Home-based tDCS for apathy in Alzheimer's disease and related dementias

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Protocol Title: Home-based tDCS for apathy in Alzheimer's disease and related dementias

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General Information

Study Title	Home-based tDCS for apathy in Alzheimer's disease and related dementias (ADRD)
Short Title	tDCS for apathy in ADRD
Study Design	This is a randomized, experimenter- and participant-blinded trial to assess feasibility, acceptability, and safety of providing transcranial direct current stimulation (tDCS) to Alzheimer's disease and related dementia (ADRD) patients with apathy. Participants will be randomized 1:1 to either treatment condition. Half of the participants will receive active (constant current intensity of 2mA), while half will receive sham tDCS. Anode and cathode electrodes will be placed over the left and right dorsolateral prefrontal cortexes, respectively, with the use of the Omni-Lateral-Electrode system. Caregivers will set up and administer tDCS for participants with ADRD at home. All sessions will be remotely supervised by trained research staff through video conferencing software (e.g., WebEx). Participants will be assessed at baseline, treatment day 14, treatment day 28, treatment day 42, and 6 weeks post-treatment. For our primary goal, we will collect clinical data related to feasibility, acceptability, and safety of providing tDCS to ADRD patients with apathy. Regarding our secondary goal (i.e., efficacy), the primary clinical outcome measure will be change on the Apathy Evaluation Scale score. The secondary clinical outcome measures will include: (1) total score on the Brief Dimensional Apathy Scale (bDAS); (2) total score on the Neuropsychiatric Inventory (NPI-Q) which evaluates 12 discrete neuropsychiatric symptoms; (3) depressive symptoms as assessed by the Cornell Scale for Depression in Dementia and (4) cognition as evaluated by the Mini-Mental State

	Examination (MMSE). Clinical and demographic data will also be collected at baseline.	
Study Participants	Patients with ADRD and apathy will be recruited at the UTHealth Geriatric Neuropsychiatry Clinic, the Harris County Psychiatric Center (HCPC) (Dr. Teixeira) and the UT Physicians Center for Healthy Aging (Dr. Holmes).	
Planned Sample Size	40 (1:1 for two groups).	
Planned Study Period	12 weeks	
	Objectives	Outcome Measures
Primary Goal	To assess feasibility, acceptability, and safety of providing tDCS to ADRD patients with apathy.	*Feasibility* measures will include recruitment rate (per month), randomization success, blind success, retention, and attrition rates. *Acceptability* will be evaluated using Likert scale (from 0 [strongly disagree] to 10 [strongly agree]) to answer ten affirmatives regarding the use of home-based tDCS. *Safety* will be assessed with a questionnaire about side effects that include itching, burning, headache, fatigue, and dizziness.
Secondary Goal	To assess the efficacy of tDCS for ADRD-related symptoms, with a primary focus on apathy.	Neuropsychiatric symptoms evaluated through validated questionnaires.

Background Information

Alzheimer's disease (AD) is the main cause of dementia and one of the great challenges of the 21st century (1). An estimated 40 million people, mostly older than 60 years, have dementia worldwide, and this number is expected to increase significantly in the next decades. Despite ongoing advances in the understanding of the pathogenesis of Alzheimer's disease and related dementias (ADRD), no treatment available can prevent or delay the cognitive decline that characterizes the condition (1). Besides cognitive impairment, nearly all patients with ADRD present behavioral and psychological symptoms, also called neuropsychiatric symptoms (NPS).

NPS have been associated with negative outcomes in ADRD, including decrease of patient and caregiver quality of life, increased risk of institutionalization, higher costs and risk of mortality (2). The expression 'NPS' is an umbrella expression that encompasses different types of behavioral problems, such as agitation, apathy, delusion, insomnia, among others (3, 4). Due to the potential complications associated with the use of psychotropic drugs (e.g. increased risk of cerebrovascular events with antipsychotics, increased risk of falls and cognitive decline with benzodiazepines) and the limited evidence of their efficacy, clinical guidelines, medical organizations and expert groups recommend non-pharmacological strategies as the first-line treatment for NPS (5, 6).

Apathy, which is defined as the loss or reduction of interest and goal-directed behaviors, is the most common NPS in ADRD, with a 5-year prevalence over 70% in this population (7, 8). Apathy has been associated with greater functional impairment, greater caregiver burden, increased risk of institutionalization and higher costs (9, 10). Because of its prevalence and clinical meaning, apathy is an important target in the management of ADRD. Standard pharmacological approach for apathy in ADRD uses cholinesterase inhibitors such as donepezil, with evidence of either no or very small effectiveness (10, 11). The stimulant methylphenidate was also shown to be effective in reducing apathy in ADRD in open studies and two double-blind randomized controlled trials (12). However, the use of methylphenidate was associated not only with reduction in apathy but also with greater anxiety and weight loss (13). Another concern with the use of stimulants is their potential cardiovascular effects, a fact particularly relevant in older adults with multiple medical comorbidities (14). Studies investigating non-pharmacological strategies for apathy in ADRD, such as music, art therapy and psychomotor activity, have modest effects and only in patients in early stages of dementia (15). Therefore, there is a great need to develop effective and safe strategies for the treatment of apathy in ADRD.

Transcranial direct current stimulation (tDCS) is a relatively novel non-pharmacological method of neuromodulation that has been evaluated in several neuropsychiatric conditions, showing promising results in depression and negative symptoms (including apathy) of schizophrenia (16, 17). tDCS modulates brain activity through low-intensity electrical currents applied over the scalp, and has been associated with significant changes in network connectivity involving the prefrontal cortex and the cingulate cortex, regions implicated in the neural basis of apathy (18-20).

In ADRD, a few controlled studies have been conducted to evaluate the role of tDCS on cognitive functioning. A recent systematic review and meta-analysis of these studies found that tDCS improved cognitive function in mild to moderate ADRD, but the stimulation parameters (multiple sites; single vs. repeated; lower vs. higher current) were very different among studies, not allowing definite conclusions (21). After this systematic review, two interesting studies were published on the matter. Khedr et al. (2019) observed cognitive improvement, as assessed by general cognitive measures (i.e., Montreal Cognitive Assessment and Mini-Mental State Examination), in patients with ADRD

submitted to 2 mA anodal tDCS for 20 minutes on each left and right temporal lobes (22). Each patient received five sessions/week for two consecutive weeks totaling 10 sessions. Im et al. (2019) investigated changes in cognitive performance, as assessed by the Mini Mental State Examination and other specific neuropsychological tests, after home-based 2 mA tDCS with anodal on the left dorsolateral prefrontal cortex (PFC) and cathodal on the right dorsolateral PFC for 30 minutes daily for 6 months in patients with early ADRD (23). Besides showing the feasibility of long-term home-based tDCS, these researchers found that daily tDCS sessions improve or stabilize cognitive decline in patients with ADRD. This clinical effect was associated with changes in regional cerebral metabolic rate for glucose in the left temporal lobe as assessed by 18F-fluoro-2-deoxyglucose positron emission tomography (23). Altogether these studies suggest that tDCS is a promising tool for cognitive stabilization in ADRD. Only one study investigated the effect of tDCS on NPS in ADRD (24). Suemoto et al. (2014) studied 40 patients with ADRD who were randomized to receive either anodal tDCS (2 mA constant current for 20 minutes) or sham-tDCS over the left dorsolateral prefrontal cortex (DLPFC) for six sessions during two weeks (25). While tDCS was safe in this population, there was no evidence of efficacy of tDCS on apathy nor on other NPS assessed. The lack of efficacy was attributed to several factors, especially the low number of sessions and the short period of intervention. One important aspect of this study – and highlighted by the authors – was the challenge to engage subjects in the trial mainly due to issues related to transportation to the medical center for tDCS application (25). Since patients with ADRD usually cannot drive safely, caregivers and/or family members need to be available to bring them into medical appointments. Home-based therapy would be very useful in this regard, as patients would not need to attend clinic as often.

Given the clinical relevance of apathy in ADRD, the equivocal results of the therapeutic resources available to address it, and the emerging evidence of safety and efficacy of tDCS in ADRD, our proposal aims to test the feasibility, safety and efficacy of home-based tDCS for the treatment of apathy in ADRD. Home-based tDCS circumvents critical problems observed in previous trials (25), including the need of multiple visits to medical centers for tDCS application, allowing a more intensive application (e.g. 5 x per week) for prolonged periods.

Objectives

Objectives	**Outcome Measures**
Primary objective To assess feasibility, acceptability, and safety of providing tDCS to ADRD patients with apathy.	*Feasibility* measures will include recruitment rate (per month), randomization success, blind success, retention, and attrition rates. *Acceptability* will be evaluated using Likert scale (from 0 [strongly disagree] to 10

	[strongly agree]) to answer ten affirmatives regarding the use of home-based tDCS. *Safety* will be assessed with a questionnaire about side effects that include itching, burning, headache, fatigue, and dizziness.
Secondary objectives To assess the efficacy of tDCS for ADRD-related symptoms, with a primary focus on apathy.	Neuropsychiatric symptoms and cognitive measures evaluated through validated tools.

Study Design

We will carry out a randomized, experimenter- and participant-blinded trial comparing home-based active tDCS and home-based sham tDCS. Participants will be randomized 1:1 to either treatment condition. Half of the participants (n=20) will receive active (constant current intensity of 2mA), while half (n=20) will receive sham tDCS. No changes to the patient's standard care medication will be made. Participants will continue to receive standard treatment for their individual health problems. Anode and cathode electrodes will be placed over the left and right dorsolateral prefrontal cortexes, respectively, with the use of the Omni-Lateral-Electrode system. Caregivers will set up and administer tDCS for participants with ADRD at home. tDCS will be applied for 30 min at an intensity of 2mA, with 30 s ramping up and down. The same procedure will be used for sham stimulation, but in this case, electric current will be applied only in the first 30s tDCS. All patients, caregivers and clinicians will be blinded to the type of stimulation delivered. We will use bi-hemispheric stimulation (anode F3/cathode F4) based on the facts that bilateral frontal circuits have been implicated in apathy, and bilateral stimulation may have wider effects on brain networks (18, 23, 26). The stimulation will last 30 min according to previous studies (17, 23, 27). According to our previous home-based tDCS protocols (28, 29), all sessions will be remotely supervised by trained research staff (RA), therefore, the sessions will run from Monday to Friday. The remote supervision of the sessions will be possible through video conferencing software (e.g., WebEx), and will ensure the use of proper technique and compliance to the study schedule, also monitoring any adverse events (Fig.1). The devices (tDCS & sham tDCS) will be programmed and cannot be tampered. Participants will be assessed at baseline,

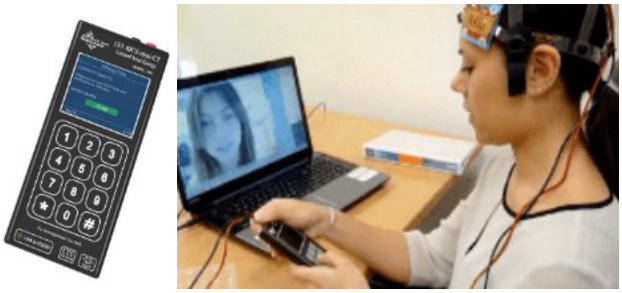
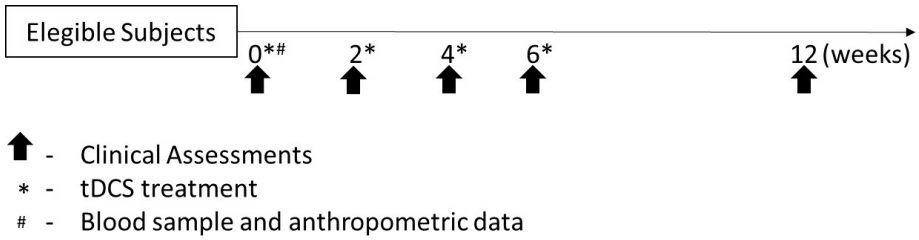


Fig. 1 Illustrative image of home-based tDCS.

treatment day 14, treatment day 28, treatment day 42, and 6 weeks post-treatment (Fig. 2). The device will be returned in person at the end of the treatment (week 6).

Fig. 2 Proposed outline of the study.



Analyses. *Inferential Paradigm and Bayesian Analyses.* Following recommendations in the clinical trial literature analyses we will proceed using parallel frequentist and Bayesian statistical inference (30, 31). The Bayesian inferential paradigm can provide probabilistic estimates of effects irrespective of sample size. Bayesian analyses will focus on posterior probabilities ≥ 0.75 (equivalent to a Bayes factor = 0.33 or 3.0) that parameter estimates are greater or less than zero to emphasize the value in discerning treatment effects in a small trial. Power calculations for the frequentist analyses are derived using G*Power v. 3.1.9.2 and focus on the residual change model described in Hypothesis 2a. As noted, the Bayesian analyses will provide the primary inferential results; sample size considerations for the frequentist analyses are limited by the small sample size and provided as due diligence. Given alpha = 0.05, a sample size N = 40 provides 80% power to detect a Cohen's f = 0.45. Frequentist analyses will provide conventional interpretation of the relationships between predictors and outcomes: the probability of the data, given the null hypothesis. Bayesian analyses will incrementally update specified prior information regarding effects to directly yield the probability of an alternative hypothesis. Bayesian analyses will employ informative priors as they develop in the literature; otherwise, weakly informative priors will be used as a default (e.g., for regression coefficients: ~N[μ=0,σ^2=100]; for non-linear outcome variables this prior applies to the coefficient within the link-function). Sensitivity analyses using optimistic and pessimistic, skeptical priors will evaluate prior assumptions. Assessing the convergence of Bayesian analyses on the posterior distributions via Monte-Carlo Markov chain (MCMC) will use diagnostic evidence including effective sample size and scale reduction factors. Evaluation of posterior distributions will permit statements regarding the probability that effects of varying magnitudes exist, given the data, even with a small sample size. *Descriptive statistics* will evaluate measures of central tendency and frequencies for all continuous and categorical variables (respectively) measured in the study. Correlation analyses (i.e., Pearson's *r*, Spearman's *rho*) will be used to evaluate broad patterns of relationships across variables. Preliminary data analyses will inspect relationships between sample characteristics (e.g., demographics), experimental group (e.g., active vs.

sham tDCS), and specified outcome variables (e.g., Apathy) via traditional statistical tests (e.g., chi-square; Mann-Whitney; *t*-tests). Any sample characteristic variables that demonstrate a relationship with both predictor and outcome variables in a given model meet criteria for being a potential confounder (32, 33) and will be included as a covariate in such models for hypothesis testing.

Statistical modeling will primarily use generalized linear modeling (GLM) with multilevel components (GLMM) for correlated observations. Potentially nonlinear relationships between predictors and outcomes will be evaluated via inclusion of polynomial or spline effects. Continuous, dichotomous, and count-distributed data will utilize linear, logistic, and Poisson/negative binomial regression, respectively (each with a canonical link function). Evaluation of distributional assumptions will use residual plots, formal statistical tests, and posterior predictive checking. Violations of assumptions will be addressed via transformation, robust estimation, stratification, and/or coefficient scaling where appropriate. Statistical analyses will be performed using the R statistical computing environment via packages lme, rstan, and brms.

Missing data will be addressed via maximum likelihood, explicit modeling of missingness, or imputation where appropriate. Each approach is robust to ignorable missingness (i.e. MCAR and MAR). Sensitivity analyses will permit evaluation of the robustness of findings to missing data assumptions. While Bayesian analyses are not influenced by traditional concerns of multiplicity, for the frequentist analyses, all primary outcome variables (those specified by name in the hypothesis statements) will be evaluated at the $\alpha = 0.05$ statistical significance level, while any secondary or otherwise post hoc analyses will employ false discovery rate (FDR) to control for Type I error.

Study Population

We will randomize 40 patients aged 60 or older with ADRD and apathy to either active home-based daily (Monday to Friday) tDCS or sham tDCS for 6 weeks (1:1 for two groups). This sample size is set to maximize the number of participants that may be enrolled over the time period of the proposal assuming a credible average recruitment rate, given the financial parameters of the funding mechanism.

Inclusion criteria will be: (1) diagnosis of possible or probable ADRD according to the National Institute of Aging – Alzheimer's Association diagnostic criteria (34); (2) mild or moderate dementia, as defined by a MMSE score between 14 and 26 (35, 36); (3) clinically meaningful apathy for at least four weeks, clinically diagnosed according to 2018 Apathy Diagnostic Criteria (37) or defined as Neuropsychiatric Inventory (NPI-Q) apathy score equal or above 4 (i.e., severity of 'moderate' or greater and caregiver distress 'mild' or greater) (38-40); (4) stable doses of cholinesterase inhibitors, memantine and other psychotropic medications for at least three months.

Exclusion criteria will be: (1) unstable medical conditions; (2) history of epilepsy; (3) metallic objects in the brain; (4) diagnosis of major depression and/or a score higher than 18 on the Cornell Scale for Depression in Dementia (41).

Recruitment and Retention. Subjects will be recruited at the *UTHealth Geriatric Neuropsychiatry Clinic, the Harris County Psychiatric Center (HCPC)* (Dr. Teixeira) and the *UT Physicians Center for Healthy Aging* (Dr. Holmes). As serious adverse effects and problems with the device use are not anticipated, it is expected a high retention rate. The remote supervision of the tDCS or tDCS sham daily sessions by trained research staff will contribute to the retention of subjects during the trial.

Training plan. Patients will be instructed on treatment at baseline, when they will receive the device. A trained research staff will instruct the participant's caregiver on how to handle the equipment. All sessions will be remotely supervised by trained research (RA) staff, who will be able to answer questions during the sessions and verify that the device is being used correctly.

Study Procedures

Feasibility measures will include recruitment rate (per month), randomization success, blind success, retention and attrition rates. Overall consent and completion rates will be evaluated via descriptive statistics. Generalized linear modeling (GLM) will evaluate treatment group differences in consent and completion rates. We expect that a high proportion of participants will consent to participate (> 80%) and complete the study (> 70%).

Acceptability will be evaluated using the method proposed by Ahn et al. (2019) (29). Participants and/or their caretakers will be asked to apply a Likert scale (from 0 [strongly disagree] to 10 [strongly agree]) to answer ten affirmatives regarding the use of home-based tDCS. For example, question 1: “It was easy to prepare the device and accessories”, question 7: “I felt confident using the device.” Overall acceptability across groups will be evaluated by descriptive measures of satisfaction ratings. GLM will model participant satisfaction ratings as a function of treatment group (active vs. sham tDCS). We expect that participant satisfaction ratings at the end of treatment will demonstrate high acceptance of tDCS treatment in the present sample.

Safety will be assessed with a questionnaire about side effects that include itching, burning, headache, fatigue, and dizziness (29). Descriptive statistics will describe raw frequencies of AEs and side effects. Treatment group differences in AEs and side effects will be evaluated via Chi-square and Fisher’s exact test of contingency tables. We expect that adverse events and side effects will be rare, and any that may occur will be mild.

The primary clinical outcome measure will be change on the Apathy Evaluation Scale score (42), the best-validated scale for measuring apathy in AD, which consists of 18 items phrased as questions that are to be answered by the caregiver on a four-point Likert scale, with higher scores indicating greater severity of apathy. Apathy will be

assessed at baseline, during treatment (weeks 2, 4 and 6) and 6 weeks post-treatment. Our hypothesis is that active tDCS group will demonstrate lower apathy scores at the end of treatment relative to sham tDCS. GLM will evaluate residual change by modeling apathy at the end of treatment as a function of treatment group, controlling for apathy at the beginning of treatment. This analysis is a regression-based analogue to ANCOVA that permits non-normally distributed outcome distributions. Follow-up analyses will evaluate change over time across groups via GLM with multilevel components (GLMM) as well as cross-sectional analyses within each measurement time point via GLM.

The secondary clinical outcome measures will include: (1) total score on the Brief Dimensional Apathy Scale (bDAS) (43); (2) total score on the NPI-Q which evaluates 12 discrete NPS considering their severity and the related caregiver distress (38-40); (3) depressive symptoms as assessed by the Cornell Scale for Depression in Dementia (41); (4) cognition as evaluated by the Mini-Mental State Examination (MMSE), which includes memory, language, praxis and orientation tasks, yielding a global cognition score ranging 0 to 30, with higher scores indicating better performance (35).

Our hypothesis is that active tDCS group will demonstrate lower scores on the bDAS, NPI-Q and Cornell Scale for Depression, and higher scores on the MMSE at the end of treatment relative to sham tDCS. GLM will evaluate residual change in each outcome (in separate models) by modeling scores at the end of treatment as a function of treatment group, controlling for baseline.

Sociodemographic data (gender, age, marital status and education) will be collected at the baseline. Clinical (health history, use of medication and life habits) and anthropometric data will be collected at the baseline and after the treatment period. These data will be control variables for the study.

Table 1. Timetable for Collection of Data

Assessment	**Baseline**	**Week 2**	**Week 4**	**Week 6**	**Week 12**
Medical History Questionnaire	X				
MMSE	X			X	X
AES (primary outcome)	X	X	X	X	X
NPI-Q	X	X	X	X	X
bDAS	X	X	X	X	X
Cornell Scale for Depression	X			X	X
tDCS experience questionnaire		X	X	X	X
Side effects questionnaire		X	X	X	X

Data and Safety Monitoring

Data will be collected from 40 human participants, and all information will be de-identified in order to protect their confidentiality. All clinical information will be stored in dedicated files at UTHealth Department of Psychiatry. We will maintain full control over the data and resources for 1 year following the completion of data collection. This will allow sufficient time for data cleaning, validation and analysis, and subsequent publication of the primary findings that address the proposed specific aims of the project. After this time, de-identified datasets with full data dictionaries will be made publicly available. The investigators are aware of and agree to abide by the principles for sharing research resources, as expected by TARCC-funded research. Before the data become publicly available, individual requests for data sharing will be considered by the PI, Co-Is, and the TARCC staff on a case-by-case basis. Evaluation of these requests will be based on the scientific validity of the proposal as well as the adequacy of plans for maintaining the security and confidentiality of the data. The data generated in this grant will be presented at national or international conferences and published in a timely fashion.

Statistics

Inferential Paradigm and Bayesian Analyses. Following recommendations in the clinical trial literature analyses we will proceed using parallel frequentist and Bayesian statistical inference (30, 31). The Bayesian inferential paradigm can provide probabilistic estimates of effects irrespective of sample size. Bayesian analyses will focus on posterior probabilities ≥ 0.75 (equivalent to a Bayes factor = 0.33 or 3.0) that parameter estimates are greater or less than zero to emphasize the value in discerning treatment effects in a small trial. Power calculations for the frequentist analyses are derived using G*Power v. 3.1.9.2 and focus on the residual change model described in Hypothesis 2a. As noted, the Bayesian analyses will provide the primary inferential results; sample size considerations for the frequentist analyses are limited by the small sample size and provided as due diligence. Given alpha = 0.05, a sample size N = 40 provides 80% power to detect a Cohen's f = 0.45. Frequentist analyses will provide conventional interpretation of the relationships between predictors and outcomes: the probability of the data, given the null hypothesis. Bayesian analyses will incrementally update specified prior information regarding effects to directly yield the probability of an alternative hypothesis. Bayesian analyses will employ informative priors as they develop in the literature; otherwise, weakly informative priors will be used as a default (e.g., for regression coefficients: $\sim N[\mu=0,\sigma^2=100]$; for non-linear outcome variables this prior applies to the coefficient within the link-function). Sensitivity analyses using optimistic and pessimistic, skeptical priors will evaluate prior assumptions. Assessing the convergence of Bayesian analyses on the posterior distributions via Monte-Carlo Markov chain (MCMC) will use diagnostic evidence including effective sample size and scale reduction factors.

Evaluation of posterior distributions will permit statements regarding the probability that effects of varying magnitudes exist, given the data, even with a small sample size.

Descriptive statistics will evaluate measures of central tendency and frequencies for all continuous and categorical variables (respectively) measured in the study. Correlation analyses (i.e., Pearson's *r*, Spearman's *rho*) will be used to evaluate broad patterns of relationships across variables. Preliminary data analyses will inspect relationships between sample characteristics (e.g., demographics), experimental group (e.g., active vs. sham tDCS), and specified outcome variables (e.g., Apathy) via traditional statistical tests (e.g., chi-square; Mann-Whitney; *t*-tests). Any sample characteristic variables that demonstrate a relationship with both predictor and outcome variables in a given model meet criteria for being a potential confounder (32, 33) and will be included as a covariate in such models for hypothesis testing.

Statistical modeling will primarily use generalized linear modeling (GLM) with multilevel components (GLMM) for correlated observations. Potentially nonlinear relationships between predictors and outcomes will be evaluated via inclusion of polynomial or spline effects. Continuous, dichotomous, and count-distributed data will utilize linear, logistic, and Poisson/negative binomial regression, respectively (each with a canonical link function). Evaluation of distributional assumptions will use residual plots, formal statistical tests, and posterior predictive checking. Violations of assumptions will be addressed via transformation, robust estimation, stratification, and/or coefficient scaling where appropriate. Statistical analyses will be performed using the R statistical computing environment via packages lme, rstan, and brms.

Missing data will be addressed via maximum likelihood, explicit modeling of missingness, or imputation where appropriate. Each approach is robust to ignorable missingness (i.e. MCAR and MAR). Sensitivity analyses will permit evaluation of the robustness of findings to missing data assumptions. While Bayesian analyses are not influenced by traditional concerns of multiplicity, for the frequentist analyses, all primary outcome variables (those specified by name in the hypothesis statements) will be evaluated at the $\alpha = 0.05$ statistical significance level, while any secondary or otherwise post hoc analyses will employ false discovery rate (FDR) to control for Type I error.

Ethics/Protection of Patient Confidentiality

The sample of this study consists of 40 older adults aged 60 years-old and over with ADRD and apathy. Study participants or their legally authorized representatives will give informed consent. Moreover, caregivers and/or relatives will be required to be present during the clinical assessments and tDCS sessions to ensure reliable information and proper use of the device. Participants will be recruited without any specific regard to sex, race, religion or ethnicity. Patients will be recruited at the UTHealth Geriatric Neuropsychiatry Clinic, the HCPC, and UTHealth Center for Healthy Aging. We will recruit ADRD patients whose dementia is of mild to moderate severity ~~(CDR 1 and 2)~~. Adults

younger than 60, adolescents and children are excluded as we are focusing on dementia, an age-related disorder that usually affects individuals aged 60 and older. No other special classes of vulnerable individuals will be included. It is anticipated that the subject demographic profile will mirror the larger population of individuals with ADRD from which they are recruited.

Informed Consent and Assent. Potential subjects and their caregivers/relatives will be informed about the study purpose, procedures, risks and benefits. They will be informed that participation in the research study is voluntary and that they are free to decline to be in the study, or to withdraw from it at any point. Study records will be kept confidential. Study information will be coded, and only study personnel will have access to the files.

Protection Against Potential Risks. The risks to the subjects involved in this study are minimal. To ensure this, we will take necessary steps to reduce risk for all study participants. We will try to create an atmosphere of security and trust prior any clinical assessment in order to minimize any discomfort with the research questions. In addition, subjects are always given permission to not answer questions with which they feel uncomfortable. A number of procedures (e.g. use of identifying numbers instead of names) will be implemented to protect subjects against loss of confidentiality. Side effects related to active tDCS application are uncommon, and mild when present, including: itching and burning sensation on the scalp, mild headache, dizziness, and fatigue. No serious adverse effects have been reported with tDCS.

Potential Benefits to Research Participants. If our hypothesis is correct, subjects in the active arm of the study might benefit from the study participation. Importantly, the results will be relevant to the field of AD and neuromodulation.

Significance

Our proposal will address a frequent and sometimes overlooked clinical problem in patients with ADRD, i.e. apathy. The proposal can advance the field of non-pharmacological strategies for NPS, also presenting a great potential for clinical translation. Home-based intervention with real-time monitoring through a secure conferencing platform is a new modality for improving symptom management in ADRD. Moreover, home-based, remotely supervised tDCS has advantages over clinic-based sessions, considering the time and cost associated with attending multiple sessions over several days. Caregivers will be trained at the in-person baseline visit, and all the tDCS sessions will be remotely supervised via secure videoconferencing software by trained research staff for the entire duration of each session to ensure the use of proper technique and to monitor any adverse events.

Costs and Compensations

Subjects will not be charged for tests, procedures or other costs incurred solely for the purposes of this research. Patients will receive a voucher of US 50.00 for their time dedicated to each evaluation (total number of assessments = 5).

This project was approved to receive financial support from Texas Alzheimer's Research and Care Consortium (TARCC) 2020 Grant Program.

Publication Plan

This study will represent an original contribution to the areas of non-pharmacological approaches for NPS in ADRD and neuromodulation in ADRD, also fostering home-based interventions. More importantly, we expect to have enough evidence on the feasibility, acceptability, safety and efficacy of tDCS for apathy in AD so we can adjust and/or expand the protocol, ultimately, aiming its translation into the clinical practice. This project, if granted, will also strength emerging clinical research groups at UTHealth working with novel technologies that can be applied to ADRD and other neuropsychiatric conditions.

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