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Older adults get episodic memory boosting from noninvasive stimulation of prefrontal cortex during learning

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Abstract

Episodic memory displays the largest degree of age-related decline, a process that is accelerated in pathological conditions such as amnesic mild cognitive impairment and Alzheimer's disease. Previous studies have shown that the left lateral prefrontal cortex (PFC) contributes to the encoding of episodic memories along the life span. The aim of this randomized, double-blind, placebo-controlled study was to test the hypothesis that anodal transcranial direct current stimulation (tDCS) over the left lateral PFC during the learning phase would enhance delayed recall of verbal episodic memories in elderly individuals. Older adults learned a list of words while receiving anodal or placebo (sham) tDCS. Memory recall was tested 48 hours and 1 month later. The results showed that anodal tDCS strengthened episodic memories, an effect indicated by enhanced delayed recall (48 hours) compared to placebo stimulation (Cohen's *d* effect size = 1.01). The observation that PFC-tDCS during learning can boost verbal episodic memory in the elderly opens up the possibility to design-specific neurorehabilitation protocols targeted to conditions that affect episodic memory such as mild cognitive impairment.

Keywords

tDCS; Aging; Encoding; Episodic memory; Prefrontal cortex

1. Introduction

Episodic memory refers to the recollection of personal experiences that contain information on what has happened and also where and when these events took place (Tulving, 1983).

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Disclosure statement

The authors have no conflicts of interest to disclose.

Appendix A. Supplementary data

Supplementary data related to this article can be found at the online version at <http://dx.doi.org/10.1016/j.neurobiolaging.2015.12.010>.

This form of long-term memory displays the largest degree of age-related decline (Ronnlund et al., 2005; Vestergren and Nilsson, 2010). Several studies in cognitive neuroscience of aging linked impairments of episodic memory to neurochemical, structural, and functional brain changes (Daselaar and Cabeza, 2008; Nyberg et al., 2012; Sala-Llloch et al., 2014).

This type of declarative memory is critical for daily life functioning, and its decline is accelerated in pathological conditions such as Alzheimer's disease (AD). AD is the leading cause of dementia, and the most prevalent neurodegenerative disease in the elderly. The prevalence of AD is predicted to rise as life expectancy grows across populations (Reitz and Mayeux, 2014). Because AD can produce tremendous chronic burdens on individuals, families, and health care systems around the world, the development of effective interventions to prevent or delay the onset of AD is an urgent priority (Buschert et al., 2011; Cotelli et al., 2012b). Early intervention appears to be more effective and research interests focus on prevention in amnesic mild cognitive impairment (aMCI) as precursors for AD (Kinsella et al., 2009; Petersen et al., 2009). The emerging categorization of aMCI is of great interest to try to identify people who are years away from showing traditional clinical symptoms and who may be well-suited for prevention studies.

Noninvasive brain stimulation (NIBS) techniques (Dayan et al., 2013; Parkin et al., 2015), such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), have been used for 2 purposes in the field of human memory: (1) to test the causal relationship between activity in specific cortical regions and memory function and (2) to test the general hypothesis that NIBS could modulate memory, an issue of relevance for research and neurorehabilitation (Sandrini and Cohen, 2013, 2014; Zimerman and Hummel, 2010).

There is evidence that NIBS influences motor (Zimerman et al., 2013) and cognitive functions (Hsu et al., 2015; Prehn and Floel, 2015) in physiological aging.

Clinical studies have shown that episodic memory is primarily dependent on the integrity of the medial temporal lobe, particularly the hippocampus (Dickerson and Eichenbaum, 2010). Functional neuroimaging (Fletcher and Henson, 2001) and NIBS studies (Brem et al., 2013; Manenti et al., 2012; Miniussi et al., 2003) have also emphasized the role of the lateral prefrontal cortex (PFC) in episodic memory processes. In addition, evidence from neuroimaging, neurophysiology, and computational modeling highlights the importance of interactions between these brain regions for memory function (Simons and Spiers, 2003).

NIBS studies have shown that the left lateral PFC contributes to verbal episodic memories along the life span (Blumenfeld et al., 2014; Brambilla et al., 2015; Floel et al., 2004; Gagnon et al., 2011; Innocenti et al., 2010; Javadi and Cheng, 2013; Javadi and Walsh, 2012; Kohler et al., 2004; Manenti et al., 2010a, 2011, 2013; Sandrini et al., 2003; Sandrini and Cohen, 2014).

Moreover, enhancement of verbal episodic memories has been reported in older adults after tDCS over the left lateral PFC (Manenti et al., 2013; Sandrini et al., 2014).

In particular, Manenti et al. (2013) found that anodal tDCS during the retrieval phase (5 minutes after the encoding session) enhanced memory in a words recognition task compared

to sham. Sandrini et al. (2014) applied tDCS 24 hours after the learning phase and showed that anodal stimulation strengthened existing memories, an effect indicated by enhanced delayed recall (24 hours) compared to sham.

However, it remains still unknown whether tDCS over the left lateral PFC during the encoding phase would enhance delayed recall on verbal episodic memories. For learning and memory formation, synchronized task- and stimulation-induced plasticity might be important. Here, stimulation might enhance task-related plasticity (Martin et al., 2014; Shin et al., 2015). To address this question is important because the development of an effective NIBS intervention requires knowledge of the best-suited timing of stimulation.

The aim of the present randomized, double-blind study was to test the hypothesis that anodal tDCS over the left lateral PFC during the learning phase would enhance delayed recall of verbal episodic memories relative to placebo (sham) stimulation in elderly individuals.

2. Material and methods

2.1. Participants

Twenty-eight healthy older individuals (17 females and 11 males; mean age = 68.9 years; mean education = 11.4 years) took part in the randomized, double-blind, placebo-controlled experiment. All the subjects had normal or corrected-to-normal vision and were native Italian speakers (see Table 1 for demographic details).

Participants reported being free of neurological and psychiatric disorders and had no history of seizures. All participants were informed about the procedures and the possible risks of tDCS, a written informed consent was obtained after a safety screening. The experimental methods got ethical approval from the local human ethics committee of Saint John of God Clinical Research Centre, IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy. Before being enrolled in the experiment, older subjects completed a Mini-Mental State Examination (Folstein et al., 1975) and a detailed neuropsychological evaluation to verify the absence of any cognitive deficit. A pathological score in one or more of the tests was an exclusion criterion. The neuropsychological test battery included measures used to assess nonverbal reasoning (Raven's Colored Progressive Matrices), verbal fluency (phonemic and semantic), visuospatial capacity (Rey-Osterrieth Complex Figure, Copy), upper-limb apraxia (De Renzi et al., 1980), and attention and executive functions (Trail Making Test A and B). Memory was assessed in depth (story recall, Rey-Osterrieth Complex Figure Recall, digit span, Auditory Verbal Learning Test, immediate and delayed recall). All the tests were administered and scored according to standard procedures (Lezak et al., 2004). In addition, we administered the Cognitive Reserve Index questionnaire, which provides a standardized measure of the cognitive reserve accumulated by individuals through their life span. The Cognitive Reserve Index questionnaire includes demographic data and items grouped into 3 sections: education, working activity, and leisure time, each of which returns a subscore and compose the total score (Nucci et al., 2012). See Table 1 for details.

2.2. Stimuli

We selected 20 concrete words from the “Corpus e Lessico di Frequenza dell'Italiano Scritto (CoLFIS)” (Laudanna et al., 1995). The words were chosen according to word length and to variables known to influence memory performance, that is, word frequency, familiarity, and imageability (see Appendix A for details). The selected words were highly imageable and concrete to ensure that participants knew all the words and were able to imagine them.

2.3. Task procedure and experimental design

The experiment consisted of 3 sessions on 3 different days (Fig. 1). Participants were informed that they would have to memorize a list of object words while receiving 15 minutes of tDCS. No information was given to participants regarding the recall sessions (48 hours and 1 month later).

On day 1, subjects were asked to learn a list of 20 object words (see Appendix A) while receiving tDCS (anodal or placebo) over the left PFC. This procedure was repeated until the participants remembered at least 17 of the 20 words (85%) or until a maximum of 5 learning trials was reached as done in a previous study (Sandrini et al., 2014). The experimenter pulled out one item at a time at random (a word written on piece of cardboard) from a white bag. Participants were asked to name each word, to pay close attention so they could remember the words later, and to place them in a blue bag. After all 20 words were placed into a blue bag, the experimenter took away this bag and asked the participants to remember as many words as possible. Before the next learning trial, the words were placed in the white bag again and mixed. The entire learning session took about 15–20 minutes to complete.

At the end of this experimental session, all the subjects were asked to fill in a “memory strategies questionnaire”. This questionnaire comprised a list of possible strategies that could be used during the task, and subjects had to assign a score from 1 to 10 (1 = never, 10 = always) to each strategy according to how often they had used each strategy during the task. The 12 listed strategies were: (1) to use words' initials, (2) to create sentences including some of the presented words, (3) to imagine the pictures corresponding to the presented words, (4) to repeat the words, (5) to create songs including some of the presented words, (6) to create rhymes between the displayed words, (7) to translate the words in a foreign language, (8) to create associations of words, (9) to create a brief story including the presented words, (10) to associate each word to a personal event, (11) to classify each word as easy or difficult, abstract or concrete, positive or negative, and so forth, (12) to imagine the words' sound, color, shape, and so forth, and (13) other strategies (Brambilla et al., 2015; Manenti et al., 2010b; Sandrini et al., 2014).

On day 3 and day 30 (respectively, 48 hours and 1 month after the learning and tDCS session), the experimenter asked the participants to recall as many words as possible from day 1, and the experimenter noted the remembered words. When participants indicated that they could not remember any more words, the experimenter engaged the participants in a figure copying task for about 30 seconds. The experimenter repeated the recall test by asking the participants to recall the words again. This procedure was repeated for a total of 4 consecutive recall trials to test reliability of recall as done in previous studies (Sandrini et al.,

2013, 2014). The recall session took about 15 minutes to complete. Intrusion errors were recorded in each day.

2.4. tDCS procedure

tDCS is a portable device which uses constant low-intensity current (usually between 1 and 2 mA) delivered directly to the cortical area for a duration of 15–20 minutes via 2 surface electrodes, anode and cathode (Dayan et al., 2013; Nitsche et al., 2008). tDCS is a neuromodulation technique and differs from TMS because it does not induce neuronal action potentials (Nitsche et al., 2008). tDCS modifies spontaneous neuronal excitability and activity by a tonic depolarization or hyperpolarization of resting membrane potential (Nitsche et al., 2008). Anodal tDCS applied to primary motor cortex generally increases cortical excitability as assessed by MEPs induced by TMS, whereas cathodal tDCS decreases cortical excitability (Nitsche et al., 2008). Regarding cognitive function, anodal tDCS applied to nonmotor areas often enhances behavioral performance, whereas cathodal tDCS does not necessarily impair performance (Jacobson et al., 2012).

A battery-driven stimulator (BrainStim, EMS, Bologna, Italy) delivered low and constant current through a pair of saline-soaked sponge electrodes ($5 \times 7 \text{ cm}^2$). A constant current of 1.5 mA was applied for 15 minutes (with a ramping period of 10 seconds at the beginning and at the end of the stimulation). The current density (0.043 mA/cm^2) was maintained below safety limits (Poreisz et al., 2007). The electrodes were secured using elastic bands, and to reduce contact impedance, an electroconductive gel was applied under the electrodes before the montage.

Fourteen subjects received anodal tDCS and 14 subjects received placebo (sham) tDCS stimulation over the left lateral PFC. The stimulation started 2 minutes before the learning session. For anodal stimulation over the left PFC, the anode was placed over F3 according to the 10-20 electroencephalogram international system for electrode placement, and the cathode was placed over the right supraorbital area as done in previous studies (Manenti et al., 2013; Sandrini et al., 2014). It has been shown that for F3 the main targeted region was Brodmann area 9 within the left lateral PFC (Herwig et al., 2003). In the placebo stimulation, the tDCS montage was the same, but the current was turned off 10 seconds after the beginning of the stimulation (plus the duration of the fade-in = 10 seconds) and was turned on for the last 10 seconds of the stimulation period (plus the duration of the fade-out = 10 seconds) (see Fig. 1).

The placement of the cathode electrode over the supraorbital region was motivated by the assumption that since this area is not specifically involved in memory processing, this electrode would not actively contribute to modulation. This montage, as all the conventional cephalic montages, delivered a diffuse current flow pattern involving both hemispheres and seems to be the better choice because the action of the current is more focused on the targeted area (Galletta et al., 2015).

Placebo or active tDCS was delivered after entering a number code to the device, and this step allows blinding of the operator before and during tDCS administration. Application time, current range, and frequencies are programmable, and settings can be saved on the

computer software. Active or placebo stimulation mode was chosen by manual entering different number codes in the computer and the stimulator was programmed via Bluetooth. These codes, delivered in the stimulator manual and distributed by the principle investigator, activated either placebo or active stimulation.

During placebo mode, the display imitated the settings of the active mode by simulating typical parameters of current strength, voltage, and impedance. The operator could not notice any difference between active and placebo stimulation.

Moreover, subjects felt the itching sensations below the electrodes at the beginning and at the end of the stimulation, making this condition indistinguishable from the experimental stimulation (Manenti et al., 2013). Potential tDCS side effects were assessed with a questionnaire administered at the end of the stimulation session. Immediately after the stimulation session, participants were required to evaluate intensity of several perceptual sensations (i.e., itching, pain, burning, heat, pinching, iron taste, fatigue, effect on performance) through a 5-point-scale (0 = none, 1 = mild, 2 = moderate, 3 = considerable, and 4 = strong) (Fertonani et al., 2015). Finally, the duration of the perceptual sensations was investigated (i.e., how long did it last? Did it stop quickly? Did it stop in the middle of the block? Did it stop at the end of the block?).

2.5. Statistical analyses

Demographic, neuropsychological variables, tDCS sensations, cognitive reserve and strategies used were compared between the 2 experimental groups using parametric (*t*-test) and nonparametric (Mann-Whitney test) analyses.

Analysis of variance (ANOVA) models for repeated measures were adopted to analyze the dependent variables individual mean percentage of words correctly recalled and mean number of intrusions according to the experimental design including one within factor, time (day 1, day 3, and day 30) and one between factor, group (anodal and placebo). Post hoc analysis was carried out using one-tailed independent *t*-tests comparing the 2 groups in each time (Bonferroni corrected for the number of comparisons, $p = 0.05/3 = 0.0166$). Statistical analyses were performed using Statistica software (version 10; www.statsoft.com).

3. Results

3.1. Sample characteristics

No differences in age ($Z = 0.41$, $p = 0.68$), education ($Z = 1.19$, $p = 0.23$), strategies used (anodal tDCS group: 7.6, standard deviation SD 3.6, placebo tDCS group: 8.2, SD 3.7; $Z = 0.28$, $p = 0.78$), and cognitive reserve ($Z = 0.16$, $p = 0.87$) were observed between the experimental groups (see Table 1). Furthermore, no differences in any other standardized neuropsychological tests were found.

Moreover, the sensations scores reported by the anodal tDCS group were similar to the sensations scores reported by the placebo tDCS group (anodal tDCS group: 1.2, SD: 0.6, placebo tDCS group: 1.0, SD: 0.5; $Z = 0.80$, $p = 0.42$). Hence, there were no reasons to reject the blinded character of this study on the basis of these results. By interpreting the

questionnaire completed by all subjects at the end of each type of stimulation, we inferred that all the subjects tolerated well the stimulation and reported only marginal perceptual sensations. Itching and irritation were the most commonly reported perceptual sensations, with light to moderate intensity. Overall, the experienced perceptual sensations started at the beginning of the experiment and quickly disappeared.

3.2. Task results

To compare the learning rate of the 3 experimental groups, we recorded how many learning trials (1–5) were necessary for each participant to recall at least 17 words (85%) on day 1. Participants who recalled <17 words during the fifth learning trial were given a score of 6. Participants needed on average 5.5 (SD: 0.9) learning trials to reach this criterion (anodal tDCS group = 5.7, SD: 0.6; placebo = 5.2, SD: 1.0). There were no significant differences between the 2 groups ($Z = 1.10$, $p = 0.27$). Furthermore, participants recalled on average 73.2% (SD: 12.6) of the words at the last learning trial (anodal tDCS group = 75.0%, SD: 7.1; placebo tDCS group = 71.4%, SD: 16.1). There were no significant differences between the 2 groups ($Z = 0.78$, $p = 0.43$).

The mean percentage of words correctly recalled was analyzed using an ANOVA with “group” (anodal and placebo) as the between subjects variable and “time” (day 1, day 3, and day 30) as the within-subjects variable.

The analyses showed significant effects for “time” [$F(2,52) = 123.27$, $p < 0.001$, $\eta_p^2 = 0.83$] and for the interaction between “group” and “time” [$F(2,52) = 3.37$, $p = 0.04$, $\eta_p^2 = 0.12$].

Interestingly, independent t -tests (Bonferroni corrected, $p < 0.0166$) showed difference between anodal and placebo stimulation at day 3 [placebo tDCS group: 34.5, SD: 17.7, anodal tDCS group: 52.1, SD: 17.1; $t(26) = 2.59$, $p = 0.007$, Cohen's d effect size = 1.01 (Soper, 2015)]. The anodal group recalled more words than the placebo group. No significant effect was found at day 30 (anodal tDCS group: 37.6, SD: 23.5, placebo tDCS group: 26.0, SD: 18.2; $t(26) = 1.41$, $p = 0.09$) (See Fig. 2).

To determine whether the facilitation effect at day 3 was due to reduced forgetting, we calculated for each participant the change in performance (delta) between the first recall test on day 3 and the last learning trial on day 1. Because recall performance generally increases across tests (Hupbach et al., 2007; Sandrini et al., 2013), the performance in the first recall test reflects a better measure of forgetting than the average performance of the 4 recall tests at day 3.

The t -test showed a significant reduction of forgetting in the anodal group relative to the placebo group (anodal tDCS group: -25.0 , SD: 14.6, placebo tDCS group: -37.5 , SD: 8.4; $t(26) = 2.67$, $p = 0.013$).

Intrusion errors were considered as mistakes and have been not computed in the total of corrected responses that composed the total score of each participant. The mean number of intrusions was analyzed with ANOVA with “group” (anodal and placebo) as the between subjects variable and “time” (day 1, day 3, and day 30) as the within-subjects variable.

The analyses showed significant effects for “time” [$F(2,52) = 17.18, p < 0.001, \eta_p^2 = 0.40$] and the interaction between “group” and “time” [$F(2,52) = 3.78, p = 0.03, \eta_p^2 = 0.13$].

Independent *t*-tests (Bonferroni corrected, $p < 0.0166$) did not show a significant difference between anodal and placebo stimulation at day 1, day 3, and day 30 (day 1: placebo tDCS group: 0.64, SD: 1.11; anodal tDCS group: 0.69, SD: 1.32, $t(26) = 0.01, p = 0.90$; day 3: placebo tDCS group: 0.93, SD: 0.88, anodal tDCS group: 1.92, SD: 1.33, $t(26) = -2.13, p = 0.04$; day 30: placebo tDCS group: 1.57, SD: 1.68, anodal tDCS group: 3.31, SD: 2.01, $t(26) = -2.29, p = 0.031$).

4. Discussion

The results of this randomized, double-blind, placebo-controlled study show for the first time that anodal tDCS over the left lateral PFC during verbal learning strengthened episodic memories and reduced forgetting up to 48 hours compared to placebo stimulation in elderly subjects. Importantly, this behavioral facilitation effect was not influenced by cognitive reserve accumulated in the life span and memory strategies measured with specific questionnaires.

Previous studies in older adults showed that anodal tDCS over the left lateral PFC enhanced recognition performance when applied during retrieval (Manenti et al., 2013) or enhanced delayed recall (24 hours) of existing memories when applied 24 hours after learning (Sandrini et al., 2014). In this study, we demonstrated an enhanced delayed recall (48 hours) obtained with the application of anodal tDCS during learning.

Interestingly, delayed free recall performance (offline effect), rather than the learning rate itself or number of words correctly recalled in the last learning trial (online effects), was enhanced by anodal tDCS, an effect evident 48 hours after the initial learning session. A better recall performance can be explained either as a more efficient encoding, which however did not manifest directly during learning phase, or as reduction of forgetting of the learned information.

There is also evidence that anodal tDCS applied during an object location memory task can improve delayed free recall in older adults (Floel et al., 2012). The results of this study reported no tDCS effects on the learning curve and on the immediate free recall (online) but enhanced delayed recall (after 1 week) compared to placebo (offline effect) (Floel et al., 2012). Similarly, in another study anodal tDCS was applied over the primary motor cortex on acquisition and retention of a motor skill-learning task in young individuals over the course of 5 days (Reis et al., 2009). The authors demonstrated that the relative increase of later performance in the anodal tDCS condition was selectively due to enhanced offline effects under anodal tDCS compared with placebo (Reis et al., 2009).

tDCS applied to the primary motor cortex also induced offline, but not online, polarity-specific changes in cortical excitability (Santarnecchi et al., 2014). Thus, the results obtained in our study are in agreement with the hypothesis that a consolidation mechanism is

susceptible to anodal tDCS and contributes to offline effects more than to online effects (Floel et al., 2012; Reis et al., 2009; Sandrini et al., 2014).

In addition, this study confirms the critical role of left PFC in the encoding of episodic memory along the life span (Blumenfeld et al., 2014; Innocenti et al., 2010; Javadi and Walsh, 2012; Rossi et al., 2001, 2004, 2011), and it supports previous data showing a positive effect of anodal tDCS on declarative memory in physiological aging (see Hsu et al., 2015 for a meta-analysis).

The neural mechanisms underlying the effects of tDCS on memory and learning are not yet understood and may involve changes in the neuromodulation efficacy of different neurotransmitters (Clark and Parasuraman, 2014; Dayan et al., 2013; Hunter et al., 2013). Interestingly, the induced excitability changes could persist after the end of the tDCS stimulation, with a duration varying as a function of tDCS parameters (Nitsche and Paulus, 2000). Both long-term potentiation and long-term depression have been postulated to explain these persistent effects (Cooke and Bliss, 2006; Thickbroom, 2007; Ziemann and Siebner, 2008) that are believed to occur at an intracortical level, perhaps mediated through N-methyl-D-aspartate receptor activity (Liebetanz et al., 2002; Nitsche et al., 2005). The long-term effects represent a crucial issue for the development of an effective intervention aimed at ameliorating cognitive deficits.

At the system-level, there is evidence that tDCS affects not only the targeted local region but also induces remote effects in regions (including subcortical) interconnected to the stimulated site (Pena-Gomez et al., 2012; Saiote et al., 2013; Stagg et al., 2013; Venkatakrishnan and Sandrini, 2012). Because variations in the strength of links between hippocampus and neocortex are at the heart of different studies in the field of system-level consolidation (Dudai, 2012), anodal tDCS over the left lateral PFC might have enhanced the functional coupling between the PFC and the hippocampus, thereby enhancing memory recollection. However, it is also possible that tDCS enhanced the functional efficacy of the PFC or promoted a feedback process that enhanced hippocampal activity in the absence of lasting change in PFC function or hippocampus–PFC connectivity. Regardless, the combination of tDCS with functional magnetic resonance imaging (Fox et al., 2014; Shafi et al., 2012) may shed light on how functional interactions between remote but interconnected brain regions may support the strengthening of episodic memories.

The relative small number of subjects represents a limitation to this study and it needs to be acknowledged. Further studies, based on larger samples, should be conducted to better investigate the long-lasting effects of this intervention. Another limitation of the present study is represented by the lack of a control stimulation site. This type of control condition is important to ensure that changes in memory performance are topographically specific. In addition to the best-suited timing of stimulation, location is another relevant variable for optimization of clinical treatment. Therefore, future studies should also investigate additional sites. For instance, there is evidence that stimulation of the posterior parietal cortex has positive effects on episodic memory (Cotelli et al., 2012a; Manenti et al., 2013; Wang et al., 2014).

In conclusion, these findings show that PFC-tDCS during learning induces beneficial effects on verbal episodic memory in physiological aging. Although further studies are needed to confirm the present results, the observation that NIBS can strengthen memory and reduce forgetting in the elderly opens up the possibility to design-specific neurorehabilitation protocols targeted to conditions that affect episodic memory such as aMCI.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1. Older adults learned 20 words on day 1 during 15 minutes of tDCS applied over the left DLPFC. Memory retrieval (free recall) was tested on day 3 (48 hours later) and day 30 (1 month later). Abbreviation: tDCS, trascranial direct current stimulation.

Fig. 2.

The plot shows the mean percentage of words correctly recalled in each group (anodal tDCS and placebo tDCS) at day 1, day 3, and day 30. Anodal tDCS enhances memory recall at day 3 (48 hours) relative to placebo tDCS. Error bars represent standard errors. Abbreviation: tDCS, transcranial direct current stimulation.

Table 1

Demographic characteristics and neuropsychological assessment of older individuals grouped according to experimental condition

Demographic characteristics and Neuropsychological assessment	Anodal tDCS (n = 14) ^a	Placebo tDCS (n = 14) ^a	Cut off	p-value
Age (y)	68.6 (4.2)	69.1 (3.4)		ns
Gender (male/female)	5/9	6/8		
Education (y)	12.4 (3.9)	10.4 (5.0)		ns
EHI	80.3 (12.1)	92.8 (11.7)		ns
Cognitive Reserve Index (CRI)				
CRI-total score	121.1 (17.5)	117.6 (20.8)		ns
CRI-education	113.3 (12.0)	106.1 (16.3)		ns
CRI-working activity	108.6 (13.3)	104.9 (19.6)		ns
CRI-leisure time	125.7 (26.5)	129.0 (22.5)		ns
Screening for dementia				
MMSE	29.1 (1.0)	29.1 (0.9)	24	ns
Nonverbal reasoning				
Raven-colored progressive matrices	30.4 (3.1)	29.4 (4.7)	>17.5	ns
Language				
Fluency, phonemic	40.6 (11.1)	41.1 (11.7)	>16	ns
Fluency, semantic	47.7 (6.8)	45.5 (9.0)	>24	ns
Memory				
Digit span	6.3 (0.7)	5.6 (0.9)	>3.5	ns
Story recall	14.1 (1.7)	13.5 (4.4)	>7.5	ns
AVLT (immediate recall)	47.0 (5.9)	43.9 (8.8)	>28.52	ns
AVLT (delayed recall)	9.9 (2.9)	9.3 (2.7)	>4.68	ns
Rey-Osterrieth complex figure, recall	15.1 (6.1)	13.7 (4.6)	>9.46	ns
Praxis				
Rey-Osterrieth complex figure, copy	32.4 (2.3)	32.0 (2.6)	>28.87	ns
De Renzi test-right upper limb	70.1 (2.0)	69.0 (2.1)	>52	ns
De Renzi test-left upper limb	70.6 (1.2)	70.4 (1.6)	>52	ns
Executive functions				
Trial Making Test-A (s)	40.8 (11.3)	36.9 (13.3)	<94	ns
Trial Making Test-B (s)	119.3 (50.5)	111.5 (42.0)	<283	ns

Cut-off scores according to Italian normative data are reported. *p*-value, comparison between the 2 experimental groups.

Key: AVLT, Rey Auditory Verbal Learning Test; EHI, Edinburgh Handedness Inventory; MMSE, Mini-Mental State Examination; ns, not significant; tDCS, transcranial direct current stimulation.

^aRaw scores are reported (standard deviation between blankets).