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

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

Principal Investigator: Dr. Kendra M. Anderson, PhD, UTHealth
Co-Investigators:
Dr. Antonio Lucio Teixeira, UT Health San Antonio
Dr. Thiago Macedo e Cordeiro, UT Health San Antonio
Dr Holly Homes, UTHealth
Dr Robert Suchting, UTHealth

General Information

Study Title	Home-based tDCS for behavioral symptoms in Alzheimer's disease and related dementias (ADRD)	
Short Title	tDCS for behavioral symptoms in ADRD	
Study Design	This is an open-label, non-randomized clinical trial to assess acceptability, safety and effi cacy of providing transcranial direct current stimulation (tDCS) to Alzheimer's disease and related dementia (ADRD) patients with behavioral symptoms. All participants will receive active tDCS with a constant current intensity of 2mA for 30 minutes, five times per week, for six weeks. Anodal tDCS will be applied to the left dorsolateral prefrontal cortex, while cathodal electrode will be positioned on the right dorsolateral prefrontal cortex. Caregivers will set up and administer tDCS for participants with AD at home. All sessions will be remotely supervised by trained research staff through video conferencing software. Participants will be assessed at baseline, treatment day 12, treatment day 28, treatment day 42, and 6 weeks	

	post-treatment.	
Study Participants	Patients with ADRD and behavioral symptoms will be recruited at the UTHealth Neurosciences Neurocognitive Disorders Center (Dr. Anderson), and UT Physicians Center for Healthy Aging (Dr. Holmes).	
Planned Sample Size	20	
Planned Study Period	12 weeks	
	Objectives	Outcome Measures
Primary Goal	To assess acceptability, and safety of providing tDCS to ADRD patients with behavioral symptoms.	*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, mainly behavioral symptoms.	Behavioral and cognitive symptoms will be evaluated through validated clinical instruments.

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 term NPS is an umbrella expression that encompasses

different types of behavioral problems, including 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).

Transcranial direct current stimulation (tDCS) is a relatively novel non-pharmacological method of neuromodulation that has been studied in several neuropsychiatric conditions with promising results in depression and negative symptoms of schizophrenia (7, 8). 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 NPS (9-11).

In ADRD, a few controlled studies have been conducted to evaluate the role of tDCS on cognitive functioning. A 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 (12) (13). Each patient received five sessions/week for two consecutive weeks totaling 10 sessions. Recently, 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 (14). 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 (14). 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 (15). 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 (16). While tDCS was safe in this population, there was no evidence of efficacy of tDCS on the 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 was the challenge to engage participants in the trial mainly due to issues related to transportation to the medical center for tDCS application (16). 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 NPS 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 acceptability, safety and efficacy of home-based tDCS for the treatment of NPS in ADRD. Home-based tDCS circumvents critical problems observed in previous trials (16), including the need of multiple visits to medical centers for tDCS application, allowing a more intensive application (e.g. 5 x per week) for long periods.

Objectives

Objectives	**Outcome Measures**
Primary objective To assess acceptability and safety of providing tDCS to ADRD patients with behavioral symptoms.	*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. Acceptability scale will be applied on Week 2, 4, 6 and 12. Side effects questionnaire will be applied on Week 2, 4 and 6.
Secondary objectives To assess the efficacy of tDCS for ADRD on clinical outcomes, mainly behavioral symptoms.	Behavioral symptoms and cognitive measures evaluated through validated tools: NPI, bDAS, CSDD, MMSE. NPI will be applied on Baseline, Week 2, 4, 6 and 12, while bDAS, CSDD and MMSE will be applied on Baseline, Week 6 and Week 12.

Study Design

We will carry out an open-label study to evaluate home-based active tDCS for AD and behavioral symptoms. There will be no randomization. All eligible patients will receive exactly the same treatment. All participants (n=20) will receive active tDCS with a constant current intensity of 2mA. Anodal tDCS will be applied to the left dorsolateral prefrontal cortex, while cathodal electrode will be positioned on the right dorsolateral prefrontal cortex. Caregivers will help setting up and administering tDCS for participants with AD at home. tDCS will be applied for 30min at an intensity of 2mA, with

30 s ramping up and down.

We will target the stimulation on the dorsolateral prefrontal cortex based on the facts that prior studies showed positive results with this strategy for behavioral and cognitive symptoms of other neuropsychiatric disorders (17-19). According to previous home-based tDCS protocols (20, 21), all sessions will be remotely supervised by trained research staff (RA), therefore, the sessions will run from Monday through Friday for four consecutive weeks. 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. The device (tDCS) will be programmed and cannot be tampered. Participants will be assessed at baseline, treatment day 14, treatment day 28, treatment day 42- and 6-weeks post-treatment (Fig.1). The device will be delivered to patients at baseline and will be returned at the end of the treatment (week 6).

Sample size

Following recommendations in the statistical literature analyses we will proceed using parallel frequentist and Bayesian statistical inference. 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 weakly informative priors as a default (e.g., for regression coefficients: ~N[μ=0,σ^2=100]). 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. Frequentist analyses will evaluate all *a priori* models at the α=0.05 (two-tailed) significance level and will employ false discovery rate (FDR) to control for Type I error across any exploratory or *post hoc* analyses. Bayesian models will be evaluated via PP threshold guidelines in the literature suggesting that PP = 75% to 90% indicates moderate evidence, PP = 91% to 96% indicates strong evidence, and PP = 97% or above indicates very strong to extreme evidence. Bayesian analyses do not conceptualize Type I error in the same way as frequentist analyses due to formally calibrating probability in the prior distribution (as opposed to long-run probabilities, as in

frequentist analyses) and are less influenced by multiple comparisons in general due to observation of the Likelihood Principle. The current Bayesian analyses stipulate posterior probabilities ≥ 0.75 (equivalent to a Bayes factor = 0.33 or 3.0) that parameter estimates are greater or less than zero provide a minimum threshold of evidence to emphasize the value in discerning effects in a small study. The Bayesian inferential paradigm can provide probabilistic estimates of effects irrespective of sample size. Power considerations focus on identifying change over time from baseline to end-of-treatment. Notably, the Bayesian analyses will provide the primary inferential results; thus considerations for the frequentist analyses are limited by the small sample size and provided solely as due diligence. Given alpha = 0.05, a sample size N = 20 provides 80% power to detect an effect size Cohen's d = 0.66.

Study Population

A maximum of 20 persons with ADRD and clinically-meaningful behavioral symptoms will be enrolled in the study. 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 resources.

Inclusion criteria. Participants who are 60 years or old will be considered eligible if they: (1) have ADRD and clinically-meaningful behavioral symptoms, (2) have a caregiver willing to participate in the study, (3) can speak and read English, (4) have stable doses of medications for at least one month. The diagnosis of ADRD will be verified by the investigators based on Mini-Mental Status Exam score (between 14 - 25) (22, 23). Clinically-meaningful behavioral symptoms will be determined by the Neuropsychiatric Inventory (NPI), and defined as a total score ≥10 arising from at least two domains (24, 25).

Exclusion criteria. Participants will be excluded if they have: (1) any unstable concurrent medical conditions, (2) history of brain surgery, seizure, or intracranial metal implantation, (3) current alcohol/substance use disorder.

Recruitment and Retention. Participants will be recruited at the *UTHealth Neurosciences Neurocognitive Disorders Center (Dr. Anderson), UT Physicians Center for Healthy Aging* (Dr. Holmes), and at the UT Health San Antonio's Glenn Biggs Institute for Alzheimer's and Neurodegenerative diseases Neurology clinic (Dr. Teixeira). Study flyers with summary and contact information about the study will be used at the *UTHealth Neurosciences Neurocognitive Disorders Center* as a mean to provide awareness and information to potential participants. Flyers will be available at the request of potential subjects at the moment of their visit with Dr. Anderson, and at dedicated spaces for research recruitment material in the *UTHealth Neurosciences Neurocognitive Disorders Center*. 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

Primary Outcome

Acceptability will be evaluated using the method proposed by Ahn et al. (2019) (21). 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. We expect that participant satisfaction ratings at the end of treatment will demonstrate high acceptance of tDCS treatment in the present sample. Acceptability scale will be applied on Week 2, 4, 6 and 12.

Safety will be assessed with a questionnaire about side effects that include itching, burning, headache, fatigue, and dizziness (21). The most common side effects of tDCS reported in the literature are very mild and include tingling, burning sensation, and skin redness, while other less common side effects may include headache, sleepiness, dizziness, and difficulty concentrating (22-23). Although rare, a possible adverse event of tDCS is the occurrence of skin lesions or small skin burns on the site where electrodes touch the skin (24-25). The side effects questionnaire will be applied on Week 2, 4 and 6 to assess the incidence and frequency of side effects in our recruited sample. We expect that the occurrence of side effects will be similar to the frequencies reported in the scientific literature, demonstrating that home-based tDCS is a safe and feasible intervention to be used on the management of ADRD patients with behavioral symptoms.

Secondary Outcome

The main efficacy measure will be change on the Neuropsychiatric Inventory (NPI) score (26), the best-validated tool for measuring NPS in dementia patients. This 12-item informant-based interview is a widely accepted measure of NPS in dementia. The NPI consists of a detailed evaluation of the following 12 neuropsychiatric domains: hallucinations, delusions, agitation/aggression, depression, anxiety, irritability, disinhibition, euphoria, apathy, aberrant motor behavior, change in night-time sleep behavior, and changes in appetite and eating (27). Each NPS domain is rated according to its severity (0-3) and frequency (0-4) (28). NPS will be assessed at baseline, during treatment (weeks 2, 4 and 6) and 6 weeks post-treatment. Our hypothesis is that patients receiving tDCS will demonstrate lower NPI scores at the end of treatment.

Other clinical outcome measures will include: (1) total score on the Brief Dimensional Apathy Scale (bDAS) (29); (2) depressive symptoms as assessed by the

Cornell Scale for Depression in Dementia (CSDD) (30); (3) 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 (31). Our hypothesis is that all participants receiving treatment will demonstrate lower scores on the bDAS and CSDD, and higher scores on the MMSE at the end of treatment.

NPI will be applied on Baseline, Week 2, 4, 6 and 12, while bDAS, CSDD and MMSE will be applied on Baseline, Week 6 and Week 12.

Sociodemographic and Clinical (health history, use of medication and life habits) *data* (gender, age, marital status and education) will be collected at the baseline.

Assessment	Baseline	Week 2	Week 4	Week 6	Week 12
Medical History Questionnaire	X				
MMSE (Secondary outcome)	X			X	X
NPI (Secondary outcome)	X	X	X	X	X
bDAS (Secondary outcome)	X			X	X
CSDD (Secondary outcome)	X			X	X
tDCS experience questionnaire (Primary outcome)		X	X	X	X
Side effects questionnaire (Primary outcome)		X	X	X	

Table 1. Timetable for Collection of Data

Data and Safety Monitoring

Data will be collected from 20 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 UT Health Department of Psychiatry and Behavioral Sciences. The data generated in this project will be presented at national or international conferences and published in a timely fashion.

Statistics

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.

Ethics/Protection of Patient Confidentiality

The sample of this study consists of 20 older adults aged 60 years-old and over with ADRD and behavioral symptoms. 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 Neurosciences Neurocognitive Disorders Center, and UTHealth Center for Healthy Aging. We will recruit ADRD patients whose dementia is of mild to moderate severity. 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. Although rare, a possible adverse event of tDCS is the occurrence of skin lesions or small skin burns on the site where electrodes touch the skin (24-25).

Potential Benefits to Research Participants. If our hypothesis is correct, all subjects 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. behavioral symptoms. 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

Participants 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).

Publication Plan

This study will represent an original contribution to the areas of non-pharmacological approaches for NPS in ADRD and neuromodulation. The results will be presented in national and international meetings, and published as a research manuscript.

References

1. Scheltens P, Blennow K, Breteler MM, de Strooper B, Frisoni GB, Salloway S, et al. Alzheimer's disease. Lancet. 2016;388(10043):505-17.
2. Cummings J, Ritter A, Rothenberg K. Advances in Management of Neuropsychiatric Syndromes in Neurodegenerative Diseases. Curr Psychiatry Rep. 2019;21(8):79.
3. Masopust J, Protopopova D, Valis M, Pavelek Z, Klimova B. Treatment of behavioral and psychological symptoms of dementias with psychopharmaceuticals: a review. Neuropsychiatr Dis Treat. 2018;14:1211-20.
4. Canevelli M, Adali N, Voisin T, Soto ME, Bruno G, Cesari M, et al. Behavioral and psychological subsyndromes in Alzheimer's disease using the Neuropsychiatric Inventory. International journal of geriatric psychiatry. 2013;28(8):795-803.
5. Dyer SM, Harrison SL, Laver K, Whitehead C, Crotty M. An overview of systematic reviews of pharmacological and non-pharmacological interventions for the treatment of behavioral and psychological symptoms of dementia. Int Psychogeriatr. 2018;30(3):295-309.
6. Abraha I, Rimland JM, Trotta FM, Dell'Aquila G, Cruz-Jentoft A, Petrovic M, et al. Systematic review of systematic reviews of non-pharmacological interventions to treat behavioural disturbances in older patients with dementia. The SENATOR-OnTop series. BMJ Open. 2017;7(3):e012759.

7. Razza LB, Palumbo P, Moffa AH, Carvalho AF, Solmi M, Loo CK, et al. A systematic review and meta-analysis on the effects of transcranial direct current stimulation in depressive episodes. Depress Anxiety. 2020.
8. Valiengo L, Goerigk S, Gordon PC, Padberg F, Serpa MH, Koebe S, et al. Efficacy and Safety of Transcranial Direct Current Stimulation for Treating Negative Symptoms in Schizophrenia: A Randomized Clinical Trial. JAMA Psychiatry. 2019.
9. Guimaraes HC, Levy R, Teixeira AL, Beato RG, Caramelli P. Neurobiology of apathy in Alzheimer's disease. Arq Neuropsiquiatr. 2008;66(2B):436-43.
10. Pena-Gomez C, Sala-Lonch R, Junque C, Clemente IC, Vidal D, Bargallo N, et al. Modulation of large-scale brain networks by transcranial direct current stimulation evidenced by resting-state functional MRI. Brain Stimul. 2012;5(3):252-63.
11. Kazui H, Takahashi R, Yamamoto Y, Yoshiyama K, Kanemoto H, Suzuki Y, et al. Neural Basis of Apathy in Patients with Amnestic Mild Cognitive Impairment. J Alzheimers Dis. 2017;55(4):1403-16.
12. Cai M, Guo Z, Xing G, Peng H, Zhou L, Chen H, et al. Transcranial Direct Current Stimulation Improves Cognitive Function in Mild to Moderate Alzheimer Disease: A Meta-Analysis. Alzheimer Dis Assoc Disord. 2019;33(2):170-8.
13. Khedr EM, Salama RH, Abdel Hameed M, Abo Elfetoh N, Seif P. Therapeutic Role of Transcranial Direct Current Stimulation in Alzheimer Disease Patients: Double-Blind, Placebo-Controlled Clinical Trial. Neurorehabil Neural Repair. 2019;33(5):384-94.
14. Im JJ, Jeong H, Bikson M, Woods AJ, Unal G, Oh JK, et al. Effects of 6-month at-home transcranial direct current stimulation on cognition and cerebral glucose metabolism in Alzheimer's disease. Brain Stimul. 2019;12(5):1222-8.
15. Vacas SM, Stella F, Loureiro JC, Simoes do Couto F, Oliveira-Maia AJ, Forlenza OV. Noninvasive brain stimulation for behavioural and psychological symptoms of dementia: A systematic review and meta-analysis. Int J Geriatr Psychiatry. 2019;34(9):1336-45.
16. Suemoto CK, Apolinario D, Nakamura-Palacios EM, Lopes L, Leite RE, Sales MC, et al. Effects of a non-focal plasticity protocol on apathy in moderate Alzheimer's disease: a randomized, double-blind, sham-controlled trial. Brain Stimul. 2014;7(2):308-13.
17. Triggs WJ, Ricciuti N, Ward HE, Cheng J, Bowers D, Goodman WK, et al. Right and left dorsolateral pre-frontal rTMS treatment of refractory depression: A randomized, sham-controlled trial. Psychiatry Research. 2010;178(3):467-74.
18. Mishra BR, Nizamie SH, Das B, Praharaj SK. Efficacy of repetitive transcranial magnetic stimulation in alcohol dependence: a sham-controlled study. Addiction. 2010;105(1):49-55.
19. Tayeb Y, Lavidor M. Enhancing switching abilities: Improving practice effect by stimulating the dorsolateral pre frontal cortex. Neuroscience. 2016;313:92-8.
20. Ahn H, Sorkpor S, Miao H, Zhong C, Jorge R, Park L, et al. Home-based self-administered transcranial direct current stimulation in older adults with knee osteoarthritis pain: An open-label study. Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia. 2019;66:61-5.
21. Ahn H, Zhong C, Miao H, Chaoul A, Park L, Yen IH, et al. Efficacy of combining home-based transcranial direct current stimulation with mindfulness-based meditation for pain in older adults with knee osteoarthritis: A randomized controlled pilot study. Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia. 2019;70:140-5.
22. Inagawa T, Yokoi Y, Narita Z, Maruo K, Okazaki M, Nakagome K. Safety and feasibility of transcranial direct current stimulation for cognitive rehabilitation in patients with mild or major neurocognitive disorders: A randomized sham-controlled pilot study. Front Hum Neurosci. 2019;13:273.
23. Yang CL, Qu Y, Huang JP, Wang TT, Zhang H, Chen Y, Tan YC. Efficacy and safety of transcranial direct current stimulation in the treatment of fibromyalgia: A systematic review and meta-analysis. Neurophysiol Clin. 2024;54(1):102944.

24. Lu H, Chan SSM, Chan WC, Lin C, Cheng CPW, Linda Chiu Wa L. Randomized controlled trial of TDCS on cognition in 201 seniors with mild neurocognitive disorder. Ann Clin Transl Neurol. 2019;6(10):1938-1948.
25. Antal A, Alekseichuk I, Bikson M, Brockmöller J, Brunoni AR, Chen R, Cohen LG, Dowthwaite G, Ellrich J, Flöel A, Fregni F, George MS, Hamilton R, Haueisen J, Herrmann CS, Hummel FC, Lefaucheur JP, Liebetanz D, Loo CK, McCaig CD, Miniussi C, Miranda PC, Moliadze V, Nitsche MA, Nowak R, Padberg F, Pascual-Leone A, Poppendieck W, Priori A, Rossi S, Rossini PM, Rothwell J, Rueger MA, Ruffini G, Schellhorn K, Siebner HR, Ugawa Y, Wexler A, Ziemann U, Hallett M, Paulus W. Low intensity transcranial electric stimulation: Safety, ethical, legal regulatory and application guidelines. Clin Neurophysiol. 2017;128(9):1774-1809.
26. Cummings JLMD. The Neuropsychiatric Inventory: Assessing psychopathology in dementia patients. Neurology. 1997;48(5) Supplement(6):10S-6S.
27. Balthazar MLF, Pereira FRS, Lopes TM, da Silva EL, Coan AC, Campos BM, et al. Neuropsychiatric symptoms in Alzheimer's disease are related to functional connectivity alterations in the salience network. Human Brain Mapping. 2014;35(4):1237-46.
28. Eikelboom WS, van den Berg E, Singleton EH, Baart SJ, Coesmans M, Leeuwis AE, et al. Neuropsychiatric and Cognitive Symptoms Across the Alzheimer Disease Clinical Spectrum: Cross-sectional and Longitudinal Associations. Neurology. 2021;97(13):e1276-e87.
29. Radakovic R, Gray D, Dudley K, Mioshi E, Dick D, Melchiorre G, et al. Reliability and validity of the brief dimensional apathy scale. Archives of clinical neuropsychology : the official journal of the National Academy of Neuropsychologists. 2020;35(5):539-44.
30. Alexopoulos GS, Abrams RC, Young RC, Shamoian CA. Cornell Scale for Depression in Dementia. Biol Psychiatry. 1988;23(3):271-84.
31. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12(3):189-98.