, $SE = 1.184$) (Fig. 1B, Sup. Tab. 2B).

A chi-square test for comparing group-allocation guesses revealed no differences between the two groups ($\chi^2(1) = 1.706$, $p = 0.191$) indicating successful blinding of stimulation.

This study provides first proof-of-principle for a sustainable beneficial effect of tDCS-enhanced CC training on memory concerns in SCD. Thus, CC training combined with tDCS appears promising as an effective and well tolerated (Sup. Tab. 3) approach to reduce the burden of memory related worries in an elderly population.

The results support our primary hypothesis that memory concerns can be reduced by a targeted activation of the CC network most likely by means of an improved executive control [6] on distractive self-focus and negative affect [4]. Based on these prior data it is plausible that a multi-session tDCS-enhanced training program can stabilize the involved CC networks and reduce the concerns about deterioration of cognitive abilities.

The lack of significant effects on processing speed as measured by PASAT performance underlines the inherently subjective nature of SCD [10] and can most likely be attributed to ceiling effects due to age-related functional limitations. However, the persistent and pronounced reduction of memory concerns by tDCS-enhanced CC training reflects a beneficial effect on prefrontal, executive control. This effect may be useful to recruit available resources to attenuate, at least temporarily, cognitive impairments caused by ongoing neurodegeneration. However, conclusions regarding the efficacy of this approach to delay cognitive decline are premature and beyond the scope of this study. Moreover, testing of optimal stimulation parameters, training schedules and individual genetic, neurophysiological, and neurocognitive response predictors are needed to optimize and stratify potential prophylactic interventions.

In conclusion, this is the first proof of concept for the efficacy of activity enhancing tDCS combined with CC training in reducing the amount of memory concerns in elderly subjects with SCD. Our findings provide a basis for the development of innovative, effective and well tolerated approaches to mobilize CC and alleviate the burden of memory related concerns in a large proportion of the elderly population.

Author contributions

Study concept and design: C.P. and N.S.; data acquisition and analysis: N.S. and C.P.; drafting and critical analysis of manuscript: C.P., N.S., and C.L.

Declaration of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2019.04.008.

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