Statistical Analysis Plan (SAP)

"Cognitive Training and Brain Stimulation in Prodromal Alzheimer's Disease" Acronym: **AD-Stim**
Version 1.1
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Intervention therapy: nine-session cognitive training over three weeks with tDCS over the left dorsolateral prefrontal cortex (DLPFC)

Control therapy: nine-session cognitive training over three weeks with sham stimulation

Study population: Older individuals with prodromal Alzheimer's disease

Clinical Phase: mono-centric randomized, double-blind, placebo-controlled trial

Clinicaltrials.gov Identifier: NCT04265378

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1 Study Background

1.1 Study Objective

Developing interventions against age-related diseases, such as Alzheimer's Disease (AD), is of growing importance, given the increases of aging populations around the world. Application of non-pharmacological therapeutic interventions could halt or at least decelerate the neurodegenerative progress. Previous studies found that combining non-invasive brain stimulation (NIBS) and multisession cognitive training may support training effects in healthy adults (1,2). So far, no studies combining those two interventions in prodromal AD populations have been conducted. Therefore, effects of a combined cognitive training and transcranial direct current stimulation (tDCS) intervention in older adults with prodromal Alzheimer's Disease are tested.

The aim of the AD-stim trial (see (3) for study protocol) is to investigate if a three week combined cognitive training and tDCS intervention yields substantial benefits and transfer effects compared to cognitive training and sham tDCS in older individuals with prodromal AD. The analyses described in this statistical analysis plan (SAP) will demonstrate the efficacy of a three-week cognitive training intervention with concurrent tDCS in older adults with prodromal AD. This SAP was prepared in accordance with the Guidelines for the Content of Statistical Analysis Plans in Clinical Trials (4).

1.2 Primary hypothesis

The primary hypothesis of the project is that the combination of cognitive training and tDCS is superior with regard to cognitive performance outcomes compared to cognitive training and sham in older individuals with prodromal AD, operationalized by the score of the letter updating task after 3 weeks of intervention (post assessment).

1.3 Secondary hypotheses

Secondary hypotheses state that the combination of cognitive training and tDCS is superior compared to cognitive training and sham with regard to cognitive training tasks, transfer tasks at all follow up measures as well as neural correlates (assessed before the intervention and at the 7-month follow up (V13) assessment) as measured by structural and functional MRI and defined by the secondary outcomes in older individuals with prodromal AD.

1.4 Study Design

The AD-Stim trial is a randomized, double-blind, placebo-controlled monocenter study. The experimental group will receive a nine-session cognitive training intervention over three weeks, accompanied by anodal tDCS over the left dorsolateral prefrontal cortex (DLPFC). The intervention of the control group will consist of the same nine-session cognitive training combined with sham stimulation over the DLPFC. Additionally, both groups will participate in follow up assessments after one and seven months.

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) and baseline performance in the letter updating task (two performance strata) as strata. We chose cut-offs of 70 years and 2 lists correct in the letter updating task. Randomization blocks with varying block sizes

will be generated for each of the four groups using R software (https://www.r-project.org/) and the blockrand package (https://CRAN.R-project.org/package=blockrand). Based on the generated randomization sequences within each block and stratum, participants will then be allocated to anodal or sham tDCS group.

1.5 Sample Size Calculation

Based on recent studies in the field using multi-session application of anodal tDCS during cognitive training compared to training with sham tDCS (5–7) we estimated an effect size of 0.85. To demonstrate an effect in the primary outcome (number of correctly recalled lists in the letter updating task), 46 participants (23 per group) need to be included in the analysis with an independent t-test using a two-sided significance level of 0.05 and a power of 80%. This conservative approach using a t-test was chosen, even though we intend to analyse the primary outcome conducting analysis of covariance (ANCOVA) models (8). Sample size estimation was conducted using nQuery Advisor 8.5.1 (9).

2 Analysis sets

2.1 Definitions

The **full analysis set** will consist of all participants who received at least one day of intervention. In case participants withdraw informed consent after baseline assessment, they will be considered as screening failures and therefore will not be included in the full analysis set. The **per protocol analysis set** comprises all subjects who received the full three-week intervention or control intervention and completed all visits in the treatment groups they were allocated to. Safety measures will be assessed during tDCS intervention and all participants who received at least one intervention will be included according to their actual treatment in **the safety analysis set**. If no participant received other treatment as intended or switched treatment groups during the study, and since no information on safety measure is available for participants who missed intervention or follow up visits or dropped out, the safety analysis set will be the same as the per protocol analysis set in this study.

2.2 Application

The primary efficacy analysis will be done using the full analysis set including estimated values from multiple imputations for missing values (Intention to treat). An analysis of the primary outcome in the per protocol analysis set will be used as sensitivity analysis. For the safety analysis, analysis will be done in the safety analysis set, which is the same as the per protocol analysis set.

3 Trial centres

Participants will be recruited in one centre: Greifswald.

3.1 Recruitment

Participants will be recruited from neurological departments of local clinics and doctors´ offices as well as through advertisements in the local newspapers and distribution of flyers in local senior citizen clubs. Telephone screenings will be conducted with all potential participants and study information will be provided. Eligible candidates will be invited for baseline assessment. Following baseline assessment (V0) participants will be included if eligibility criteria are met (3).

Information on recruitment flow can be found in the CONSORT flow diagram (Figure 1).

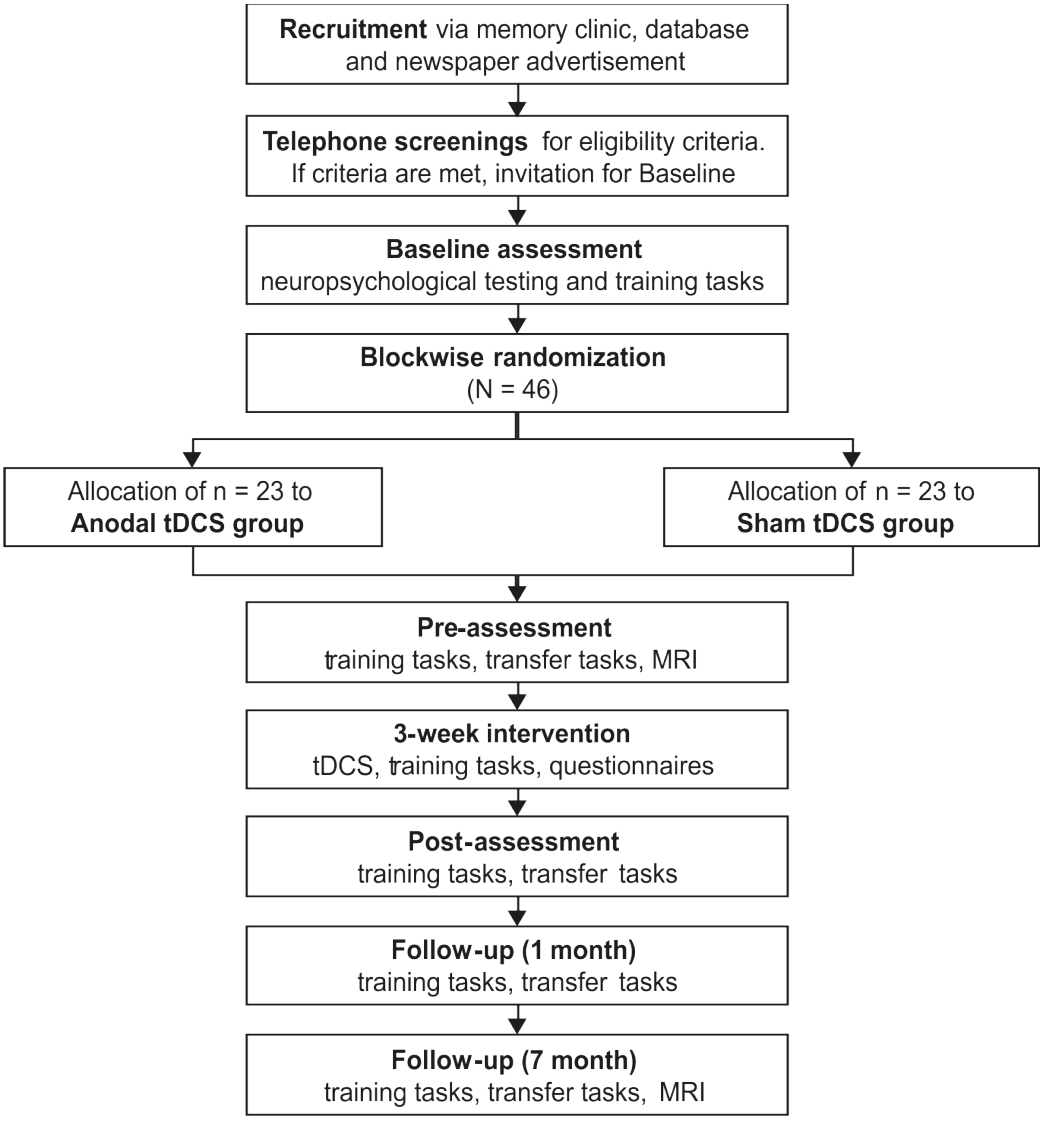

Figure 1. TrainStim-Cog study flowchart. tDCS, transcranial direct current stimulation; MRI, magnetic resonance imaging. Obtained from **(3)**.

4 Analysis variables

Table 1. AD-Stim outcome measures.
Adapted from **(3)**

Table 2. *AD-Stim outcome measures.*

				Post-allocation				
			Base-line	Pre	T1-T9 (3 weeks)	Post (3 days)	FU (1 month)	FU (7 months)
			~ 2h	~ 3h	~ 1h	~ 3h	~ 3h	~ 3h
Time point	**Measurement**	**Mode**	**V0**	**V1**	**V2-V10**	**V11**	**V12**	**V13**
Enrollment								
Eligibility screening		Paper	x					
Informed consent		Paper	x					
Neuro-psycho-logical Screening	Demographic data	Paper	x					
	Geriatric Depression scale (10)	Paper	x					
	Oldfield handedness inventory (11)	Paper	x					
	CERAD (memoryclinic.ch)	Paper	x					
	Digit span (12)	Paper	x					
	Identical pictures (13) Spot-a-word (14)	Computer	x					
Intervention					♦——♦			
Training tasks	Letter updating (15) **primary endpoint at V11**	Tablet-PC	x	x	x	**x**	x	x
	Markov decision making (16,17)	Computer	x	x	x	x	x	x
Brain stimulation	tDCS (anodal vs. sham)	Device			x			
Question-naires	Initial state questionnaire	Paper		x	x	x	x	x
	PANAS (18)	Paper			x			
	Adverse Events Questionnaire* (19)	Paper			x			
Additional assessments								
Transfer tasks	n-back	Computer		x		x	x	x
	AVLT (12,20)	Paper		x		x	x	x
	Wiener Matrices Test 2 (21)	Paper		x		x	x	x
Physical measures	MRI, optional			x				x
	Blood draw			once at any of these visits				

Abbreviations: T1-T9, training 1-9. FU, follow-up assessment. V0-V13, visits 0-13. CERAD: The Consortium to Establish a Registry for Alzheimer's Disease, neuropsychological battery. Fragebogen zur Ausgangslage (Questionnaire about the current state). PANAS, Positive and negative affect schedule. VLMT, Verbaler Lern- und Merkfähigkeitstest (German version of the auditory verbal learning test). tDCS, transcranial direct current stimulation. MRI, magnetic resonance imaging. All measures were acquired on site, except for screening, which was done via telephone. * assessed only at the end of each training week (V4, 7,10).

4.2 Primary Outcome

Performance in the letter updating task at post-assessment, operationalized by number of correctly recalled lists (maximum 15 lists) will be the primary outcome measure.

4.3 Secondary Outcomes

At post- and follow-up assessments (V11, V12, V13) the following secondary outcome measures will be analyzed:

Training tasks

- Number of correctly recalled lists (as secondary outcome at follow-up sessions)
- Proportion of optimal actions in the Markov decision-making task

Transfer tasks

- Performance on numeric n-back task (% correct, d-prime)
- Performance on German version of the auditory verbal learning test (12,20) (# words recalled, total amount of words learned, number of recalled words at delayed recall)
- Performance on Wiener matrices test (WMT-2) (21) (% correct)
- All transfer measures will be corrected for performance at pre-assessment.

MRI measures

- structural neural correlates; assessed by grey matter volumes, cortical thickness, white matter microstructure (diffusion tensor imaging, DTI)
- functional neural correlates; assessed by resting-state fMRI analyses to obtain functional connectivity
- MRI measures will be taken at pre and 7-month follow-up assessments (V1 and V13), therefore analyses will focus on structural and functional correlates of task performance at the respective sessions

In case of effects of interest in primary and / or secondary analyses, effects during the intervention (V2-V10) will be analyzed for both training tasks:

- online effects; assessed by within session performance changes
- offline effects; assessed by performance changes from the last trial of the previous visit to the first trial of the next visit
- direct interventional effects; assessed as performance change from first to last training session (learning curves)

4.4 Safety Outcomes

Safety parameters are assessed via self-report questionnaire every third day of training (V4, V7, V10). The questionnaire was adapted from (19) and includes intensity ratings with regard to itching, pain, burning, warmth/heat, metallic/iron taste, fatigue/decreased alertness and other sensations.

5 Handling of missing values

In case of missing values and under the assumption of missing at random (MAR) or missing completely at random (MCAR) as missing data mechanism, data will be estimated using multiple imputation methods with 30 imputed data sets. To estimate values in a realistic range and with

values similar as in complete cases, we will use predictive mean matching. Multiple imputation by chained equations will be performed by using the following variables in the imputation model: sex, age, stimulation condition, education, letter updating performance at pre-assessment, all outcome measures over all time points.

6 Statistical analyses

For all analyses (including analysis of primary outcome) appropriate descriptive statistics (mean, standard deviation, median, interquartile range, absolute and relative frequencies) depending on the scale and distribution of the outcome variable will be presented.

Statistical analyses will be divided to analyze

1. immediate treatment effects by including all measures until include V11 (post assessment)
2. long-term treatment effects by focusing on V12 (1 month follow up) and V13 (7 months follow up)

6.1 Primary analysis

Using a linear mixed model, the measures of the letter updating task over the study period until include V11 (post assessment, 10 time points), will be used as dependent variable, stimulation group (tDCS, sham) as factor, and letter updating performance at pre-assessment, time point of measure, as well as age and sex as covariates. Time dependent changes will be tested with a continuous time variable (centered) for training days and an additional quadratic time (centered) term to account for a curvilinear time trend. To model differences in time changes between groups an interaction term for intervention group*time will be included. The primary outcome (letter updating task score at post assessment) will be evaluated between treatment groups based on this regression model via marginal means. We will use random intercept models that account for the clustering of measures within individuals (3). The primary analysis will be conducted in a multiple imputed dataset.

6.2 Secondary analyses

<u>Immediate treatment effects</u>

Performance on the second training task (Markov decision-making task) will be analyzed in the same manner as the primary outcome, using linear mixed models for performance on the Markov decision-making task over the study period until include V11 (post-assessment) as dependent variable, stimulation group (tDCS, sham) as factor, and letter updating and Markov decision-making performance at pre-assessment, time point of measure (centered linear and quadratic term, as well as age as covariates, and additionally and interaction term of time point* stimulation group. We will use random intercept models that account for the clustering of measures within individuals.

In case of numeric instability of mixed models for outcomes, generalized estimating equations will be used instead of mixed models.

Transfer tasks and other secondary outcomes that are measured pre and post assessment will be compared in both groups at post-assessment (V11, dependent variable), using separate ANCOVA models for each outcome. In these models treatment allocation will be tested as covariate of interest.

Age and sex as well as interaction terms (age*stimulation group, specific baseline measures*stimulation group) will be included to adjust for possible confounders or to test subgroup differences. The pre-assessment value of the letter updating task and the particular pre-assessment value of the measure of interest will be used as covariates.

Long-term treatment effects

Long term treatment effects will be analyzed using mixed models over the time points: post assessment, 1 month follow up, 7 months follow up. These models will include the pre-assessment scores of the letter updating task and the respective measure of interest, age and sex as covariates and a random effect for the participant (random intercept) as well as a dummy variable for the time point and an interaction term for time point and stimulation group. Type of link function (logistic, linear, ordinal) will depend on the scaling of the dependent variable. In case of skewed continuous data, variables will be transformed before analysis.

All secondary analyses will be done using the full analysis set with multiple imputed data in case of missing values. Per protocol analyses will be done as sensitivity analyses. All secondary analyses will be done in an exploratory framework.

Online and offline training effects

Analyses of online and offline training effects (22) for detailed examination of learning during training will be performed for the main measures of the two training tasks, in case primary and secondary analyses yield any effects worth further exploring. Online learning is defined as performance difference from beginning to end of a training task within each session. Offline effects will regard between session retention (overnight / over the weekend) and will be computed as performance difference from end of the previous session to the beginning of the next session. For the analysis of online training effects, we will use the outcome directly after a training task as dependent variable over the complete training period in a linear mixed model (random intercept model). As independent variables we will use the pre-training measure of the specific training day, the pre-assessment value, age, sex, time point of measurement, group allocation and the interaction of group*time point. To account for possible curvilinear changes of measures over time, a continuous time variable will be included as linear and as quadratic (centred) effect). Offline effects will be analyzed similarly with measures over night / weekend after training as dependent variable, including the measure direct after training (from the day or some days before) as independent measure as well as the other covariates.

Analysis of MRI data

Structural and functional MRI data analyses will be performed using well-established pipelines from MATLAB-based toolboxes such as SPM (Statistical Parametric Mapping software, http://www.fil.ion.ucl.ac.uk/spm/), CONN toolbox (www.nitrc.org/projects/conn, (23), FSL (Analysis Group, FMRIB, Oxford, UK; fsl.fmrib.ox.ac.uk/fsl/fslwiki/, (24), the computational anatomy toolbox (CAT12, http://www.neuro.uni-jena.de/cat/) or Freesurfer (http://surfer.nmr.mgh.harvard.edu/). Functional connectivity within and between large-scale networks will be assessed using functional resting-state fMRI scans (25,26). Segmentation on structural scans will be performed to assess volume of cortical and subcortical gray matter (15,27) and white matter microstructure in white matter tracts will be extracted from diffusion-weighted images using common tractography methods (28–31).

6.3 Safety/Tolerability

Safety outcomes will be reported separately as incidences (n, incidence rate with 95%CI) in total and by intervention group based on the safety analysis set. Participants will be grouped according to their actually received treatment. Incidence rates and 95%CI will be based on poisson regression models that account for the different observation periods for each participant. Group comparisons will be done using incidence rate ratios and 95%CI. Results of safety analysis will be interpreted and discussed thoroughly also for minor group differences, since statistically significance is not of importance here.

6.7 Planned subgroup analyses

For primary and secondary outcomes main subgroups analyses will be done by sex. Therefore, as a first step we will include an interaction term of sex*intervention allocation in the regression models to test whether there are differential treatment effects with regard to sex. Similarly, this will be done as first step for all subgroup analyses. All subgroup analyses will be done within an exploratory framework.

To further explore learning effects, we will perform sensitivity analyses using only measures on time points on which participants felt well enough, based on initial self-rating questionnaires at each visit. To obtain more detailed information on the two training tasks, exploratory models will be calculated on measures, such as performance dependent on list length in the letter updating task (32) or parameters from a drift diffusion model and change-points for the Markov decision-making task (16,17,33,34).

To assess possible predictors of training task performance and responsiveness to the intervention, measures of cognitive reserve (e.g. education, baseline cognitive ability or neuropsychological status) will be entered into analyses.
Cerebrospinal fluid (CSF) biomarkers are an important tool for specification of different etiologies of cognitive decline. We will perform subgroup analysis for participants where information on CSF diagnostic is available from clinical files: To assess possible influence of CSF biomarkers on responsiveness to the intervention, we will perform primary and secondary outcome analysis comparing participants with reduced β-amyloid-ratio (Aβ1-42/Aβ1-40) and participants with no signs of AD pathology.

6.8 Example table for the description of baseline characteristics

Table 3. Baseline characteristics of the study sample.

	All n =	TDCS group n =	Sham group n =
Age (years)			
Gender (n, % female)			
Education (years)			
GDS			
Semantic fluency			
BNT (max. 15)			
MMSE (max. 30)			
Word list learning			
Total (max. 30)			
Trial 1 (max. 10)			
Trial 2 (max. 10)			
Trial 3 (max. 10)			
Word list retrieval (max. 10)			
Word list intrusions			

Figure copying (max. 11)	
Figure retrieval (max. 11)	
Phonematic fluency	
Trail-making test	
Part A (sec)	
Part B (sec)	
Digit-span	
Forward	
Backward	
Identical pictures	
Accuracy	
RT	
Spot-a-word	
Accuracy	
RT	

Data are shown as the mean (SD) or n(%). GDS, Geriatric Depression Scale. BNT, Boston Naming Test. MMSE, Mini Mental Status Examination. RT, reaction time.

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