TITLE: Combined effect of tDCS and motor or cognitive activity in patients with Alzheimer's Disease: a proof-of-concept pilot study

NCT Number: NCT06619795

02/10/2024

The aim of this study will be to evaluate the effectiveness of combining tDCS with motor or cognitive activities on cognitive functions in patients with AD. A secondary aim will be to investigate whether tDCS will have a different impact when combined with motor versus cognitive activities.

Materials and Methods

The study will be a double-blind randomized controlled trial (RCT) that will compare the effects of anodal and sham tDCS combined with motor or cognitive activity on cognitive performance in AD patients. The research team will consist of "evaluators" and "treatment providers." The neuropsychologist evaluator will be responsible for measuring outcomes and will remain unaware of the group assignments. Additionally, to assess the presence of a placebo effect or the absence of an effect from the anodal stimulation, and to reduce potential bias, participants will also be kept unaware of the type of stimulation being administered. In contrast, the treatment providers, including neuropsychologists and physiotherapists, will be informed about the treatment but will not know the type of tDCS stimulation used (anodal or sham) (Cotelli et al., 2014).

Participants

Patients with AD will be recruited from the Mons. A. Mazzali Foundation (Mantua). The inclusion criteria will be: Mini Mental State Examination (MMSE) >15, good level of compliance, treatment with acetylcholinesterase inhibitors (e.g., donepezil, rivastigmine), and no modifications to medication in the last four months. The exclusion criteria will be: behavioral disorders (e.g., aggressiveness), alcohol abuse, orthopedic conditions with a risk of falls, respiratory disorders, uncorrected severe auditory or visual deficits, history of epileptic fits, use of anti-epileptic medication, metallic body implants, pacemaker, and psychiatric, neurological, systemic, or metabolic disorders.

Following a simple software-generated randomization scheme (www.randomization.org), patients will be allocated to one of four groups after the baseline evaluation. Unbalanced randomization will be applied. The randomization list will not be disclosed to the assessors or treatment providers but will be known only to the principal investigator (CF).

Treatment procedures

The real tDCS groups will receive anodal stimulation combined with either motor activity (MotA) or cognitive activity (CogA). The sham tDCS groups will receive sham stimulation combined with motor activity (MotS) or cognitive activity (CogS).

Each group will undergo 45 minutes of activity, with the first 15 minutes performed simultaneously with tDCS stimulation. Treatments (45 minutes) will be administered for two weeks, five times per week (Cotelli et al., 2014)..

During the study, participants will not engage in any other motor or cognitive activities.

Motor activity

A standardized sequence of motor exercises will be established. A physiotherapist will conduct the individual motor activity, which will include moderate-intensity endurance and resistance training. Each session will begin with a 5-minute warm-up and conclude with a 5-minute cool-down, including active joint mobilization. Subsequently, patients will engage in endurance exercises, which will be

randomly ordered and divided among cycling on a cycle ergometer, walking on a platform, and arm cranking on a specialized ergometer (Fonte et al., 2019).

Cognitive activity

A neuropsychologist will conduct individual cognitive activities, focusing on stimulating residual cognitive abilities, particularly memory. The cognitive stimulation will be tailored to the severity of each patient's cognitive decline. Each session will begin with an orientation exercise, followed by oral and paper-and-pencil tasks targeting specific cognitive functions. These exercises will aim to encourage natural reminiscence processes while also focusing on the present, enhancing social interaction and mood. Multisensory stimulation will also be incorporated.

The structure of the neuropsychological treatment will be modeled after a study conducted by Spector et al. in 2003, which involved 201 dementia patients (Spector et al., 2003). This approach demonstrated positive outcomes in several cognitive domains, as well as improvements in quality of life, while maintaining a high level of feasibility and adaptability (Fonte et al., 2019; Spector et al., 2003).

tDCS procedure

The tDCS stimulation will be performed using a BrainSTIM stimulator (EMS). A pair of saline-soaked electrodes will be placed and secured on the patients. The anode (25 cm^2, 5x5 cm) will be positioned over the left dorsolateral prefrontal cortex (DLPFC) following the 10–20 system (F3-F7 position), and the cathode (35 cm^2, 7x5 cm) will be placed above the shoulder on the opposite side. The stimulation procedure will be adapted to align with the prevalent literature, as the DLPFC montage is widely used (Pilloni et al., 2022; Fonte et al.,2021). The intensity of the stimulation will be set at 2mA and applied for the first 15 minutes of either cognitive or motor activity (45 minutes total).

The electrode placement and parts of the stimulation procedure will follow the protocol described by Cotelli and colleagues in 2014 (Cotelli et al., 2014). To ensure safety, the current density of the active electrode will be kept within the limits established by Poreisz and collaborators in 2007 and Nitsche and collaborators in 2008. In the sham condition, the current will be turned off 10 seconds after the stimulation starts and turned back on during the final 10 seconds, so that participants will be unable to discern whether the stimulation is real or sham (Poreisz et al., 2007; Nitsche et al., 2008).

Evaluation procedures

Primary and secondary outcomes will be measured by the same blinded examiner. Patients will be evaluated before treatment (T0), immediately after treatment (T1), and at a one-week follow-up (T2). Cognitive assessments will be conducted in a single session lasting one hour. The tests used in the assessment are described below.

- Primary Outcome

The primary outcome will be the Mini Mental State Examination (MMSE), used to assess global cognitive impairment (Folstein et al., 1975).

- Secondary Outcomes

The secondary outcomes will include:

- Picture Recognition (PR) is a subtest of the Rivermead Behavioral Memory Test-3, an ecological memory battery resembling everyday tasks, with the aim to measure daily memory function (Beschin et al., 2013).
- Digit Span Test- Forward (DSF), used to measure span of immediate verbal recall. The examiner presents digits verbally at a rate of one per second (Monaco et al., 2013).
- Digit Span Test- Backward (DSB), used to measure working memory (Monaco et al., 2013).
- Phonemic Fluency Test (PFT), used to measure processing speed, language production and executive functions (Zappalà et al., 1995).
- Visual Search Test (VST), to assess visual-selective attention (Spinnler & Tognoni, 1987).
- Sustained Attention to Response Test (SART): used to evaluate sustained attention and control inhibition. In the test, participants view a computer monitor on which a random series of single digits are presented at the regular rate of 1 per 1.15 seconds (Robertson et al., 1997).
- Neuropsychiatric Inventory (NPI) to evaluate the presence, frequency and severity of behavioral disorders (Cummings et al., 1994).

Statistical analysis

Data from all randomized patients will be assessed. The Kruskal-Wallis test will be used to measure baseline homogeneity for all outcome measures across the four groups. The Mann-Whitney U test will be employed to examine the effects of tDCS by comparing MotA+CogA versus MotS+CogS between T1 and T0 (T1-T0) and between T2 and T0 (T2-T0). Further analysis will investigate differences in performance between the MotA and CogA groups from T1 to T0 (T1-T0) and from T2 to T0 (T2-T0). The alpha level for significance will be set at $P < 0.05$.

Statistical analysis will be conducted using the Statistical Package for Social Science (SPSS) for Macintosh, version 26.0 (IBM SPSS Inc, Armonk, NY, USA).

To determine the sample size, based on the study by Khedr and colleagues, an effect size of 1.15 will be calculated using G*Power 3.1.9.4 software. With an effect size of 1.15, an alpha of 0.01, and a power of 0.90, a total of 48 patients will be required to detect a significant treatment effect Khedr et al., 2019).

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