


BMJ Open Feasibility of Cognitive Training in Combination With Transcranial Direct Current Stimulation in a Home-Based Context (TrainStim-Home): study protocol for a randomised 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 centres 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 multisession 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, randomised, double-blind, placebo-controlled study. Thirty healthy participants, aged 60–80 years, will receive 2 weeks of combined cognitive training and anodal tDCS over left dorsolateral prefrontal cortex (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, operationalised by two-thirds successfully completed sessions per participant. Additionally, performance in the training task and an untrained task will be analysed.

Ethics and dissemination Ethical approval was granted by the ethics committee of the University Medicine Greifswald. Results will be available through publications

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This is the first trial to investigate the feasibility of self-application of cognitive training combined with transcranial direct current stimulation in older adults.
- ⇒ We implement thorough training of older adults in handling devices and materials and collect structured feedback on satisfaction with procedure 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 programme including tasks from multiple cognitive domains (in contrast to the one task trained in this study) could possibly show more general behavioural effects. Nonetheless, for the primary purpose of assessing feasibility, our planned training regimen is well justified.

in peer-reviewed journals and presentations at national and international conferences.

Trial registration number NCT04817124.

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 been shown to be sensitive to age-related changes such as cortical atrophy and functional reorganisation.^{14–16} Research combining training of executive functions with tDCS over the dorsolateral prefrontal cortex (dlPFC) 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 (eg, 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 predefined 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% only²⁶ 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 with 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 behavioural 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, ie, 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-Elvira *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 with previous home-based trials administering solely tDCS.³⁰

In the TrainStim-Home study, we will therefore investigate the feasibility (primary) and explore the effects on cognitive function of home-based cognitive training and tDCS in a monocentric, randomised, double-blind, placebo-controlled design. We will assess feasibility and behavioural outcome measures, such as direct training effects, transfer to untrained domains and performance sustainability for 1 month.

We hypothesise 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 (ie, at the participant's home) by the participants themselves is feasible (ie, the participants complete two-thirds of the home-based sessions successfully (primary outcome)

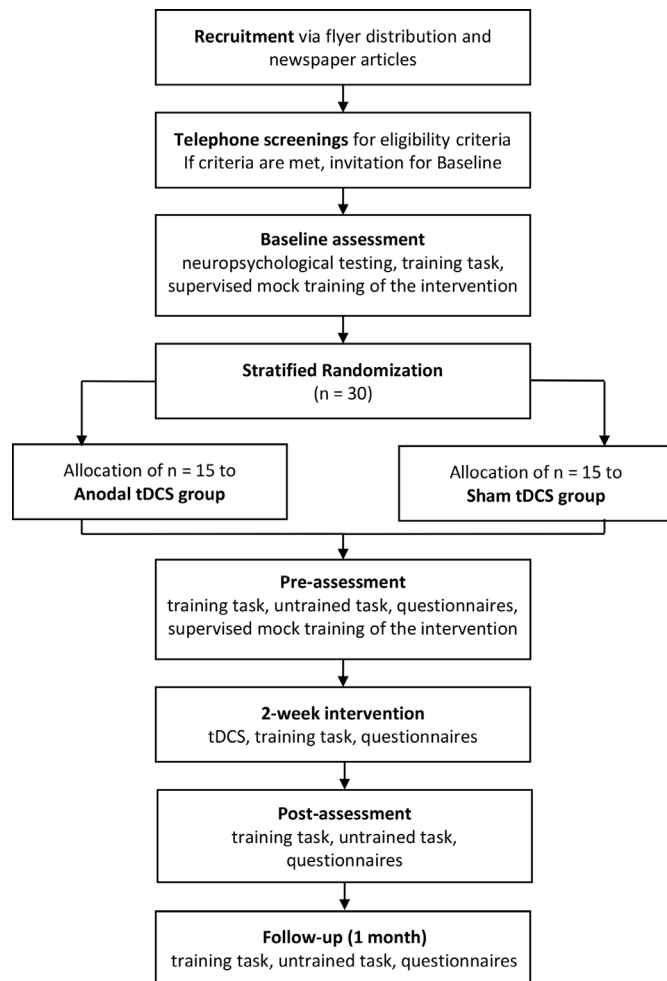


Figure 1 TrainStim-Home study flowchart. tDCS, transcranial direct current stimulation.

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 behavioural outcomes, the purpose of the present study is to collect data on direct training performance, transfer to untrained domains and performance sustainability for 1 month, in order to inform planning (eg, power analysis) of future, definitive randomised controlled trials (RCTs) 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 randomised pilot and feasibility trials.²⁹

METHODS

Participants, intervention and outcomes

Design and setting

This is a monocentric, randomised, double-blind, placebo-controlled study to evaluate the feasibility and explore the effects of a 2-week combined cognitive training and tDCS intervention administered by participants themselves. Participants will accomplish a letter updating (LU) task over six training sessions (three per

week) with concurrent tDCS over the left 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-assessment and post-assessment will be carried out at the University Medicine Greifswald. A follow-up assessment will follow 1 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 randomisation, 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 SD from the normative samples mean).^{33 34}

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

- ▶ Mild cognitive impairment, subjective cognitive decline or dementia (participants reporting a 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 and previous stroke.
- ▶ Severe untreated medical conditions that preclude participation in the training, as determined by the 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 an LU task (cf. Passow *et al*⁵ and Dahlin *et al*³⁶) on a tablet computer. This task targets working memory updating. The letters A–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 2000 ms, inter-stimulus interval (ISI) 500 ms), 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 min,



simultaneously to the stimulation. The LU task will be the only task trained by the participants in this study. A more comprehensive training programme including tasks from multiple cognitive domains (in contrast to the one task trained in this study) could possibly show more general behavioural 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; Neuroelectronics, Barcelona, Spain). Two sponge-based electrodes (Sponstim, NE026; Neuroelectronics) 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 colour coded, matching the respective coloured 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 halfway distances between nasion and inion and preauricular 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 (eg, the rim of the cap has to be aligned with the eyebrows). This hands-on approach using caps with predefined 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 s 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 two times 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 2 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 1 day before the intervention. Furthermore, they will be instructed to avoid excessive caffeine consumption, that is, more than the usual amount for the participant,

and, if possible, 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-assessment, post-assessment and follow-up assessment, 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 analysed regarding potential differences between intervention groups (anodal vs sham tDCS).

Primary outcomes

Primary outcome measure will be the feasibility of home-based tDCS as operationalised by at least two-thirds of successfully performed interventional sessions per participant for at least 60% of all participants (corresponding to the lower bound of 95% CI; see the Sample size section). A session is considered successful when it is 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 behaviourally relevant effects requires completion of 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 analysed as a secondary outcome. A single-item self-rate questionnaire on participant satisfaction, independence and self-confidence in the handling of the devices and programme (adapted from Cha *et al*.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' (ie, 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, operationalised by the number of correctly recalled lists in the LU task.⁴¹ Performance in the untrained task (n-back) will be assessed as secondary outcome at post-assessment and follow-up assessments, operationalised by percentage of correct answers in 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 (V0 and

Table 1 TrainStim-Home outcome measures

Time point	Measurement	Mode	Baseline	Pre	T1–T6	Post	FU
			~3 hours	~1.5 hours	(2 weeks)	(3 days)	(1 month)
			V0	V1	V2–V7	V8	V9
Enrolment							
	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	

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).
 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); FU, follow-up-assessment; PANAS, Positive and Negative Affect Schedule; tDCS, transcranial direct current stimulation; T1–T6, training 1–6; V0–V9, visits 0–9.

V1) will take place at the University Medicine Greifswald; the training sessions (V2–V7) 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 (V8) will be conducted immediately and follow-up assessment (V9) will be administered 4 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 Consortium to Establish a Registry for Alzheimer's Disease (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 organisation 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-assessment, post-assessment and follow-up assessment

Self-reported well-being, quality and duration of sleep as well as potential stressors in the last 2 hours prior to the visit will be assessed in the form of a semistructured interview. Then, the participants will complete the working memory training task (LU task³⁶) and a working memory task that will not be trained (n-back task⁴²). 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% CI of the proportion of participants who fulfilled the feasibility criterion needs to be at 60%. Thus, 76%, that is, $n=23$ participants will have to meet the feasibility criterion.

With 15 participants per stimulation group (anodal vs sham stimulation), we will be able to 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 RCTs.^{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 behavioural performance.

Recruitment

Participants will be recruited via adverts in the local newspaper and via the distribution of flyers at senior and adult education centres, 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.

Assignment of interventions

Allocation to anodal and sham tDCS group will be performed using stratified block randomisation. 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 and 71–80) and cognitive performance at baseline assessment (≤ 5 , $> 5/25$ corrects lists in the LU task). Randomisation 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 randomisation 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 and sham) will be labelled with unidentifiable labels such as A and B. A staff member not involved in data collection will perform the randomisation as described earlier 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 labelled protocol that corresponds to the participants' identification (ID) numbers 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 20s ramp-up and ramp-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.

Data collection, management and analysis

Data collection methods

Neuropsychological and behavioural data 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 behavioural assessment

Neuropsychological testing at the baseline visit (V0) will comprise paper–pencil as well as computer-based assessment. The Geriatric Depression Scale⁴⁵ and the Edinburgh Handedness Inventory⁴⁴ will be administered. Cognitive function in different domains will be quantified using a comprehensive battery of neuropsychological tests including the CERAD (German version), extended to CERAD-Plus (<https://www.memoryclinic.ch/de/main-navigation/neuropsychologen/cerad-plus/>) with the Trail Making Test A+Band 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-assessment, post-assessment

and follow-up-assessment (V1 and V8–V9), an untrained task is administered: participants will perform a numeric n-back task (1-back and 2-back) to assess working memory function (18 trials total, 9 trials 1-back and 9 trials 2-back with 10 items each, presentation duration 1500 ms, ISI 2500 ms). 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 postassessments, participants will complete a 17-item feasibility questionnaire concerning independence and self-confidence in the handling of the devices and programme as well as the participant satisfaction and comfort during the at-home part of the study participation (cf. Cha *et al*²⁶).

Retention and adherence

Participants will be provided with information on their appointments via telephone and if possible via email to maximise 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 email 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, that is, 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 pseudonymised. 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 digitalised by one staff member and double-checked by another. The progress of data acquisition and digitalisation will be documented. All digitally acquired data, such as task output files, will be saved on a secure server and protected with password known only 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 for at least 10 years will be stored.

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 protocol⁵⁵), 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 checklist 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 semistructured 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 optimise 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 analysed using descriptive statistics. Feasibility will be inferred when participants complete at least two-thirds of the home-based sessions successfully. Secondary feasibility outcomes, as measured by questionnaire, will be analysed 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 behavioural tasks from all participants included at randomisation and completed post-assessment will be analysed within an exploratory framework. Additionally, a subgroup analysis will include only those participants who successfully completed two-thirds of the home-based sessions (thus fulfilling the criterion for feasibility). In detail, descriptive statistics (ie, mean and SD) will be reported for the post- and follow-up-assessment working memory score (number of correctly recalled lists in the LU 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, that is, not powered for testing hypotheses about effectiveness, group differences between anodal and sham stimulation groups will be calculated reporting means and 95% CIs.²⁹ Data analysis will be conducted using IBM SPSS Statistics for Windows, MatLab (The Mathworks V.016) 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 pseudonymised. The results of this study

will be made accessible to scientific researchers and healthcare 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.

TRIAL STATUS

Recruitment of participants started in April 2021.

CONSENT OR ASSENT

A member of the investigational team (study coordinator or study assessor) will collect written informed consent during study enrolment 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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Contributors FT, DA and AF conceptualised and designed this trial. AF supervised its implementation. FT implemented the trial and supervised 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 performed recruitment and assessments. FT and MR drafted the study protocol. UG performed statistical analyses. All authors contributed 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.

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

Patient and public involvement Patients and/or the public were involved in the design, conduct, reporting or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Consent obtained directly from patient(s) / participant(s).

Ethics approval This study involves human participants and was approved by the ethics committee of the University Medicine Greifswald, Germany (BB02 /21, date of first approval: 5 February 2021). The participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Anonymised data will be made available to the scientific community upon request.

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