Official title: Non-invasive Transcranial Direct Current Stimulation to Improve Cognitive Efficiency

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Study Protocol

Eligibility Criteria:

Participants eligible for inclusion in the study must meet specific criteria based on their age, cognitive status, and health condition. For healthy older adults, the minimum age requirement is 65 years, and they must have a Montreal Cognitive Assessment (MEC) score greater than 26 points and a Geriatric Depression Scale (GDS) score between 1 and 3. Individuals classified as having Mild Cognitive Impairment (MCI) must also be at least 65 years old and have a MEC score between 21 and 26 points, with a GDS score falling between 1 and 3. Those categorized as having mild Alzheimer's disease (EA) must meet the same minimum age requirement of 65 years, with a MEC score ranging from 18 to 23 points and a GDS score between 3 and 4.

Exclusion Criteria:

Certain conditions disqualify individuals from participating in the study. These include contraindications to transcranial Direct Current Stimulation (tDCS), such as the presence of intracranial metal implants, intracranial hypertension, or a high risk of seizures. Additionally, significant asymptomatic neurovascular disease, a history of previous symptomatic stroke, alcohol or drug abuse/dependence, severe psychiatric symptoms, or depressive symptoms higher than mild are grounds for exclusion from the study.

Randomisation

Once patients were available, allocation to the anodal and sham tDCS groups was carried out by stratified block randomisation. Participants were randomly assigned using a random number system. They were randomly assigned to the experimental groups (anodal vs. sham) with a 1:1 ratio, with gender as the stratum. Participants did not know which group they had been placed in until the intervention ended, this being a single-blind study.

Procedure

Stimulation was performed using an HDC stimulator (Newronika TM, Milan, Italy), which is battery-driven and delivers a direct current. The current intensity was 2 mA, and the stimulation lasted 20 minutes. In addition, a current ramp was delivered for 30 seconds prior to the start and end of stimulation. A pair of 25 cm2 rubber electrodes

transferred the direct current. These electrodes were inserted into sponge pads soaked with sterile water. The electrodes and sponges were placed in a neoprene headcap with predefined and clearly annotated positions, based on a subset of the international 10-10 EEG system. The anode was placed on F3 at left dorsolateral prefrontal cortex (DLPFC), and the cathode was placed on the right frontal lobe (Fp2). Electrode placement and session duration were identical in active and placebo tDCS. However, in the placebo tDCS condition, at the end of the onset ramp, the current was automatically turned off for 20 minutes and then turned on again for the last 30 seconds.

In addition, to check the stimulations carried out, the HDCstim® stimulator is connected to the HDCprog, which has a "treatment report" in its menu. These reports show: a. Time and date of each stimulation, b. Average impedance of each stimulation (a suitable impedance range would be from 4 kOhm to 12 kOhm, and c. Result of the treatment (completed, failed or cancelled).

Additionally

Participants were fully informed about the study's blinding design and provided informed consent acknowledging their understanding and acceptance of the blinding procedure. Quality control measures were implemented to maintain consistency and accuracy in tDCS administration. Personnel received training in standardized electrode placement procedures and stimulation administration. Ongoing supervision ensured proper electrode placement and adherence to established protocols in all stimulation sessions, ensuring uniform treatment administration throughout the study.

Outcome

The primary outcome measures were general cognitive function, immediate and delayed memory, and learning ability. The secondary outcome measures included executive function tests. The selection of primary outcomes was based on the DSM-5 criterion (APA, 2013) that states that mild neurocognitive disorder due to possible Alzheimer's disease should show clear evidence of a decline in memory and learning. The assessment of memory and learning is a main criterion in the characterisation of the pathology, and we aimed to analyse the possible change in measures that analyse these variables. In addition, given that the progression of these patients to major neurocognitive disorder due to Alzheimer's disease is usually accompanied by a deterioration in executive control, change in the measures that assess this variable was proposed as a secondary outcome.

The Mini-Mental State Examination (MMSE; Folstein et al., 1975) was used as an index of global cognitive functioning; the maximum score is 30 points. This test was designed to estimate the existence and severity of cognitive impairment; it is a brief and quantitative test that measures general cognitive function.

Test de Aprendizaje Verbal Complutense (TAVEC; Benedet and Alejandre, 1998). This test presents a list of 16 words which, after being read by the evaluator, have to be repeated by the participant. The list is repeated five times (trials), and after 20 minutes, the participant is again asked to remember the 16 words. The test was administered to evaluate the participant's immediate memory (Trial 1), learning ability (analysing Trial 5 and the total number of correct answers on the five trials), and delayed memory.

Memory Alteration Test (M@T; Rami et al., 2007). The M@T provides efficient and valid screening for A-MCI and early-stage AD. The test evaluates different abilities such as: encoding, orientation, semantic memory, and free recall. The maximum score is 50 points.

Direct and inverse digits of the Wechsler Intelligence Scale for Adults-III (Wechsler, 2001). These tests assess attentional capacity by exposing the participant to increasing amounts of information. On the direct digits task, which is used to assess immediate recall, the subject must repeat the sequence of numbers in the same order in which they are read by the examiner. On the inverse digits task, which assesses working memory and mental flexibility, the subject must say the digits backwards from the way they were presented by the examiner. Both tests are evaluated in the same way, assigning one point for each correct item, with a maximum score of 16 for both tests.

Rey's Complex Figure (Rey, 1984). This test is used to evaluate both memory and executive capacity, such as planning, motor skills, working memory, and visuocontructive and spatial ability. For its execution, the subject has to attentively reproduce a complex geometric drawing and later reproduce it after a three-minute delay.

Semantic fluency and phonological fluency subtests of the Barcelona Test Revised (TBR; Peña-Casanova 2005). The semantic fluency subtest requires the subject to evoke the maximum number of words linked to a specific category, “animals”, in one minute. In the case of phonological verbal fluency, the subject is asked to recall the maximum number of words beginning with the letter “p” in a maximum of 3 minutes. This test evaluates the ability to access and recall elements from the lexical and semantic store. Among the processes involved, information processing speed, cognitive flexibility, and

working memory have been pointed out.

Statistical Analysis

A priori power calculation for ANOVA repeated-measures within-between interaction required a total sample of 32 participants to detect an effect size of .30 with 90% power, with alpha set at .05. Power calculations were carried out using GPower 3.1.7.

To analyse the sociodemographic variables, we used independent samples t-tests and chi-square tests. To analyse the cognitive variables, mixed ANOVAs with 2 groups (active vs. sham; between-subjects) X 2 sessions (before vs. after intervention; within-subjects) were conducted. The effectiveness of the tDCS should be reflected by finding a significant interaction between the two independent variables (in which the active group should improve across sessions, whereas the sham or control group would not). Post-hoc simple effects tests were conducted to analyse these significant interactions. A value of $p \leq .05$ was considered statistically significant. Data were analysed using SPSS 28.