Temporal cortex direct current stimulation enhances performance on a visual recognition memory task in Alzheimer disease

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Received 7 December 2007
Revised 20 May 2008
Accepted 17 June 2008
Published Online First
31 October 2008

ABSTRACT

Several studies have reported that transcranial direct current stimulation (tDCS), a non-invasive method of neuromodulation, enhances some aspects of working memory in healthy and Parkinson disease subjects. The aim of this study was to investigate the impact of anodal tDCS on recognition memory, working memory and selective attention in Alzheimer disease (AD). Ten patients with diagnosis of AD received three sessions of anodal tDCS (left dorsolateral prefrontal cortex, left temporal cortex and sham stimulation) with an intensity of 2 mA for 30 min. Sessions were performed in different days in a randomised order. The following tests were assessed during stimulation: Stroop, Digit Span and a Visual Recognition Memory task (VRM). The results showed a significant effect of stimulation condition on VRM ($p = 0.0085$), and post hoc analysis showed an improvement after temporal ($p = 0.01$) and prefrontal ($p = 0.01$) tDCS as compared with sham stimulation. There were no significant changes in attention as indexed by Stroop task performance. As far as is known, this is the first trial showing that tDCS can enhance a component of recognition memory. The potential mechanisms of action and the implications of these results are discussed.

The development of novel non-invasive methods of brain stimulation has increased the interest in neuromodulatory approaches as potential therapeutic tools for cognitive rehabilitation such as in Alzheimer disease (AD). Two techniques of non-invasive brain stimulation—transcranial magnetic stimulation and transcranial direct current stimulation—have been shown to induce cognitive improvements in healthy subjects[1–3] and patients with neuropsychiatric disorders such as major depression[4 5] and Parkinson diseases.[6 7]

Transcranial direct current stimulation (tDCS) is a simple, but powerful tool to modulate brain activity in which low-intensity currents (1 to 2 mA) are applied to the brain using two large saline-soaked sponge electrodes. The effects of tDCS are dependent on the current direction—whereas anodal stimulation increases cortical excitability, cathodal stimulation decreases it.

We therefore aimed to investigate the cognitive effects of tDCS in AD patients. We chose to assess visual recognition memory, working memory and selective attention, as the most affected cognitive domain in AD is declarative memory. This memory disturbance is related to the degree of brain atrophy especially that observed in medial temporal lobe involving entorhinal cortex and hippocampus, and also prefrontal areas.

METHODS

Subjects

We studied 10 patients (four men and six women) aged 70 to 92 years (table 1) that met criteria for AD as defined by the National Institute of Neurological Communicative Disorders and Stroke—Alzheimer disease and Related Disorders Association (NINCDS/ADRDA). Patients were excluded if they had other neuropsychiatric diseases. We included patients with a Mini-Mental State Examination (MMSE) between 12 and 25 points (the MMSE was adjusted to the level of education of this population).[8] The study was approved by the local and national research ethics committee (process approval number 0035.0.272.000-06; http://portal.saude.gov.br/sisnep).

Experimental protocol

At day 1, we collected demographic and clinical characteristics. Patients were then randomised to receive tDCS of the left temporal cortex, left dorsolateral prefrontal cortex (LDLPFC) and sham tDCS in a counterbalanced order, and were tested at day 2, 3 and 4, during sham and active conditions using VRM, Stroop, and Digit Span (order randomised across subjects). Testing started 10 min after stimulation onset and lasted until the end of stimulation. Each condition was separated by at least 48 h to wash out the effects of the previous run.

Transcranial direct current stimulation

Direct current was transferred by a saline-soaked pair of surface sponge electrodes (35 cm^2) and delivered by a battery-driven, constant current stimulator. To stimulate the LDLPFC, the anode electrode was placed over F3 according to the 10–20 international system for EEG electrodes placement. The left temporal cortex (LTC) was stimulated with an anode electrode placed over T7 (10–20 EEG system). For both conditions, the reference, cathode electrode was placed over the right supraorbital area.

Regarding the sites of stimulation (DLPFC and left temporal cortex), we chose DLPFC, as this area has been critically associated with working memory performance as shown by neuroimaging,[9] rTMS[10] and tDCS[3] studies—indeed this tDCS study showed that anodal tDCS improves working memory in healthy subjects.[3] Regarding the other

Table 1 Clinical and demographic characteristics

Subjects	Age (years)	Gender	Education (years)	Clinical Dementia Rating*	Mini-Mental State Examination	Hamilton Depression Scale	Duration of disease (years)	Medication
1	74	M	4	1	22	2	4	†
2	69	M	12	1	20	2	6	Pimozide, Bromazepam, Periciazine
3	85	F	4	2	12	1	6	†
4	92	F	8	1	13	0	9	Hydergine
5	88	F	16	1	15	7	5	†
6	70	F	4	3	13	6	2	Imipramine, Haloperidol, Clonazepam
7	72	F	4	3	14	0	2	Galantamine, Sertraline
8	80	F	8	3	13	8	4	Rivastigmine, Olanzapine
9	72	M	16	1	23	2	2	Clonazepam
10	89	M	11	1	25	2	5	Periciazine, Fluoxetine
Mean (SD)	79.1 (8.8)	6F/4M	8.7 (4.9)	1.7 (0.9)	17.0 (4.9)	3.0 (2.9)	4.5 (2.2)	

*Index as described by Montanõ and Ramos [16]: 0, normal; 0.5, questionable; 1, mild; 2, moderate; 3, severe.
†The medication column of this table reports neuropsychoactive medications only. Other medications such as for hypertension and heart disease are not indicated in this table. One point is that, besides the diagnostic of Alzheimer disease, some of these patients were not taking anticholinergic drugs. This is a result of difficult access to these drugs by some patients due to elevated costs.

area of stimulation—temporal cortex—the medial temporal cortex, including the hippocampus and adjacent cortical areas, is a critical area for long-term, declarative memory.[11]

For the active conditions, subjects received 2 mA tDCS for 30 min (with 10 s of ramp down and up). The same procedure was used for sham stimulation, but current was applied just for the first 30 s. This procedure is reliable to blind subjects for the respective stimulation condition.[12]

Neuropsychological assessment

Three cognitive domains were evaluated: selective attention, working memory and recognition memory. Selective attention was assessed by the Stroop test (Victoria version). Working memory was evaluated by the digit span test—backward and forward.

Recognition memory was assessed using a visual memory task specially designed for this purpose using the IBV software.[13] Patients were exposed during 10 s (encoding phase) to a screen containing two, four, six or eight pictures (figures of animals, persons and objects). They were then shown a single picture and instructed to respond as to whether this picture had been presented before (recognition phase). After a screen with two, four, six or eight stimuli, three, six, eight or 10 screens with one item (the response set) were presented, respectively. Two trials were performed for each condition (DLPFC, Temporal, or sham tDCS). We developed four alternative versions of this task and randomised them between group conditions to avoid learning. We also randomised the group conditions between the application days. We also had alternative versions for the Stroop and Digit Span test.

Data analysis

The primary outcome for this study was the number of correct responses on VRM task. The time to complete the Stroop task and backward and forward digit span were analysed as secondary outcomes. We analysed differences in task performance, as indexed by correct responses (VRM), time (Stroop), and score (digit span) following each condition (anodal

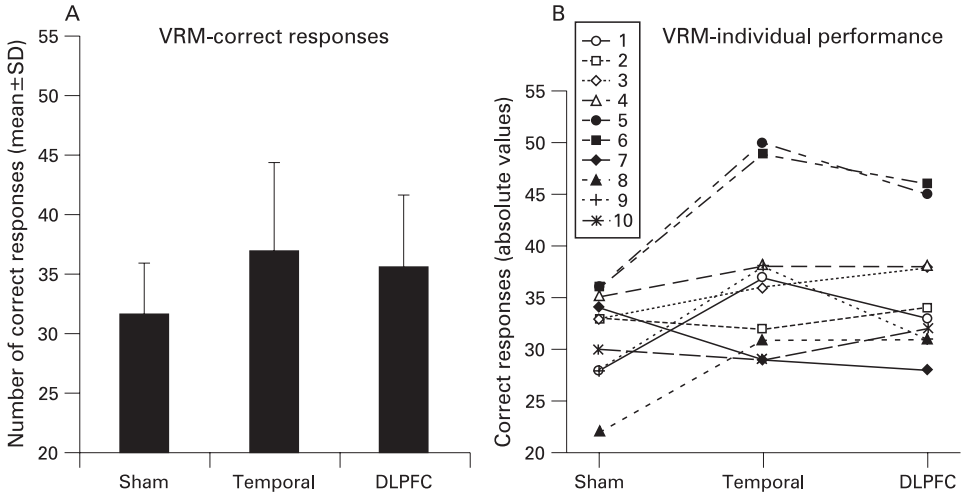

Figure 1 (A) Number of correct responses on the visual recognition memory task across groups (mean ± SD). (B) Individual performance (correct responses) during dorsolateral prefrontal cortex, temporal and sham transcranial direct current stimulation on the Visual Recognition Memory (VRM) task (note that order of stimulation was randomised across subjects).

LDLPFC, LTC and Sham stimulation). We performed an analysis of variance (ANOVA) to test whether there was an overall effect of the intervention (stimulation condition) on each primary outcome measure. When appropriate, we performed posthoc paired comparisons using Bonferroni correction for multiple comparisons. Results are expressed as mean (SD) unless otherwise stated. Statistical significance refers to a p value of <0.05.

RESULTS

Subjects tolerated treatment well. There were no adverse effects associated with a single application of tDCS.

The analysis of correct responses on VRM detected a significant difference across groups as shown on fig 1A. One-way ANOVA revealed that the main effect of stimulation condition was significant ($F_{(2,18)} = 6.28$; $p = 0.0085$). Posthoc comparisons revealed that there was a significant difference between temporal and sham ($p = 0.01$), and between prefrontal and sham ($p = 0.01$), but not between prefrontal and temporal ($p = 0.24$). Performances after temporal and prefrontal stimulation were 18.03% and 13.80% superior in comparison with sham stimulation, respectively (fig 1B). All groups increased the number of correct answers with the increase in memory set size.

The analysis of stroop and digit span did not reveal any significant difference between groups ($F<1$ for the three analyses—main effect of condition of stimulation). This lack of changes in the stroop test suggests that the improvement in VRM test was not due to a general effect on attention.

In order to understand if there was any correlation between the response to tDCS and AD severity, we performed a Pearson correlation between scores of the Clinical Dementia Rating (CDR) and the difference on performance (active—sham) for LTC and DLPFC tDCS. These tests showed no significant correlations ($p>0.5$ for both tests). Correlation plots of these analyses can be seen in figs 2, 3. Finally, we analysed whether age and use of anticholinergic drugs were associated with the outcome (VRM performance) adding these terms to the model. Analysis showed that both terms were not significant ($p>0.2$ for both terms).

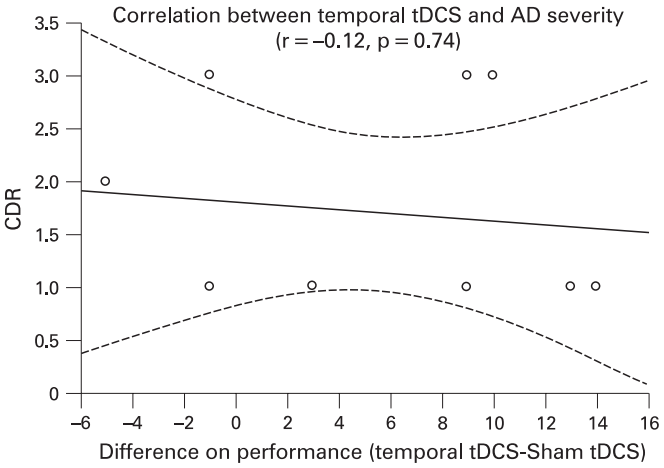

Figure 2 Correlation between difference on Visual Recognition Memory performance (temporal transcranial direct current stimulation (tDCS)—sham tDCS) and Alzheimer disease (AD) severity as measured by the Clinical Dementia Rating (CDR).

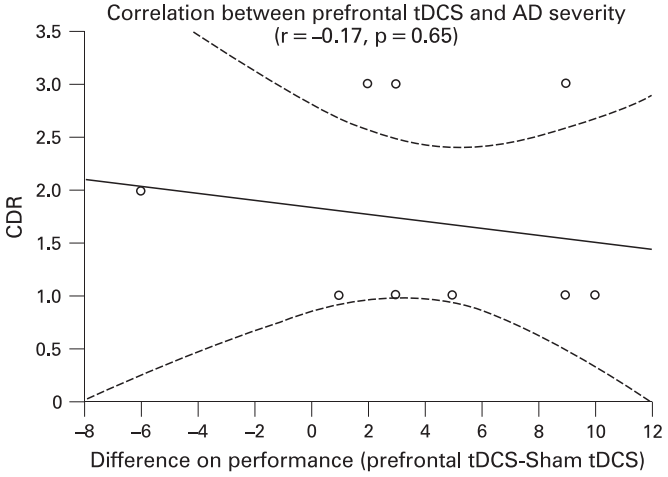

Figure 3 Correlation between difference on Visual Recognition Memory performance (prefrontal tDCS—sham tDCS) and Alzheimer disease (AD) severity as measured by the Clinical Dementia Rating (CDR).

DISCUSSION

The main finding of this study was an enhancement on a visual recognition memory task after tDCS of DLPFC and LTC as compared with sham stimulation.

The use of tDCS to improve some aspects of cognition has been investigated before. With respect to memory, Fregni *et al*[3] and Boggio *et al*[7] showed that tDCS over LDLPFC improves the performance of healthy volunteers and PD patients on a working memory task, respectively. The effects of tDCS might be related to a facilitation of this brain area induced by the anodal electrode, and as a consequence this neuronal network became more reactive during the encoding phase of the task. In this context, the effects of tDCS are task-dependent, as tDCS is only responsible for priming the area to receive additional behavioural intervention.

Although we found significant effects in the declarative memory task, we did not find any significant effects in the other test such as Digit Span (backward and forward), a task commonly used as a measure of working memory; this lack of effect could be explained by the low sensitivity of the digit span to the effects of tDCS, since previous studies showed a positive effect of this same technique on an n-back task.[3 7]

Importantly, we showed that our results are not because of an increase in attention—in other words, due to non-specific processes—as the results of the Stroop test show no significant changes after stimulation of both temporal and prefrontal cortex as compared with sham stimulation.

This study has several limitations. First, we used a bipolar montage (ie, two electrodes were placed in the scalp); therefore, the results observed in this study might be the result of the stimulation from the reference electrode. We chose to use bipolar, rather than monopolar (as described by Ferrucci *et al*[14] and Monti *et al*),[15] stimulation, as we showed in our previous study that bipolar stimulation is effective in improving working memory in healthy subjects.[3] A further step in this field is the investigation of monopolar stimulation in patients with AD. Second, although this study evaluated only a single session of tDCS, we did not measure whether the effects of our study were long-lasting and were observed on the next day of stimulation. In addition, we did not perform any other behavioural assessment to measure whether the effects observed in this study are clinically relevant.

Acknowledgements: The authors thank C Campanha and TM Rossi for support on data acquisition.

Funding: This work was supported by a grant from CNPq (401701/2007-7) to PSB. LPK was supported by a research grant from CNPq, São Paulo, Brazil (PIBIC—CNPq). DCSM was supported by a research grant from Mackenzie, São Paulo, Brazil (PIBIC—Mackenzie). ECM is supported by a CNPq grant (305356/2005-4). FF is supported by an AHA grant (0735535T).

Competing interests: None.

Ethics approval: Ethics approval was provided by the Institutional Ethics Committee from Mackenzie Presbyterian University, Brazil.

Patient consent: Obtained.

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J Neurol Neurosurg Psychiatry 2009 80: 444-447 originally published online October 31, 2008
doi: 10.1136/jnnp.2007.141853