Official title: Combined Intervention Using Transcranial Direct Current Stimulation and Cognitive Training in Alzheimer's Type Dementia Patients

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Study Protocol

Eligibility Criteria

Participants are eligible for inclusion in the study if they meet predefined criteria related to age, cognitive status, and clinical condition. Specifically, participants must be aged 65 years or older and have a diagnosis of mild cognitive impairment due to Alzheimer's disease (MCI due to AD). This includes a score of ≥23 on the Mini-Mental State Examination (MMSE) and a score of 3 on the Global Deterioration Scale (GDS), consistent with MCI. In addition, participants must fulfil the clinical and cognitive criteria for MCI due to AD according to the NIA-AA guidelines, including evidence of progressive cognitive decline, particularly in memory and learning; relatively preserved independence in activities of daily living; and the absence of alternative medical or psychiatric conditions that could explain the symptoms. The age threshold of 65 years was selected to focus on Alzheimer's disease in older adults and to reduce clinical heterogeneity by excluding cases of early-onset cognitive impairment, which may differ in etiology and clinical course.

Exclusion Criteria

Certain conditions disqualify individuals from participating in the study. These include contraindications to transcranial direct current stimulation (tDCS), such as intracranial metallic implants, intracranial hypertension, or a high risk of seizures; the presence of significant cerebrovascular disease, including asymptomatic neurovascular pathology or a history of symptomatic stroke; diagnosis of neurodegenerative diseases other than Alzheimer's disease; severe psychiatric symptoms or depressive symptoms greater than mild; significant functional dependency; and plans to relocate during the intervention period that could interfere with study participation.

Randomisation

A single-blind design was employed, whereby participants and outcome assessors were blinded to group allocation throughout the study in order to minimize potential bias in outcome evaluation. The psychologist administering the intervention was not blinded, due to the practical requirements of delivering the treatment. Participants were not informed of their assigned group and were instructed not to disclose any details of the intervention during assessments to help maintain blinding.

Procedure

tDCS was delivered using a battery-operated HDC stimulator (Newronika™, Milan, Italy) providing non-invasive direct current at an intensity of 2 mA for 20 minutes (current density: 0.08 mA/cm²). Stimulation was applied using a pair of 5 × 5 cm (25 cm²) rubber electrodes enclosed in saline- or sterile water–soaked sponge pads to optimize conductivity and minimize skin resistance. Electrodes were positioned on a neoprene headcap according to predefined locations based on the international 10–10 EEG system, with the anode placed at F3 (left dorsolateral prefrontal cortex, DLPFC) and the cathode at Fp2 (right supraorbital area). Electrode–skin impedance was assessed prior to each session, and stimulation was initiated only when impedance values were within the acceptable range. Each session included 30-second ramp-up and ramp-down phases to facilitate sensory habituation. Procedures, electrode placement, and session duration were identical in both active and sham conditions. In the sham condition, current was delivered only during the initial and final 30 seconds, with no stimulation administered during the intervening period, thereby preserving participant blinding.

To verify stimulation delivery, the HDCstim® device was interfaced with the HDCprog software, which includes a "treatment report" function. These reports provide detailed information for each session, including (a) date and time of stimulation, (b) average electrode–skin impedance (acceptable range: 4–12 kΩ), and (c) treatment status (completed, failed, or cancelled).

Additionally

Participants were fully informed about the study's blinding design and provided written informed consent confirming their understanding and acceptance of this procedure. Quality control procedures were implemented to ensure consistency and accuracy in tDCS administration. Study personnel received standardized training in electrode placement and stimulation delivery. In addition, ongoing supervision was conducted to ensure correct electrode positioning and adherence to the study protocol across all sessions, thereby guaranteeing uniformity in treatment administration throughout the study.

Outcome

The primary outcome measure was global cognitive functioning. Secondary outcome measures included immediate and delayed memory, as well as learning ability.

The selection of these cognitive domains was guided by their clinical relevance in mild cognitive impairment in Alzheimer's disease. Global cognitive functioning was included to capture overall cognitive change associated with disease progression, while verbal episodic memory and learning were selected due to their early impairment and central role in diagnostic characterization. Immediate verbal memory span was included as an index of short-term and working memory processes, which are frequently targeted in cognitive training protocols and have shown sensitivity to prefrontal tDCS in previous studies. Together, these measures encompass core cognitive functions commonly affected in the early stages of Alzheimer's disease.

The Mini-Mental State Examination (MMSE; Folstein et al., 1975) was used as a measure of global cognitive functioning and served as the primary outcome variable. It is a brief, standardized, and quantitative instrument designed to assess the presence and severity of cognitive impairment, with a maximum score of 30 points. The Spanish validated version, widely used in both clinical and research settings in Spain, was administered in this study.

The Test of Verbal Learning Complutense (TAVEC; Benedet and Alejandre, 1998) was administered to assess immediate memory, learning ability, and delayed memory. The test consists of a list of 16 words that are read aloud by the evaluator and subsequently recalled by the participant. The list is presented over five learning trials, and after a 20-minute delay, participants are asked to freely recall the words. Immediate memory was indexed by performance on the first trial, learning ability by performance on the fifth trial and the total number of correct responses across the five trials, and delayed memory by free recall after the 20-minute interval.

The forward and backward digit span subtests from the Wechsler Adult Intelligence Scale–III (WAIS-III; Wechsler, 2001) were used to assess attentional capacity, immediate verbal memory span, and working memory. In the forward digit span task, participants are required to repeat sequences of numbers in the same order as presented by the examiner, providing a measure of immediate verbal memory. In the backward digit span task, participants must recall the digits in reverse order, which assesses working memory and mental flexibility. Both tasks are scored by assigning one point for each correctly recalled sequence, with a maximum total score of 16 for each subtest.

The semantic and phonological fluency subtests of the Barcelona Test Revised (TBR; Peña-Casanova, 2005) were administered to assess lexical retrieval and executive

functioning. In the semantic fluency task, participants were asked to generate as many words as possible belonging to a specific category (“animals”) within one minute. In the phonological fluency task, participants were required to produce as many words as possible beginning with the letter “p” within a maximum of three minutes. These tasks evaluate the ability to access and retrieve information from lexical and semantic stores. Performance is influenced by multiple cognitive processes, including processing speed, cognitive flexibility, and working memory.

The Memory Alteration Test (M@T; Rami et al., 2007) is a brief and valid screening instrument for amnestic mild cognitive impairment (a-MCI) and early-stage Alzheimer’s disease. It assesses multiple cognitive domains, including encoding, orientation, semantic memory, and free recall. The maximum possible score is 50 points.

Statistical Analysis

Considering the study groups, 3 repeated measures (pre, post, and follow-up), a statistical power of 95%, and a 95% confidence interval with an estimated effect size of $\eta^2 = 0.16$, it is estimated that an N = 30 participants would be needed, which means 15 subjects per group. However, due to recruitment constraints, the final sample consisted of 22 participants, which may have reduced the statistical power of the study.

The data will be analyzed using linear mixed-effects models to account for the repeated measures structure of the data, with group (active vs. sham) as a between-subjects factor and time (pre, post, follow-up) as a within-subjects factor. The efficacy of tDCS will be assessed by examining the interaction between group and time.