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Prolonged visual memory enhancement after direct current stimulation in Alzheimer's disease

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Background
Immediately after patients with Alzheimer's disease (AD) receive a single anodal transcranial direct current stimulation (tDCS) session their memory performance improves. Whether multiple tDCS sessions improve memory performance in the longer term remains unclear.

Objective
In this study we aimed to assess memory changes after five consecutive sessions of anodal tDCS applied over the temporal cortex in patients with AD.

Methods
A total of 15 patients were enrolled in two centers. Cognitive functions were evaluated before and after therapeutic tDCS. tDCS was delivered bilaterally through two scalp anodal electrodes placed over the temporal regions and a reference electrode over the right deltoid muscle. The stimulating current was set at 2 mA intensity and was delivered for 30 minutes per day for 5 consecutive days.

Results
After patients received tDCS, their performance in a visual recognition memory test significantly improved. We found a main effect of tDCS on memory performance, i.e., anodal stimulation improved

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it by 8.99% from baseline, whereas sham stimulation decreased it by 2.62%. tDCS failed to influence differentially general cognitive performance measures or a visual attention measure.

Conclusions

Our findings show that after patients with AD receive anodal tDCS over the temporal cerebral cortex in five consecutive daily sessions their visual recognition memory improves and the improvement persists for at least 4 weeks after therapy. These encouraging results provide additional support for continuing to investigate anodal tDCS as an adjuvant treatment for patients with AD.

Keywords Alzheimer's disease; memory; tDCS; brain polarization

Alzheimer's disease (AD) is the most common cause of dementia in the elderly. A total 26.6 million people had AD in 2006 and by 2050 this number is estimated to increase four times owing to progressive population aging.[1] People with dementia live mostly in developing countries.[2] Given this scenario, investigating new therapeutic approaches for AD–especially low-cost therapies–is a critical need in medicine. Currently available AD medications have poor efficacy, are expensive, and induce adverse effects.[3] Mesial temporal lobe atrophy related to AD produces severe memory problems, especially episodic memory impairment.[4] AD typically begins with mild memory difficulties and the symptoms progress slowly toward severe impairment involving memory, executive function, visuospatial abilities, language, and other cognitive domains. Neuroimaging studies investigating mild cognitive impairment increasingly disclose memory circuit dysfunction in humans with AD and other memory disorders.[5] Because AD in its earliest stages affects the medial temporal lobe memory system, particularly the hippocampus and entorhinal cortex, numerous studies have focused on this brain region. By the time individuals are diagnosed clinically with AD dementia, the substantial memory impairments appear to be associated not only with medial temporal lobe atrophy but also with temporal lobe hypoactivation during the performance of memory tasks.[5]

Increasing evidence over recent years shows that memory performance improves after patients with AD receive transcranial direct current stimulation (tDCS), a neuromodulation technique that entails applying a weak direct current to the scalp.[6,7] In patients with AD, a single anodal tDCS session improves recognition memory as tested by a visual memory task[6] and by a verbal memory task.[7] What remains unclear is how many anodal tDCS sessions patients should undergo to obtain longer-lasting memory improvement. This information is essential for developing therapeutic protocols using this safe, noninvasive neurostimulation technique to improve memory in patients with AD or other neurodegenerative disorders.

We designed this study to investigate whether applying anodal tDCS over the temporal cortex in five consecutive daily sessions would prolong the cognitive improvement in patients with AD. To do so, as the primary outcome variable, we assessed visual recognition memory at various time points before and after therapy and 4 weeks after therapy ended.

Material and methods

Subjects

We selected 15 patients with AD diagnosed according to the National Institute of Neurology and Communication Disorder and Stroke-The Alzheimer's Disease and Related Disorders Association Criteria (NINCDS-ADRDA)[8] and the Diagnostic and Statistical Manual–IV (DSM-IV).[9] According to the DSM-IV, to be diagnosed with AD, subjects need to fulfill the following: memory impairment; one or more of the following cognitive disturbances (aphasia, apraxia, agnosia, impaired executive functioning); cognitive deficits causing severe impairment in social and occupational functioning; a gradually progressive disease course; and cognitive deficits not due to other neurologic (cerebrovascular disease, Parkinson's disease, Huntington's disease, subdural hematoma, normal-pressure hydrocephalus, brain tumor) or systemic conditions (hypothyroidism, vitamin B or folic acid deficiency, niacin deficiency, hypercalcemia, neurosyphilis, HIV infection, substance abuse) (Table 1).

The 15 subjects were recruited from two AD centers: eight subjects (group 1) were screened and recruited in the AD Center at the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy, and seven subjects (group 2) were recruited from the Estância Vale Verde, Sao Paulo, Brazil. The patients were screened by a team of experienced neurologists and neuropsychologists and underwent the appropriate diagnostic tests.

Participants were included in the study if their Mini-Mental State Examination (MMSE)[10] score was above 15 (the MMSE was adjusted to the population's educational level) and if they had no other neuropsychiatric diseases.

The study was performed according to the Declaration of Helsinki and approved by the local institutional review board. Patients and their caregivers gave their informed consent before participation.

Table 1 Demographic characteristics

	Italian patients	Brazilian patients	P^a
Number (n)	8	7	
Gender (males [%])	4 (50%)	4 (57.1%)	0.6
Duration of disease–y (SD)	5.0 (1.1)	3.7 (2.4)	0.20
Age–y (SD)	77.5 (6.9)	80.6 (9.5)	0.48
Education–y (SD)	13.3 (4.8)	15.7 (0.8)	0.21
MMSE (SD)	21.0 (3.2)	19.0 (2.8)	0.22
CDR – Classification (n)			
1	6	7	0.3
2	2	0	

[a] Student *t* test for the comparison of continuous variables and Fisher exact test for the comparison of categoric variables.

Experimental protocol

We investigated the effects of anodal tDCS applied daily to the temporal cortex for 5 consecutive days in the 15 patients with AD. We tested anodal and sham (i.e., placebo) tDCS, in separate experimental sessions. All subjects received both types of stimulation tested in random order and to avoid carry-over effects an average 71.1 ± 5.8 days (range: 60-151) elapsed between sessions. We collected demographic and clinical characteristics and then randomized patients in a counterbalanced order to receive active treatment first and sham second or vice versa. Cognitive functions were assessed at four time points: before the first tDCS session for each condition (real and sham) (T0), at the end of treatment day 5 (T1), 1 week later (T2), and then 4 weeks later (T3) (Figure 1).

tDCS

tDCS was bilaterally delivered with a constant direct current stimulator connected to three sponge electrodes, two placed on the scalp over the temporal lobes bilaterally and one placed over the right deltoid muscle. To avoid bias arising from the use of two electrodes with opposite polarities over the scalp, we used a noncephalic reference electrode. Scalp electrodes were positioned over T3 and T4 according to the 10-20 EEG international system. The electrodes used for tDCS were thick (0.3 cm), rectangular, saline-soaked synthetic sponges (each scalp electrode measured 35 cm^2 in area; the deltoid electrode measured 64 cm^2). The stimulus was anodal DC at 2 mA intensity delivered for 30 minutes (with 10 seconds for ramping up and down) over the temporal lobes bilaterally. The same procedure was used for sham stimulation, but current was applied only for the first 30 seconds. This procedure reliably blinds subjects for the respective stimulation condition.[11] All patients and raters were blinded to the type of tDCS delivered in each session but no index was calculated to measure blinding.

Cognitive assessment

Cognitive functions were evaluated with four different tasks: MMSE[10]; Alzheimer's Disease Assessment Scale-cognitive sub scale (Adas-Cog)[12]; a Visual Recognition Task (VRT)[6]; and a Visual Attention Task (VAT)[13] using the computer-controlled procedure Cog-lab Software Wadsworth (Wadsworth Publishing, Belmont, CA) to investigate whether tDCS induced specific changes in arousal or attention.

To screen patients with AD for cognitive impairment and dementia and to measure cognitive changes in response to tDCS therapy over time, we used the MMSE or Folstein test, a brief 30-point questionnaire commonly used for these purposes in medicine.[10]

To assess the intensity of cognitive and noncognitive changes typical of AD, we used the Alzheimer's Disease Assessment Scale (ADAS). The scale comprises two parts with a maximum score of 120 points. One part is cognitive (Adas-Cog), includes items 1-11 and has a maximum score of 70. The other part is noncognitive, assesses behavioral disturbances, includes items 12-21 and has a maximum score of 50. The main cognitive domains evaluated are memory (50%), language (28%), praxis (14%), and command understanding (8%).

Visual recognition memory was assessed using a visual memory task specifically designed for this purpose using IBV (software for the development of computerized

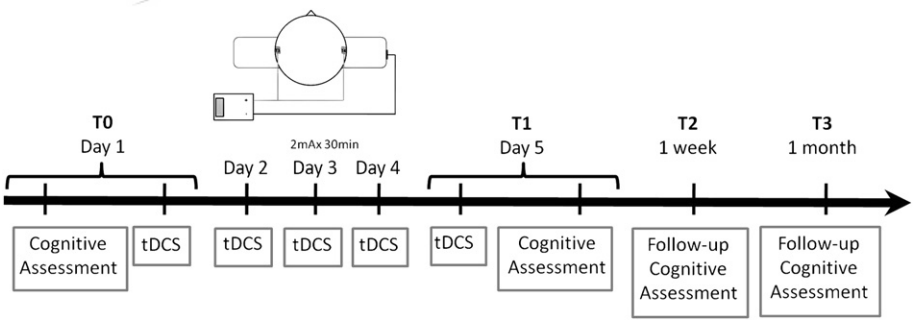

Figure 1 Experimental protocol for transcranial direct current stimulation (tDCS).

assessment tasks). The task comprised item encoding and recognition phases. It started with the encoding phase, two items, drawings of animals, persons, and objects, displayed on a computer screen for 10 seconds, followed 1 second later by the recognition phase, when patients were shown a single picture (test trial) and asked to say whether the picture had been presented before. Patients underwent this procedure eight times during the test. These eight encoding/recognition sequences included two study trials of two, four, six, and eight stimuli. Patients therefore studied a total 40 drawings during the test. Each study trial included test trials (recognition phase), three test trials were presented after each two-item study trial; six test trials after each four-item study trial; eight test trials after each six-item study trial; and 10 test trials after each eight-item study trial. To avoid learning, we developed alternative versions of this task and randomized them between assessment sessions.

For the VAT, we used an endogenous cue version of the Posner task.[13] In this task, patients responded to targets that appeared at one of two locations on either side of a fixation mark. Before the target appeared, one of these locations was cued so that subjects focused their attention on this location. This experimental procedure used three types of cues: valid cues, invalid cues, and neutral cues. Valid cues appeared on the same side as the target, invalid cues appeared on the side opposite the target, and neutral cues always appeared without the target. The patients were asked to answer by pressing the "b" key on the keyboard. We evaluated the total reaction time (RT) as the dependent variable.

Statistical analysis

For demographic characteristics, Student *t* test was used to compare continuous variables and Fisher exact test for categorical variables. To investigate the effects of anodal tDCS on cognitive functions, we ran a repeated measures analysis of variance (ANOVA) with scores on MMSE, Adas-Cog, and VAT as dependent variables and "stimulation" (two levels: anodal and sham), "time" (four levels: T0, T1, T2, and T3) and "gender" (two levels: male and female) as independent variables. For VRT, we ran a repeated measures ANOVA with the percentage change from baseline (T0) as the dependent variable and "stimulation" (two levels: anodal and sham), "time" (three levels: T1, T2, and T3), and "gender" (two levels: male and female) as the independent variables. Percentage variations in VRT test scores were used to control for baseline imbalance. When appropriate, a Bonferroni test for multiple comparisons was used for post hoc analysis. Because testing patients several times might have increased their understanding of the test structure thus influencing encoding and recognition strategies during the various assessment sessions to control for a possible learning effect, we ran a repeated measures ANOVA with percentage changes on VRT from baseline for all time points after treatment ended as the dependent variable and order (two levels: first or second time that the patients participated in the experiment regardless of whether they received active or sham tDCS) and time (three levels: T1, T2, and T3) as the independent variables. To investigate possible effects as a function of whether subjects received anodal tDCS first, we conducted a repeated measures ANOVA with the task performance at baseline and T3 (relative to sham tDCS) as dependent variables and order of stimulation (sham first or sham second) as a factor. Finally, exploratory repeated ANOVAs were run on three Adas-Cog memory subscales (Word Recall, Word Recognition, and Instruction Remembering). All data are presented as means $\pm$ SE. P values < 0.05 were considered to indicate statistical significance. Statistical calculations were done with Statistica (version 6.1, Stat-Soft Inc., Tulsa, OK).

Results

All 15 patients tolerated tDCS therapy well and none of them reported adverse effects. When we checked comparability by analyzing the patients' baseline performance on MMSE, VAT, and ADAS-Cog scales we found no significant differences between patients for any of the cognitive measures tested ($P > 0.05$) (Table 2). Nor were differences found in baseline VRT performance scores for each condition (Figure 2).

Repeated measures ANOVA detected no effects of the dependent variables MMSE, Adas-Cog, and VAT scores on tDCS, Time, Time*tDCS, Time*Gender, tDCS*Gender, or Time*tDCS*Gender for these three cognitive tasks (Table 3). Hence, no differential effect was found between active and sham tDCS for these variables. Conversely, repeated measures ANOVA disclosed a gender-related effect on VAT. This effect depended on slower RTs among women than among men (1043 $\pm$ 87 milliseconds, vs 613 $\pm$ 81 milliseconds) independently of the type of stimulation or evaluation session.

An exploratory repeated measures ANOVA testing the memory subscales (Word Recall, Word Recognition, and Instruction Remembering) run because Adas-Cog comprises several cognitive domains showed that tDCS had no significant effects on memory subscales (Table 4).

When we analyzed differences in VRT task performance indexed by the mean percentage change in correct responses at T1, T2, and T3 from baseline, we detected a significant main effect for tDCS performance changes from baseline: 8.99% after anodal and 2.62% after sham tDCS) (Figure 3). No significant effects were found for time, gender, and the interactions stimulation versus time, stimulation versus gender, gender versus time, or stimulation versus time versus gender.

The repeated measures ANOVA with scores on the task at T1, T2, and T3 as dependent variables and with tDCS (anodal and sham) and time (T1, T2, and T3) as the independent variables found no significant effects for stimulation ($P = 0.52$), time ($P = 0.78$), or the interaction stimulation versus time ($P = 0.49$).

Table 2 Performance on MMSE, VAT, and ADAS-Cog

	T0	T1	T2	T3
MMSE				
Anodal	20.3 ± 1.0	20.4 ± 1.2	21.3 ± 1.2	20.2 ± 1.1
Sham	19.2 ± 1.1	19.5 ± 1.3	20.2 ± 1.2	19.4 ± 1.1
VAT				
Anodal	865.5 ± 96.6	828.9 ± 83.2	843.8 ± 90.0	676.7 ± 90.0
Sham	868.0 ± 103.8	862.0 ± 89.4	826.8 ± 96.9	855.2 ± 96.7
ADAS-Cog-total				
Anodal	29.2 ± 2.5	28.0 ± 2.8	29.0 ± 3.1	28.4 ± 2.6
Sham	30.6 ± 2.6	30.4 ± 2.9	30.1 ± 3.2	30.0 ± 2.7
ADAS-Cog-subscales				
Word recall				
Anodal	8.3 ± 0.5	8.6 ± 0.4	8.6 ± 0.4	8.6 ± 0.4
Sham	9.1 ± 0.5	9.0 ± 0.4	9.0 ± 0.4	9.0 ± 0.4
Word recognition				
Anodal	7.2 ± 0.9	7.2 ± 0.9	7.4 ± 0.9	7.8 ± 0.9
Sham	9.4 ± 1.0	8.1 ± 0.9	6.9 ± 1.0	8.5 ± 0.9
Instruction remembering				
Anodal	2.4 ± 0.5	2.3 ± 0.6	1.9 ± 0.5	2.2 ± 0.4
Sham	2.1 ± 0.5	2.8 ± 0.6	2.4 ± 0.5	1.9 ± 0.5

Values are described as mean ± SEM.

The repeated measures ANOVA testing the possible influence of the order in which patients received anodal and sham tDCS with dependent variables task performance at baseline and T3 (relative to sham tDCS) as the dependent variables and order of tDCS (sham first or sham second) as a factor disclosed no significant effects because of order ($F_{1,12} = 0.08$; $P = 0.8$), time (no difference between baseline and T3) ($F_{1,12} = 1.30$; $P = 0.3$), or the interaction Time*Order of Stimulation ($F_{1,12} = 0.72$; $P = 0.41$) (Table 5). Nor did the repeated measures ANOVA controlling for a possible learning effect detect significant effects for order ($F_{1,28} = 1.615$; $P = 0.3$), Time ($F_{2.56} = 0.115$; $P = 0.9$), or the interaction Time*Order ($F_{2.56} = 0.701$; $P = 0.5$).

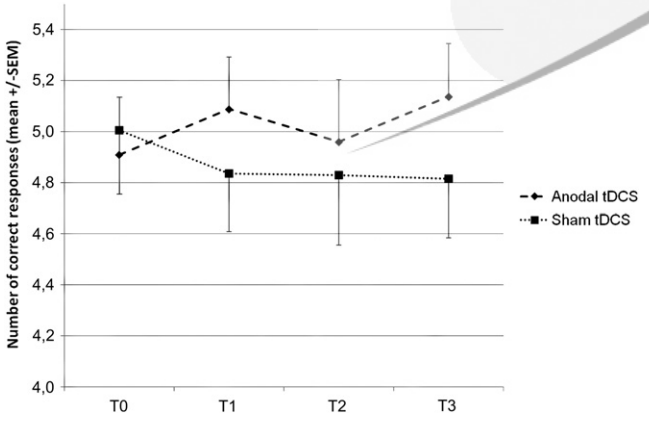

Figure 2 Mean accuracy of visual recognition task (VRT) at baseline (T0), T1, T2, T3 in the 15 patients with Alzheimer's disease tested. Error bars represent the SEM.

Of the 15 patients with AD we studied, eight were receiving cholinesterase inhibitors. ANOVA showed no significant interactions between covariate medication and outcome ($P = 0.08$) and its interactions with tDCS ($P = 0.35$) and tDCS*Time ($P = 0.9$) (Table 6).

Discussion

The main findings in this study are that visual recognition memory improved after patients with AD received anodal tDCS over the temporal cortex daily for 5 days and the improvement persisted for 4 weeks after neurostimulation therapy ended. We found no significant changes in Adas-Cog, MMSE, or a VAT tested after tDCS. This study therefore extends our previous findings showing significant improvement in recognition memory after patients with AD undergo a single session of temporal tDCS. We also extend previous findings by showing that in patients with AD these memory benefits last several weeks after therapeutic tDCS sessions end.

Providing evidence that the improvement in recognition memory depended only on changes induced by temporal anodal tDCS, in all the patients with AD we tested, recognition memory improved significantly more after anodal tDCS than after sham stimulation (8.99% versus 2.62% from baseline). And most important, 4 weeks after anodal tDCS sessions ended, patients recognition memory had improved by 11.4% from baseline. We therefore confirm results from previous studies, including those from our two laboratories,[6,7] showing that tDCS is a noninvasive neuromodulatory technique able to induce cognitive changes.

Table 3 F and *P* values of ANOVAs for the cognitive tasks

Cognitive task	Degrees of freedom	F	*P*
VRT			
Gender	1.26	3.782	0.06
tDCS		5.777	0.02
tDCS*Gender		2.343	0.14
Time	2.52	0.107	0.90
Time*Gender		0.003	>0.99
Time*tDCS		0.935	0.40
Time*tDCS*Gender		0.074	0.93
MMSE			
Gender	1.25	3.383	0.08
tDCS		0.474	0.50
Gender*tDCS		0.153	0.70
TIME	3.75	1.458	0.23
TIME*Gender		0.081	0.97
TIME*tDCS		0.039	0.99
TIME*Gender*tDCS		1.416	0.24
VAT			
Gender	1.24	12.925	0.001
tDCS		0.169	0.68
Gender*tDCS		0.103	0.75
TIME	3.72	1.797	0.16
TIME*Gender		2.031	0.12
TIME*tDCS		1.854	0.15
TIME*Gender*tDCS		0.985	0.40
ADAS-Cog			
Gender	1.25	0.221	0.64
tDCS		0.196	0.66
Gender*tDCS		0.027	0.87
TIME	3.75	0.164	0.92
TIME*Gender		0.677	0.57
TIME*tDCS		0.103	0.96
TIME*Gender*tDCS		2.431	0.07

Table 4 F and *P* values of ANOVAs for ADAS-Cog subscales

ADAS-Cog subscales	Degrees of freedom	F	*P*
Word recall			
Gender	1.25	0.0002	0.990
tDCS		0.821	0.373
tDCS*Gender		0.024	0.878
Time	3.75	0.184	0.907
Time*Gender		0.521	0.669
Time*tDCS		0.742	0.530
Time*tDCS*Gender		0.559	0.644
Word recognition			
Gender	1.25	4.06	0.055
tDCS		0.63	0.434
Gender*tDCS		0.59	0.451
TIME	3.75	1.42	0.245
TIME*Gender		1.74	0.166
TIME*tDCS		1.60	0.197
TIME*Gender*tDCS		1.66	0.184
Instruction remembering			
Gender	1.25	0.840	0.368
tDCS		0.029	0.867
Gender*tDCS		0.010	0.923
TIME	3.75	0.708	0.550
TIME*Gender		1.790	0.156
TIME*tDCS		1.056	0.373
TIME*Gender*tDCS		1.479	0.227

Although the results are encouraging, our study has several limitations. An important limitation is that for the analysis of VAT scores we only found a significant effect of group—indeed the interaction time versus group was not significant. This indicates that there was an overall difference between groups in post-tDCS assessments as compared with baseline when all post-tDCS time points were analyzed together. Though it is not possible to specify in which time points performance in VAT was different between the two groups. One reason to explain the lack of significance for the interaction effect was the small sample size and significant variability of VAT assessment. Future studies should assess other outcomes and larger sample sizes. The second limitation is that the cognitive improvement after patients with AD underwent tDCS was specific to visual recognition memory, and we did not investigate the cognitive effects induced by a single tDCS session day by day. Although we cannot yet say how the elicited changes in visual recognition memory will influence our patients' daily life, our study nonetheless encourages broader research protocols. One possibility for a further study is to explore whether this memory enhancement is lost over time and whether maintenance treatment with tDCS can preserve and perhaps increase the gains. Another limitation is that even though we conducted our study as a double-blind trial we did not explicitly assess whether subjects were truly blind to receiving tDCS or sham

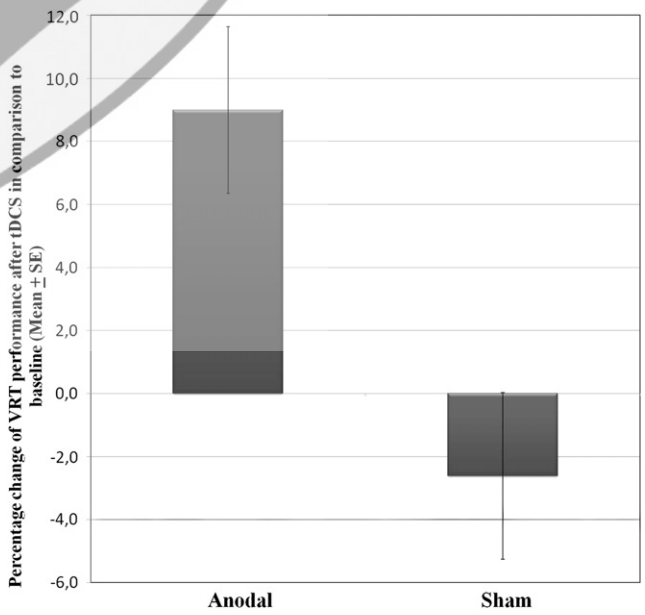

Figure 3 Percentage changes in visual recognition task (VRT) after anodal and sham stimulation in the 15 patients with Alzheimer's disease tested.

Table 5 Performance on VRT considering tDCS order

	Sham first/Anodal second		Anodal first/ Sham second	
	T0	T3	T0	T3
Sham	5.06 ± 0.31	5.02 ± 0.37	5.06 ± 0.27	4.78 ± 0.32
Anodal	4.73 ± 0.35	5.11 ± 0.25	5.06 ± 0.33	5.16 ± 0.24

Values are described as mean ± SEM.

stimulation. Our results could therefore in theory reflect participants' awareness of condition or nonspecific arousal. We nevertheless consider this possibility unlikely given that anodal tDCS left patients' performance in other cognitive tasks unchanged and affected VRT alone.

Another confounding factor in this study is that the worse performance observed in the placebo group may depend on the fact that some patients received active stimulation first. Again, testing effects seem unlikely given that the repeated measures ANOVA testing participants' performance in cognitive tasks at baseline and 1 month after tDCS placebo treatment ended showed no significant effect of order.

The tests we used to assess general cognitive functions and tests of attention, such as Adas-Cog, found no differences in scores related to tDCS. A possible explanation is that Adas-Cog measures several cognitive domains including memory, language, and praxis. Hence, this scale may be capable of detecting improvement for only a restricted range of severity levels.[14] Similarly, MMSE scores were similar between conditions, and although this instrument has also been widely used as an outcome measure in AD clinical trials, it is a poor outcome measure for AD drug trials because it was not designed to measure subtle changes in cognition.[14]

An important finding relevant to future technologic advances in therapeutic tDCS is that no adverse effects were recorded after five daily tDCS sessions, thereby extending previous data on the technique's satisfactory safety profile.[15] The absence of adverse effects is especially important given that our electrode montage used two active anodal electrodes. In addition, in normal subjects, magnetic resonance spectroscopy failed to detect changes in acetylaspartate, thus showing that anodal tDCS induced no neurotoxic effects.[16] Other neuroimaging studies indicate that anodal and cathodal tDCS protocols applied to the human brain neither induce structural changes in brain tissue nor cause alterations in the blood brain barrier.[17] In a study evaluating the effects of DC stimulation over the motor cortical area, serum neuron specific enolase (NSE)—a marker of neuronal damage—detected no noticeable changes in humans, thus indicating that DC stimulation induced no harmful effects.[18] These results were confirmed in a study evaluating the effects of DC stimulation over the spinal cord.[19]

Table 6 Performance on VRT considering the use of cholinesterase inhibitor medication

	Use of cholinesterase inhibitor medications	
	On	Off
Anodal	6.0 ± 5.3	12.4 ± 5.7
Sham	−0.7 ± 5.3	−4.8 ± 5.7

Values are described as mean ± SEM.

Though the memory effect we observed in patients with AD is small, it encourages research to develop better protocols for improved memory enhancement. For instance, tDCS applied twice a day effectively improves memory in patients with severe depression.[20] Prolonging tDCS treatment for 2 or 3 weeks may also boost the beneficial effects we observed after only 5 days in patients with AD. Further studies should evaluate memory improvement after tDCS combined with neuropsychologic intervention and rehabilitation or with pharmacologic treatments.

The mechanisms underlying tDCS-induced visual memory enhancement remain unclear. Anodal tDCS used over longer periods might interact with basic mechanisms involved in neurodegeneration (e.g., oxidative stress and gene expression) with potential beneficial (delayed deterioration) or unsought effects (accelerated deterioration). Along this line, prolonged tDCS treatment might prevent further memory decline by acting as a neuroprotective agent.

In conclusion, although further controlled studies with larger sample sizes and longer stimulation periods are needed, our results encourage continued research to investigate anodal tDCS as an adjuvant treatment for patients with AD.

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