

Transcranial direct current stimulation in mild cognitive impairment: methodology for a randomized controlled trial

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Abstract

Background: Transcranial direct current stimulation (tDCS) is a non-invasive neuromodulatory technique that has shown encouraging results regarding performance improvement of normal subjects in tests of executive functions. Moreover, when applied repeatedly in daily sessions, tDCS has shown therapeutic potential in various neuropsychiatric disorders. However, there is a need for double-blind, placebo-controlled studies to determine the true therapeutic potential of this portable, low-cost and non-invasive treatment. Mild cognitive impairment (MCI) of the amnesic subtype may evolve into Alzheimer's dementia (AD) and pharmacological approaches have not been successful in ameliorating symptoms or halting progression to AD. Here we propose a protocol for studying a possible role for tDCS on improvement of MCI symptoms in older patients.

Methods/Design: This will be a double-blind, placebo-controlled study of the effects of anodal tDCS over the left dorsolateral prefrontal cortex of patients with MCI. Patients aged 60-90 years will be randomly assigned to either real tDCS or sham stimulation. Twenty-minute real or sham tDCS sessions, 5 days a week, will be performed over the course of two weeks. The Rivermead Behavioural Memory Test (RBMT), California Verbal Learning Test, Rey Verbal Auditory Learning Test (RVALT) and Digit Span (WAIS-IV) will be assessed at baseline, after the first and second weeks of treatment, as well as one and three months after the last tDCS session. The primary outcome will be change in test scores over time.

Secondary outcomes will be self-reported memory improvement and possible side effects of tDCS.

Discussion: This study will evaluate possible therapeutic applications of tDCS for treatment of MCI. tDCS is a portable and low-cost neuromodulatory technique that has been found to increase performance of both normal subjects and patients in many cognitive tasks. It will also examine the tolerability, program adherence and possible side effects of this novel technique in this age group. The information obtained in this study should be useful in planning further studies in which tDCS could be combined with other treatment modalities, such as cognitive training.

Keywords: mild cognitive dysfunction; dementia; transcranial direct current stimulation; tDCS

Background

Life expectancy of the world population has been rapidly increasing, but has also been linked to a higher prevalence of chronic diseases such as dementia. Nowadays the population over 60 years old is near 900 million.

The number of dementia cases in 2016 (Alzheimer's Disease International, 2016) was close to 50 million, whereas in 2015 this number was 46.8 million (Alzheimer's Disease International, 2015). This number will almost double every 20 years. It is estimated that the prevalence of dementia will reach 74.7 million in 2030 and 131.5 million in 2050. These estimates are 12-13 % higher than those presented by the World Alzheimer Report of 2009 (Alzheimer's Disease International, 2016). The economic impact of the disease, therefore, is high, and whereas in 2010 its overall cost was 604 billion dollars, it climbed to 818 billion dollars by 2015. In 2018, the global cost of dementia is estimated to rise above a US\$ trillion dollars, or more than 1% of the global GDP (Alzheimer's Association, 2018).

Every dementia, regardless of its etiology, progressively affects cognitive, behavioral and functional abilities. Limitations in everyday life activities compromise functional abilities and increase the risk of fatal accidents and constitute a burden to the patient, family members and

public health care facilities, directly impacting the quality of life (Fuentes, 2008; Brodaty & Donkin, 2009; World Health Organization, 2012).

Between 2000 and 2015, deaths resulting from stroke, heart disease, and prostate cancer decreased, whereas deaths from Alzheimer Disease (AD) increased 123%. In 2017, more than 16 million family members and other unpaid caregivers provided an estimated 18.4 billion hours of care, resulting in increased risk of emotional and negative mental and physical health outcomes also for these caregivers. Total payments in 2018 for health care, long-term care for people aged ≥ 65 years with dementia are estimated to reach \$277 billion (Alzheimer's Association, 2018).

Mild cognitive impairment is thought to represent a transitional period between normal ageing and the diagnosis of clinically probable very early Alzheimer's disease (AD) (Petersen, 2004, 2016; Petersen et al., 2014). The diagnosis of MCI can be done by taking a history and performing a mental status exam, possibly complemented with neuropsychological testing (Petersen, 2016). The construct of mild cognitive impairment (MCI) has evolved over the past 10 years since the publication of the new MCI definition at the Key Symposium in 2003, but the core criteria have remained unchanged. The construct has been extensively used worldwide, both in clinical and in research settings, to define the grey area between intact cognitive functioning and clinical dementia. A rich set of data regarding occurrence, risk factors and progression of MCI has been generated (Petersen et al., 2014; Petersen, 2016).

Although patients with MCI may represent an optimal target population for pharmacological and non-pharmacological interventions, results from clinical trials have been mixed and an effective treatment remains elusive (Vega & Newhouse, 2014). Several attempts have been made at developing a pharmacological treatment to ameliorate symptoms or to decrease the rate of progression of dementia of the Alzheimer type, but so far no drug has achieved this goal (Petersen & Negash, 2008; Vega & Newhouse, 2014).

Recently, a non-pharmacological, non-invasive neuromodulatory technique, namely repetitive transcranial magnetic stimulation (TMS), has been found to improve memory in both normal volunteers and older patients with mild cognitive impairment (MCI) (Drumond Marra et al., 2015). Good results have also been reported concerning memory and language in patients with mild Alzheimer's disease when TMS was administered together with cognitive training (Rabey et al., 2013; Rabey & Dobronevsky, 2016). Furthermore, TMS can influence brain function if delivered repetitively; repetitive TMS (rTMS) is capable of modulating cortical

excitability and inducing long-lasting neuroplastic changes. Preliminary findings have suggested that rTMS can enhance performances on several cognitive functions impaired in AD and MCI (Cotelli et al., 2012; Nardone et al., 2014).

TMS is able to induce electric currents in the cerebral parenchyma, according to Faraday's Law (Hasey, 1999; Priori, 2003; Brunoni et al., 2010a). The effects of electric currents upon neuronal function have been studied for decades (Priori, 2003). More recently, after several reports of beneficial effects of TMS upon symptoms of many neuropsychiatric disorders, such as depression (Pascual-Leone et al., 1996; Boechar-Barros, 2004; Boechar-Barros & Brasil-Neto, 2004; Leo & Latif, 2007; O'Reardon et al., 2007; Brunoni et al., 2010b; Holtzheimer & Mayberg, 2012; Rothwell, 2012; Iannone et al., 2016) and chronic pain (Nguyen et al., 1999; Leo & Latif, 2007; Rosen et al., 2009; Galhardoni et al., 2015) and neuropathic pain (Brown & Barbaro, 2003; Fagundes-Pereyra et al., 2010; Nguyen et al., 2011; Nizard et al., 2012), transcranial direct current stimulation (tDCS) has also been the subject of many studies due to its ability to modulate cortical function in a non-invasive manner. For that reason, there is a great deal of interest in its potential applications in the fields of neurology and psychiatry (Alonzo et al., 2012; Demirtas-Tatlidede, Vahabzadeh-Hagh & Pascual-Leone, 2013; Elder & Taylor, 2014; Flöel, 2014; Kuo, Paulus & Nitsche, 2014; Dedoncker et al., 2016; Iannone et al., 2016). tDCS employs direct current to modulate neuronal excitability according to the polarity of stimulation: anodal stimulation has been found to increase neuronal excitability, whereas cathodal stimulation decreases excitability of the underlying cortical region (Javadi & Walsh, 2012). The technique of tDCS is not new (Priori, 2003), but the interest in it has just recently been renewed, after decades of oblivion. This was due to new discoveries in the field of neuroscience, including the development of TMS (Brunoni et al., 2010a).

Many studies are currently under way to explore possible applications of tDCS in the treatment of neuropsychiatric disorders; in one of those clinical trials, anodal tDCS has been performed in post-stroke aphasia with good results (Baker, Rorden & Fridriksson, 2010). In patients with Alzheimer's disease, anodal stimulation has led to improvements in declarative memory (Javadi & Walsh, 2012). Especially noteworthy, however, are the results obtained in normal subjects: tDCS to specific cortical areas has been shown to increase memory and learning. The effects are not only present during the stimulation period, but usually persist for hours to days after the stimulation session (Brasil-Neto, 2012). Moreover, repeated tDCS sessions have been found to extend the benefit to weeks, or even months, in several neuropsychiatric disorders (Alonzo et al., 2012; Dedoncker et al., 2016).

Although both TMS and tDCS show promise as potential non-pharmacological treatments for many neuropsychiatric disorders, tDCS is especially interesting due to its simplicity, low cost and portability. Thus, in view of the recent demonstration of beneficial effects of TMS in patients with MCI (Nardone et al., 2014; Drumond Marra et al., 2015), it would be interesting to verify whether tDCS would be able to produce similar results. MCI may be divided into amnesic and non-amnesic subtypes (Petersen & Negash, 2008; Petersen et al., 2014; Petersen, 2016). The amnesic subtype strongly predisposes the individual toward Alzheimer's disease (Petersen & Negash, 2008). Here we propose a study protocol to test for possible effects of anodal tDCS sessions targeting the left dorsolateral prefrontal cortex on memory of patients with the amnesic subtype of MCI. Since anodal stimulation increases cortical excitability, the rationale would be the same as that of applying high-frequency rTMS to the same cortical region, as in the study by Marra et al (Drumond Marra et al., 2015). The primary aim of this randomized controlled trial is to determine the effectiveness of 10 sessions of anodal left prefrontal cortex stimulation in improving everyday memory in patients with the amnesic subtype of MCI. In addition, patients will be retested at 1 and 3 months to verify the duration of any beneficial effects.

Methods

Design

A prospective, randomized controlled trial will be conducted with 80 community-dwelling participants with a diagnosis of MCI.

Participant selection

To be included in the study participants must meet the following inclusion criteria: (i) diagnosis of MCI; (ii) aged 60 to 90 years; (iii) educational level of 4 or more school years; (iv) duration of MCI symptoms of at least one year.

Participants will be excluded if they take any drugs acting on the central nervous system, if they have a history of neurological disorders, or if focal neurological deficits are present at examination.

Screening tests

Cognitive

All subjects will be tested for depression using the 17-item Hamilton Depression (HAMD-17) Scale (Hamilton, 1960; Depression & Scale, 2004), since depression can be a confounding factor in the diagnosis of MCI. The Clinical Dementia Rating (CDR)(Morris, 1993), Mini-Mental State Examination-2: EV(MMSE)(Folstein et al., 1975) and the Philadelphia Brief Assessment of Cognition (PBAC)(Pereira et al., 2012) will also be assessed. To evaluate everyday memory and its possible improvement with tDCS the Rivermead Behavioral Memory Test (RBMT)(Wilson et al., 1989), California Verbal Learning Test (CVLT)(Delis et al., 2000), Rey Auditory-Verbal Learning Test (RAVLT)(Schmidt, 1996; Malloy-Diniz et al., 2007), and Digit Span (WAIS-IV)(Wechsler, 2008) will be employed.

Medical and laboratory tests

All subjects will undergo a neurological examination and blood will be drawn for lab tests to exclude clinical secondary causes of dementia or cognitive deficits, such as hypothyroidism, AIDS, vitamin B12 and folate deficiency, and syphilis. Brain MRI scans will be obtained to exclude focal or lacunar ischemia, brain tumors, and hydrocephalus. Table 1 details the planned assessment schedule.

Randomization

After completion of the initial assessment, participants will be formally entered into the study and randomized to intervention or control group. Randomization will be done using computer-generated random numbers and will be performed by an investigator not involved in patient assessments. The same investigator will perform real and sham tDCS sessions.

Intervention group

The intervention group will undergo ten daily sessions of anodal tDCS targeting the left dorsolateral prefrontal cortex, five days a week, for two weeks. Stimulation will be delivered by a custom-made, battery-driven, direct current stimulator through electrodes embedded in sponges (area: 35 cm²) soaked with NaCl 0.9 %. The anode will be placed over F3 (10-20 EEG electrode positioning system) and the cathode over the contralateral supraorbital region. Current intensity will be kept at 1.5 mA and stimulation duration will be 20 min.

Control group

Patients in the control (sham) group will undergo the same procedure as the intervention group, but the current will be tapered off over 5 seconds after the initial 10 seconds ramp-up period. This maneuver will provide the subjects with the same initial tingling sensation experienced during a real tDCS session, but with no physiological effects.

Cognitive testing

Patients will undergo The Rivermead Behavioral Memory Test (RBMT) before the first tDCS session (baseline), after the first and second weeks of tDCS and at one and three months after treatment.

Outcome measures

The primary outcome measure will be RBMT scores. Secondary outcome measures will be the patient's self-reported memory improvement, if any, and complaints of possible tDCS side effects, as well as perception of having been subject to the real or to the sham procedure.

Statistical analysis

A two-way ANOVA will be used to compare test scores at baseline (T0), after 5 and 10 tDCS sessions (T1 and T2, respectively), and after 1 and 3 months' post-treatment (T3 and T4). Student's t test will be used to compare baseline mean scores for the intervention and control groups. Besides frequentist analysis, we also take advantage of Bayesian statistics to maximize information retrieval and possibly minimize the length of the trial and the number of patients studied in case of efficacy of the intervention.

Sample power estimation

Although Bayesian statistics may allow for a reduction in the required number of patients, a preliminary estimation of such number has been made. The sample size has been estimated with using GPower 3.1(Berry, 2004). Measurements will be evaluated comparing the RBMT test performance across time and intervention groups. The potential effect size of anodal tDCS sessions upon performance in the RBMT has been estimated from the findings of a previously published work in which MCI patients underwent 10 sessions of rTMS. Thirty subjects in each group will be required to achieve a power of 0.8 in detecting improvements with intervention. Taking into account the dropout rate of 25 %, 40 participants per arm should be recruited.

Discussion

tDCS has been able to improve performance of normal subjects in learning and memory tasks (Brasil-Neto, 2012). It remains to be seen whether patients with MCI would benefit from such an approach. The effects of tDCS tend to be relatively non-focal, but neurons actively engaged in a given task seem to be more prone to its effects, i.e., it is possible to achieve a certain degree of functional focalization by applying tDCS in conjunction with cognitive tasks. In fact, tDCS-linked working-memory has been found to provide long-term benefits in maintaining cognitive training benefits and extending them to untrained tasks in healthy older adults (Jones et al., 2015; Looi & Cohen Kadosh, 2015; Stephens & Berryhill, 2016). However, in a study with Alzheimer's patients, adding anodal tDCS to memory training did not result in a synergistic effect (Cotelli et al., 2014). In this regard, it is noteworthy that a protocol for studying the effects of tDCS combined with cognitive training in patients with mild AD has been recently published (Cheng et al., 2015). However, the authors intend to stimulate the left temporal cortex rather than the left dorsolateral prefrontal cortex. The great variability in tDCS montages, intensity of stimulation and targeted cortical areas across studies has hampered progress in its clinical application. Therefore, it is important that study protocols be published to allow a more efficient discussion of paradigms, aiming at improving study comparability. Should the present study demonstrate a beneficial effect of tDCS sessions upon RBMT scores in MCI patients, a study using the same stimulation paradigm combined with cognitive training would be warranted.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

ASA and JPB conceived the idea for the protocol. All authors contributed to the design and development of the trial protocol. ASA, JPB and AA drafted the manuscript. All authors critically reviewed and approved the final version of the manuscript.

Table 1

Assessment schedule.

	Baseline (T0)	First week (T1)	Second week (T2)	One Month (T3)	Three Months (T4)
Neurological exam	x				
Blood tests	x				
MRI	x				
CDR	x				
HAMD-17	x		x	x	x
MMSE-2:EV	x	x	x	x	x
PBAC	x	x	x	x	x
CVLT	x	x	x	x	x
RVALT	x	x	x	x	x
Digit Span	x	x	x	x	x
RBMT	x	x	x	x	x

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