Clinical Trial Protocol

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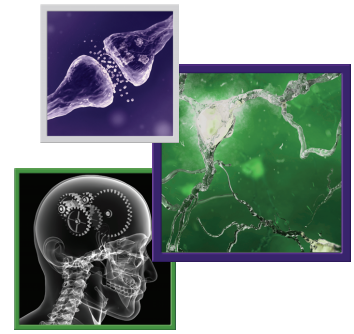
Neurodegenerative Disease Management



Neurostimulation for cognitive enhancement in Alzheimer's disease (the NICE-AD study): a randomized clinical trial

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Practice points

- As Alzheimer's disease (AD) among older adults is on the rise and current treatments have only limited efficacy, novel treatments for cognitive decline and associated symptoms in AD are urgently needed.
- We present a randomized, double-blind, sham-controlled clinical trial to examine efficacy of noninvasive neuromodulation using transcranial direct current stimulation (tDCS) applied for 6 months at home to enhance cognitive performance and brain neuroplasticity in older patients with mild-to-moderate AD.
- The noninvasive neurostimulation with tDCS represents a cutting-edge, nonpharmacological approach to symptom management in AD patients.
- The technology can be applied alongside other pharmacological treatments for AD.
- Major contraindications to tDCS in our study include history of head trauma, seizures, brain surgery, stroke or cancer affecting head, metal implants in the head or neck, compromised integrity or sensitivity of the skin at or near locations where electrodes will be placed.
- This study will provide insights into neuroplasticity effects of tDCS in patients with AD.
- This trial will also examine durability of cognitive benefits beyond the intervention period.
- If efficacy of the at-home tDCS protocol is proven in this study, it could be examined in combination with other pharmacological and nonpharmacological approaches.

New therapies for symptoms in Alzheimer's disease (AD) are urgently needed. Prior studies suggest that transcranial direct current stimulation (tDCS), a noninvasive neuromodulatory method, may be a safe and potentially effective treatment, but conclusions have been limited by small-sample sizes and brief stimulation protocols. This double-blind randomized trial involving 100 older adults with mild-to-moderate AD examines effects of 6 months of at-home active tDCS or sham delivered over the dorsolateral prefrontal cortex. The primary outcome is global cognitive performance. Secondary outcomes include executive-control/spatial selective attention, functional neuroplasticity, depressive symptoms, quality of life and the durability of effects 3 months after the stimulation period. The results will provide evidence on the efficacy of multimonth at-home tDCS in the AD treatment.

Clinical trial identifier: NCT 04404153 (Clinicaltrials.gov).

First draft submitted: 19 November 2020; Accepted for publication: 23 June 2021; Published online: 9 July 2021

Keywords: Alzheimer's disease • at-home tDCS • clinical trial protocol • dementia • noninvasive neurostimulation • transcranial direct current stimulation (tDCS)

The NICE-AD study is a randomized double-blind sham-controlled two-parallel-arm clinical trial investigating if 6 months of at-home tDCS can improve cognitive performance, symptoms and functional neuroplasticity in 100

patients with mild-to-moderate AD. The study includes participants' follow-up for 9 months (3 months after the end of the stimulation period) to gain insight into time characteristics/durability of the effects.

The prevalence of Alzheimer's disease (AD) is increasing, and the burden it imposes on patients and their families, the healthcare system and society at large is immense [1]. In the US, more than 5 million individuals have AD, most of whom are older adults with medical co-morbidities. In the absence of an effective disease-modifying therapy, treatment currently focuses on interventions that mitigate cognitive and behavioral symptoms. The few US FDA-approved medications provide only modest benefits and risk-troubling side effects. There is a compelling need for novel treatment approaches, particularly those that pose minimal risk of adverse effects in a medically fragile population.

Transcranial direct current stimulation (tDCS) is a nonpharmacological, noninvasive neurostimulation method that employs a battery-powered device to painlessly transfer electrical current of low intensity (usually 1–2 mA) to the surface of the head, typically with two large (20–35 cm^2) saline-soaked sponge electrodes [2–4]. Clinical effects result from tDCS-induced changes in excitability and activation of brain neurons and neuronal circuits. These changes have not been associated with significant adverse outcomes and tDCS is considered by the US FDA to be a nonsignificant risk method.

The neuromodulatory effects of tDCS are multifaceted. The primary effect is a subthreshold modulation of neuronal resting membrane potential. Based on electrode position, this modulation can be activating or inhibiting – increasing or decreasing the likelihood of neuronal firing. In addition, stimulation for several minutes induces glutamatergic calcium-dependent neuroplasticity involving *N*-methyl-D-aspartate (NMDA) receptors that play a role in synaptic connectivity [5,6]. The latter effects may explain the potential for tDCS to produce enduring changes of functional and structural connectivity within brain networks [7–10]. In addition, tDCS interacts with various cerebral neurotransmitter systems, such as those mediated by dopamine or serotonin, that are directly related to cognitive function and emotional/affective regulation [11,12].

The neural changes induced by tDCS produce activity alterations in remote interconnected cortical and subcortical areas [13,14]. This is important in the context of cognitive disturbances and related symptoms in AD. Neurophysiological and neuroimaging findings in AD have consistently revealed disturbances in neural connectivity, and a decrease in brain metabolism, especially in the parieto-temporal, frontal and posterior cingulate cortices. The decreases correlate with the severity of dementia and accompanying symptoms [15].

Preclinical studies of tDCS in rodent models of AD suggest that this neuromodulatory tool could potentially ameliorate this debilitating disease [16,17]. In these rodent models, tDCS produces an improvement of spatial learning and memory, and histological analysis and immunohistochemistry of the hippocampus indicates a protective effect of repetitive tDCS on these neurons, keeping them from being damaged by the β-amyloid neurotoxicity.

Initial human studies applying 1–10 tDCS sessions in early-stage AD patients yielded mixed results [18–22]. The findings called for additional studies with larger sample sizes and longer stimulation protocols. The feasibility of longer stimulation protocols has greatly improved with the advent of reliable at-home tDCS devices [3,23–28]. A small-sample (N = 18), sham-controlled pilot study in patients with early-stage AD evaluated 6 months of daily at-home tDCS over the dorsolateral prefrontal cortex (DLPFC), which is a significant cortical target for neuromodulation of cognitive outcomes (we use this DLPFC target/montage in this trial) [28]. The study revealed a significant treatment effect in general cognitive performance and preserved regional brain metabolic activity in the temporal lobe [28]. This study, however, which was limited by a small sample, the inclusion of a narrow segment of population with mild AD and a lack of postintervention follow-up, provides a strong rationale for a larger study of tDCS using a DLPFC montage and relatively long treatment period.

We propose to conduct an adequately powered, randomized, sham-controlled trial of 6-month at-home tDCS in 100 older adults with mild-to-moderate AD. This study will provide high-quality evidence concerning the effects of tDCS applied to the DLPFC on global cognitive performance, and secondarily, on executive control/spatial selective attention, mood, quality of life and patient satisfaction with both the device and procedure (Aim 1). The trial will also determine functional and structural changes in brain activation/deactivation patterns and connectivity in response to the intervention (Aim 2), and explore time characteristics (durability) of the tDCS effects for up to 3 months following the intervention period (Aim 3, exploratory). This will be the first rigorous test of efficacy of a feasible at-home tDCS protocol for possible remedy of cognitive decline and associated symptoms in mild-to-moderate AD.

Hypothesis

We hypothesize that 6 months of at-home tDCS for 30 min per day, 5 days per week, over the DLPFC at the intensity of 2 mA, will induce neuroplasticity in cerebral networks associated with cognitive processing and result in significant differences compared with sham stimulation in both behavioral measures of cognitive performance and neural activation patterns and functional connectivity, particularly in fronto-parietal and salience networks. More specifically, we hypothesize that behavioral cognitive measures and neural activation in the cognitive processing networks will decline in the group receiving sham stimulation during the 9-month assessment period while remaining relatively preserved in the group receiving active tDCS.

Design & methods

Study design

The study is a randomized clinical trial that employs a double blind, sham-controlled two-parallel arm design. A total of 100 older adults who have been diagnosed with mild-to-moderate AD are randomly assigned to active tDCS or sham, with stratification by sex and disease stage (mild vs moderate). Coparticipation of patients' informal caregiver is encouraged, but not mandatory, and participants who lack an informal caregiver are offered an assistance from the study personnel via scheduled video connection and via technical-support visits at home. The group assigned to active tDCS receives stimulation at 2 mA and be applied for 30 min 5 days/week. Those assigned to sham intervention follow the same procedures but employ a device that does not deliver the stimulation. The daily treatment is implemented at home, with or without assistance by a caregiver, and with remote involvement of study personnel, for a total of 26 weeks (6 months, during daytime by an awake participant). No issues were reported in previous studies regarding patients staying awake during the 20–30 min stimulation [18–22,28]. This is a pragmatic study delivering tDCS for 6 months and therefore the timing of the daily remotely supervised sessions is based on mutually convenient schedule for the patient and the study staff supervising the session. The study duration for each participant is up to 10 months, including the baseline with tDCS familiarization and training, the 6-month tDCS/sham intervention and the 3-month postintervention follow-up. There are six study visits:

Visit 1: Consenting and screening.

Visit 2: Baseline neuropsychological testing and tDCS familiarization/training: Participants undergo the baseline assessments, familiarization with tDCS device and in-person training in tDCS procedure.

Visit 3: Neuroimaging, tDCS refresher training, device deployment and first tDCS/sham application. After neuroimaging, patients are randomly assigned 1:1 to active tDCS or sham. Training in tDCS procedure is refreshed and the at-home device, which is preprogrammed for active tDCS or sham, is dispensed. Participants perform the first application under in-person supervision by study personnel. Following this visit, the patient/caregiver apply the study intervention at home for 26 weeks (6 months).

Visit 4–Visit 6: Outcome assessments occur at 6 months (Visit 4, immediately upon conclusion of the intervention), 7 months (Visit 5, 1 month postintervention) and 9 months (Visit 6, 3 months postintervention).

All study procedures have been approved by the Albert Einstein College of Medicine Institutional Review Board as well as the National Institute on Aging approved Data and Safety Monitoring Board of this study.

Screening, recruitment & randomization

Clinicians from New York-based dementia and geriatric clinical sites identify patients potentially interested in participating in the research study who preliminarily meet inclusion criteria. A study coordinator meets with a prospective participant and his/her informal caregiver over Zoom to conduct the informed consent process. Our process of obtaining informed consent from chronically ill individuals is designed as a multistep procedure that allows enough time for the patient and family to obtain sufficient information about the study in the manner that is not overwhelming, and allows enough time to answer all study-related questions the patient and family may have. After reading the informed consent document, the coordinator assesses participant's ability to consent using a modified version of the University of California, San Diego Brief Assessment of Capacity to Consent (UBACC) measure. The UBACC was found to have good internal consistency, inter-rater reliability, concurrent validity, high sensitivity and acceptable specificity [29]. For individuals who do not meet the criteria for capacity to consent, consent is obtained from their designated healthcare proxy with assent obtained from the participant.

After obtaining the consent, the study eligibility is evaluated by a research coordinator and confirmed by study clinicians, including screening for MRI contraindications such as pacemaker or any permanent magnetic metal implants like hip prosthesis (other than tooth fillings) and claustrophobia. The full list of the eligibility criteria is

Box 1. Inclusion and exclusion criteria.

Inclusion criteria:
- Community-dwelling male or female age 60 or older
- AD diagnosed by neurologist or geriatrician at our dementia and geriatric clinical sites using established criteria, and confirmed by study clinicians [30]
- Mild-to-moderate stage AD (0.5–2) determined by clinicians using the Clinical Dementia rating scale [31]
- If receiving a dementia medication regimen, the regimen is stable for at least 4 weeks prior to enrollment
- Able to speak and understand English at a level sufficient to undergo study procedures and testing protocols
- Willing to complete an functional MRI
- Able to provide Informed Consent independently, or able to provide assent with a legal surrogate providing informed consent

Exclusion criteria:
- Unstable medical or major psychiatric illnesses or unstable treatments for medical or major psychiatric illnesses
- History of head trauma, seizures, brain surgery, stroke or cancer affecting head, metal implants in the head or neck, compromised integrity or sensitivity of the skin at or near locations where electrodes will be placed
- Currently participating in another intervention study or using a neurostimulation device
- Exclusions specific to neuroimaging procedure (e.g., presence of metallic devices such as aneurysm clips or pacemakers, large amounts of dental or surgical hardware, subjects with history of claustrophobia or subjects with weight greater than 350 pounds or waist circumference >55 inches)

presented in Box 1. An eligible participant undergoes familiarization with tDCS and completes baseline assessments, followed by 1:1 random assignment, stratified by sex and AD stage (mild vs moderate), to the sham or active tDCS group.

The tDCS device is be programmed by the manufacturer team to active tDCS or sham mode. The device is delivered to study personnel labeled with a participant's study ID. The trial is double-blind; all participants and members of the study team, except for the biostatistician and manufacturer representative, are blinded to the programming of the device. Postintervention evaluation of blinding based on participants' belief regarding received modality (real tDCS or sham) is included in data analysis.

Study measures

A complete list of all evaluation tools conducted at baseline and follow-up visits is delineated in Table 1. These measures also serve to define the baseline characteristics of the groups, assess confounding and provide data for covariate analyses.

Primary outcomes

Our primary outcome for Aims 1 and 3 is cognitive improvement as measured by the Alzheimer's disease assessment scale – cognitive subscale (ADAS-Cog). The ADAS-Cog is the most widely used general cognitive measure in clinical trials of AD [32,37–39]. Developed as an outcome measure for treatment trials in samples with mild-to-moderate AD, its primary purpose was to be an index of global cognition in response to therapies. It has been used in previous tDCS studies, facilitating outcome comparisons [40]. Multiple cognitive domains are assessed by the 11 items of the ADAS-Cog: Word Recall Task, Naming Objects and Fingers, Following Commands, Constructional Praxis, Ideational Praxis, Orientation, Word Recognition Task, Remembering Test Directions, Spoken Language, Comprehension and Word-Finding Difficulty. The score ranges from 0–70, with higher scores (≥18) indicating greater cognitive impairment. A four-point ADAS-cog change at 6 months is clinically meaningful, with decline of two points (standard deviation [SD]: 4 points) in mild AD cases reported over 6 months [41,42]. Table 1 shows that assessments for ADAS-Cog and other cognitive tests are done at baseline, immediate postintervention and postinterventions at months 7 and 9. We avoided an interim assessment during the 6-month intervention period to reduce practice effects due to repeated administrations of the same test.

Aim 2 will be accomplished using resting-state and task-based functional MRI (fMRI), as functional brain changes may be a more sensitive biomarker of AD than is structural brain changes. The primary outcome for this aim is functional neuroplasticity measured by changes in functional connectivity and activation/deactivation patterns during rest and fMRI-adapted versions of the Digit Symbol Substitution Test and Flanker Interference test. tDCS has been shown to affect resting-state functional activation patterns, but it is still unknown how these functional networks are used, especially when performing cognitive tasks that are particularly affected by AD. For

Table 1. Summary of outcome measures.

	Measure	Variable	Instrument	Assessment				Ref.
				B	6M	7M	9M	
Aim 1 and Aim 3 – Exploratory	Primary	Global cognitive performance	ADAS-Cog	x	x	x	x	[32]
	Secondary	Multiple-domain cognitive dysfunction	Digit Symbol Substitution Test	x	x	x	x	[33]
		Executive control/spatial selective attention	Eriksen Flanker Test	x	x	x	x	[34]
		Quality of life	QoL-AD	x	x	x	x	[35]
		Depressive symptoms	Geriatric Depression Scale	x	x	x	x	[36]
		Satisfaction with tDCS	tDCS User Satisfaction Survey		x			
		Tolerability	Adverse events		x	x	x	
	Covariates	Gender, age, medication, chronic illness and baseline cognitive status	Sociodemographics self-report; baseline results of ADAS-Cog	x				
	Process measures	Intervention fidelity	Missed or incomplete sessions Data from evaluation of blinding, i.e., patient's impression, obtained after the study, of having received either active or sham treatment		x			
Aim 2	Primary	Functional activation/deactivation patterns	fMRI during Digit Symbol Test and Eriksen Flanker test	x	x		x	
	Secondary exploratory	Structural connectivity	Diffusion-weighted imaging	x	x		x	
	Covariates	Gender, age, medication, chronic illness and baseline cognitive status	Sociodemographics; self-report; baseline results of ADAS-Cog	x				

ADAS-Cog: Alzheimer's disease assessment scale–cognitive subscale; fMRI: Functional MRI; QoL-AD: Quality of life-Alzheimer's disease; tDCS: Transcranial direct current stimulation.

these reasons, we will examine functional network connectivity and activation/de-activation patterns during both rest and during Flanker interference and digit symbol substation tasks. Flanker interference test and digit symbol substitution test are particularly challenging to individuals with AD. The Flanker interference test has also been shown to be sensitive to other noninvasive interventions such as exercise [34,43,44].

Other study outcomes

Secondary outcomes include multiple domain cognitive dysfunction, executive control and spatial selective attention, quality of life, depressive symptoms and satisfaction and tolerability with tDCS device and procedures, as well as changes in cerebral markers of structural connectivity. In addition, we will assess intervention fidelity by evaluating quality of blinding and number of incomplete applications of study intervention during the 26-week interventional period. Covariates include age, sex, medication, chronic illness and baseline cognitive status.

Study intervention

Participants randomized to the active tDCS group receive 30 min of direct current at the intensity of 2 mA once a day five times per week for 26 weeks (6 months), delivered via two sponge electrodes of size 5 cm × 5 cm presoaked by the manufacturer with normal saline (9 g of NaCl/l). Electrodes are placed on the head over the area of the DLPFC with the anode on the left and cathode on the right using an EasyStrap headband, which can be applied by the participant and yield accurate and replicable electrode placement. DLPFC is a significant cortical target for neuromodulation of cognitive outcomes; this montage has been used in the pilot study that informed the intervention parameters for this trial. Participants randomized to the sham group receive 1 min of direct current that is ramped up to 2 mA over 30 s, ramped down over 30 s and stay at 0 current for the remaining time of the 30-min period. This model of sham successfully mimics the sensory sensation of real stimulation without inducing neuroplasticity changes and has been successfully employed in numerous tDCS studies [45,46].

The tDCS device to deliver the study intervention is a model Soterix Mini-CT (Soterix Medical Inc., NY, USA), programmed either to active tDCS or sham in double-blind manner. This device is suitable for tDCS administration at home and has a built-in dose control that allows the user to apply only the predetermined dose each day. the tDCS device CT-mini has specific features for adherence tracking: an electronic code provided by study staff to start the device, and an electronic end-code generated by the device upon completion of each session. The device is paired with a tablet with WiFi capability that enables video connection providing a real-time linkage

to study personnel who can remotely supervise tDCS application and provide remote assistance with technical aspects of tDCS. The cellular connection for the system is provided by the study site; participants do not need to have Internet connection at home in order to participate.

Coparticipation of participant's informal caregiver for assistance with at-home tDCS is encouraged, but not required. Participants who do not have access to an informal caregiver and decide to participate alone are offered assistance via scheduled video connection and via scheduled technical-assistance visits by the field study personnel.

At study visit 2, a research coordinator provides an overview of tDCS functionalities and teaches the participant and informal caregivers to use the tDCS device. This training is refreshed at study visit 3. Upon conclusion of training during study visit 3, the study coordinator dispenses the randomized tDCS device programmed either to sham or active tDCS to the participant, who performs the first application in the presence of the coordinator. For the remaining 6-month period, participants apply the study intervention at home. Study personnel contacts participants by phone and/or video prior each tDCS application to provide the electronic code that unlocks the daily stimulation dose. This ensures that the tDCS device is being used in compliance with the protocol and provides an opportunity to ask about adverse events. Refamiliarization on tDCS equipment is offered as often as is necessary should participants or caregivers need to review correct usage.

The intervention spans 6 months and sustaining adherence represents a major challenge in any randomized controlled trial (RCT) involving cognitively impaired seniors. For this reason, we have many plans in place to promote adherence to the study protocol. A permanent staff contact is provided for participants in both groups, written materials on study contacts and tDCS usage are provided to participants and caregivers, and involvement of family members and caregivers is encouraged; all of this should promote adherence. Furthermore, research assistants are in contact with participants after each session to further promote adherence and, if necessary, document instances of nonadherence. Additionally, participants are reminded of all appointments and visits, receive compensation for their time and receive free transportation to the study offices.

MRI acquisition

Baseline and postintervention MRI are performed at the Gruss Magnetic Resonance Research Center at Albert Einstein College of Medicine. MRI scanning will be performed with a Philips 3T system (Ingenia Elition). All BOLD (T2*-weighted) images are acquired with multiband echo planar imaging using a whole brain gradient over a 224 × 224 × 128 mm field of view on a 112 × 112 acquisition matrix, 2-mm slice thickness (no gap); time to echo (TE) = 28 ms, time of repetition (TR) = 2000 ms, flip angle = 90° and 64 *trans*-axial slices per volume. A T1-weighted whole-head structural image is also acquired using axial 3D-MP-RAGE parameters over a 240 × 188 × 220 mm field of view and 1.0-mm isotropic resolution, TE = 4.6 ms, TR = 9.9 ms, $\alpha = 8o$, with SENSE factor 2.6. Diffusion-weighted images are acquired at b = 1000 s/mm^2 for 66 gradient directions. Six b = 0 s/mm^2 volumes will also be collected, half with opposing phase encoding directions to correct for distortions. Other diffusion-weighted images parameters include TE = 97 ms, TR = 4299 ms, voxel size 2 × 2 mm, 68 slices and slice thickness of 2 mm with no gap. Additional MRIs are also acquired to be included as potential covariates in our analyses, including white matter hyperintensities using FLAIR. Each neuroimaging examination takes less than 1 to 1/2 h – including safety screening, task training, set up and approximately 45 min of actual scanning time.

MRI procedure

We use a Digit symbol substitution test (DSST) task adapted for use in an fMRI environment and validated in older adults [47]. This task has been further adapted for our sample and takes about 7 min divided over two blocks, with 27 items each (total 54 test items). During each item, a code table with numbers 1–9 paired with a symbol is presented on the screen. Below the code table, an individual number–symbol pair is presented. Participants are asked to indicate if the individual number–symbol pair is the same as (or different from) the code table with a button press. We use a Flanker task optimized for fMRI environment that takes about 5 min with a total of 60 test items (30 congruent and 30 incongruent) presented with jittered interstimulus intervals (4–8 s) [48]. During each item, a series of five arrows are presented on the screen. Participants are asked to indicate if the central/middle is in the same direction (> > **>** > >; < < **<** < <) or in a different direction (<< **>** < <; > > **<** > >) from the other arrows. Our DSST and Flanker protocols are written in E-Prime 2.0 (Psychology Software Tools Inc.) and are presented with an *in vivo* Eloquence fMRI system. Prior to the completing the tasks in the MRI, participants

complete at least one 3-min training block for each task. If needed, these training blocks can be repeated up to five times to ensure task comprehension.

MRI processing & analysis

Resting-state fMRI

Standard preprocessing steps will be performed with FSL to prepare for functional connectivity analyses of resting-state fMRI data (FMRIB's Software Library [http://fsl.fmrib.ox.ac.uk/fsl]) [49–51]. Group-level analyses will then be implemented with FSL MELODIC Independent Component Analysis software [52]. FSL MELODIC separates multivariate data into statistically independent spatial components and their associated time series. When applied to resting-state fMRI data, Independent Component Analysis decomposes the BOLD dataset into components representing neural signals of interest, structured noise and random noise [53–57]. We will use this technique to identify components that change as a function of time and intervention arm. We will limit each analysis to 20 components, a dimensionality utilized in previous resting-state studies [58]. Criterion for statistical significance will be set at $p < 0.05$. We will also use an additional fMRI denoising procedure to manually classify components as representing artifacts or neural signals of interest via visual inspection. The protocol dictates that components are labeled as artefactual when the thresholded component spatial map shows 90% or more activation or deactivation in peripheral areas or in a random-scattered pattern over a quarter or more of the brain without correspondence to functional-anatomical boundaries. Components are labeled as neural signals of interest when the thresholded component spatial map shows 10% or more activation or deactivation in small to large gray matter clusters localized to nonperipheral regions of the brain. Secondary considerations include indications of noise such as high frequency activity, spikes, saw tooth pattern and sinus coactivation. This procedure has been shown to be reliable and to improve the sensitivity of results from resting-state fMRI data analysis [59].

Task-based fMRI: DSST & Flanker task

Standard preprocessing and first-level analyses will be performed with statistical parametric mapping (SPM; https://www.fil.ion.ucl.ac.uk/spm/software/spm12/).

Group level

Ordinal Trend Covariance Analyses (OrT-CVA; http://www.nitrc.org/projects/gcva_pca) will then be used to analyze the DSST and Flanker Tasks. OrT-CVA will be used to identify covariance patterns in the fMRI signal as a function of trial type (task and rest blocks on the DSST, incongruent and congruent trials on Flanker Task) at each study visit (pre- and postintervention). OrT-CVA employs a principal component analysis (PCA) to the data matrix that is then transformed to a matrix of the experimental design. Linear regression is then applied to detect a covariance pattern (ordinal trend) in the fMRI signal as a function of task conditions that is based on a linear combination of a small set of principal components. An ordinal trend is a monotonic change in pattern expression as a function of task conditions, in this case as a function of trial type. The expression of an ordinal trend is quantified in terms of a participant-specific expression score that is derived by projecting the covariance pattern onto a participant's scan for each task condition.

Statistical plan

Our goal in this RCT is to determine whether tDCS is efficacious in maintaining cognition and functional and structural brain activation/connectivity, during a 6-month period in patients with mild-to-moderate AD. Differences between the group of participants randomly assigned to tDCS and the group assigned to sham will be determined for these primary outcomes and an array of secondary outcomes related to cognitive functioning, depressive symptoms and quality of life. Outcomes will be measured 3 months after the intervention to explore the durability of tDCS effects. Baseline distribution of covariates will be compared with assess adequacy of randomization to produce comparable groups of participants using appropriate graphical procedures and summary statistics. A prespecified set of these baseline covariates – age, sex, education, chronic illnesses and baseline ADAS-Cog score – will be used in the analyses to determine whether they influence treatment comparisons. This method is preferred to adjusting for covariates that are imbalanced between treatment groups using significance testing, because it is possible for a covariate to have a strong confounding effect even if the difference in the average value of that variable between the parallel arms is not significant [60]. Differences between groups at cross-section and in changes in the continuous study outcomes after intervention will be evaluated using linear regression and

linear mixed effects models, respectively, adjusting covariates aforementioned. Medication changes by physician are allowed under the study protocol. We will track new medications or changes in medication doses during the trial. We will compare medication changes between study arms, and address analytically if there is an imbalance. We will use intention-to-treat (ITT) analysis, which includes all randomized participants in the groups assigned, regardless of their adherence with the entry criteria, whether tDCS was received and subsequent withdrawal or deviation from the protocol [61]. ITT analysis is pragmatic because it admits noncompliance and protocol deviations, and gives an unbiased estimate of the intervention effect. Handling missing data is a major issue in ITT, and is dealt with by imputation methods or sensitivity analysis [62–64]. The linear mixed effects model is good in handling missing data due to drop out assuming missing at random mechanism. We do not discount residual/unmeasured confounding, but this is more of a concern in observational studies without randomization. We will report adjusted and crude estimates of association and discuss limitations of the study design in our publications. If sessions attended vary (adherence), potential 'dose' effect on outcomes based on number of tDCS sessions completed will be examined within the tDCS group.

Sample size

This randomized study has 50 participants for each of the two groups (tDCS and sham). Based on previous studies, we expect correlations of at least 0.80 between repeated ADAS-Cog scores [65]. With 50 participants in each group and assuming 20% drop out rate at postintervention, we can detect a difference of 0.6 SD in the change in ADAS-Cog score at postintervention from baseline between the two groups with 80% power using two-sided tests with alpha level 0.05. A meta-analysis of neurostimulation on AD patients, including 11 studies with a total of 200 patients, showed a significant effect size of 1.35 was found for the cognitive outcomes [66]. However, we assumed a more conservative effect size to estimate our power as this meta-analysis was based on smaller sample sized studies [66].

Cohort retention is not a major issue for this RCT. Given the safety of tDCS and the convenience of a home-based therapeutic intervention, we do not anticipate a high dropout rate. Nonetheless, we have accounted for dropout rates of 25 and 30% at 7- and 9-month assessments (i.e., 1 and 3 months postintervention), respectively. We will be able to detect differences of 0.63 and 0.64 SD in the change in ADAS-Cog score at the 7- and 9-month assessment, respectively, between the two groups with 80% power using two-sided tests with alpha level 0.05.

For the neuroplasticity evaluation to detect a signal change at the individual participant level (i.e., first-level time-series modeling using SPM) at $p < 0.001$, a percent signal change of 0.34% is required using a published method and estimate of noise at a magnet strength of 3.0 Tesla. Based on this estimate, to detect a difference in contrast values between groups (i.e., second level analyses using SPM) at $p < 0.001$ and a power of at least 0.80, where the mean of one group's signal change is 50% of the other, 16 subjects per group are required. Thus, our goal of 50 participants in each group is more than sufficient to detect a main effect of condition (tDCS vs sham), and leaves us with room to examine more specific components of derived network covariance patterns.

Discussion

To our knowledge, this is the first adequately powered RCT testing the efficacy of long-term (multimonth) home-based tDCS therapy to relieve cognitive decline and associated symptoms in older adults with mild-to-moderate AD. The study has innovative elements and is relevant for the fields of dementia care, geriatrics, nursing and neurostimulation. Among the notable aspects are the following:

- The noninvasive neurostimulation with tDCS represents a cutting-edge, nonpharmacological approach to disease and symptom management in AD patients; it is clearly distinct from conventional medication-based interventions that provide only modest benefits and have risks of troubling side effects;
- The at-home application of tDCS is a recent advance and could allow long-term treatment of chronic conditions while addressing unmet needs of patients in home settings; it greatly facilitates clinical trials, which were heretofore conducted in research centers;
- Our at-home application has a novel remote-supervision component, allowing for enhanced outreach, adherence promotion and support for communication and interaction among patients, caregivers and research staff;
- This study will provide insight into underlying mechanisms and neuroplasticity effects of tDCS in patients with AD by evaluating differences between active tDCS and sham control;

- Prior studies have not explored the durability tDCS effects, typically evaluating effects for only 2–4 weeks. This study will evaluate outcomes for 3 months after the intervention ends, providing important data for translation of this intervention to the real world and potentially rationalizing the use of booster sessions;
- If efficacy of the at-home tDCS protocol is proven in this study, it could be examined in combination with other pharmacological or nonpharmacological approaches.

This trial will substantially enhance the understanding of the effects of tDCS on the Alzheimer's brain and determine whether 6 months of at-home tDCS is efficacious in ameliorating cognitive decline and associated symptoms in patients with mild-to-moderate AD. Furthermore, by exploring tDCS effects during a 3-month postintervention period, the trial will provide insight into the durability and time characteristics of the effects.

Conclusion

The information obtained from this trial should advance the development of a potentially important treatment for patients with AD, one that may substantially reduce the burden associated with this debilitating illness by lessening symptoms and improving quality of life of AD patients and their families.

Financial & competing interests disclosure

This work is supported by a grant from the National Institutes of Health (1 R01 AG068167-01). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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