Effects of transcranial direct current stimulation on episodic memory in amnestic mild cognitive impairment: A pilot study

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Abstract (187 words)

Objectives. Episodic memory is impaired in amnestic mild cognitive impairment (aMCI), which is posited as a potential prodromal form of Alzheimer's disease. Reactivated existing memories become sensitive to modification during reconsolidation. There is evidence that the lateral prefrontal cortex (PFC) plays causal role in episodic memory reconsolidation. Transcranial direct current stimulation (tDCS) applied to the PFC after a contextual reminder enhanced episodic memory performance up to one month, conceivably through reconsolidation, in older adults with subjective memory complaints, a condition that may represent a "pre-MCI" stage.

The aim of this pilot study was to test the effect of PFC-tDCS (anode over left lateral PFC, cathode over right supraorbital area) after a contextual reminder on episodic memory in older adults with aMCI.

Method. Older adults with aMCI learned a list of words. 24 hours later, tDCS (active or sham) was applied after a contextual reminder. Memory retrieval (free recall and recognition) was tested 48 hours and one month after the learning session.

Results. Active tDCS enhanced recognition memory relative to sham stimulation.

Discussion. Modulating reconsolidation with PFC-tDCS might be a novel intervention to enhance episodic memories in aMCI.

Introduction

Alzheimer's Disease (AD) is a progressive neurodegenerative disorder characterized by several cognitive disturbances, the earliest and most prominent being impaired episodic memory, the ability to recall specific episodes from one's personal past (Tulving, 1983). What is new and exciting in AD research is the idea of prevention trials, such as helping healthy people reduce their risk of developing AD (primary prevention), or delaying the progression of amnestic mild cognitive impairment (aMCI) to AD (secondary prevention). aMCI is posited as a potential prodromal form of AD (Petersen, 2004).

Given the increased risk of developing AD in people with aMCI (Jessen et al., 2014), there is a strong argument for developing effective interventions aimed at reducing episodic memory decline in aMCI. Since pharmacological interventions have failed to show efficacy in clinical trials with aMCI (Karakaya, Fusser, Schroder, & Pantel, 2013), non-pharmacological interventions, such as transcranial direct current stimulation (tDCS), have received increasing attention. tDCS is a safe, painless and portable technique in which weak constant current, delivered through electrodes (anode and cathode) placed over the scalp, modulates cortical excitability by changing spontaneous neural activity (Dayan, Censor, Buch, Sandrini, & Cohen, 2013). Remarkably, the effects of tDCS outlast the stimulation period, sharing significant analogies to the synaptic phenomena of long-term potentiation (Fritsch et al., 2010).

Limited evidence suggests a potential role for tDCS in improving cognitive functions in MCI (Murugaraja, Shivakumar, Sivakumar, Sinha, & Venkatasubramanian, 2017). Using a concurrent fMRI-tDCS protocol, Meinzer et al. (2015) applied tDCS over the prefrontal cortex (PFC) during a semantic word retrieval task in aMCI patients. Semantic memory performance increased in the active tDCS condition, associated with reduced task-related lateral PFC hyperactivity and normalized resting state functional connectivity. Yun et al. (2016) reported that multiple sessions of active PFC-tDCS (3 sessions per week for 3 consecutive weeks) increased regional cerebral metabolism measured with positron emission tomography (PET). In addition,

subjective memory satisfaction and enhancement of memory strategies of aMCI patients were observed only in the active group after the multiple sessions of tDCS. Finally, a recent open-label study (Murugaraja et al., 2017) showed that active PFC-tDCS (5 consecutive sessions) enhanced immediate and delayed recall performance in a picture memory impairment test, with most of the facilitation effects persisting at 1 month follow‐up.

Accumulating evidence has shown that consolidated memories can return to fragile states when they are reactivated during retrieval or by a reminder cue (Dudai, 2012). The process that re-stabilizes the existing memories after their reactivation is known as memory reconsolidation (Sandrini, Cohen, & Censor, 2015). Importantly, during this time-limited reconsolidation window, existing memories can be modified (e.g., strengthened) through behavioral, pharmacological or noninvasive brain stimulation interventions (Sandrini et al., 2015). It has been shown that the PFC, a critical node in the episodic memory network (Manenti, Cotelli, Robertson, & Miniussi, 2012), plays a causal role in strengthening verbal episodic memories through reconsolidation, an effect only observed when the existing memories were reactivated during retrieval (Javadi & Cheng, 2013) or by a contextual reminder cue (Sandrini, Censor, Mishoe, & Cohen, 2013).

In healthy older adults, it has been shown that tDCS applied during intentional encoding (Antonenko et al., 2018; Floel et al., 2012; Medvedeva et al., 2018; Sandrini et al., 2016) or retrieval (Manenti, Brambilla, Petesi, Ferrari, & Cotelli, 2013) enhanced episodic memory performance. Other studies in the same population applied tDCS to enhance episodic memory performance through reconsolidation (Manenti, Sandrini, Brambilla, & Cotelli, 2016; Manenti et al., 2017; Sandrini et al., 2014). A subsequent study showed that a single session of tDCS applied over the PFC after a contextual reminder cue enhanced episodic memory recall up to one month in healthy older adults (Sandrini et al., 2014). A recent study with the same paradigm showed memory enhancement up to one month in recognition memory, but not recall, in older adults with subjective memory complaints (SMC) (Manenti et al., 2017; Sandrini et al., 2014). SMC may indicate a “pre-MCI” stage in the progression from normal aging to clinical AD. In addition, evidence from AD

transgenic model mice showed that disrupted reconsolidation might be involved in AD-related memory dysfunction (Ohno, 2009).

The main focus of this pilot study was whether active relative to sham tDCS applied over the PFC after a contextual reminder cue would enhance episodic memory in older adults with aMCI as measured by recall and recognition both after 48 hours and one month after the learning session.

As done in a previous study (Manenti et al., 2017), participants learned a list of 20 words on Day 1. 24h later (Day 2), tDCS (anode over left lateral PFC, cathode over right supraorbital area) was applied shortly after a contextual reminder cue. Memory retrieval was tested 48 hours (Day 3) and one month (Day 30) after the learning session (Day 1).

Based on our previous tDCS work showing enhancement in recognition memory up to one month in older adults with SMC (Manenti et al., 2017), we hypothesized that active tDCS would enhance recognition memory up to one month relative to the sham tDCS in older adults with aMCI.

Methods

Participants

Between January 2017 and April 2018, older adults with aMCI were recruited at the MAC Memory Center of IRCCS Fatebenefratelli of Brescia (Italy). All participants were living independently in the community at the time of their baseline evaluation and were followed up annually during at least the 2 years before the recruitment in the present study.

The sample size calculation was based on our previous study using the same paradigm in SMC (Manenti et al., 2017) with an effect size of 1.49 (Cohen's d) for memory recognition performance (hits-false alarms rate) at Day 30, a significance level (α) of 0.05 and power ($1-\beta$)=80 (two-tailed independent t-test). The estimated sample size was nine participants for each group.

The sample included eighteen older adults (mean age 75.3 ± 3.7 years; mean education level 7.7 ± 3.3 years; mean monitoring period prior inclusion 37 ± 11 months) fulfilling the Petersen (Petersen, 2004) criteria for aMCI. All of the participants had normal or corrected-to-normal vision,

were native Italian speakers and were characterized by: a) subjective memory complaints; b) preservation of general cognitive functioning documented by Mini Mental State Examination (MMSE) score between 24 and 30 (Folstein, Folstein, & McHugh, 1975); c) global Clinical Dementia Rating score of 0.5; d) predominant episodic impairment on a standard neuropsychological test (i.e. story recall; Rey Auditory Verbal Learning Test, recall; Rey-Osterrieth Complex Figure, recall); e) preservation of functional activities; f) absence of criteria for a diagnosis of dementia according to DSM-V (American Psychiatric Association, 2014); g) absence of mood and anxiety disorders.

Participants were excluded from the study if they had: a) other prior or current neurological or major psychiatric disorders; b) history of traumatic brain injury, brain tumor or stroke; c) a history of alcohol abuse; d) any contraindication to tDCS such as presence of pacemakers, aneurysm clips, artificial heart valves, ear implants or foreign metal objects and history of seizures. Moreover, brain magnetic resonance imaging (MRI) performed within the 6 months before inclusion in the study was required to exclude patients with focal lesions, including brain tumor, subdural hematoma, stroke, central nervous system infection, multiple lacunar strokes, or extensive white matter hyperintensities.

Prior to being enrolled in the study all participants were informed about the study and the possible risks of tDCS and signed a written informed consent after a safety screening. The local Human Ethics Committee of IRCCS Fatebenefratelli of Brescia (Italy) approved the protocol and it was conducted in accordance with the Declaration of Helsinki.

Clinical and functional assessment

Baseline assessment, performed by trained clinicians, included family history of dementia, record of medical events, current medication and complete neurologic examination. The Clinical Dementia Rating scale (CDR) was completed. The evaluation of subjective memory complaints was conducted using the 20-item version (range: 20-180) of the Everyday Memory Questionnaire

(Calabria et al., 2011). Functional abilities were evaluated using basic (BADL) and instrumental activity of daily living (IADL) scales (Katz, 1983; Lawton & Brody, 1988). Depression was assessed by the 30-item version of the Geriatric Depression Scale (GDS - Yesavage et al., 1983) and anxiety by the State-Trait Anxiety Inventory (STAI - Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983).

Neuropsychological assessment

In addition to clinical and functional assessments, all participants were tested at inclusion by a standardized neuropsychological battery. Cognitive tests were selected to assess a broad range of cognitive abilities commonly affected by aging and MCI. The battery took approximately 90 minutes and included Mini Mental State Examination (MMSE) (Folstein et al., 1975) for assessment of global cognition, Raven's Colored Progressive Matrices for nonverbal reasoning, verbal fluency (phonemic and semantic) for language production, Token Test for language comprehension, Rey–Osterrieth Complex Figure Copy for visuo-constructional abilities, Trail Making Test part A and part B for attention and executive function, Auditory Verbal Learning Test (AVLT), immediate and delayed recall, and Story Recall for verbal episodic memory, Rey–Osterrieth Complex Figure Recall for non-verbal episodic memory and Digit Span for verbal short term memory. Moreover, participants completed the Cognitive Reserve Index questionnaire (CRIq) in order to obtain a standardized measure of the cognitive reserve accumulated by individuals across their lifespan (Nucci, Mapelli, & Mondini, 2012).

The results of all these assessments are reported in Table1 for the two tDCS groups.

Procedure

The present work was a randomized, double-blind, sham-controlled study. Participants and the study team members did not know the tDCS condition applied at any point in the experiment. Patients were randomized into two groups: *a)* active tDCS (anode over the left lateral PFC –cathode

over right supraorbital area) or *b)* sham tDCS. The tDCS group assigned to each participant was obtained by stratified randomization according to MMSE and age. Stratified randomization is achieved by generating a separate block for each combination of covariates and participants are assigned to the appropriate block of covariates by a researcher blinded to the study aims. Details of the allocated group were given on cards contained in sequentially numbered, opaque and sealed envelopes.

The study protocol was executed with no changes from the beginning.

tDCS

A tDCS stimulator (BrainStim, EMS, Bologna, Italy) delivered constant low intensity (1.5 mA) current for 15 minutes through two saline-soaked sponge electrodes (7 cm x 5 cm, current density: 0.043 mA/cm^2) (Antal et al., 2017; Bikson et al., 2016). The electrodes were secured using elastic bands, and to reduce contact impedance, an electroconductive gel was applied under the electrodes before the montage (Manenti et al., 2013; Sandrini et al., 2014; Sandrini et al., 2016). Active or Sham stimulation mode was selected by entering different codes so that the experimenter that applied tDCS did not know the type of stimulation applied.

The targeted region was the PFC: the anode electrode was placed over F3 (left lateral PFC) and the cathode electrode was located over Fp2 (right supraorbital) according to the 10-20 EEG international system as in previous studies (Manenti et al., 2013; Sandrini et al., 2014; Sandrini et al., 2016). The anode was placed over F3 with the long side parallel to the sagittal line, while the cathode was positioned above the arcus superciliaris on the right with the long side of the rectangular pad parallel to the horizontal line (DaSilva, Volz, Bikson, & Fregni, 2011).

See Figure 1 for a graphical representation of the computerized modeling of tDCS-induced current flow in the brain (Soterix Medical https://soterixmedical.com). In the Active tDCS, the current was applied for 15 minutes (with a ramping period of 10 seconds (s) at the beginning and at the end of the tDCS session). In sham tDCS condition, the current was turned off 10 s after the beginning and

was turned on for 10 s at the end of the stimulation period so that the participants could not distinguish between Active and Sham stimulation (Manenti et al., 2013). Sensations induced by tDCS were assessed immediately after the stimulation session. Perceptual sensations induced by the active and sham tDCS conditions were assessed with standardized questionnaire developed by Fertonani, Ferrari and Miniussi (2015). Participants were asked to evaluate the intensity of seven perceptual sensations (i.e. itching, pain, burning, heat, pinching, iron taste, fatigue) on a 5-point-scale (0=none, 1=mild, 2=moderate, 3=considerable, and 4=strong). This questionnaire provides an evaluation of the general perceived discomfort induced by tDCS. The total score ranges from 0 to 28.

Experimental memory task

We applied the experimental protocol used in our previous study with older adults with SMC (Manenti et al., 2017; Sandrini et al., 2014). There were four sessions on four different days: Day 1 (learning session), Day 2 (24 hours after Day 1), Day 3 (48 hours after Day 1) and Day 30 (one month from Day 1). Patients were informed about the learning phase on Day 1 and about the tDCS session on Day 2, but no information on the retrieval sessions were provided. Participants returned to the institute on Day 3 and Day 30 without expecting a memory test since when contacted for the present study the two visits on Day 3 and on Day 30 were not described as directly linked with the experimental memory procedure conducted on Day 1. See Figure 1 for a summary.

Day 1 – learning session

Twenty concrete (concreteness value >5.5), high frequency (Frequency value > 20) two- or three-syllabic words were selected (Barca, Burani, & Arduino, 2002; Bertinetto et al., 2005). On average, the words were 6.3 (SD: 1.0) letters and 2.5 (SD: 0.5) syllables long, word frequency was 24.5 (SD: 23.2), imageability was 5.9 (SD: 0.31) and concreteness scores 6.3 (SD: 0.5).

The experimenter pulled out one item at a time at random (a word printed on piece of card)

from a white bag and gave it to the participants. Participants were asked to pay close attention so they could remember the words later and to place them in a blue bag when ready. When all 20 words were placed into a blue bag, the experimenter took away this bag and asked the participants to recall as many words as possible. Before the next learning trial, the words were placed in the white bag again and mixed. The procedure was repeated five times. At the end of this session participants were asked to complete a memory strategies questionnaire (Manenti, Tettamanti, Cotelli, Miniussi, & Cappa, 2010), which comprises 12 possible strategies that can be used to enhance the learning of information. Participants rated how often they had used each strategy during the learning session using a 5-point-scale (0, never; 1, rarely; 2, sometimes; 3, often; and 4, always). The total score of this questionnaire ranges between 0 and 52.

Day 2 – reactivation and tDCS session

Twenty-four hours later, the same experimenter involved in Day 1 in the same experimental room, showed the empty blue bag and asked, "Do you remember this blue bag and what we did with it yesterday?" Participants were encouraged to describe the procedure, but were stopped if they started to recall any specific words. tDCS (Active or Sham) was applied 10 minutes after the contextual reminder cue as in previous studies (Manenti et al., 2017; Sandrini et al., 2014; Sandrini et al., 2013). It has been shown that existing episodic memories are automatically reactivated if the original spatial context (i.e. same experimental room of Day 1) is part of the reminder (Hupbach, Hardt, Gomez, & Nadel, 2008; Sandrini et al., 2013).

Day 3 and Day 30 – retrieval sessions

Forty-eight hours (Day 3) and one month (Day 30) after the learning session (Day 1), the experimenter asked the participants to recall the words learned during Day 1 (free recall task) and when participants could not remember any more words, the experimenter engaged the participants in an old/new recognition task that consisted in the written randomized presentation of the 20

learned words along with 20 new words (two different lists of new words at Day 3 and Day 30). Target words encoded on Day 1, new words displayed at Day 3 and new words used at Day 30 were balanced according to word length and to variables known to influence memory performance. There were not significant differences between the three lists with respect to "concreteness" (Target words= 6.3 ± 0.5; new words at Day 3= 5.8 ± 0.8; new words at Day 30= 5.9 ± 0.8; $p > 0.05$), "imageability" (Target words= 5.9 ± 0.3; new words at Day 3= 5.7 ± 0.7; new words at Day 30= 5.7 ± 0.5; $p > 0.05$), "word frequency" (Target words= 24.5 ± 23.2; new words at Day 3= 25.9 ± 31.2; new words at Day 30= 35.1 ± 25.8; $p > 0.05$), length in letters (Target words= 6.3 ± 1.0; new words at Day 3= 6.5 ± 1.9; new words at Day 30= 5.9 ± 1.4; $p > 0.05$) or in syllables (Target words= 2.5 ± 0.5; new words at Day 3= 2.75 ± 0.7; new words at Day 30= 2.4 ± 0.5; $p > 0.05$) based on "Corpus e Lessico di Frequenza dell'Italiano Scritto (CoLFIS)" and "LEXVAR" (Barca et al., 2002; Bertinetto et al., 2005; Laudanna, Thornton, Brown, Burani, & Marconi, 1995). The assignment of the three words lists to the three conditions (Target words on Day 1, new words at Day 3 and new words at Day 30) was fixed across participants.

Statistical analyses

Demographic, clinical and neuropsychological characteristics, sensations induced by tDCS, cognitive reserve, subjective memory complaints and memory strategies used were compared between the active and sham groups using Mann–Whitney U test. We analyzed d' and C to estimate detection sensitivity and decision criterion in the recognition task. In particular, ANOVA models were adopted to analyze the dependent variables percentage of correctly recalled words (free recall task) and d' and C criterion (recognition task) at Day 3 and Day 30 including one within-subjects variable "Time" (Day 3 and Day 30) and one between-subjects variable "Group" (Active tDCS and Sham tDCS). Statistical analyses were performed using Statistica software (version 10; www.statsoft.com). Statistical power and Effect Sizes (Cohen's d) analyses were estimated using GPower 3.1 (Faul, Erdfelder, Lang, & Buchner, 2007).

Results

Sample characteristics

All the 18 MCI participants included in the study completed all the assessments. Overall, the participants showed isolated episodic memory impairment, as recorded by scores below cut-off according to Italian normative data (1.5 SD under performance of matched controls) in at least one of the following standardized tests: Auditory-Verbal Learning Test (Carlesimo et al., 1995), recall of Rey-Osterrieth Complex Figure (Caffarra, Vezzadini, Dieci, Zonato, & Venneri, 2002) or Story recall (Novelli, Papagno, Laiacona, Vallar, & Cappa, 1986). On the other hand, they performed in the normal range in other cognitive domains such as reasoning, visuo-constructional abilities, language and executive functions.

No differences were found between groups for demographic variables and for neuropsychological assessment. Moreover, no differences were observed between the Active and Sham groups for cognitive reserve (U=39.5, p=0.96), GDS (U=33.5, p=0.57), STAI - State (U=39.0, p=0.93), STAI - Trait (U=26.0, p=0.22) and EMQ (U=36.0, p=0.72). See table 1 for details. No differences were found between the Active and Sham groups in the strategies questionnaire (Active tDCS group: 3.7 (2.1), Sham tDCS group: 4.6 (3.3); U=37.0, p=0.79). Finally, the tDCS sensations scores reported by the Active and Sham groups were similar (Active tDCS group: 1.4, SD 1.1, Sham tDCS group: 1.0, SD 0.9; U=30.0, p=0.38). Hence, there are 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 the stimulation well 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 did not last long.

Experimental memory task

There were no significant differences in the percentages of words correctly recalled after the last learning trial of Day 1 between the Active and Sham groups (Active= 27.8%, SD 8.3; Sham= 34.4%, SD 11.0; $t(16)=-1.45$, $p=0.17$, Cohen's $d=0.67$, $1-\beta=0.27$), showing that the two groups are relatively equal in baseline word recall performance.

We analyzed changes on memory performance (recognition and free recall) at different time points (Day 3 and Day 30) using ANOVA with "Group" (Active and Sham tDCS) as the between-subjects variable and "Time" (Day 3 and Day 30) as the within-subjects variable.

The analysis of d' on recognition task showed a significant effect for "Group" ($F(1,16)=4.75$, $p=0.044$, $\eta p^2=0.23$, $1-\beta=0.89$), indicating better performance in Active tDCS group compared to Sham Group, and a significant effect of "Time" ($F(1,16)=6.60$, $p=0.020$, $\eta p^2=0.29$, $1-\beta=0.96$), showing a decrease of performance from Day 3 to Day 30. The interaction between "Group" and "Time" did not reach the significance ($F(1,16)=0.009$, $p=0.922$, $\eta p^2=0.0006$, $1-\beta=0.01$). The analysis on C criterion on recognition task did not show any significant effect on "Group" ($F(1,16)=0.348$, $p=0.563$, $\eta p^2=0.02$, $1-\beta=0.01$), "Time" ($F(1,16)=0.049$, $p=0.826$, $\eta p^2=0.003$, $1-\beta=0.01$) and the interaction between "Group" and "Time" ($F(1,16)=1.18$, $p=0.293$, $\eta p^2=0.07$, $1-\beta=0.03$). In Table 2 we reported d' and C values from the Recognition Task. The analysis of percentages of words correctly recalled showed only a significant effect of "Time" ($F(1,16)=4.94$, $p=0.041$, $\eta p^2=0.24$, $1-\beta=0.99$), showing a decrease of performance from Day 3 to Day 30. "Group" ($F(1,16)=0.25$, $p=0.626$, $\eta p^2=0.02$, $1-\beta=0.01$) and the interaction between "Group" and "Time" did not reach the significance ($F(1,16)=0.37$, $p=0.553$, $\eta p^2=0.02$, $1-\beta=0.01$; Active tDCS: Day 3 3.3%, SD 4.3; Day 30 1.1%, SD 3.3; Sham tDCS: Day 3 5.0%, SD 7.1; Day 30 1.1%, SD 2.2).

In summary, active tDCS enhanced recognition but not free recall relative to sham tDCS. In Figure 2 we showed the d' values from the recognition task in the Active and Sham groups at Day 3 and Day 30.

Discussion

This study shows for the first time that active tDCS applied over the PFC after a contextual reminder cue enhanced recognition memory, relative to sham tDCS, in older adults with aMCI. Importantly, there were no differences between groups in the memory strategies and number of words correctly recalled after the last learning trial of Day 1.

Our findings also support previous work suggesting a potential facilitation effect of tDCS on memory function in MCI (Meinzer et al., 2015; Murugaraja et al., 2017; Yun et al., 2016).

As in our previous study in older adults with SMC (Manenti et al., 2017), the results of the current study show that recognition memory, rather than free recall, was enhanced by active tDCS. The effect of active tDCS might be related to a facilitation of accessibility of the memory trace. Most studies have described episodic memory impairment in MCI using both free recall and cued recall (Belleville, Sylvain-Roy, de Boysson, & Menard, 2008; Ivanoiu et al., 2005; Perri, Carlesimo, Serra, & Caltagirone, 2005; Petersen et al., 1999). Interestingly, free recall tests have been used to diagnose the episodic memory difficulties in MCI subjects and several works have shown that free recall is systematically impaired in older adults with aMCI (Bennett, Golob, Parker, & Starr, 2006; Sarazin et al., 2007).

A number of studies supported the hypothesis that word recall failure reflects intratrial forgetting, which refers to the decay of traces during the time between the presentation and the requested recall of an item (Tulving, 1964). One possibility is that memory trace would be available, but not accessible for recall. A considerable body of evidence confirms that retrieval success is closely related to the number and quality of the available retrieval cues (Hunt & Smith,

1996; Tulving, 1972; Tulving & Pearlstone, 1966).

Since aMCI is associated with large decreases in recollection (Koen & Yonelinas, 2014), it is also possible that tDCS had a facilitation effect on a task thought to depend more on familiarity (old/new recognition) but not on a task believed to rely primarily on recollection (free recall).

The results of the current study are in line with previous findings of enhanced recognition induced by tDCS in AD patients. In particular, Boggio and collaborators (2009) reported improvements in visual recognition memory in AD following stimulation of the left PFC and temporoparietal cortex (TPC). Ferrucci et al. (2008) showed that bilateral tDCS applied over the TPC improved word recognition in AD patients.

Regarding the putative brain mechanisms underlying this facilitation effect, resting-state functional MRI studies in older adults with aMCI have reported reduced functional connectivity between regions of the default mode network (DMN) (Binnewijzend et al., 2012; Wang et al., 2013), a well-established large-scale brain network subserving episodic memory processes (Jeong, Chung, & Kim, 2015). Considering the role of hippocampus in contextual reconsolidation (Morris et al., 2006) and the idea that tDCS acts by modulating functional connectivity (Krause et al., 2017; Meinzer et al., 2015), PFC-tDCS after a contextual reminder cue in our study might have increased the functional connectivity between the hippocampus and other DMN nodes. The combination of tDCS with resting state fMRI (Shafi, Westover, Fox, & Pascual-Leone, 2012) might shed light into the neural mechanisms of the PFC-tDCS after a contextual reminder and help identify brain regions where tDCS may exert greater beneficial effects.

Facilitation of the consolidation processes might be a mechanism acting during the hours or days after tDCS (Au, Karsten, Buschkuehl, & Jaeggi, 2017). Since the reactivation of newly encoded memories during subsequent waking state (Au et al., 2017; Karlsson & Frank, 2009; Sirota & Buzsaki, 2005) may be important for memory consolidation, tDCS applied during waking rest, as in our study during reconsolidation, might have facilitated neural reactivation and consequently boosted systems-level consolidation for long-term retention (Au et al., 2017).

Some limitations of the current study should be mentioned. First, given that our sample size was relatively small, findings reported here should be reproduced in larger cohorts before firm conclusions can be drawn. Second, because of the lack of a control stimulation site nonspecific effects of the stimulation cannot be ruled out. Third, we cannot rule out an intergroup variability in experimental memory performance because we did not test pre-tDCS recognition memory performance at Day 1.

Future work is needed to determine whether the tDCS effect on recognition could have a clinical impact, since enhanced ability to recall information would have greater impact on daily living than improved ability to recognize. Although it is still unknown whether tDCS interventions can ameliorate episodic memory in everyday life, we believe that the evidence is sufficiently promising to merit future research.

Finally, since the effects of anodal tDCS outlast the stimulation period and share significant analogies to the synaptic phenomena of long-term potentiation (LTP) (Fritsch et al., 2010), it is possible to hypothesize that multiple-sessions of tDCS after a contextual reminder could enhance episodic memory performance in aMCI. Previous works in healthy older subjects and in patients with neurodegenerative disease provided a framework for testing the long-term behavioral facilitation effects of repeated tDCS on functional scales and standard memory tests (Brunoni et al., 2012; Floel, 2014; Hsu, Ku, Zanto, & Gazzaley, 2015; Lefaucheur et al., 2017).

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Table 1. Demographical, clinical and neuropsychological data

	Active tDCS (n=9)	Sham tDCS (n=9)	Cut-off	p-value
Age (years)	75.3 (4.8)	75.3 (2.2)		ns
Gender (male/female)	5/4	5/4		
Education (years)	7.7 (3.6)	7.8 (3.1)		ns
Mood and Anxiety Assessment				
Geriatric Depression Scale (GDS)	5.2 (3.0)	5.6 (3.8)	< 11	ns
State-Trait Anxiety Inventory (STAI)				
STAI-State	42.6 (8.4)	45.0 (3.4)		ns
STAI-Trait	40.9 (6.7)	45.6 (4.4)		ns
Functional Assessment				
BADL (number of unspared functions)	0.1 (0.3)	0 (0)		ns
IADL (number of unspared functions)	0.3 (0.7)	0 (0)		ns
Cognitive Reserve				
Cognitive Reserve Index questionnaire (CRI-q)				
CRI-Total Score	108.1 (20.0)	108.7 (11.0)		ns
CRI-Education	98.0 (13.1)	100. 8 (7.8)		ns
CRI-Working Activity	95.6 (24.6)	93.8 (8.1)		ns
CRI-Leisure Time	124.8 (19.1)	124.7 (18.7)		ns
Subjective Memory Complaints				
Everyday Memory Questionnaire (EMQ)	64.1 (19.9)	74.6 (38.7)		ns
Screening for dementia				
MMSE	26.0 (1.2)	26.3 (1.7)	≥ 24	ns

Non-Verbal Reasoning				
Raven's colored progressive matrices	25.9 (3.6)	25.0 (4.5)	> 17.5	ns
Language				
Token Test	32.6 (1.8)	31.0 (1.9)	> 26.25	ns
Fluency, phonemic	28.0 (5.8)	29.7 (9.3)	> 16	ns
Fluency, semantic	28.9 (7.1)	27.3 (9.5)	> 24	ns
Memory				
Digit Span (forward)	5.2 (0.8)	5.4 (0.7)	> 4.25	ns
Story Recall	**5.3 (1.9)**	**5.5 (2.2)**	> 7.5	ns
AVLT (Immediate recall)	28.6 (3.8)	28.8 (6.3)	> 28.52	ns
AVLT (Delayed recall)	**3.8 (2.5)**	**3.8 (3.4)**	> 4.68	ns
Rey-Osterrieth Complex Figure, recall	**6.2 (4.8)**	**6.3 (4.7)**	> 9.46	ns
Visuo-constructional functions				
Rey-Osterrieth Complex Figure, copy	31.6 (4.4)	31.3 (2.4)	> 28.87	ns
Executive functions				
Trial Making Test-A (seconds)	68.2 (18.5)	64.3 (26.2)	< 94	ns
Trial Making Test-B (seconds)	247.0 (107.7)	271.4 (126.5)	< 283	ns

* Raw scores are reported (SD in parentheses).

p-value column reports nonparametric Mann-Whitney test. BADL: Activities of Daily Living, IADL: Instrumental Activities of Daily Living, MMSE: Mini Mental State Examination, AVLT: Rey Auditory Verbal Learning Test, p-value: comparison between Active and Sham groups, ns: not significant. Cut-off scores according to Italian normative data are reported. Bold font indicates scores below cut-off.

Table 2. d' and C values from the Recognition Task

	Active tDCS (n=9)			
	d'		**C**	
	Day 3	**Day 30**	**Day 3**	**Day 30**
Participant 1	0,87	1,73	0,23	-1,07
Participant 2	0,97	0,18	-0,22	-0,36
Participant 3	1,44	0,74	-0,89	0,00
Participant 4	1,53	0,77	-0,79	-0,42
Participant 5	1,90	1,07	0,43	0,12
Participant 6	0,74	0,91	0,00	-0,91
Participant 7	1,64	0,30	-0,69	-0,66
Participant 8	0,51	1,01	0,68	0,46
Participant 9	1,47	1,18	0,00	0,63
Mean (SD)	**1.23 (0.44)**	**0.88 (0.56)**	**-0.14 (0.52)**	**-0.24 (0.28)**
	Sham tDCS (n=9)			
	d'		**C**	
	Day 3	**Day 30**	**Day 3**	**Day 30**
Participant 10	0,82	0,51	-1,00	-0,68
Participant 11	1,16	0,82	1,16	0,64
Participant 12	1,44	0,66	0,89	0,30
Participant 13	-0,18	-0,46	-0,36	0,28
Participant 14	0,68	0,89	-0,51	-1,44
Participant 15	1,09	0,43	-2,55	-1,38
Participant 16	0,46	-0,20	1,01	-0,75
Participant 17	0,42	0,73	-0,77	-1,09
Participant 18	1,64	0,57	0,69	0,39
Mean (SD)	**0.84 (0.53)**	**0.44 (0.77)**	**-0.16 (1.15)**	**-0.41 (0.22)**

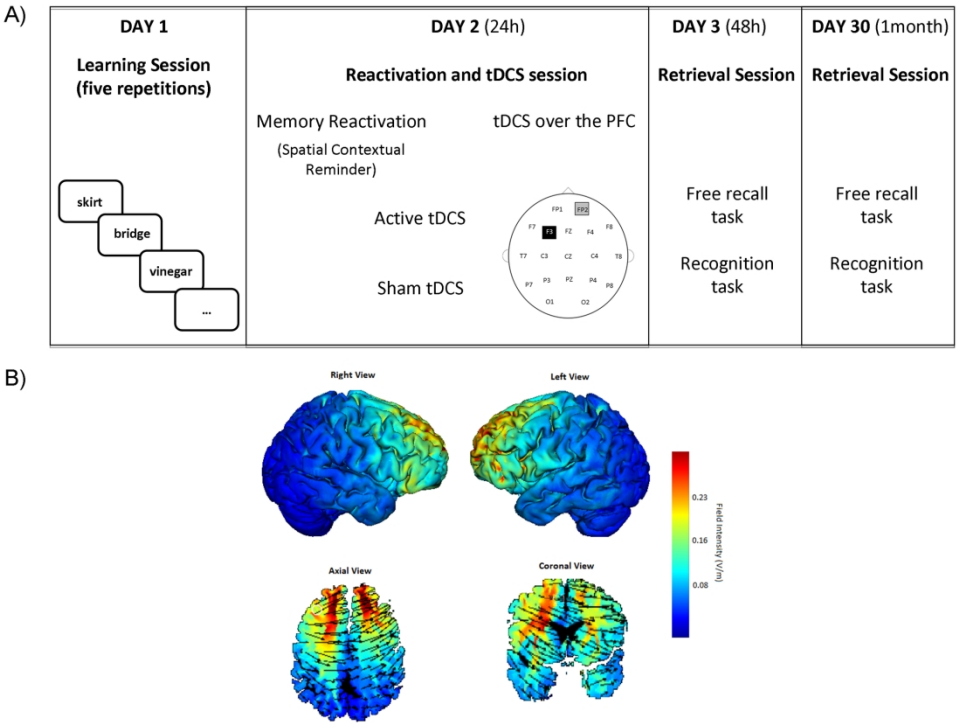
Figures Captions

Figure 1. Experimental procedure.

A. Experimental protocol design. Participants learned 20 words on Day 1. On Day 2 (24h later), tDCS (active or sham) was applied after a spatial contextual reminder. Memory retrieval (free recall and recognition) was tested 48h (Day 3) and one month (Day 30) after the learning session (Day 1).

B. Current flow model of tDCS montage. Current flow model of tDCS montage (anode over F3 and cathode over the right supraorbital area), using two 7×5 sponge pads is represented in a 3D and in a 2D view from the Male 1 model in the Soterix HD Targets software (Soterix Medical).

Figure 2. Effects of tDCS on memory recognition. The plot shows the d' values from the recognition task in the Active and Sham groups at Day 3 and Day 30. Active tDCS enhanced memory recognition (d') relative to Sham tDCS. Error bars represent standard errors. *=$p<0.05$



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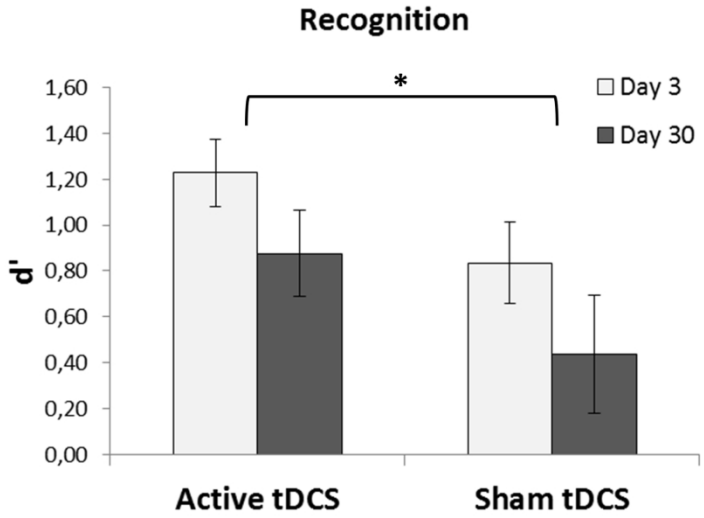
190x142mm (300 x 300 DPI)



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