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Feasibility and pilot efficacy of self-applied home-based cognitive training and brain stimulation: A randomized-controlled trial

Dear Editor,

Non-pharmacological interventions to enhance cognitive functions and decelerate neurodegenerative processes are urgently needed [1]. In this context, pairing cognitive training with transcranial direct current stimulation (tDCS) is a safe, low-cost, and potentially effective treatment option [2]. Previously, we conducted clinical trials involving older adults without and with cognitive impairment, administering multi-session cognitive training (i.e., intense practicing of working memory updating and decision-making) with anodal tDCS over left dorsolateral prefrontal cortex [3,4]. These studies were performed in the laboratory, requiring frequent visits to the facility, thus necessitating not only high motivation, but also placing high demands on temporal availability and flexibility for patients, often challenging, especially for older adults in rural areas due to long distances and limited mobility. Moreover, limited clinical resources would not support such interventions in the population at large. Importantly, the use of therapies in clinical routine is not only related to their effectiveness but also to their feasibility and acceptability [5]. Thus, remotely controlled and independently self-applied tES approaches for at-home use may be a crucial step forward [6].

We therefore conducted a monocentric, randomized, placebo-controlled clinical trial in older adults to determine the feasibility (primary), acceptability and efficacy (secondary) of a home-based independently self-applied tDCS-accompanied cognitive training [7]. This approach has not yet been evaluated in a home environment without "real-time" supervision. We hypothesized that appropriate training and instruction will allow for at least 60 % of all participants to successfully complete at least two-thirds of all sessions, rendering the intervention feasible. Thirty older adults (aged 60–80 years) were randomly assigned to either an active or sham tDCS group ($n = 15$ per group). Participants completed six at-home sessions over two weeks, with pre-, post-, and follow-up assessments in the lab. During at-home sessions, participants performed a working memory (letter updating, LU) task while self-administering tDCS (1.5 mA for 20 minutes). See Supplementary Material for details on study design and participants, randomization and blinding, intervention, and statistical analysis.

From March 2021 to July 2023, 30 participants were included in the trial and randomly assigned to either active (target intervention, $n = 15$) or sham tDCS (control intervention group, $n = 15$) combined with cognitive training (mean/SD age 69 ± 5 years, 19 women). Twenty-nine participants completed four or more of the six sessions successfully, which amounts to 96.7 % (95%-CI: [81.9 to 100.0]), confirming that the intervention was feasible (Fig. 1A). On the acceptability questionnaire, the item that assessed overall satisfaction with the intervention was rated "agree" ($n = 10$) or "strongly agree" ($n = 18$) by 93 % of participants ($n = 28$). Overall, the mean for acceptability (i.e., satisfaction and feasibility) ratings was 93 % (95%-CI: [77.6 to 99.2]) on a 5-point Likert scale (Fig. 1B). Most of the items of the questionnaire were rated high by the majority of participants (i.e., confidence in setting up the system: 93 %, comfort with tDCS: 83 %). The target group showed superior performance on the LU training task compared to the control group ($\beta = 3.5$, 95%-CI: [0.5, 6.6], $p = 0.037$; Fig. 1C). There was no significant difference in the transfer task (N-back, $\beta = -5.1$, 95%-CI: [−14.6, 4.5], $p = 0.23$). See Supplementary Material for further details about cognitive effects and a report on adverse events and blinding.

Our findings demonstrate excellent feasibility and acceptability of the combined self-administered at-home intervention in older adults. The prespecified criterion for inference of feasibility was exceeded. Only one participant did not complete all sessions, thus overall commitment and retention rates were very high, with no dropouts or losses to follow-up. A questionnaire further showed overall high acceptability, with excellent scores for tolerability and satisfaction with the intervention and very low discomfort ratings, with only two participants reporting minor side effects. To the best of our knowledge, this is the first Phase II clinical trial of self-administered approach of cognitive training combined with tDCS in a cohort of older adults [8]. Combined approaches challenge participants in terms of assembling study material, such as inserting electrodes into the cap, putting on the cap, switching on the stimulator, checking electrode impedances, as well as starting the training session on the tablet computer, a concern particularly valid for older adults who are often less experienced in handling technical devices and software [9]. Our findings confirm an exploratory analysis of five older participants (however of "younger old" age, i.e., 51–68 years) who performed a motor training together with tDCS on their own at home [10]. Our participants particularly appreciated detailed guidance and training on the practical aspect of this approach. Given that no "real-time" or video supervision is needed for this approach, demands on personnel and laboratory space are reduced for the investigator. Moreover, the at-home approach reduces time and travel commitment for participants, and may thus overcome barriers to neuromodulation as a treatment for routine clinical use. Secondary analyses on efficacy of active stimulation revealed superior training (LU task), but no robust effects for transfer task performance (N-back task). Overall, the behavioral results were in line with beneficial effects of the combined approach for cognitive outcomes in our previous clinical trials conducted in the laboratory in healthy older adults [4] and older adults with cognitive impairment [3]. However, while these trials showed group differences for transfer working memory (N-back) task performance only, we observed an effect of tDCS on the trained (LU) task performance in the current study. The training task effect in the present study may be related to higher stimulation intensity (1.5 instead of 1 mA). With regard to the lack of transfer effects, we can only speculate that more

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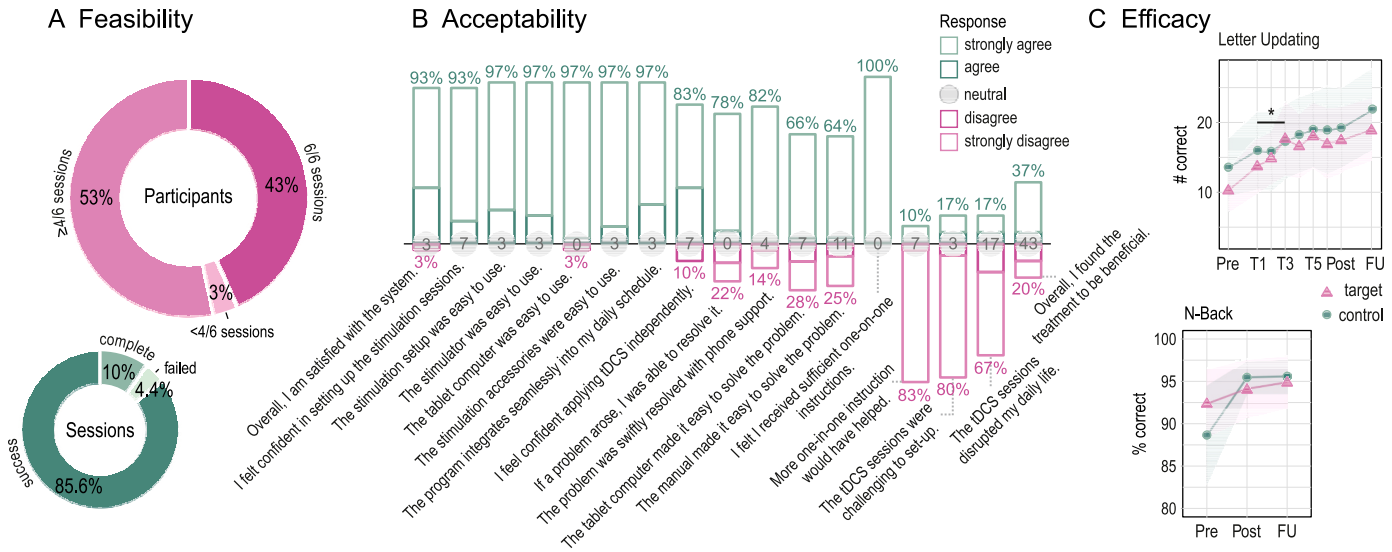

Fig. 1. (A) Percentage of participants by session completion. The top pie chart shows the percentage of participants based on the number of sessions they completed. A session was considered successful if it was recorded as completed in the cloud and the participant had not contacted the study staff to report issues or request rescheduling. Among the participants, 16 (53.3 %) completed all 6 sessions, 13 (43.3 %) completed 4 or 5 sessions, and 1 (3.3 %) completed fewer than 4 sessions. Thus, 29 participants met the feasibility criterion. One participant experienced technical issues (abort of the stimulation due to high impedance and bad Wi-Fi connection and, thus, incomplete synchronization with the cloud server). The bottom pie chart displays the percentage of sessions based on their outcomes. Of all sessions, 154 (85.5 %) were successful, 18 (10 %) were completed but with issues that were resolved, and 8 (4.4 %) failed due to unsolvable problems (i.e., system abortion, scheduling issues). (B) Acceptability questionnaire. Responses to all items by all participants in percent. (C) Performance on training and transfer tasks. Overall improvement over the intervention period in letter updating training task with superior performance in the target compared to the control group ($\beta = 3.5$, 95%-CI: [0.52 to 6.58], $p = 0.037$ (model-derived marginal means: 18.9, 95%-CI: [16.7 to 21.1] for target and 15.7, 95%-CI: [13.6 to 17.8] for sham control group; $n = 30$ participants, 206 data points). For the N-back transfer task, performance did not differ between groups ($\beta = -5.1$, 95%-CI: [-14.6 to 4.5], $p = 0.23$ (model-derived marginal means: 80.5, 95%-CI: [73.7 to 87.2] for the target group and 85.5, 95%-CI: [79.2 to 91.8] for the sham control group; $n = 30$ participants, 60 data points). tDCS, transcranial direct current stimulation. Pre, pre-assessment. T1 to T6, timepoints during training. FU, follow-up assessment (one month after the intervention).

concurrent training and stimulation sessions may be needed (i.e., nine [3,4] instead of six sessions in the present report). Moreover, our previous studies included an additional decision-making training in each session, which may have contributed to the transfer effects.

In conclusion, feasibility and acceptability of self-administered cognitive training combined with tDCS in older adults were clearly demonstrated, with indications for efficacy in terms of cognitive outcome in an at-home approach, which shows significant advantages for both investigators and patients. These findings warrant a subsequent Phase III trial, which would, if successful, introduce a safe and feasible approach to prevent cognitive decline into clinical practice.

CRediT authorship contribution statement

Merle Rocke: Writing – review & editing, Writing – original draft, Visualization, Investigation, Formal analysis. **Anna E. Fromm:** Visualization, Project administration, Investigation, Formal analysis, Data curation. **Nora Jansen:** Investigation. **Friederike Thams:** Supervision, Project administration, Investigation, Conceptualization. **Catalina Trujillo-Llano:** Writing – original draft, Visualization, Investigation, Formal analysis. **Ulrike Grittner:** Visualization, Formal analysis. **Daria Antonenko:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Project administration, Investigation, Formal analysis, Data curation, Conceptualization. **Agnes Flöel:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Funding acquisition, Conceptualization.

Authorship statement

The authors confirm that they meet the requirement for authorship.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2024.10.009.

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Merle Rocke
Department of Neurology, University Medicine Greifswald, Greifswald, Germany

Anna E. Fromm
Department of Neurology, University Medicine Greifswald, Greifswald, Germany

Nora Jansen
Department of Neurology, University Medicine Greifswald, Greifswald, Germany

Friederike Thams
Department of Neurology, University Medicine Greifswald, Greifswald, Germany

Catalina Trujillo-Llano
Department of Neurology, University Medicine Greifswald, Greifswald, Germany

Ulrike Grittner
Berlin Institute of Health, Charité University Medicine Berlin, Berlin, Germany
Institute of Biometry and Clinical Epidemiology, Charité University Medicine Berlin, Corporate Member of Freie Universität Berlin, Humboldt-University Berlin and Berlin Institute of Health, Berlin, Germany

Daria Antonenko [*,1]
Department of Neurology, University Medicine Greifswald, Greifswald, Germany
German Centre for Neurodegenerative Diseases (DZNE), Greifswald, Germany

Agnes Flöel[1,**]
Department of Neurology, University Medicine Greifswald, Greifswald, Germany
German Centre for Neurodegenerative Diseases (DZNE), Greifswald, Germany

[*] Corresponding author. Department of Neurology, University Medicine Greifswald, Ferdinand-Sauerbruch-Straße, D-17475 Greifswald, Germany.

[**] Corresponding author. Department of Neurology, University Medicine Greifswald, Ferdinand-Sauerbruch-Straße, D-17475, Greifswald, Germany.
E-mail address: daria.antonenko@med.uni-greifswald.de (D. Antonenko).
E-mail address: agnes.floeel@med.uni-greifswald.de (A. Flöel).

[1] Shared-last authorship.