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Feasibility of Cognitive Training in Combination With Transcranial Direct Current Stimulation in a Home-based Context (TrainStim-Home) – Study Protocol for a Randomized Controlled Trial

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Abstract

Introduction: With the worldwide increase of life expectancy leading to a higher proportion of older adults experiencing age-associated deterioration of cognitive abilities, the development of effective and widely accessible prevention and therapeutic measures has become a priority and challenge for modern medicine. Combined interventions of cognitive training and transcranial direct current stimulation (tDCS) have shown promising results for counteracting age-associated cognitive decline. However, access to clinical centers for repeated sessions is challenging, particularly in rural areas and for older adults with reduced mobility, and lack of clinical personnel and hospital space prevents extended interventions in larger cohorts. A home-based and remotely supervised application of tDCS would make the treatment more accessible for participants and relieve clinical resources. So far, studies assessing feasibility of combined interventions in a home-based setting are missing. With this study, we aim to provide evidence for the feasibility and the effects of a multi-session home-based cognitive training in combination with tDCS on cognitive functions of healthy older adults.

Methods and analysis: The TrainStim-Home trial is a monocentric, randomized, double-blind, placebo-controlled study. Thirty healthy participants, aged 60 to 80 years, will receive two weeks of combined cognitive training and anodal tDCS over left dorsolateral prefrontal cortex (dlPFC, target intervention), compared with cognitive training plus sham stimulation. The cognitive training will comprise a letter updating task, and the participants will be stimulated for 20 min with 1.5 mA. The intervention sessions will take place at the participants' home and primary outcome will be the feasibility, operationalized by 2/3 successfully completed sessions per participant. Additionally, performance in the training task and an untrained task will be analyzed.

Ethics and dissemination: Ethical approval was granted by the ethics committee of the University Medicine Greifswald. Results will be available through publications in peer-reviewed journals and presentations at national and international conferences.

Trial registration: The study was registered prospectively on 26 March 2021 at ClinicalTrials.gov with the Identifier: NCT04817124.

Keywords: home use, neuromodulation, working memory, transfer, executive function, brain stimulation, behavioral intervention, multi-session

Strengths and limitations of this study

- This is the first trial to investigate the feasibility of self-application of cognitive training combined with tDCS in older adults
- We implement thorough training of older adults in handling devices and materials, and collect structured feedback on satisfaction with procedures from participants, to obtain successful delivery of the intervention and high adherence rates
- A possible selection bias towards technical experienced participants may occur, as due to remote connection requirements we can only include participants with an internet access in their homes

Background

With the worldwide increase of life expectancy[1], an increasing proportion of older adults will experience age-associated deterioration of cognitive abilities which will lead, in addition to individual suffering, to social and health economic strains[2 3]. Thus, investigation of non-invasive interventions to counteract cognitive decline and restore impaired functions, such as combined cognitive training and transcranial direct current stimulation (tDCS) protocols, is particularly relevant [4-7]. In general, combined approaches of training and tDCS have been shown to elicit immediate effects on cognitive abilities, transfer to untrained domains, and long-term effects, which persisted up to several months[8-12]. Mechanistically, tDCS is thought to additionally boost the effect of cognitive training by supporting already ongoing brain activity in task-related neural areas[10 13]. Possible underlying physiological mechanisms are tDCS-induced alterations of resting membrane potentials and long-term potentiation via glutamatergic neurotransmission[14-16]. However, multi-session interventions of combined cognitive training and tDCS involve frequent visits to the facility, which requires high compliance and motivation from the participants, especially from participants living in rural areas with no easy access to research facilities or from adults that are limited in their mobility due to advanced age or comorbidities. Additionally, the facilities need space and personnel to administer the intervention, which puts further limits on interventions applied over multiple sessions in large cohorts. As promising results of combined cognitive training and tDCS have been shown in on-site studies (i.e., in the clinic or lab environment)[8-12], translation of the intervention to remotely-controlled self-administration in a home-based context would be the next necessary step for a widely accessible intervention.

Remotely-controlled tDCS enables the trained staff to monitor the intervention from a distance, for example from the hospital (e.g., by tracking the completed sessions, the quality, length, and any problems during the sessions remotely or via direct phone contact) [17]. The devices for the stimulation are programmed specifically for home-based use before being handed over to the participants. This programming only allows a pre-defined strength and length of the stimulation, thereby ensuring the

safety of the participants [17]. A recent review of 22 studies of home-based tDCS interventions without cognitive training has given a positive outlook on home-based tDCS [17]. So far, studies that investigated home-use tDCS for the treatment of diseases such as trigeminal neuralgia, vascular-related dementia, or multiple sclerosis, showed that a remote application of tDCS at home could lead to an improvement in symptoms [18-20]. As the participants were, however, mostly young adults, and most of the studies focused on effectiveness, research on the feasibility of home-based tDCS in older adults is particularly relevant. Previous home-based tDCS studies with a wide age range reported a large variance in the level of the participant's commitment. Dropout rates ranged from 4% only [21] to high rates of 41% [20]. An easy, self-explanatory application, good communication, and unsolicited support in keeping the participants engaged seem to be key factors for higher adherence rates [17 21 22]. Thus, research assessing the feasibility of a combined home-based cognitive training and tDCS approach is needed. Compared to home-use tDCS feasibility trials published so far, a combined approach poses a bigger challenge for participants in terms of assembly of the study materials and execution of the stimulation and behavioral task, especially in an older population, who is often less experienced in handling of technical devices and software[17]. Nonetheless, when well instructed on how to administer the intervention, the effectiveness of the combined approach and the possibility of participating from home could serve as a motivator for long-term adherence. Moreover, a combined approach of training and concurrent tDCS, will control for the participants' activity during stimulation compared to previous home-based trials administering solely tDCS[23].

In the TrainStim-Home study, we will therefore investigate the feasibility (primary) and the effects on cognitive function of home-based cognitive training and tDCS in a monocentric, randomized, double-blind, placebo-controlled design. Participants will accomplish a letter updating task over six training sessions with concurrent tDCS over left dorsolateral prefrontal cortex (dlPFC) administered by the participants themselves in their own home. Half of the study cohort will receive anodal tDCS while performing the cognitive training, whereas the other half will undergo sham stimulation during training. The intervention will span two weeks, with three training sessions per week. We will assess

feasibility and behavioral outcome measures, such as direct training effects, transfer to untrained domains and performance sustainability for one month. We hypothesize that with appropriate instruction and close supervision via remote cloud system and phone, the use of combined cognitive training and tDCS (or sham) in an ecologically valid environment (i.e., at the participant's home) by the participants themselves is feasible (i.e., the participants complete 2/3 of the home-based sessions successfully (primary outcome) and achieve a high score in a feasibility questionnaire at post-assessment). For assessment of feasibility, both groups will be included in the analysis. For the assessment of efficacy, we hypothesize increased performance on the trained and untrained tasks at post-assessment in the anodal compared to the sham stimulation group. Moreover, we expect sustainability of the effects at four-week follow-up to be superior in the anodal group. This protocol, describing the design and methods of the TrainStim-Home study, was prepared in accordance with the SPIRIT guidelines [24 25].

METHODS: Participants, intervention, and outcomes

Design and setting

This is a monocentric, randomized, double-blind, placebo-controlled study to evaluate the feasibility and effectiveness of a two-week combined cognitive training and tDCS intervention administered by participants themselves. The intervention spans two weeks and comprises six sessions (3 per week) of cognitive training, accompanied by tDCS over the left dlPFC compared to sham tDCS. The intervention will take place at the participants' home. Additionally, pre- and post-assessments will be carried out at the University Medicine Greifswald. A follow-up assessment will follow one month after the intervention to assess possible long-term effects. In total, participants will complete 10 sessions. A flowchart of the study is shown in Figure 1.

Eligibility criteria

Before randomization, participants eligible for the study must meet all the following criteria:

- Age: 60-80 years
- Right-handedness
- Internet access at the home of the participants
- Performance in neuropsychological screening at baseline within normal range (defined as performance of each subtest within -1.5 standard deviations (SD) from the normative samples mean) [26 27].

In case one or more of the following criteria are present at randomization, potential participants will be excluded:

- Mild cognitive impairment (MCI), subjective cognitive decline (SCD), or dementia (participants reporting decline in cognitive functions or performing below -1.5 SD in any neuropsychological screening subtest will be excluded).
- Other neurodegenerative neurological illnesses, epilepsy or history of seizures, close relatives with epilepsy or history of seizures; previous stroke.
- Severe untreated medical conditions that preclude participation in the training, as determined by responsible physician
- History of severe alcoholism or use of drugs
- Severe psychiatric disorders such as depression (if not in remission) or psychosis
- Contraindication to tDCS application [28].

If all eligibility criteria are met and participants provide written informed consent, they will be included in the study sample.

Intervention

At each training session, participants will participate in a cognitive training with concurrent administration of either anodal or sham stimulation. Participants will be presented with a letter updating task (LU task, cf. [5 29]) on a tablet computer. This task targets working memory updating. The

letters A to D will be presented one letter at a time in random order, and with differing list lengths (5, 7, 9, 11, 13 or 15 letters, six times each; total of 36 lists). After the presentation of each list (presentation duration 2000ms, ISI 500ms), the participants will be asked to recall the last four letters that were presented.

tDCS will be administered via a battery-operated stimulator (Starstim Home, Neuroelectrics, Barcelona, Spain). Two sponge-based electrodes (Sponstim, NE026, Neuroelectrics, Barcelona, Spain) will be mounted on the head in a neoprene cap using the 10-20 EEG grid. The anodal electrode will be placed over the left dlPFC, in the position of F3, the cathodal electrode will be placed over the right orbita in the Fp2 position. A current of 1.5 mA will be applied for 20 min, with 20 additional seconds of ramping in the beginning and at the end of the stimulation. In the sham group, the current will only be applied for 30 sec in total at the beginning of the 20 min, to elicit the typical tingling sensation of stimulation on the scalp and to blind the participants regarding their stimulation condition. Ramp times and montage will be equivalent to the anodal stimulation group. The cognitive training task and the stimulation will be started simultaneously. Every three sessions, thus twice over the intervention time, participants will be asked to complete an adverse events questionnaire [28]. At each training session, the participants will be asked to fill in a questionnaire regarding self-reported well-being, quality and duration of sleep as well as potential stressors in the last two hours prior to the session. They will also be asked to complete the German version of the Positive and Negative Affect Schedule (PANAS[30]), both before and after the session. Participants will be asked to avoid excessive consumption of alcohol and nicotine on the day of the intervention, and one day prior. Furthermore, they will be instructed to forgo caffeine 90 min before a session and adhere to their regular sleep schedule.

Outcome measures

Feasibility will be assessed directly after the intervention. Outcome measures of the training task will be acquired at each visit. Additionally, at pre-, post- and follow-up assessments outcomes for

possible transfer effects will be acquired. All outcome measures and assessment time points are displayed in Table 1. Each outcome measure will be analyzed regarding potential differences between intervention groups (anodal vs. sham tDCS).

Primary outcomes

Primary outcome measure will be the feasibility of home-based tDCS as operationalized by at least 2/3 of successfully performed interventional sessions per participant for at least 60 % of all participants. A session is considered successful when its registered as fully completed in the cloud and the participant has not initiated contact concerning a problem or rescheduling.

Secondary outcomes

Feasibility will further be measured by questionnaire and analyzed as a secondary outcome. A single-item self-rate questionnaire on participant satisfaction, independence and self-confidence in the handling of the devices and program (adapted from Cha et al., 2016[21]) will be filled out by the participants. Feasibility will be assumed, if at least 60 % of all participants rated to "agree" or "strongly agree" (i.e., 4 or 5 on 5-point Likert scale) on the questionnaire item assessing overall satisfaction with the tDCS and training equipment. Additionally, working memory performance in the trained task will be assessed at each session, operationalized by number of correctly recalled lists in the letter updating task[31]. Performance in the untrained tasks will be assessed as secondary outcome at post- and follow-up assessments, operationalized by percentage of correct answers in the n-back task [32].

Participant timeline

Participants will have to adhere to 10 sessions over the course of the study. Baseline and pre-assessment (V1, V2) will take place at the University Medicine Greifswald, the training sessions (V3-V8) will take place at the participants' own home during two consecutive weeks on 3 days a week. The first of the training sessions will be accompanied by a study investigator, the following five sessions will be performed independently and tracked via a cloud system. After the training, post-

assessment (V9) will be conducted immediately and follow-up assessment will be administered four weeks later, both at the University Medicine Greifswald.

Baseline measures

At baseline assessment, the study and its execution will be explained to the participant by a member of the study staff. Subsequently, the participants will be asked to provide written informed consent and a demographic interview will be carried out. This interview will be followed by a comprehensive battery of neuropsychological tests to quantify cognitive function on different domains, including the CERAD-Plus test battery[33]. Additionally, handedness will be assessed with the Oldfield Handedness Questionnaire[34] and possible depressive symptoms will be explored with the Geriatric Depression Scale[35].

Following the tests and questionnaires, an instructional video explaining the assembly, disassembly, handling and care of the devices and of the supplies for the stimulation will be shown to the participants. Any questions and critical points will be discussed with a staff member. The participant will then be asked to replicate the assembly and disassembly of an interventional session with the help of a checklist and the study staff, and subsequently perform the training task as described above. At baseline assessment, the training task will include 25 lists (36 lists at training sessions) and a practice trial with four lists will be performed.

Pre-, post- and follow-up-assessments

Self-reported well-being, quality and duration of sleep as well as potential stressors in the last two hours prior to the visit will be assessed in the form of a semi-structured interview. Then, the participants will complete the working memory training task (LU task[29]) and a working memory task that will not be trained (n-back task[32]). At pre-assessment participants will additionally be instructed once more in the handling of the stimulation set. The feasibility questionnaire will be completed at post-assessment.

Sample size

As the primary goal of this study will be to assess feasibility, and as it is recommended to employ results of feasibility trials for sample size calculation of a planned subsequent trial[36], we chose a sample size of N = 30[37]. To infer feasibility, the lower bound of the 95 % confidence interval of the proportion of participants who fulfilled the feasibility criterion needs to be at 60 %. Thus, 76 %, i.e., n = 23 participants will have to meet the feasibility criterion.

With 15 participants per stimulation group (anodal vs. sham stimulation), we will be able to additionally explore the benefit of anodal tDCS over sham with regard to performance after the training on the trained working memory, and the untrained working memory tasks[38 39]. Using an independent t-test with a two-sided significance level of 0.05 and a power of 80 % we will be able to demonstrate an effect of Cohen's d = 1.06 or higher on behavioral performance.

Recruitment

Participants will be recruited via adverts in the local newspaper and via the distribution of flyers at senior and adult education centers, local shops, restaurants and museums. All potential participants will be provided with information about the study over the phone, and a screening assessing exclusion and inclusion criteria will be carried out. All eligible participants will be invited for baseline assessment.

METHODS: Assignment of interventions

Allocation to anodal and sham tDCS group will be performed using stratified block randomization. Participants will be randomly allocated by a researcher not involved in assessments. Allocation to the experimental groups (anodal vs. sham) will be performed with a 1:1 ratio with age (two age strata; 60-70, 71-80) and cognitive performance at baseline assessment (≤5, >5/25 corrects lists in the LU task). Randomization blocks with varying block sizes will be generated for each of the four groups,

using R software (http://www.R-project.org) and the blockrand package (https://CRAN.R-project.org/package=blockrand). Participants will then be allocated to anodal or sham tDCS group, based on the generated randomization sequences within each block and stratum.

Blinding

In this double-blind trial, both investigators and study participants and investigators will be blinded regarding the stimulation condition. The two stimulation protocols (anodal, sham) will be labeled with unidentifiable labels such as A and B. A staff member not involved in data collection will perform the randomization as described above and will subsequently assign the label of the stimulation protocol accordingly to each participant. The investigator will schedule stimulation sessions for each participant individually via a cloud-system. This investigator will select the labeled protocol that corresponds to the participants ID number and will be able to plan the stimulation without knowledge of the respective stimulation condition. As for participant blinding, study participants will only be able to use the device if a stimulation session with given duration and current intensity was scheduled beforehand in the online cloud-system. Participants will be unaware whether the session entails active or sham stimulation. In the sham group the current will only be applied at the beginning of the stimulation session for 20 sec ramp-up and -down respectively. This method is used to elicit the typical tingling sensation under the electrodes during the stimulation and to ensure blinding of the participants to the respective stimulation condition. Previous studies have shown that sham tDCS is a safe and valid method of participant-blinding [40-43]. At post-assessment, participants will be asked to state if they believe they received anodal or sham stimulation.

METHODS: Data collection, management and analysis

Data collection methods

Neuropsychological and behavioral will be collected from each participant. Study investigators will be thoroughly trained in administering the assessments. Time points of data collection are shown in **Table 1.**

Neuropsychological and behavioral assessment

Neuropsychological testing at the baseline visit (V0) will comprise paper-pencil as well as computer-based assessment. The Geriatric Depression Scale[35] and the Edinburgh Handedness Inventory[34] will be administered. Cognitive function in different domains will be quantified using a comprehensive battery of neuropsychological tests including the CERAD (Consortium to Establish a Registry for Alzheimer's Disease, German version), extended to CERAD-Plus (https://www.memoryclinic.ch/de/main-navigation/neuropsychologen/cerad-plus/) with the Trail Making Test A + B and Phonematic Fluency (S-Words)[33], and the digit span test[44].

The training and transfer tasks are computer-based. Detailed description of the training task is provided in the intervention section. At pre-, post-, and follow-up-assessment (V2, V9-V10) an untrained task is administered: Participants will perform a numeric n-back task (1 and 2 back) to assess working memory function (18 trials total, 9 trials 1back and 9 trials 2back with 10 items each, presentation duration 1500ms, ISI 2500ms). A sequence of numerical stimuli is presented one after another, and the participants will have to state if the number that is currently presented is identical to the stimulus "n"-steps back.

Additionally, at post-assessments, participants will complete a 17-item feasibility questionnaire concerning independence and self-confidence in the handling of the devices and program as well as the participant satisfaction and comfort during the at-home part of the study participation (cf. Cha et al.[21]).

Retention and adherence

Participants will be provided with information on their appointments via telephone and if possible via e-mail to maximize retention over the course of the study. A few days prior to pre-assessment, participants will be contacted by a study investigator and will be reminded of the upcoming

appointments. A copy of all study appointments will be handed out at pre-assessment. At every appointment and during each phone call, the investigator will actively seek out any open questions and remarks regarding the intervention and will provide assistance accordingly. Furthermore, the online cloud-system, which interacts with the application on the tablet computer, allows the investigators involved in this study to schedule and monitor stimulation sessions individually for each participant. During stimulation and simultaneous performance of the training task, the participant will be able to abort the stimulation at any time via button press, if necessary. After the completion of the task, the stimulation will be turned off automatically, and information on whether the session was completed or not will be transferred to the cloud-system, to be checked by the investigator. Additionally, investigators will be notified automatically via e-mail alert about any reported adverse events or problems. In such case, participants will be contacted immediately. The participants will be reminded that their progress will be monitored closely through the cloud-system and that they should not hesitate to contact the investigator in case problems or questions arise. If no contact is initiated by the participant, they will be contacted by the day of their sixth training sessions. To assist the participant in solving problems, the investigator has the possibility to remotely control the tablet computer. Participants will be encouraged to use the 24/7 study answering machine if they cannot attend a visit and want to reschedule. They will then be contacted by a member of the study team as soon as possible. At the end of the study, i.e. at follow-up assessment, participants will receive a financial reimbursement of 130 € and a report about their neuropsychological test performance. If for whatever reason complete adherence is not possible, an effort will be made to collect as much data as possible from the respective participant.

Data management and monitoring

All collected data will be pseudonymized. Paper-based data such as questionnaires and the scoring sheets of the neuropsychological test will be stored in lockable cabinets in rooms with restricted access, sorted by participant ID for easy access at each stage of the study. Data acquired on paper

will be manually digitalized by one staff member, and double-checked by another. The progress of data acquirement and digitalization will be documented. All digitally acquired data, such as task output files, will be saved on a secure server and protected with password only known to the staff involved in this project. Protocols of the tDCS stimulation of each participant and session will also be stored on this server. Spreadsheets concerning sensitive data, such as names, addresses and contact information, will be further protected with another password if acquired digitally, and stored in a separate lockable cabinet if in paper form. Following good scientific practice, data will be stored for at least 10 years.

Patient and public involvement

In order to involve older adults, in December of 2020, we asked five former participants of our TrainStim-Cog trial (study protocol, see [45]) which comprised a very similar procedure, to participate in trial sessions. During these trial sessions, we simulated the home-based training sessions including the assembly and disassembly of the stimulation set and the handling of the tablet computer. Any difficulties, such as the complicated order of mounting the stimulation equipment, were identified in these trial sessions and were solved by developing further aids, such as a check-list and a detailed instruction manual. Using this check-list and manual, trial participants were then able to mount the stimulation set confidently and correctly. Similarly, we were made aware of the importance of a visual demonstration and consequently filmed an instruction video of 20 min duration, which will be shown to every participant at baseline assessment and will be available over the treatment period as on-demand video on the tablet computer. Continuing this feedback-based development of the home-based approach during the feasibility trial, we will carry out a semi-structured interview at post-assessment concerning ease of use, opinions and feelings of the participants about the system and of our assistance, as well as concerning perceived challenges with this home-based approach. Information obtained through these interviews will help optimize the trial design for a possible subsequent clinical trial.

Adverse events monitoring

The risk of health damage associated with anodal tDCS is expected to be minimal. Known adverse effects (AEs) with the study parameters (20 min, 1.5 mA) are skin tingling, reddening and occasionally a mild headache. These potential AEs will be monitored after each third stimulation session via an adverse events questionnaire[28]. We will refrain from assessing AEs at every session, as we believe it would only draw the participants' attention to minor sensations during the stimulation and ultimately act as a distractor from the cognitive task. Investigators will be instructed to monitor for and document all AEs and serious AEs throughout the trial. Participants will be informed about possible risks and AEs at baseline assessment and can withdraw consent at any time without providing reason. If a serious AE occurs, the study physician will be consulted and asked to make an assessment whether or not a causal relationship with the intervention is considered possible. If more than three of the enrolled participants suffer from serious AEs that are likely to be associated with the intervention (as assessed by the study physician), the trial will be discontinued.

Statistical analysis

Feasibility data (primary outcome) will be analyzed using descriptive statistics. Feasibility will be inferred when participants complete at least 2/3 of the home-based sessions successfully. Secondary feasibility outcomes, as measured by questionnaire will be analyzed similarly. Data distributions of the questionnaire items will be visually assessed for normality using q-q plots, and statistically using the Shapiro-Wilk test[37,46]

Secondary outcome data on behavioral tasks from all participants included at randomization will be analyzed including data from all participants who finished post-assessment. Additionally, a "per protocol" analysis will be conducted, including only those participants, who successfully completed 2/3 of the home-based sessions (thus fulfilling the criterion for feasibility). Focusing on the trained task, we will conduct an ANCOVA model with the post-assessment working memory score (number

of correctly recalled lists in the letter updating task) as dependent variable, stimulation group (anodal, sham) as factor, and working memory performance at pre-assessment as well as age as covariates. We will furthermore analyze outcome measures from untrained WM tasks and their interactions, using linear mixed models with time-point (e.g., pre- / post-assessment) as within-subject factor and stimulation group (anodal, sham) as between-subject factor. In case of violation of requirements for parametric methods, appropriate non-parametric tests will be conducted. Data analysis will be conducted using IBM SPSS Statistics for Windows (IBM Corp., Armonk, NY, United States), MatLab (The Mathworks Inc., 2016), and R software.

Ethics and Dissemination

This study was approved by the ethics committee of the University Medicine Greifswald and will be conducted in accordance with the Helsinki Declaration. All data collected will be pseudonymized. The results of this study will be made accessible to scientific researchers and health care professionals via publications in peer-reviewed journals and presentations at national and international conferences. Furthermore, the scientific and lay public can access the study results on the ClinicalTrials.gov website (Identifier: NCT04817124).

Conclusion

With this trial, we will assess feasibility and efficacy a home-based combined cognitive training and tDCS intervention in older adults. A successful implementation of the intervention in the home-based setting will contribute to the development of home-based tDCS as a widely available therapy option in clinical populations.

Trial status

Recruitment of participants has started in April 2021.

Declarations

Consent or assent

A member of the investigational team (study coordinator or study assessor) will collect written informed consent during study enrollment after having reviewed the participant information sheet, participant's questions, and study inclusion and exclusion criteria.

Confidentiality

The collected data will be treated as confidential. Direct access to personal information and source data documentation will only be given to study monitors, study assessors, and the research team.

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Availability of data and materials

Anonymized data will be made available to the scientific community upon request.

Authors' contributions

FT, DA and AF conceptualized and designed this trial. AF is supervising its implementation. FT is implementing the trial and supervising its conduct. RN assisted in programming and software development of the home-based stimulation application. RM programmed the training task and implemented it to work with the stimulation application. MR is performing recruitment and assessments. FT and MR drafted the study protocol. UG will be performing statistical analyses. All authors will be contributing to interpretation of the data. All authors read and revised the original draft and consecutive versions of the manuscript. All authors read and approved the final version of the study protocol.

Ethics approval and consent to participate

The study was approved by the ethics committee of the University Medicine Greifswald, Germany (BB02 /21, date of first approval: 05 Feb 2021). All procedures conducted during the TrainStim-Home trial will be carried out in compliance with the Declaration of Helsinki.

Competing interests

RN is a part-time employee with NE. The other authors declare no actual or potential conflicts of interest.

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Tables and Figures

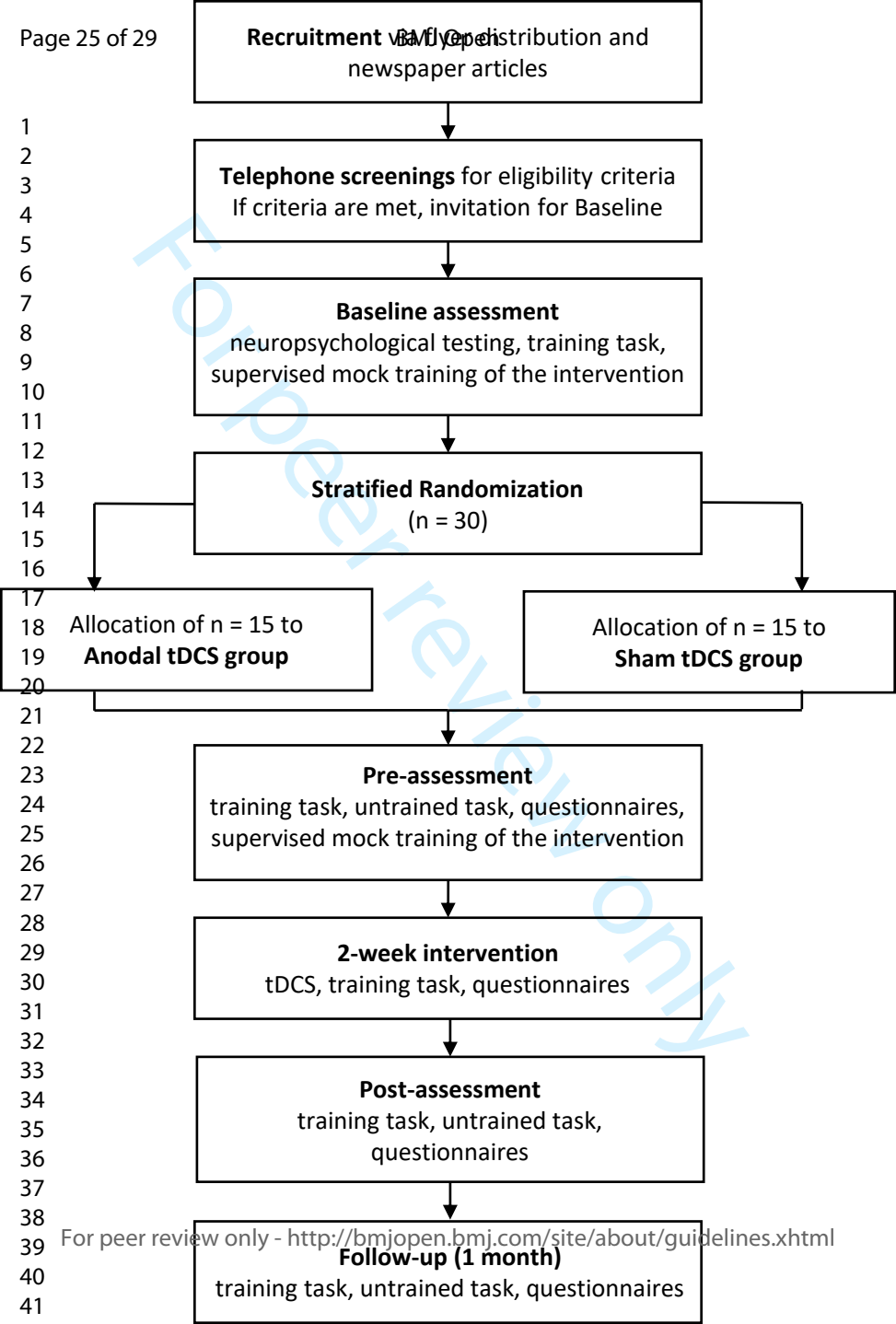
Table 1. *TrainStim-Home outcome measures.*

			Baseline	Pre	T1-T6 (2 weeks)	Post (3 days)	FU (1 month)
			~3h	~1,5h	~1h	~1,5h	~1,5h
Time point	**Measurement**	**Mode**	**V0**	**V1**	**V2-V7**	**V8**	**V9**
Enrollment							
Eligibility screening		Paper	x				
Informed consent		Paper	x				
Neuropsychological Screening	Demographic data	Paper	x				
	Geriatric depression scale[35]	Paper	x				
	Oldfield handedness inventory[34]	Paper	x				
	CERAD Plus[33]	Paper	x				
	Digit Span[44]	Paper	x				
Intervention					↔		
Training task	Letter updating[5 29]	Tablet computer	x	x	x	x	x
Brain stimulation	tDCS (anodal vs. sham)	Device			x		
Questionnaires	Self-reported well-being questionnaire	Paper		x	x	x	x
	PANAS[30]	Paper			x		
	Adverse events questionnaire[28]*				x		
Additional assessments							
Untrained task	n-back[32]	Computer		x		x	x
Feasibility	Sessions completed (primary outcome)	Cloud system			x	x	
	Feasibility questionnaire	Paper				x	

Abbreviations: T1-T6, training 1-6; FU, follow-up-assessment; V0-V9, visits 0-9; CERAD Plus, The Consortium to Establish a Registry for Alzheimer's Disease, neuropsychological test battery, German version, extended to CERAD Plus with the Trail Making Test A + B and Phonematic Fluency (S-Words); tDCS, transcranial direct current stimulation; PANAS, positive and negative affect schedule. All measures were acquired on site or at the respective participants home, except for screening which was done via telephone. *assessed only at the end of each training week (V4 and V7).

Figure Legend

Figure 1. TrainStim-Home study flowchart. *tDCS*, transcranial direct current stimulation.



SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Adressed on page no.
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1, 3
	2b	All items from the World Health Organization Trial Registration Data Set	Yes (available under NCT04817124)
Protocol version	3	Date and version identifier	3
Funding	4	Sources and types of financial, material, and other support	18
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	18
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4, 5, 6
	6b	Explanation for choice of comparators	4, 5, 6
Objectives	7	Specific objectives or hypotheses	5, 6, 9
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6, 11, 12
Methods: Participants, interventions, and outcomes			

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	9, 10
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6, 7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7, 8, 13
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	16
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	13, 14
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8, 13, 14
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9, 10, 11, Figure 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	11
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	11, 12
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	11,12
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	12

Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	12
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	12, 13, Table 1
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	13, 14
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	14, 15
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16, 17
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	17
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	16, 17
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n/a
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	16
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	17, 18
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	18
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10,18
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14,15,18
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	19
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	18
	31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	18
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Feasibility of Cognitive Training in Combination With Transcranial Direct Current Stimulation in a Home-based Context (TrainStim-Home) – Study Protocol for a Randomized Controlled Trial

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Feasibility of Cognitive Training in Combination With Transcranial Direct Current Stimulation in a Home-based Context (TrainStim-Home) – Study Protocol for a Randomized Controlled Trial

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Abstract

Introduction: With the worldwide increase of life expectancy leading to a higher proportion of older adults experiencing age-associated deterioration of cognitive abilities, the development of effective and widely accessible prevention and therapeutic measures has become a priority and challenge for modern medicine. Combined interventions of cognitive training and transcranial direct current stimulation (tDCS) have shown promising results for counteracting age-associated cognitive decline. However, access to clinical centers for repeated sessions is challenging, particularly in rural areas and for older adults with reduced mobility, and lack of clinical personnel and hospital space prevents extended interventions in larger cohorts. A home-based and remotely supervised application of tDCS would make the treatment more accessible for participants and relieve clinical resources. So far, studies assessing feasibility of combined interventions with a focus on cognition in a home-based setting are rare. With this study, we aim to provide evidence for the feasibility and the effects of a multi-session home-based cognitive training in combination with tDCS on cognitive functions of healthy older adults.

Methods and analysis: The TrainStim-Home trial is a monocentric, randomized, double-blind, placebo-controlled study. Thirty healthy participants, aged 60 to 80 years, will receive two weeks of combined cognitive training and anodal tDCS over left dorsolateral prefrontal cortex (dlPFC, target intervention), compared with cognitive training plus sham stimulation. The cognitive training will comprise a letter updating task, and the participants will be stimulated for 20 min with 1.5 mA. The intervention sessions will take place at the participants' home and primary outcome will be the feasibility, operationalized by 2/3 successfully completed sessions per participant. Additionally, performance in the training task and an untrained task will be analyzed.

Ethics and dissemination: Ethical approval was granted by the ethics committee of the University Medicine Greifswald. Results will be available through publications in peer-reviewed journals and presentations at national and international conferences.

Trial registration: The study was registered prospectively on 26 March 2021 at ClinicalTrials.gov with the Identifier: NCT04817124.

Keywords: home use, neuromodulation, working memory, transfer, executive function, brain stimulation, behavioral intervention, multi-session

Strengths and limitations of this study

- This is the first trial to investigate the feasibility of self-application of cognitive training combined with tDCS in older adults
- We implement thorough training of older adults in handling devices and materials, and collect structured feedback on satisfaction with procedures from participants, to obtain successful delivery of the intervention and high adherence rates
- A possible selection bias towards technical experienced participants may occur, as due to remote connection requirements we can only include participants with an internet access in their homes
- A more comprehensive training program including tasks from multiple cognitive domains (in contrast to the one task trained in this study) could possibly show more general behavioral effects. Nonetheless, for the primary purpose of assessing feasibility, our planned training regimen is well justified.

Background

With the worldwide increase of life expectancy [1], an increasing proportion of older adults will experience age-associated deterioration of cognitive abilities which will lead, in addition to individual suffering, to social and health economic strains [2, 3]. Thus, investigation of non-invasive interventions to counteract cognitive decline and restore impaired functions, such as combined cognitive training and transcranial direct current stimulation (tDCS) protocols, is particularly relevant [4-7]. In general, combined approaches of training and tDCS have been shown to elicit immediate effects on cognitive abilities, transfer to untrained domains, and long-term effects, which persisted up to several months [8-12]. Executive functions, including working memory, are especially prone to age-related decline [13]. Brain regions implicated primarily in these functions, including the prefrontal cortex and associated functional networks, have shown to be sensitive to age-related changes such as cortical atrophy and functional reorganization [14-16]. Research combining training of executive functions with tDCS over the dorsolateral prefrontal cortex provided promising, but highly variable, results so far [8-12, 17]. Mechanistically, tDCS is thought to additionally boost the effect of cognitive training by supporting already ongoing brain activity in task-related neural areas[10, 18]. Possible underlying physiological mechanisms are tDCS-induced alterations of resting membrane potentials and long-term potentiation via glutamatergic neurotransmission[19-21]. However, multi-session interventions of combined cognitive training and tDCS involve frequent visits to the facility, which requires high compliance and motivation from the participants, especially from participants living in rural areas with no easy access to research facilities or from adults that are limited in their mobility due to advanced age or comorbidities. Additionally, the facilities need space and personnel to administer the intervention, which puts further limits on interventions applied over multiple sessions in large cohorts. In light of promising results of combined cognitive training and tDCS interventions in an outpatient clinic, or laboratory environment [8-12], translation to remotely-controlled self-administration in a home-based context would be the next necessary step for a widely accessible intervention, requiring feasible and easy-to handle intervention protocols.

Remotely-controlled tDCS enables the trained staff to monitor the intervention from a distance, for example from the hospital (e.g., by tracking the completed sessions, the quality, length, and any problems during the sessions remotely or via direct phone contact) [22]. The devices for the stimulation are programmed specifically for home-based use before being handed over to the participants. This programming only allows a pre-defined strength and length of the stimulation, thereby ensuring the safety of the participants [22]. Two recent reviews, of 22 studies and 24 studies respectively, of home-based tDCS interventions without cognitive training have given a positive outlook on feasibility and possibly effectiveness of home-based tDCS in a number of cognitive functions in various patient populations [22]. So far, studies that investigated home-use tDCS for the treatment of diseases such as trigeminal neuralgia, vascular-related dementia, or multiple sclerosis, showed that a remote application of tDCS at home could lead to an improvement in symptoms [23-25]. As the participants were, however, mostly young adults, and most of the studies focused on effectiveness, research on the feasibility of home-based tDCS in older adults is particularly relevant. Previous home-based tDCS studies with a wide age range reported a large variance in the level of the participant's commitment. Dropout rates ranged from 4% only [26] to high rates of 41% [25]. An easy, self-explanatory application, good communication, and unsolicited support in keeping the participants engaged seem to be key factors for higher adherence rates [22, 26, 27].

Thus, research assessing the feasibility of a combined home-based cognitive training and tDCS approach is needed. Compared to home-use tDCS feasibility trials published so far, a combined approach poses a bigger challenge for participants in terms of assembly of the study materials and execution of the stimulation and behavioral task, especially in an older population, who is often less experienced in handling of technical devices and software [22]. To our knowledge there is only one previous feasibility study of a combined home-based tDCS and training intervention, i.e. an intervention where participants performed the training as well as the stimulation on their own. What turned out to be particularly important is a detailed training and guidance on the practical aspect of this approach, as well as readily available support via telephone and regular contact with the study

team to keep participants engaged and to prevent drop-out out of frustration [28]. In contrast to the present study, in their exploratory feasibility analysis, Maceira et al. included five participants of younger age (51-68 years) than in the present trial and focused their home-based approach on learning in the motor domain. Consequently, the requirements for setting up the equipment differ from our trial and an older cohort may have difficulties in handling the technical equipment. Our study will thus add to the already identified aspects by systematically assessing feasibility of a cognitive training and tDCS approach in the form of a clinical feasibility trial in a larger cohort of older adults [29].Nonetheless, when well instructed on how to administer the intervention, the effectiveness of the combined approach and the possibility of participating from home could serve as a motivator for long-term adherence. Moreover, a combined approach of training and concurrent tDCS, will control for the participants' activity during stimulation compared to previous home-based trials administering solely tDCS[30].

In the TrainStim-Home study, we will therefore investigate the feasibility (primary) and the effects on cognitive function of home-based cognitive training and tDCS in a monocentric, randomized, double-blind, placebo-controlled design. We will assess feasibility and behavioral outcome measures, such as direct training effects, transfer to untrained domains and performance sustainability for one month. We hypothesize that with appropriate instruction and close supervision via remote cloud system and phone, the use of combined cognitive training and tDCS (or sham) in an ecologically valid environment (i.e., at the participant's home) by the participants themselves is feasible (i.e., the participants complete 2/3 of the home-based sessions successfully (primary outcome) and achieve a high score in a feasibility questionnaire at post-assessment). For assessment of feasibility, both groups will be included in the analysis. With regard to behavioral outcomes, the purpose of the present study is to collect data on direct training performance, transfer to untrained domains and performance sustainability for one month, in order to inform planning (e. g., power analysis) of future, definitive randomized controlled trials in older adults. This protocol, describing the design and

methods of the TrainStim-Home study, was prepared in accordance with the SPIRIT guidelines [31, 32] and in adherence with the CONSORT extension to randomized pilot and feasibility trials [29].

METHODS: Participants, intervention, and outcomes

Design and setting

This is a monocentric, randomized, double-blind, placebo-controlled study to evaluate the feasibility and effectiveness of a two-week combined cognitive training and tDCS intervention administered by participants themselves. Participants will accomplish a letter updating task over six training sessions (3 per week) with concurrent tDCS over the left dorsolateral prefrontal cortex (dlPFC) administered by the participants themselves in their own home. Half of the study cohort will receive anodal tDCS while performing the cognitive training, whereas the other half will undergo sham stimulation during training. The intervention will take place at the participants' home. Additionally, pre- and post-assessments will be carried out at the University Medicine Greifswald. A follow-up assessment will follow one month after the intervention to assess possible long-term effects. In total, participants will complete 10 sessions. A flowchart of the study is shown in Figure 1.

Eligibility criteria

Before randomization, participants eligible for the study must meet all the following criteria:

- Age: 60-80 years
- Right-handedness
- Internet access at the home of the participants
- Performance in neuropsychological screening at baseline within normal range (defined as performance of each subtest within -1.5 standard deviations (SD) from the normative samples mean) [33, 34].

In case one or more of the following criteria are present at randomization, potential participants will be excluded:

- Mild cognitive impairment (MCI), subjective cognitive decline (SCD), or dementia (participants reporting decline in cognitive functions or performing below -1.5 SD in any neuropsychological screening subtest will be excluded).
- Other neurodegenerative neurological illnesses, epilepsy or history of seizures, close relatives with epilepsy or history of seizures; previous stroke.
- Severe untreated medical conditions that preclude participation in the training, as determined by responsible physician
- History of severe alcoholism or use of drugs
- Severe psychiatric disorders such as depression (if not in remission) or psychosis
- Contraindication to tDCS application [35].

If all eligibility criteria are met and participants provide written informed consent, they will be included in the study sample.

Intervention

At each training session, participants will participate in a cognitive training with concurrent administration of either anodal or sham stimulation. Participants will be presented with a letter updating task ([LU task, cf. 5, 36]) on a tablet computer. This task targets working memory updating. The letters A to D will be presented one letter at a time in random order, and with differing list lengths (5, 7, 9, 11, 13 or 15 letters, six times each; total of 36 lists). After the presentation of each list (presentation duration 2000ms, ISI 500ms), the participants will be asked to recall the last four letters that were presented. With a list length of 36 lists, participants are expected to complete the task in about 20-25 minutes, simultaneously to the stimulation. The letter updating task will be the only task trained by the participants in this study. A more comprehensive training program including tasks from multiple cognitive domains (in contrast to the one task trained in this study) could

possibly show more general behavioral effects [37, 38]. Nonetheless, for the primary purpose of assessing feasibility, our planned training regimen is well justified.

tDCS will be administered via a battery-operated stimulator (Starstim Home, Neuroelectrics, Barcelona, Spain). Two sponge-based electrodes (Sponstim, NE026, Neuroelectrics, Barcelona, Spain) will be mounted on the head in a neoprene cap using the 10-20 EEG grid. The anodal electrode will be placed over the left dlPFC, in the position of F3, the cathodal electrode will be placed over the right orbita in the Fp2 position. In preparation for the independent electrode mounting done by the participants over the intervention period (working memory training and tDCS), the participants will be trained on the positioning and mounting of the cap with additional care. To ensure correct assembly, the two electrode positions in the neoprene head-cap are color coded, matching the respective colored cables to connect the electrodes with the device. During the training to assemble the set-up, the electrode positions in the cap and on the head will be checked by study staff. For this purpose, study staff will identify the 10-20 EEG system Cz position (vertex) by measuring half-way distances between nasion and inion and pre-auricular points and check whether the cap is correctly placed. Together with the participants, individual markers to find the correct positioning of the cap on the head will be identified (e.g., the rim of the cap has to be aligned with the eyebrows).This hands-on approach using caps with pre-defined electrode positions is suited for at home use by participants and allows for precise electrode placement in a non-lab environment [28]. A current of 1.5 mA will be applied for 20 min, with 20 additional seconds of ramping in the beginning and at the end of the stimulation. In the sham group, the current will only be applied for 30 sec in total at the beginning of the 20 min, to elicit the typical tingling sensation of stimulation on the scalp and to blind the participants regarding their stimulation condition. Ramp times and montage will be equivalent to the anodal stimulation group. The cognitive training task and the stimulation will be started simultaneously. Every three sessions, thus twice over the intervention time, participants will be asked to complete an adverse events questionnaire [35]. At each training session, the participants

will be asked to fill in a questionnaire regarding self-reported well-being, quality and duration of sleep as well as potential stressors in the last two hours prior to the session. They will also be asked to complete the German version of the Positive and Negative Affect Schedule [PANAS, 39], both before and after the session. Participants will be asked to avoid excessive consumption of alcohol and nicotine on the day of the intervention, and one day prior. Furthermore, they will be instructed to avoid excessive caffeine consumption, i.e. more than the usual amount for the participant, and if possible forgo caffeine 90 min before a session and adhere to their regular sleep schedule.

Outcome measures

Feasibility will be assessed directly after the intervention. Outcome measures of the training task will be acquired at each visit. Additionally, at pre-, post- and follow-up assessments outcomes for possible transfer effects will be acquired. All outcome measures and assessment time points are displayed in Table 1. Each outcome measure will be analyzed regarding potential differences between intervention groups (anodal vs. sham tDCS).

Primary outcomes

Primary outcome measure will be the feasibility of home-based tDCS as operationalized by at least 2/3 of successfully performed interventional sessions per participant for at least 60 % of all participants (corresponding to the lower bound of 95 % confidence interval, see section Sample size). A session is considered successful when its registered as fully completed in the cloud and the participant has not initiated contact concerning a problem or rescheduling. The thresholds were chosen based on previous reports of dropout rates of up to 41 % in self-administered tDCS studies [25, 40]. The criterion for the amount of successfully performed sessions per participant is based on the idea that the induction of behaviorally relevant effects requires completion off a certain training amount. Additionally, an overall high dropout rate of participants would indicate the need for additional initial instructions and further training of setting-up and performing the intervention, or changes in the usability of the set-up. Thus, our thresholds were set considering to not be too

conservative (taking into account the high dropout rates found by previous studies), but nonetheless maintain a level that would allow to infer feasibility.

Secondary outcomes

Feasibility will further be measured by questionnaire and analyzed as a secondary outcome. A single-item self-rate questionnaire on participant satisfaction, independence and self-confidence in the handling of the devices and program [adapted from 26], see supplementary material for feasibility questionnaire) will be filled out by the participants. Feasibility will be assumed, if at least 60 % of all participants rated to “agree” or “strongly agree” (i.e., 4 or 5 on 5-point Likert scale) on the questionnaire item assessing overall satisfaction with the tDCS and training equipment. Additionally, working memory performance in the trained task will be assessed at each session, operationalized by number of correctly recalled lists in the letter updating task[41]. Performance in the untrained task (n-back) will be assessed as secondary outcome at post- and follow-up assessments, operationalized by percentage of correct answers the sensitivity measure d-prime [42].

Participant timeline

Participants will have to adhere to 10 sessions over the course of the study. Baseline and pre-assessment (V1, V2) will take place at the University Medicine Greifswald, the training sessions (V3-V8) will take place at the participants’ own home during two consecutive weeks on 3 days a week. The first of the training sessions will be accompanied by a study investigator, the following five sessions will be performed independently and tracked via a cloud system. After the training, post-assessment (V9) will be conducted immediately and follow-up assessment will be administered four weeks later, both at the University Medicine Greifswald.

Baseline measures

At baseline assessment, the study and its execution will be explained to the participant by a member of the study staff. Subsequently, the participants will be asked to provide written informed consent and a demographic interview will be carried out. This interview will be followed by a comprehensive battery of neuropsychological tests to quantify cognitive function on different domains, including the CERAD-Plus test battery [43]. Additionally, handedness will be assessed with the Oldfield Handedness Questionnaire (to exclude variance due to functional hemispheric asymmetries and therefore ensure consistent organization of the targeted brain areas)[44]. Possible depressive symptoms will be explored with the Geriatric Depression Scale [45].

Following the tests and questionnaires, an instructional video explaining the assembly, disassembly, handling and care of the devices and of the supplies for the stimulation will be shown to the participants. Any questions and critical points will be discussed with a staff member. The participant will then be asked to replicate the assembly and disassembly of an interventional session with the help of a checklist and the study staff, and subsequently perform the training task as described above. At baseline assessment, the training task will include 25 lists (36 lists at training sessions) and a practice trial with four lists will be performed.

Pre-, post- and follow-up-assessments

Self-reported well-being, quality and duration of sleep as well as potential stressors in the last two hours prior to the visit will be assessed in the form of a semi-structured interview. Then, the participants will complete the working memory training task (LU task [36]) and a working memory task that will not be trained (n-back task [42]). At pre-assessment participants will additionally be instructed once more in the handling of the stimulation set. The feasibility questionnaire will be completed at post-assessment.

Sample size

As the primary goal of this study will be to assess feasibility, and as it is recommended to employ results of feasibility trials for sample size calculation of a planned subsequent trial [46], we chose a sample size of N = 30 [47]. To infer feasibility, the lower bound of the 95 % confidence interval of the proportion of participants who fulfilled the feasibility criterion needs to be at 60 %. Thus, 76 %, i.e., n = 23 participants will have to meet the feasibility criterion.

With 15 participants per stimulation group (anodal vs. sham stimulation), we will be able to able to scope the general feasibility of this home-based intervention, and will be able to plan follow-up trails accordingly. Additionally, we will be able to explore descriptively the benefit of anodal tDCS over sham with regard to performance after the training on the trained and untrained working memory tasks to obtain estimates of effect sizes for power calculations of future randomized controlled trials[48, 49]. Using an independent t-test with a two-sided significance level of 0.05 and a power of 80 % we will be able to demonstrate an effect of Cohen's d = 1.06 or higher on behavioral performance.

Recruitment

Participants will be recruited via adverts in the local newspaper and via the distribution of flyers at senior and adult education centers, local shops, restaurants and museums. All potential participants will be provided with information about the study over the phone, and a screening assessing exclusion and inclusion criteria will be carried out. All eligible participants will be invited for baseline assessment.

METHODS: Assignment of interventions

Allocation to anodal and sham tDCS group will be performed using stratified block randomization. Participants will be randomly allocated by a researcher not involved in assessments. Allocation to the experimental groups (anodal vs. sham) will be performed with a 1:1 ratio with age (two age strata; 60-70, 71-80) and cognitive performance at baseline assessment (≤5, >5/25 corrects lists in the LU task). Randomization blocks with varying block sizes will be generated for each of the four groups,

using R software (http://www.R-project.org) and the blockrand package (https://CRAN.R-project.org/package=blockrand). Participants will then be allocated to anodal or sham tDCS group, based on the generated randomization sequences within each block and stratum.

Blinding

In this double-blind trial, both investigators and study participants and investigators will be blinded regarding the stimulation condition. The two stimulation protocols (anodal, sham) will be labeled with unidentifiable labels such as A and B. A staff member not involved in data collection will perform the randomization as described above and will subsequently assign the label of the stimulation protocol accordingly to each participant. The investigator will schedule stimulation sessions for each participant individually via a cloud-system. This investigator will select the labeled protocol that corresponds to the participants ID number and will be able to plan the stimulation without knowledge of the respective stimulation condition. Thus, study staff performing cognitive assessments will be blinded to the stimulation condition. As for participant blinding, study participants will only be able to use the device if a stimulation session with given duration and current intensity was scheduled beforehand in the online cloud-system. Participants will be unaware whether the session entails active or sham stimulation. In the sham group the current will only be applied at the beginning of the stimulation session for 20 sec ramp-up and -down respectively. This method is used to elicit the typical tingling sensation under the electrodes during the stimulation and to ensure blinding of the participants to the respective stimulation condition. Previous studies have shown that sham tDCS is a safe and valid method of participant-blinding [50-53]. At post-assessment, participants will be asked to state if they believe they received anodal or sham stimulation.

METHODS: Data collection, management and analysis

Data collection methods

Neuropsychological and behavioral will be collected from each participant. Study investigators will be thoroughly trained in administering the assessments. Time points of data collection are shown in **Table 1.**

Neuropsychological and behavioral assessment

Neuropsychological testing at the baseline visit (V0) will comprise paper-pencil as well as computer-based assessment. The Geriatric Depression Scale [45] and the Edinburgh Handedness Inventory[44] will be administered. Cognitive function in different domains will be quantified using a comprehensive battery of neuropsychological tests including the CERAD (Consortium to Establish a Registry for Alzheimer's Disease, German version), extended to CERAD-Plus (https://www.memoryclinic.ch/de/main-navigation/neuropsychologen/cerad-plus/) with the Trail Making Test A + B and Phonematic Fluency (S-Words)[43], and the digit span test [54].

The training and transfer tasks are computer-based. Detailed description of the training task is provided in the intervention section. At pre-, post-, and follow-up-assessment (V2, V9-V10) an untrained task is administered: Participants will perform a numeric n-back task (1 and 2 back) to assess working memory function (18 trials total, 9 trials 1back and 9 trials 2back with 10 items each, presentation duration 1500ms, ISI 2500ms). A sequence of numerical stimuli is presented one after another, and the participants will have to state if the number that is currently presented is identical to the stimulus "n"-steps back.

Additionally, at post-assessments, participants will complete a 17-item feasibility questionnaire concerning independence and self-confidence in the handling of the devices and program as well as the participant satisfaction and comfort during the at-home part of the study participation (cf. [26]).

Retention and adherence

Participants will be provided with information on their appointments via telephone and if possible via e-mail to maximize retention over the course of the study. A few days prior to pre-assessment, participants will be contacted by a study investigator and will be reminded of the upcoming appointments. A copy of all study appointments will be handed out at pre-assessment. At every appointment and during each phone call, the investigator will actively seek out any open questions and remarks regarding the intervention and will provide assistance accordingly. Furthermore, the online cloud-system, which interacts with the application on the tablet computer, allows the investigators involved in this study to schedule and monitor stimulation sessions individually for each participant. During stimulation and simultaneous performance of the training task, the participant will be able to abort the stimulation at any time via button press, if necessary. After the completion of the task, the stimulation will be turned off automatically, and information on whether the session was completed or not will be transferred to the cloud-system, to be checked by the investigator. Additionally, three investigators will be notified automatically via e-mail alert about any reported adverse events or problems. In such case, participants will be contacted immediately. At the end of each day, study staff will check the cloud system and participants will then be contacted if anything is out of the ordinary. The participants will be reminded that their progress will be monitored closely through the cloud-system and that they should not hesitate to contact the investigator in case problems or questions arise. For acute problems participants will be made aware of the study mobile phone number and the office telephone number. If no contact is initiated by the participant, they will be contacted by the day of their sixth training sessions. To assist the participant in solving problems, the investigator has the possibility to remotely control the tablet computer. Participants will be encouraged to use the 24/7 study answering machine or write an email to the study's email address if they cannot attend a visit and want to reschedule. They will then be contacted by a member of the study team as soon as possible. At the end of the study, i.e. at follow-up assessment, participants will receive a financial reimbursement of 130 € and a report about their neuropsychological test

performance. If for whatever reason complete adherence is not possible, an effort will be made to collect as much data as possible from the respective participant.

Data management and monitoring

All collected data will be pseudonymized. Paper-based data such as questionnaires and the scoring sheets of the neuropsychological test will be stored in lockable cabinets in rooms with restricted access, sorted by participant ID for easy access at each stage of the study. Data acquired on paper will be manually digitalized by one staff member, and double-checked by another. The progress of data acquirement and digitalization will be documented. All digitally acquired data, such as task output files, will be saved on a secure server and protected with password only known to the staff involved in this project. Protocols of the tDCS stimulation of each participant and session will also be stored on this server. Spreadsheets concerning sensitive data, such as names, addresses and contact information, will be further protected with another password if acquired digitally, and stored in a separate lockable cabinet if in paper form. Following good scientific practice, data will be stored for at least 10 years.

Patient and public involvement

In order to involve older adults, in December of 2020, we asked five former participants of our TrainStim-Cog trial ([study protocol, 55]) which comprised a very similar procedure, to participate in trial sessions. During these trial sessions, we simulated the home-based training sessions including the assembly and disassembly of the stimulation set and the handling of the tablet computer. Any difficulties, such as the complicated order of mounting the stimulation equipment, were identified in these trial sessions and were solved by developing further aids, such as a check-list and a detailed instruction manual. Using this check-list and manual, trial participants were then able to mount the stimulation set confidently and correctly. Similarly, we were made aware of the importance of a visual demonstration and consequently filmed an instruction video of 20 min duration, which will be

shown to every participant at baseline assessment and will be available over the treatment period as on-demand video on the tablet computer. Continuing this feedback-based development of the home-based approach during the feasibility trial, we will carry out a semi-structured interview at post-assessment concerning ease of use, opinions and feelings of the participants about the system and of our assistance, as well as concerning perceived challenges with this home-based approach. Information obtained through these interviews will help optimize the trial design for a possible subsequent clinical trial.

Adverse events monitoring

The risk of health damage associated with anodal tDCS is expected to be minimal. Known adverse effects (AEs) with the study parameters (20 min, 1.5 mA) are skin tingling, reddening and occasionally a mild headache. These potential AEs will be monitored after each third stimulation session via an adverse events questionnaire [35]. We will refrain from assessing AEs at every session, as we believe it would only draw the participants' attention to minor sensations during the stimulation and ultimately act as a distractor from the cognitive task. Investigators will be instructed to monitor for and document all AEs and serious AEs throughout the trial. Participants will be informed about possible risks and AEs at baseline assessment and can withdraw consent at any time without providing reason. If a serious AE occurs, the study physician will be consulted and asked to make an assessment whether or not a causal relationship with the intervention is considered possible. If more than three of the enrolled participants suffer from serious AEs that are likely to be associated with the intervention (as assessed by the study physician), the trial will be discontinued.

Statistical analysis

Feasibility data (primary outcome) will be analyzed using descriptive statistics. Feasibility will be inferred when participants complete at least 2/3 of the home-based sessions successfully. Secondary feasibility outcomes, as measured by questionnaire will be analyzed similarly. Data distributions of

the questionnaire items will be visually assessed for normality using q-q plots, and statistically using the Shapiro-Wilk test [47, 56].

Secondary analysis of measures for future RCT

Data on behavioral tasks from all participants included at randomization and completed post-assessment will be analyzed within an exploratory framework. Additionally, a subgroup analysis will include only those participants, who successfully completed 2/3 of the home-based sessions (thus fulfilling the criterion for feasibility). In detail, descriptive statistics (i.e., mean and SD) will be reported for the post- and follow-up-assessment working memory score (number of correctly recalled lists in the letter updating task) and outcome measures from the untrained working memory task (% correct and d-prime from the n-back task). As this is a feasibility trial, i.e., not powered for testing hypotheses about effectiveness, group differences between anodal and sham stimulation groups will be calculated reporting means and 95 % confidence intervals [29]. Data analysis will be conducted using IBM SPSS Statistics for Windows (IBM Corp., Armonk, NY, United States), MatLab (The Mathworks Inc., 2016), and R software.

Ethics and Dissemination

This study was approved by the ethics committee of the University Medicine Greifswald and will be conducted in accordance with the Helsinki Declaration. All data collected will be pseudonymized. The results of this study will be made accessible to scientific researchers and health care professionals via publications in peer-reviewed journals and presentations at national and international conferences. Furthermore, the scientific and lay public can access the study results on the ClinicalTrials.gov website (Identifier: NCT04817124).

Trial status

Recruitment of participants has started in April 2021.

Declarations

Consent or assent

A member of the investigational team (study coordinator or study assessor) will collect written informed consent during study enrollment after having reviewed the participant information sheet, participant's questions, and study inclusion and exclusion criteria.

Confidentiality

The collected data will be treated as confidential. Direct access to personal information and source data documentation will only be given to study monitors, study assessors, and the research team.

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Availability of data and materials

Anonymized data will be made available to the scientific community upon request.

Authors' contributions

FT, DA and AF conceptualized and designed this trial. AF is supervising its implementation. FT is implementing the trial and supervising its conduct. RN assisted in programming and software development of the home-based stimulation application. RM programmed the training task and implemented it to work with the stimulation application. MR is performing recruitment and assessments. FT and MR drafted the study protocol. UG will be performing statistical analyses. All authors will be contributing to interpretation of the data. All authors read and revised the original draft and consecutive versions of the manuscript. All authors read and approved the final version of the study protocol.

Ethics approval and consent to participate

The study was approved by the ethics committee of the University Medicine Greifswald, Germany (BB02 /21, date of first approval: 05 Feb 2021). All procedures conducted during the TrainStim-Home trial will be carried out in compliance with the Declaration of Helsinki.

Competing interests

RN is a part-time employee with NE. The other authors declare no actual or potential conflicts of interest.

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Tables and Figures

Table 1. *TrainStim-Home outcome measures.*

			Baseline	Pre	T1-T6 (2 weeks)	Post (3 days)	FU (1 month)
			~3h	~1,5h	~1h	~1,5h	~1,5h
Time point	**Measurement**	**Mode**	**V0**	**V1**	**V2-V7**	**V8**	**V9**
Enrollment							
Eligibility screening		Paper	x				
Informed consent		Paper	x				
Neuropsychological Screening	Demographic data	Paper	x				
	Geriatric depression scale[45]	Paper	x				
	Oldfield handedness inventory[44]	Paper	x				
	CERAD Plus[43]	Paper	x				
	Digit Span[54]	Paper	x				
Intervention					↔		
Training task	Letter updating[5, 36]	Tablet computer	x	x	x	x	x
Brain stimulation	tDCS (anodal vs. sham)	Device			x		
Questionnaires	Self-reported well-being questionnaire	Paper		x	x	x	x
	PANAS[39]	Paper			x		
	Adverse events questionnaire[35]*				x		
Additional assessments							
Untrained task	n-back[42]	Computer		x		x	x
Feasibility	Sessions completed (primary outcome)	Cloud system			x	x	
	Feasibility questionnaire	Paper				x	

Abbreviations: T1-T6, training 1-6; FU, follow-up-assessment; V0-V9, visits 0-9; CERAD Plus, The Consortium to Establish a Registry for Alzheimer's Disease, neuropsychological test battery, German version, extended to CERAD Plus with the Trail Making Test A + B and Phonematic Fluency (S-Words); tDCS, transcranial direct current stimulation; PANAS, positive and negative affect schedule. All measures were acquired on site or at the respective participants home, except for screening which was done via telephone. *assessed only at the end of each training week (V4 and V7).

684 **Figure 1.** TrainStim-Home study flowchart. *tDCS*, transcranial direct current stimulation.

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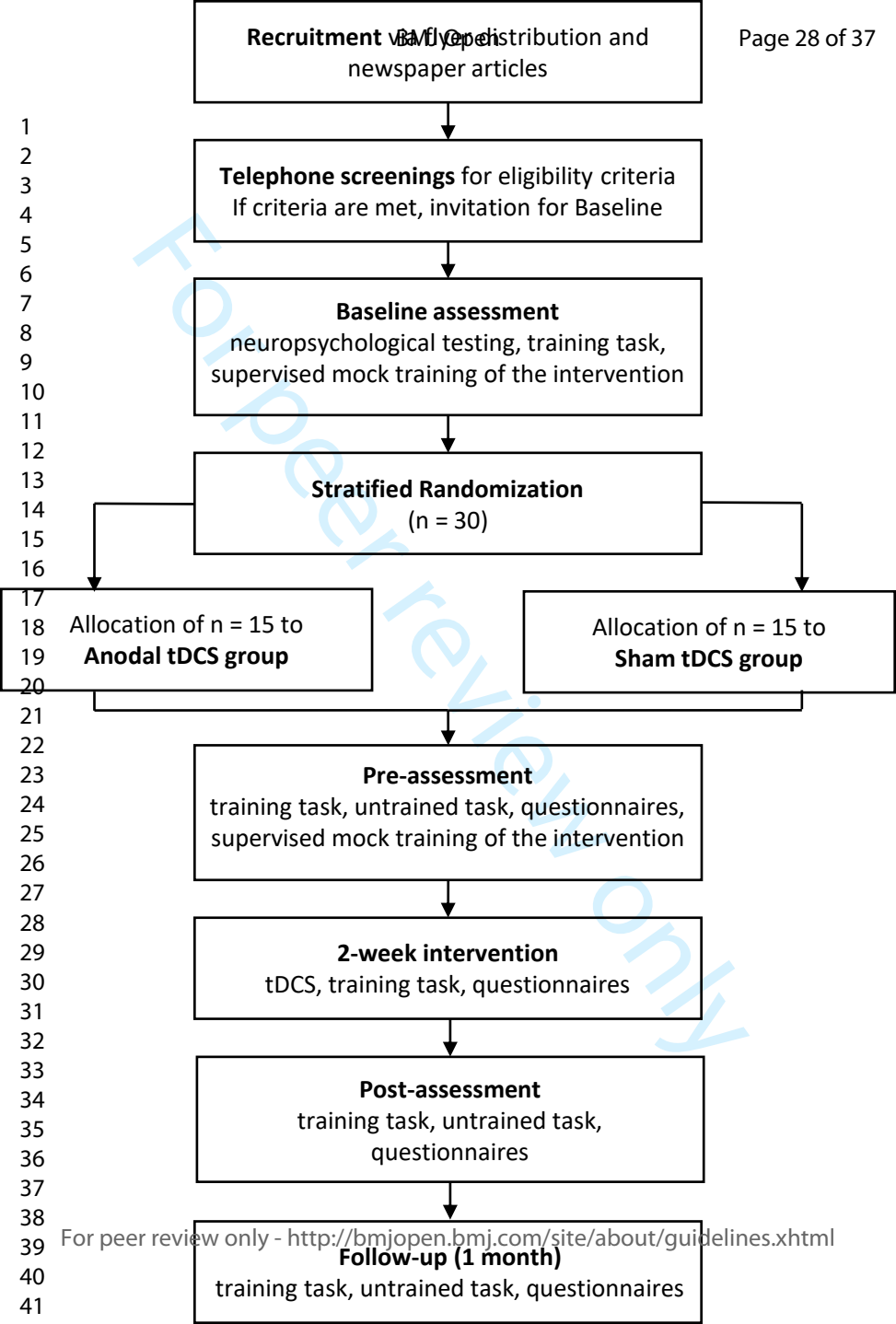

TS4-OG-____ Feasibility ___.___._____

Machbarkeits-Fragebogen

Bitte lesen Sie sich die nachfolgenden Aussagen sorgfältig durch und kreuzen Sie an wie sehr diese Aussagen auf Sie und Ihre Erfahrungen bei den Trainingssitzungen zutreffen!

	Trifft zu	Trifft eher zu	Neutral	Trifft eher nicht zu	Trifft nicht zu
Es war insgesamt einfach dieses Stimulationsset zu verwenden.	☐	☐	☐	☐	☐
Es war einfach den Stimulator zu verwenden.	☐	☐	☐	☐	☐
Es war einfach das Tablet zu verwenden.	☐	☐	☐	☐	☐
Es war einfach das Stimulator-Zubehör (Kappe, Elektroden, etc.) zu verwenden.	☐	☐	☐	☐	☐
Ich habe mich bei der Vorbereitung der Trainingssitzungen sicher gefühlt.	☐	☐	☐	☐	☐
Es ist mir schwergefallen, die Trainingssitzungen vorzubereiten.	☐	☐	☐	☐	☐
Ich konnte die Trainingssitzungen gut in meinen Alltag integrieren.	☐	☐	☐	☐	☐
Die Trainingssitzungen haben meinen Alltagsablauf gestört.	☐	☐	☐	☐	☐
Ich wurde ausreichend persönlich betreut und geschult.	☐	☐	☐	☐	☐
Mehr persönliche Betreuung und Schulung hätte mir geholfen.	☐	☐	☐	☐	☐
Wenn ein Problem aufgetreten ist, konnte ich dieses insgesamt gut lösen.	☐	☐	☐	☐	☐
Das Problem war mithilfe des Tablets gut zu lösen.	☐	☐	☐	☐	☐
Das Problem war mithilfe des Manuals gut zu lösen.	☐	☐	☐	☐	☐
Das Problem war mithilfe der telefonischen Betreuung gut zu lösen.	☐	☐	☐	☐	☐
Insgesamt glaube ich, dass ich von der elektrischen Stimulation profitiert habe.	☐	☐	☐	☐	☐

TS4-OG-____ Feasibility ___.___._____

Wie selbstsicher schätzen Sie sich bei der Durchführung der Trainingssitzungen ohne Kontrolle und Hilfestellung durch ein*e Studienmitarbeiter*in ein?	Sehr selbst-sicher ☐	Selbst-sicher ☐	Neutral ☐	Unsicher ☐	Sehr Unsicher ☐
Zusammengefasst bin ich zufrieden mit diesem Stimulationsset.	Trifft zu ☐	Trifft eher zu ☐	Neutral ☐	Trifft eher nicht zu ☐	Trifft nicht zu ☐
Haben Sie noch Kommentare oder Wünsche?					

CONSORT 2010 checklist of information to include when reporting a pilot or feasibility trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a pilot or feasibility randomised trial in the title	1
	1b	Structured summary of pilot trial design, methods, results, and conclusions (for specific guidance see CONSORT abstract extension for pilot trials)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale for future definitive trial, and reasons for randomised pilot trial	1-7
	2b	Specific objectives or research questions for pilot trial	6
Methods			
Trial design	3a	Description of pilot trial design (such as parallel, factorial) including allocation ratio	7
	3b	Important changes to methods after pilot trial commencement (such as eligibility criteria), with reasons	n/a
Participants	4a	Eligibility criteria for participants	7-8
	4b	Settings and locations where the data were collected	7
	4c	How participants were identified and consented	13
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	8-10
Outcomes	6a	Completely defined prespecified assessments or measurements to address each pilot trial objective specified in 2b, including how and when they were assessed	10-11
	6b	Any changes to pilot trial assessments or measurements after the pilot trial commenced, with reasons	n/a
	6c	If applicable, prespecified criteria used to judge whether, or how, to proceed with future definitive trial	10
Sample size	7a	Rationale for numbers in the pilot trial	13
	7b	When applicable, explanation of any interim analyses and stopping guidelines	n/a
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	13-14
	8b	Type of randomisation(s); details of any restriction (such as blocking and block size)	13-14
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	13-14

Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	13-14
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	13-14
	11b	If relevant, description of the similarity of interventions	14
Statistical methods	12	Methods used to address each pilot trial objective whether qualitative or quantitative	15
Results		***(not applicable as the present work is a study protocol)***	
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were approached and/or assessed for eligibility, randomly assigned, received intended treatment, and were assessed for each objective	n/a
	13b	For each group, losses and exclusions after randomisation, together with reasons	n/a
Recruitment	14a	Dates defining the periods of recruitment and follow-up	n/a
	14b	Why the pilot trial ended or was stopped	n/a
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	n/a
Numbers analysed	16	For each objective, number of participants (denominator) included in each analysis. If relevant, these numbers should be by randomised group	n/a
Outcomes and estimation	17	For each objective, results including expressions of uncertainty (such as 95% confidence interval) for any estimates. If relevant, these results should be by randomised group	n/a
Ancillary analyses	18	Results of any other analyses performed that could be used to inform the future definitive trial	n/a
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	n/a
	19a	If relevant, other important unintended consequences	n/a
Discussion		***(not applicable as the present work is a study protocol)***	
Limitations	20	Pilot trial limitations, addressing sources of potential bias and remaining uncertainty about feasibility	n/a
Generalisability	21	Generalisability (applicability) of pilot trial methods and findings to future definitive trial and other studies	n/a
Interpretation	22	Interpretation consistent with pilot trial objectives and findings, balancing potential benefits and harms, and considering other relevant evidence	n/a
	22a	Implications for progression from pilot to future definitive trial, including any proposed amendments	n/a
Other information			
Registration	23	Registration number for pilot trial and name of trial registry	3 / 19
Protocol	24	Where the pilot trial protocol can be accessed, if available	n/a
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	20
	26	Ethical approval or approval by research review committee, confirmed with reference number	19

Citation: Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. BMJ. 2016;355.
*We strongly recommend reading this statement in conjunction with the CONSORT 2010, extension to randomised pilot and feasibility trials, Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Adressed on page no.
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1, 3
	2b	All items from the World Health Organization Trial Registration Data Set	Yes (available under NCT04817124)
Protocol version	3	Date and version identifier	3
Funding	4	Sources and types of financial, material, and other support	20
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	20
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4, 5, 6, 7
	6b	Explanation for choice of comparators	4, 5, 6, 7
Objectives	7	Specific objectives or hypotheses	6, 10
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7, 12, 13
Methods: Participants, interventions, and outcomes			

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7, 8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8, 9, 10, 12
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	18
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	15, 16
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	15, 16
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10, 11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	11, 12, Figure 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	13
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	13, 14
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	13,14
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	13, 14

Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	14
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	12, 13, 14, Table 1
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	15, 16
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	17
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	18, 19
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	19
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	18, 19
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n/a
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	18
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	19
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	19
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	12, 19
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14,17
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	21
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	20
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	19
	31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	19
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.