ORIGINAL ARTICLE

Effects on cognition of 20-day anodal transcranial direct current stimulation over the left dorsolateral prefrontal cortex in patients affected by mild cognitive impairment: a case-control study

Enrico Fileccia[1] · Vitantonio Di Stasi[2] · Roberto Poda[2] · Giovanni Rizzo[1,2] · Michelangelo Stanzani-Maserati[2] · Federico Oppi[2] · Patrizia Avoni[1,2] · Sabina Capellari[1,2] · Rocco Liguori[1,2]

Abstract

Background Mild cognitive impairment (MCI) is a common disorder affecting as much as 15% of the elderly population. Transcranial direct current stimulation (tDCS) is a non-invasive technique of neuromodulation that has proven to influence performance in different cognitive domains.

Objective/hypothesis We investigated the effects on cognition of 20-day anodal tDCS in 17 MCI patients compared with 17 matched MCI patients.

Methods Patients underwent neuropsychological evaluation at baseline and then were randomly assigned to the anodal or sham group. The tDCS protocol consisted in 20 min, 5 days per week (up to a total of 20 days), of 2-mA anodal stimulation over the left dorsolateral prefrontal cortex (DLPFC). The location of anodal electrode was chosen in accordance with previous reports which relate anodal stimulation of this site with cognitive enhancement. At the end of the last day of stimulation, a second neuropsychological evaluation was performed. We compared baseline and post-stimulation neuropsychological results in the anodal vs sham group using repeated measures ANOVA as a statistical analysis test.

Results At follow-up, patients exposed to anodal stimulation showed improvement in episodic verbal memory ($p < 0.001$) and figure naming test ($p < 0.01$), in a general index of cognitive function (Brief Mental Deterioration Battery) ($p < 0.0001$) and in a mood measurement test (Beck Depression Inventory) ($p < 0.01$).

Conclusion Anodal tDCS could be a useful tool to improve cognitive symptoms in MCI although more evidence is needed to understand the exact underlying mechanisms. Confirmation of its potential benefits in MCI would be significant.

Keywords MCI · tDCS · DLPFC · Cognition · Neuropsychology · Mild cognitive impairment · Transcranial direct current stimulation

Introduction

Mild cognitive impairment (MCI) is a common medical condition with a prevalence in the elderly estimated between 4.9 and 25.2% [1, 2]. Patients affected by MCI have an annual risk between 5 and 15% of progression to dementia (mainly Alzheimer's disease) [3, 4], with a cumulative risk in the longest studies estimated between 20 and 30% [5]. Our experience reported cumulative conversion rate to dementia of 18.4% (mean, 4.6% per year) [6].

According to international criteria, MCI is characterised by an under-average performance in at least one cognitive domain in such a way that everyday life is not affected [7, 8]. Executive and perceptual motor functions, complex attention, language, memory and social cognition represent the domains commonly assessed for diagnosis [7, 8]. Several pharmacological and physical interventions have been evaluated in MCI, and unfortunately, to date, no consistent reports of long-term efficacy have been demonstrated [9–14]. Transcranial direct current stimulation (tDCS) is a safe, low-cost [15], non-invasive neurophysiological technique that

---

V. Di Stasi and R. Poda contributed equally to this work.

✉ Enrico Fileccia
  enrico.fileccia@studio.unibo.it

[1] Department of Biomedical and Neuromotor Sciences, University of Bologna, Bologna, Italy

[2] Institute of Neurological Sciences of Bologna, Bologna, Italy

consists in the application of mild (1–2 mA) electrical current on the scalp [16]. Effects of tDCS vary based on current polarity, intensity, time and site of application [17, 18]. There are reports of improvement in different aspects of cognition after anodal stimulation, such as working memory, visuomotor coordination and naming in healthy subjects [19–22], recognition memory in Alzheimer's disease [23] and working memory and mood in depression [24]. To our knowledge, there is only one report in literature that studied the neuropsychological effects of tDCS on MCI [25], as also confirmed by this recent review [26]. In this paper, we describe the neuropsychological effects of long-lasting anodal tDCS on MCI subjects.

Methods

Subject recruitment and procedure

We studied 34 patients admitted to our observation for mild cognitive impairment. Diagnosis was performed by different neurologists, according to the previously described criteria [8, 27]. Inclusion criteria were cognitive symptoms affecting one or more domains without loss of independence in everyday life. Exclusion criteria were taking medications affecting the central nervous system, brain MRI abnormalities, history of anxiety or depression. All patients had normal brain MRI and normal neurological examination performed before our observation. No patient in both groups was under medication treatment which could affect cognitive performances or was affected by mood or anxiety disorders. Patients underwent neuropsychological evaluation at baseline and then were randomly assigned to either the anodal or sham stimulation group. All patients underwent 5 days a week, up to a total of 20 days, of stimulation. A single-day session lasted 20 min in both the anodal and sham groups. At the end of the last day of stimulation, the patients underwent a second neuropsychological evaluation.

Neuropsychological evaluation

Neuropsychological evaluation consisted of Mini Mental State Examination (MMSE, range, 1.93–35.24; cut-off, < 23.8) [28, 29], Brief Mental Deterioration Battery (BMDB) with final result (FR) (cut-off, < 0) [6, 30], Rey Auditory Verbal Learning Test: immediate recall (range, 0–75; cut-off, < 28.53) and delayed recall (range, 0–15; cut-off, < 4.69) [31], Immediate Visual Memory (range, 0–22; cut-off, < 13.85) [31], Copy Design: simple (range, 0–12; cut-off, < 7.18) [31], Barrage test (time cut-off, ≥ 90; score cut-off, ≤ 9; errors cut-off, ≥ 2; result cut-off, > 2.5) [30, 32], Stroop test (time cut-off, > 27.5; errors cut-off, > 7.5) [33], verbal fluency: phonemic (range, 0–infinite; cut-off, < 17.35) [31] and semantic (range, 0–infinite; cut-off, < 25) [34], naming to description

test (cut-off, < 15) [35], figure naming (cut-off, < 58.5) [36, 37], analogies (range, 0–20; cut-off, < 15.1) [30, 32], State-Trait Anxiety Inventory–Y (range, 20–80; cut-off, < 50 T points) [38] and Beck Depression Inventory (range, 0–63; cut-off, > 9) [39]. The figure naming test is composed of two different sets of 24 pictures derived from the list of Snodgrass and Vanderwart [37]. Each set was homogeneous for frequency of use and familiarity according to Laiacona et al. [36]. Test score for each set depended on response time: 3 points for correct answer within 5 s, 1 point between 5 and 10 s, 0 point for correct answer after 10 s or wrong answers.

The BMDB is based on results obtained by patients on the Rey Auditory Verbal Learning Test (RAVLT) with immediate and delayed recall, Immediate Visual Memory, visual search test (Barrage test) and verbal abstract thinking test (analogies test) and allows us to calculate a final result (FR) that expresses a measure of global cognition functioning of the subject; normality threshold is set at zero, and negative scores are considered pathological.

The neuropsychologist who administered the evaluation was blind to the stimulation received by patients. Parallel forms (same tests but with different subject matters) were used on follow-up evaluation to eliminate any learning effect.

tDCS

tDCS was administered by the HDC stimulator (Newronica s.r.l.). Two electrodes, (7×5) 35 cm^2 and (7×6) 42 cm^2 in size, were used as anode and cathode respectively. Electrodes were inserted into holding bags soaked with saline solution and placed over the left dorsolateral prefrontal cortex (DLPFC) and the right deltoid muscle, positions of anode and cathode respectively. The location of the latter electrode was selected to be extra-cephalic in order to avoid inhibitory effects due to cathodal stimulation. We used this site for the cathode in order to have the possibility to consider any possible subsequent measured neuropsychological result at follow-up as an effect of anodal stimulation. Conductivity gel was applied over the skin in contact with the electrode-holding bags. The location of the active electrode was selected in accordance with the EEG International 10–20 system, corresponding to F3 location.

Current was increased during the first 10 s to a maximum of 2 mA, then maintained constant for the rest of the 20-min stimulation. The subjects often complained, at the beginning of the procedure, of a slight itching sensation over the electrode sites, usually lasting only few seconds. In the sham group, the current was gradually decreased after the first 20 s in order to have patients perceive the same itching sensation.

Statistical analysis

Statistical analyses were performed using SPSS 24.0. We verified normal distribution of the variable using the

Kolmogorov-Smirnov test. In the case of non-normal distribution, the variables were rank transformed.

The differences in the demographic and baseline neuropsychological data between the two groups were evaluated using the unpaired t test for continuous variables and by the χ^2 test for categorical variables. The intervention effect of tDCS was evaluated by conducting a repeated measures analysis of variance (ANOVA) on the neuropsychological data, taking the condition (tDCS vs sham) as a between-subject factor and the time point (before vs after sessions) as a within-subject factor. We corrected for multiple comparisons using the false discovery rate (FDR). P values < 0.05 were considered significant.

Results

The two groups did not differ in age, sex, years of schooling and baseline neuropsychological evaluation (Table 1). Neuropsychological evaluation after 20 days of both anodal and sham stimulation groups is displayed in Tables 2 and 3. Compared with their baseline results, patients belonging to the anodal group showed at follow-up significantly better performance in Brief Mental Deterioration Battery ($p < 0.0001$), RAVLT: immediate recall ($p < 0.001$), figure naming test ($p < 0.01$) and Beck Depression Inventory ($p < 0.01$) (significant interaction between time, pre/post and intervention in the repeated measures ANOVA) (Fig. 1). Furthermore, MMSE, Immediate Visual Memory, Barrage test (time employed to perform) and Rey's 15 Words: delayed recall showed a clear trend of improvement in the tDCS group (uncorrected $p = 0.02$, $p = 0.02$, $p = 0.03$ and $p = 0.03$ respectively), but non-surviving after FDR correction ($p > 0.05$).

Discussion

In this paper, we describe the effects on cognition of long-lasting anodal tDCS in patients affected by MCI.

Compared with the baseline and with the sham groups, after 20 days of stimulation of the anodal group, our patients showed better performance on global cognition functioning test (BMDB) and, more selectively, in neuropsychological

Table 1 Demographic features of the two group studied

Demographic features	Anodal group	Sham group
Sex, female	4	6
Sex, male	13	11
Age	71.6 (SE 1.4)	69.7 (SE 1.6)
Years of schooling	10.5 (SE 1)	11.5 (SE 0.9)

The two groups did not differ in age, sex and years of schooling. SE standard error

assessments exploring immediate verbal memory and naming skills (RAVLT: immediate recall and figure naming respectively). In addition, mood evaluation through the Beck Depression Inventory disclosed lower scoring, suggesting improvement of depressive symptoms. Although several studies described tDCS effects on cognition, only one study [25] reported tDCS neuropsychological effects on MCI [26]. Meinzer and colleagues described improved semantic word-retrieval scoring after 5 days of 1-mA anodal stimulation over the left ventral inferior frontal junction (IFJ). A concomitant fMRI study of brain metabolism showed the reduction of bilateral prefrontal cortex (including the left IFJ) and right middle temporal gyrus metabolic activity. This observation was considered the result of a facilitatory effect in the stimulated neuronal network which causes a decrease requirement of energy [25]. However, this explanation partially contrasts with the results of a following work on MCI patients disclosing increased glucose metabolism in dorsolateral, ventrolateral, medial prefrontal and dorsal anterior cingulate, anterior and posterior insular regions, and hippocampal and parahippocampal regions on cerebral PET after 3 weeks of three times/week, 30 min, 2-mA anodal tDCS stimulation over the left DLPFC [40]. Compared with the study of Meinzer, our study differs in intensity of the current applied (1 mA vs 2 mA), site of stimulation (left DLPFC vs left IFJ) and days of stimulation (20 vs 5). Left DLPFC is the most common area targeted for transmagnetic stimulation (TMS) and tDCS stimulation studies concerning cognitive enhancement in the elderly [41]. Previous works describe improvement in episodic memory retrieval after anodal tDCS over the left DLPFC in healthy elderly adults [42, 43].

Furthermore, working memory and dual tasking skills, two functions which both decline early during ageing, showed also improvement after anodal TDCS over DLPFC in healthy-aged persons [41, 44].

In addition, the left DLPFC has been used as target for TMS study which showed improvement in Stroop test [45]. Some of our findings are consistent with the clinical-anatomical expectations based on the site of stimulation; on the other hand, some are less clear. Executive function networks which are thought to rely anatomically mainly on left prefrontal cortex are usually studied assessing skills in the subdomains of inhibition, set shifting, working memory and fluency [46, 47].

Unexpectedly, we did not observe improvement in Stroop test which evaluate the former subdomain neither in phonemic verbal fluency tests. We did not perform trial making test and digit span which selectively assess set shifting and working memory respectively. Despite analogies test depends upon proper function of pre-frontal areas and it allows to assess inhibition, working memory and selective attention subdomains [48], we did not found better scores in patients after anodal stimulation. Improvement in Beck Depression Inventory is

Table 2 Neuropsychological evaluation (global cognitive function indices) of anodal and sham groups at baseline and follow-up

Global cognitive functions indices	Anodal group baseline	Sham group baseline	Anodal group follow-up	Sham group follow-up
Mini Mental State Examination (MMSE) (range, 1.93–35.24; cut-off, < 23.8)	25.9 (SE 0.5)	26.1 (SE 0.6)	26.6 (SE 0.5)	25.1 (SE 1.2)
Brief Mental Deterioration Battery (BMDB) (cut-off, < 0)	1.1 (SE 0.2)	0.74 (SE 0.3)	1.97 (SE 0.3) $p < 0.0001$	0.84 (SE 0.3)

Mean results of neuropsychological evaluation at baseline and follow-up (rounded to first decimal) in the anodal and sham groups: global cognitive function indices. The two groups did not differ in baseline neuropsychological evaluation. Compared with their baseline results, patients belonging to the anodal group showed at follow-up significantly better performances in Brief Mental Deterioration Battery ($p < 0.0001$) (significant interaction between time, pre-post and intervention in the repeated measures ANOVA). MMSE showed a clear trend of improvement in the anodal group (uncorrected $p = 0.02$), but non-surviving after false discovery rate correction. *SE* standard error

Table 3 Neuropsychological evaluation (specific domains) of anodal and sham groups at baseline and follow-up

	Anodal baseline	Sham baseline	Anodal follow-up	Sham follow-up
Episodic verbal memory				
Rey Auditory Verbal Learning Test: immediate recall (cut-off, < 28.53)	31.5 (SE 1.7)	32.2 (SE 2.4)	39.1 (SE 3) $p < 0.001$	33 (SE 2.5)
Rey Auditory Verbal Learning Test: delayed recall (cut-off, < 4.69)	5.3 (SE 0.7)	4.6 (SE 0.6)	7.3 (SE 1.2)	5.2 (SE 0.7)
Episodic visual memory				
Immediate Visual Memory (range, 0–22; cut-off, < 13.85)	17.7 (SE 1.2)	15.1 (SE 1.9)	20.2 (SE 0.5)	17.2 (SE 1.1)
Attention				
Barrage test time (cut-off, ≥ 90)	65.8 (SE 9.2)	62.6 (SE 10.2)	50.9 (SE 5.3)	74.6 (SE 13.6)
Barrage test score (cut-off, ≤ 9)	10.7 (SE 0.5)	9.47 (SE 5.8)	9.9 (SE 0.5)	9.6 (SE 0.7)
Barrage test errors (cut-off, ≥ 2)	0.8 (SE 0.4)	2.5 (SE 0.8)	0.6 (SE 0.6)	1.8 (SE 0.6)
Barrage test result (cut-off, > 2.5)	1 (SE 0.6)	3.2 (SE 1)	0.5 (SE 0.6)	2.8 (SE 1)
Constructional praxis				
Copy Design: simple (cut-off, < 7.18)	10.6 (SE 0.4)	10.2 (SE 0.6)	10.9 (SE 0.4)	10.4 (SE 0.5)
Executive functions				
Analogies (cut-off, < 15.1)	14.6 (SE 0.9)	12.8 (SE 1.3)	16.2 (SE 0.7)	13.2 (SE 1.2)
Stroop test time (cut-off, > 27.5)[§]	23.4 (SE 5)	32.5 (SE 6.9)	22.1 (SE 4.5)	28.7 (SE 9.1)
Stroop test errors (cut-off, > 7.5)[§]	3.5 (SE 2.2)	5.3 (SE 2.1)	0 (SE 0.7)	6.2 (SE 3.1)
Language				
Verbal fluency: phonemic (cut-off, < 17.35)[°]	27.2 (SE 2.2)	20.3 (SE 2.4)	30.1 (SE 2.5)	19.9 (SE 2.9)
Verbal fluency: semantic (cut-off, < 25)*	32 (SE 2.7)	26.3 (SE 2.9)	35.6 (SE 2.4)	26.1 (SE 3.2)
Verbal naming (cut-off, < 15)	12.8 (SE 0.8)	12.1 (SE 0.9)	13.1 (SE 0.8)	12 (SE 0.9)
Figure naming (cut-off, < 58.5)	60.7 (SE 3.5)	61.5 (SE 4.1)	64.8 (SE 2.7) $p < 0.01$	60.3 (SE 4)
Social cognition				
State Anxiety Inventory (cut-off, > 50 points)	38.9 (SE 9.5)	38.6 (SE 9.4)	39 (SE 1.5)	41.5 (SE 1.7)
Trait Anxiety Inventory (cut-off, > 50 points)	41.1 (SE 10.5)	42.5 (SE 10.4)	41 (SE 2.2)	39 (SE 1.5)
Beck Depression Inventory (cut-off, > 9)	11.5 (SE 2.1)	6.5 (SE 1.4)	6.7 (SE 1.7) $p < 0.01$	7.4 (SE 1.2)

Mean results of neuropsychological evaluation at baseline and follow-up (rounded to first decimal) in anodal and sham groups: specific domains. The two groups did not differ in baseline neuropsychological evaluation. Compared with their baseline results, patients belonging to the anodal group showed at follow-up significantly better performances, RAVLT: immediate recall ($p < 0.001$), figure naming ($p < 0.01$) and Beck Depression Inventory ($p < 0.01$) (significant interaction between time, pre-post and intervention in the repeated measures ANOVA). Furthermore, Immediate Visual Memory, Barrage test (time employed to perform) and Rey's 15 Words: delayed recall showed a clear trend of improvement in the tDCS group (uncorrected $p = 0.02$, $p = 0.02$, $p = 0.03$ and $p = 0.03$ respectively), but non-surviving after false discovery rate correction. *SE*, standard error. *Semantic fluency and figure naming tests relates also with semantic memory. °Phonemic fluency test relates also with executive functions. § Stroop test depends also on selective attention
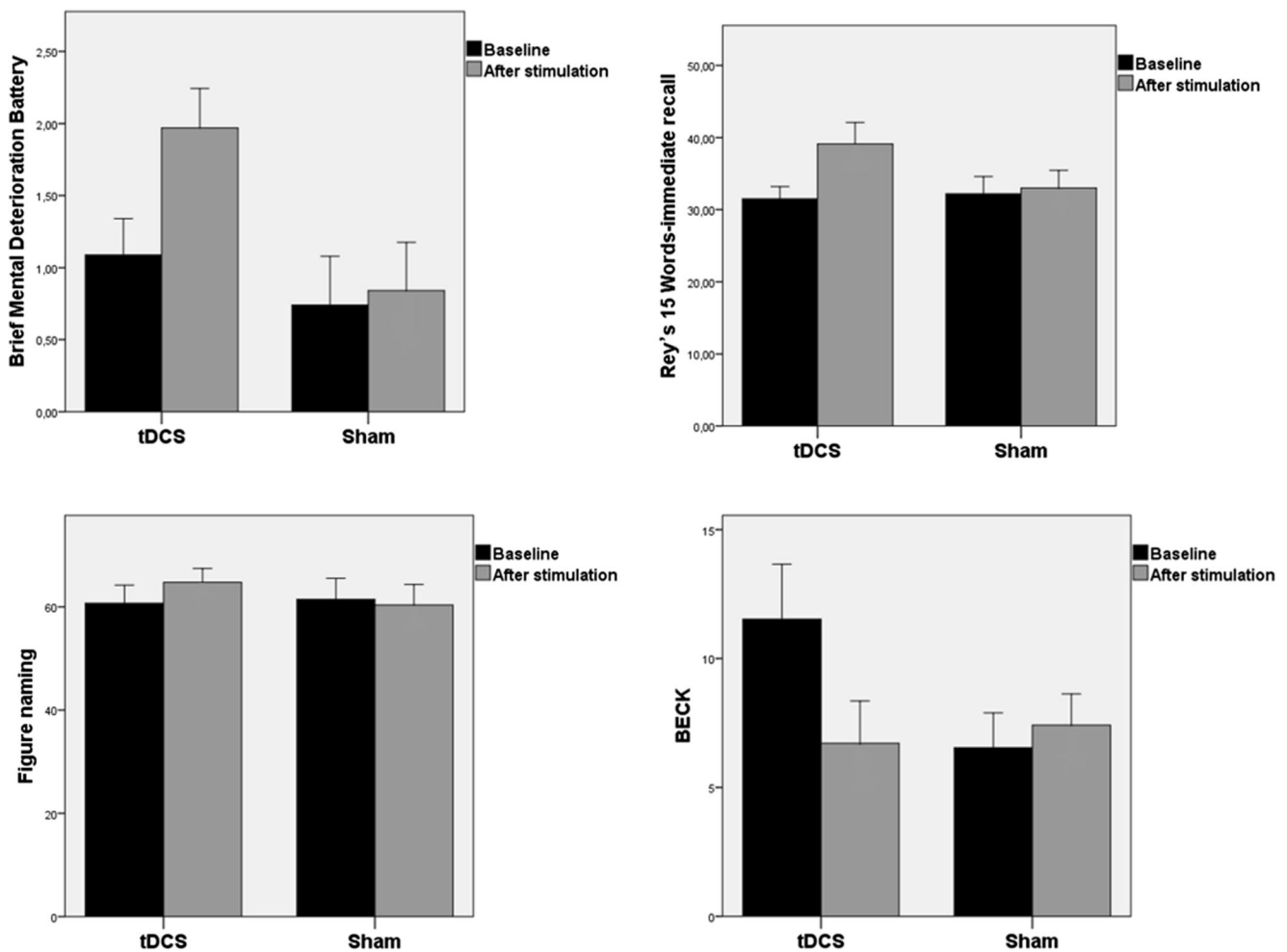
Fig. 1 Compared with their baseline results, patients belonging to the anodal group showed at follow-up significantly better performances in Brief Mental Deterioration Battery ($p < 0.0001$), RAVLT: immediate recall ($p < 0.001$), figure naming ($p < 0.01$) and Beck Depression Inventory ($p < 0.01$) (significant interaction between time, pre-post and intervention in the repeated measures ANOVA)

consistent with previous studies which described, along with a definite positive effect of TMS on mood disorders, a possible therapeutic role of anodal stimulation of the left DLPFC in these conditions [49]. Whether the above effects are directly mediated by left DLPFC, or indirectly through its connection with the frontal insular, anterior cingulate and ventromedial pre-frontal cortex is not known. However, although baseline measurements in Beck Depression Test were not significantly different in anodal and sham groups, the latter showed a lower baseline score. Thus, it cannot be defined whether the above effects are mediated by left DLPFC, directly or indirectly through its connections, or they represent regression to mean in the anodal group. It is also to be defined the reason why selective stimulation of the left DLPFC area results in a better performance on general cognition, as evidenced by the Brief Mental Deterioration Battery score or why anodal stimulation of the left DLPFC improves cognitive performance thought to be mainly dependent upon other cortical areas, such as verbal episodic memory assessed through Rey's 15 Words: immediate recall test, a function thought to rely mainly upon left mid

temporal neuronal activity [50]. Moreover, the reason underlying selective improvement of general cognition index such as BMDB but not MMSE is also unclear. It could be speculated that using MMSE is less sensible to identify cognitive alterations that depended upon pre-frontal lobe functions; an improvement in BMDB could reflect better results in the subtest of analogies of BMDB. However, the latter view contrasts with the fact that in our patients, improvement of BMDB relates better with RAVLT results rather than with analogies test. On the other hand, a contribution of working memory in RAVLT results cannot be excluded. Nevertheless, as already expressed above, the anodal group did not show better scores in tests which selectively explore other subdomains of executive functions such as Stroop test or analogies test.

Besides, we cannot exclude a contribution of arousal reaction to our results; however, this interpretation would contrast with data that showed increased pain threshold in healthy individuals after anodal tDCS applied over the left DLPFC [51]. The neurological impact of tDCS stimulation has been theorised at different levels. It has been described that 13 min

of anodal stimulation of the motor cortex is sufficient to induce threshold excitability modification lasting up to 1 h [16, 17, 52]. TMS-coupled studies showed tDCS during stimulation effects depends only on membrane polarity changes whilst after effects are consequences of glutamatergic- and GABAergic-mediated synaptic plasticity mechanisms [53]. Long-lasting effects of both anodal and cathodal stimulation are blocked by the use of NMDA antagonists suggesting a reliance mediated by long-term potentiation (LTP)-dependent mechanisms [52, 54].

An in vitro study showed that anodal tDCS increases AMPA receptor translocation in the hippocampus and a promoting effect of tDCS on S831 phosphorylation of the receptor. Interestingly, both phenomena relate with synaptic strength and LTP induction [55]. It has been reported that working memory can be impaired by temporary TMS-mediated inhibition of the left prefrontal cortex [56] and a subsequent work demonstrated improvement in working memory performances after anodal tDCS application over the left DLPFC [22]. We can speculate that using LTP important for learning [57] interventions facilitating its physiological activity could improve memory fruition.

Nevertheless, to date, some results concerning tDCS effectiveness in specific neurological disorders such as aphasia are still conflicting [58, 59] and additional studies are needed in order to better clarify biological aspects and clinical purposes of tDCS.

Conclusion

We found that long-lasting anodal tDCS over the left DLPFC stimulation improves overall cognition scores (BMDB), immediate verbal memory (RAVLT: immediate recall) and figure naming performance in patients affected by MCI. In addition, tDCS seems to improve a standardised measure of mood in the same population. Notwithstanding the foregoing, the following limitations of the study demand caution in interpretation: lack of long-term follow-up, lack of information about in vivo biomarkers of degenerative conditions (such as CSF tau, P-tau and beta amyloid) or functional imaging (FDG-PET). Furthermore, the biological mechanisms behind our observed results and the site of stimulation need to be clarified. Future studies are needed to confirm the promising therapeutical opportunities which tDCS seems to have in MCI. In this perspective, overcoming the aforementioned limitations will help to standardise more precisely the effects of the technique in the condition and to understand the exact mechanisms underlying improvement and its duration over time. tDCS, due to its low-cost and relative risk-free profile, could be a useful tool to improve cognitive symptoms in MCI. Considering the high prevalence of the condition, confirmation of effectiveness of tDCS application in MCI would have significant social and economic benefits.

Compliance with ethical standards

The study followed the Helsinki Declaration regarding international clinical research on human beings and was approved by the local Ethics Committee. All subjects gave their written informed consent to the study.

Competing interests The authors declare that they have no competing interests.

References

1. Alexander M, Perera G, Ford G, Arrighi HM, Foskett N, Debove C, Novak G, Gordon FM (2015) Age-stratified prevalence of mild cognitive impairment and dementia in European populations: a systematic review. J Alzheimers Dis 48:355–359. https://doi.org/10.3233/JAD-150168 IOS Press355

2. Petersen RC, Lopez O, Armstrong MJ, Getchius TSD, Ganguli M, Gloss D, Gronseth GS, Marson D, Pringsheim T, Day GS, Sager M, Stevens J, Rae-Grant A (2018) Practice guideline update summary: Mild cognitive impairment report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology Neurology® 90:1–10. https://doi.org/10.1212/WNL.0000000000004826

3. Petersen RC, Roberts RO, Knopman DS, Boeve BF, Geda YE, Ivnik RJ, Smith GE, Jack CR Jr (2009) Mild cognitive impairment: ten years later. Arch Neurol 66(12):1447–1455

4. Ritchie C, Smailagic N, Noel-Storr AH, Ukoumunne O, Ladds EC, Martin S (2017) CSF tau and the CSF tau/ABeta ratio for the diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI). Cochrane Database Syst Rev (3):CD010803. https://doi.org/10.1002/14651858.CD010803.pub2

5. Mitchell AJ, Shiri-Feshki M (2008) Temporal trends in the long term risk of progression of mild cognitive impairment: a pooled analysis. J Neurol Neurosurg Psychiatry 79:1386–1391. https://doi.org/10.1136/jnnp.2007.142679

6. Gallassi R, Oppi F, Poda R, Scortichini S, Stanzani Maserati M, Marano G, Sambati L (2010) Are subjective cognitive complaints a risk factor for dementia? NeurolSci 31:327–336. https://doi.org/10.1007/s10072-010-0224-6

7. American Psychiatric Association (2013) Diagnostic and statistical manual of mental disorders, Fifth Edition (DSM-5). American Psychiatric Association, Arlington

8. Petersen RC, Caracciolo B, Brayne C, Gauthier S, Jelic V, Fratiglioni L (2014) Mild cognitive impairment: a concept in evolution. J Intern Med 275(3):214–228. https://doi.org/10.1111/joim.12190

9. Cooper C, Li R, Lyketsos C, Livingston G (2013) Treatment for mild cognitive impairment: systematic review. Br J Psychiatry 203(3):255–264. https://doi.org/10.1192/bjp.bp.113.127811

10. Doody RS, Ferris SH, Salloway S, Sun Y, Goldman R, Watkins WE, Xu Y, Murthy AK (2009) Donepezil treatment of patients with MCI: a 48-week randomized, placebo-controlled trial. Neurology 72(18):1555Y1561. https://doi.org/10.1212/01.wnl.0000344650.95823.03

11. Feldman HH, Ferris S, Winblad B, Sfikas N, Mancione L, He Y, Tekin S, Burns A, Cummings J, del Ser T, Inzitari D, Orgogozo JM, Sauer H, Scheltens P, Scarpini E, Herrmann N, Farlow M, Potkin S, Charles HC, Fox NC, Lane R (2007) Effect of rivastigmine on delay to diagnosis of Alzheimer's disease from mild cognitive impairment: the InDDEx study. Lancet Neurol 6(6):501Y512. https://doi.org/10.1016/S1474-4422(07)70109-6

12. Lautenschlager NT, Cox KL, Flicker L, Foster JK, van Bockxmeer FM, Xiao J, Greenop KR, Almeida OP (2008) Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: a randomized trial. JAMA 300(9):1027Y1037. https://doi.org/10.1001/jama.300.9.1027

13. Petersen RC, Thomas RG, Grundman M, Bennett D, Doody R, Ferris S, Galasko D, Jin S, Kaye J, Levey A, Pfeiffer E, Sano M, van Dyck CH, Thal LJ, Alzheimer's Disease Cooperative Study Group (2005) Vitamin E and donepezil for the treatment of mild cognitive impairment. N Engl J Med 352(23):2379Y2388. https://doi.org/10.1056/NEJMoa050151

14. Thal LJ, Ferris SH, Kirby L et al (2005) A randomized,double-blind, study of rofecoxib in patients with mild cognitive impairment. Neuropsychopharmacology 30(6):1204Y1215. https://doi.org/10.1038/sj.npp.1300690

15. Bikson M, Grossman P, Thomas C, Zannou AL, Jiang J, Adnan T, Mourdoukoutas AP, Kronberg G, Truong D, Boggio P, Brunoni AR, Charvet L, Fregni F, Fritsch B, Gillick B, Hamilton RH, Hampstead BM, Jankord R, Kirton A, Knotkova H, Liebetanz D, Liu A, Loo C, Nitsche MA, Reis J, Richardson JD, Rotenberg A, Turkeltaub PE, Woods AJ (2016) Safety of transcranial direct current stimulation: evidence based update 2016. Brain Stimul 9(5):641–661. https://doi.org/10.1016/j.brs.2016.06.004

16. Woods AJ, Antal A, Bikson M, Boggio PS, Brunoni AR, Celnik P, Cohen LG, Fregni F, Herrmann CS, Kappenman ES, Knotkova H, Liebetanz D, Miniussi C, Miranda PC, Paulus W, Priori A, Reato D, Stagg C, Wenderoth N, Nitsche MA (2016) A technical guide to tDCS, and related non-invasive brain stimulation tools. ClinNeurophysiol. 127(2):1031–1048. https://doi.org/10.1016/j.clinph.2015.11.012

17. Nitsche MA, Paulus W (2000) Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol 527(Pt 3):633–639. https://doi.org/10.1111/j.1469-7793.2000.t01-1-00633.x

18. Jamil A, Batsikadze G, Kuo HI, Labruna L, Hasan A, Paulus W, Nitsche MA (2017) Systematic evaluation of the impact of stimulation intensity on neuroplastic after-effects induced by transcranial direct current stimulation. J Physiol 595(4):1273–1288. Published online 2016 Nov 8. https://doi.org/10.1113/JP272738

19. Antal A, Nitsche MA, Kruse W, Kincses TZ, Hoffmann K-P, Paulus W (2004) Direct current stimulation over V5 enhances visuomotor coordination by improving motion perception in humans. J Cogn Neurosci 16:521–527

20. Fertonani A, Rosini S, Cotelli M, Rossini MP, Miniussi C (2010) Naming facilitation induced by transcranial direct current stimulation. Behav Brain Res 208:311–318

21. Reis J, Schambra HM, Cohen LG, Buch ER, Fritsch B, Zarahn E, Celnik PA, Krakauer JW (2009) Non invasive cortical stimulation enhances motor skill acquisition over multiple days through an effect on consolidation. Proc Natl Acad Sci U S A 106:1590–1595

22. Zaehle T, Sandmann P, Thorne J, Jäncke L, Herrmann C (2011) Transcranial direct current stimulation of the prefrontal cortex modulates working memory performance: combined behavioural and electrophysiological evidence. BMC Neurosci 12:2

23. Ferrucci R, Mameli F, Guidi I, Mrakic-Sposta S, Vergari M, Marceglia S, Cogiamanian F, Barbieri S, Scarpini E, Priori A (2008) Transcranial direct current stimulation improves recognition memory in Alzheimer disease. Neurology. 71(7):493–498. https://doi.org/10.1212/01.wnl.0000317060.43722.a3

24. Loo CK, Alonzo A, Martin D, Mitchell PB, Galvez V, Sachdev P (2012) Transcranial direct current stimulation for depression: 3-week, randomised,sham-controlled trial. Br J Psychiatry 200:52–59

25. Meinzer M, Lindenberg R, Phan MT, Ulm L, Volk C, Floel A (2014) Transcranial direct current stimulation in mild cognitive impairment: Behavioral effects and neural mechanisms. Alzheimers Dement 1–9. https://doi.org/10.1016/j.jalz.2014.07.159

26. Liu CS, Rau A, Gallagher D, Rajji TK, Krista L, Lancto T, Herrmann N Using transcranial direct current stimulation to treat symptoms in mild cognitive impairment and Alzheimer's disease. Neurodegener Dis Manag. Published online: 18 October 2017. https://doi.org/10.2217/nmt-2017-0021

27. Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, Gamst A, Holtzman DM, Jagust WJ, Petersen RC, Snyder PJ, Carrillo MC, Thies B, Phelps CH et al (2011) Alzheimers Dement 7(3):270Y279. https://doi.org/10.1016/j.jalz.2011.03.008

28. Folstein MF, Folstein SE, McHugh PR (1975) "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 12(3):189–198. https://doi.org/10.1016/0022-3956(75)90026-6

29. Measso G, Cavarzeran F, Zappalà G et al (1993) The Mini-Mental State Examination: normative study of an Italian random sample. Dev Neuropsychol 9:77–85

30. Gallassi R, Lenzi P, Stracciari A, Lorusso S, Ciardulli C, Morreale A, Mussuto V (1986) Neuropsychological assessment of mental deterioration: purpose of a brief battery and a probabilistic definition of 'normality' and 'non normality'. Acta Psychiatr Scand 75:62–67

31. Carlesimo GA, Caltagirone C, Gainotti G (1996) The Mental Deterioration Battery: normative data, diagnostic reliabilityand qualitative analyses of cognitive impairment. The Group for the Standardization of the Mental Deterioration Battery. Eur Neurol 36(6):378–384

32. Gallassi R, Morreale A, Di Sarro R, Lorusso S (2002) Value of clinical data and neuropsychological measures in probable Alzheimer's disease. Arch Gerontol Geriatr 34(2):123–134

33. Caffarra P, Vezzadini G, Dieci F, Zonato F, Venneri A (2002) Una versione abbreviata del test di Stroop: Dati normativi nella popolazione Italiana. Nuova Riv Neurol 12(4):111–115

34. Novelli G, Papagno C, Capitani E et al (1986) Tre test clinici di ricerca e produzione lessicale. Taratura su soggetti normali. Arch Psicol Neurol Psichiatr 47:279–296

35. Cavalli M, De Renzi E, Faglioni P, Vitale A (1981) Impairment of right brain-damaged patients on a linguistic cognitive task. Cortex 17(4):545–555

36. Laiacona M, Barbarotto R, Trivelli C, Capitani E (1993) Dissociazioni semantiche intercategoriali: descrizione di una batteria standardizzata e dati normativi [category specific semantic defects: a standardised test with normative data]. Arch Psicol Neurol Psichiatr 54(2):209–248

37. Snodgrass JG, Vanderwart M (1980) A standardized set of 260 pictures: norms for name agreement, image agreement, familiarity, and visual complexity. J Exp Psychol Hum Learn 6(2):174–215

38. Spielberger CD, Vagg PR, Barker LR et al (1980) The factor structure of the State-Trait Anxiety Inventory. In: Sarason IG, Spielberger CD (eds) Stress and anxiety. Hemisphere/Wiley, New York, pp 95–109

39. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J (1961) An inventory for measuring depression. Arch Gen Psychiatry 45:561–571

40. Yun K, Songand I-U, Chung Y-A (2016) Changes in cerebral glucose metabolism after 3 weeks of noninvasive electrical stimulation of mild cognitive impairmentpatients. Alzheimers Res Ther 8:49. https://doi.org/10.1186/s13195-016-0218-6

41. Tatti E, Rossi S, Innocenti I, Rossi A, Santarnecchi E (2016) Non-invasive brain stimulation of the aging brain: state of the art and future perspectives. Ageing Res Rev 29:66–89. https://doi.org/10.1016/j.arr.2016.05.006

42. Manenti R, Brambilla M, Petesi M, Ferrari C, Cotelli M (2013) Enhancing verbal episodic memory in older and young subjects after non-invasive brain stimulation. Front Aging Neurosci 5:1–9. https://doi.org/10.3389/fnagi.2013.00049

43. Sandrini M, Brambilla M, Manenti R, Rosini S, Cohen LG, Cotelli M (2014) Noninvasive stimulation of prefrontal cortex strengthens existing episodic memories and reduces forgetting in the elderly. Front Aging Neurosci 6:289. https://doi.org/10.3389/fnagi.2014.00289

44. Manor B, Zhou J, Jor'dan A, Zhang J, Fang J, Pascual-Leone A (2016) Reduction of dual-task costs by noninvasive modulation of prefrontal activity in healthy elders. J Cogn Neurosci 28:275–281. https://doi.org/10.1162/jocn_a_00897

45. Kim SH, Han HJ, Ahn HM, Kim SA, Kim SE (2012) Effects of five daily high frequency rTMS on Stroop task performance in aging individuals. Neurosci Res 74:256–260. https://doi.org/10.1016/j.neures.2012.08.008

46. Fisk JE, Sharp CA (2004) Age-related impairment in executive functioning: updating, inhibition, shifting, and access. J Clin Exp Neuropsychol 26(7):874Y890. https://doi.org/10.1080/13803390490510680

47. Rabinovici GD, Stephens ML, Possin KL (2015) Executive dysfunction. Continuum (Minneap Minn) 21(3):646–659

48. Gallassi R, Sambati L, Stanzani Maserati M, Poda R, Oppi F, De Matteis M, Marano G (2014) Simple verbal analogies test: normative data on a short task exploring abstract thinking. Aging Clin Exp Res 26:67–71. https://doi.org/10.1007/s40520-013-0180-0

49. Milev RV, Giacobbe P, Kennedy SH, Blumberger DM, Daskalakis ZJ, Downar J, Modirrousta M, Patry S, Vila-Rodriguez F, Lam RW, MacQueen GM, Parikh SV, Ravindran AV, CANMAT Depression Work Group (2016) Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: section 4. Neurostimulation treatments. Can J Psychiatr 61(9):561–575. https://doi.org/10.1177/0706743716660033

50. Matthews BR (2015) Memory dysfunction. Continuum (Minneap Minn) 21(3):613–626

51. Mariano TY, Van't Wout M, Garnaat SL, Rasmussen SA, Greenberg BD (2016) Transcranial direct current stimulation (tDCS) targeting left dorsolateral prefrontal cortex modulates task-induced acute pain in healthy volunteers. Pain Med 17(4): 737–745. https://doi.org/10.1093/pm/pnv042

52. Nitsche MA, Fricke K, Henschke U, Schlitterlau A, Liebetanz D, Lang N, Henning S, Tergau F, Paulus W (2003) Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans. J Physiol 553:293–301

53. Stagg CJ, Nitsche MA (2011) Physiological basis of transcranial direct current stimulation. Neuroscientist 17:37–53

54. Liebetanz D, Nitsche MA, Tergau F, Paulus W (2002) Pharmacological approach to the mechanisms of transcranial DC-stimulation-induced after-effects of human motor cortex excitability. Brain J Neurol 125:2238–2247

55. Stafford J, Brownlow ML, Qualley A, Jankord R (2018) AMPA receptor translocation and phosphorylation are induced by transcranial direct current stimulation in rats. Neurobiology of Learning and Memory. Available online 11 November 2017 In Press, Accepted Manuscript https://doi.org/10.1016/j.nlm.2017.11.002,

56. Mull BR, Seyal M (2001) Transcranial magnetic stimulation of left prefrontal cortex impairs working memory. Clin Neurophysiol 112: 1672–1675

57. Whitlock JR, Heynen AJ, Shuler MG, Bear MF (2006) Learning induces long-term potentiation in the hippocampus. Science. 313(5790):1093–1097

58. de Aguiar V, Paolazzi C, Miceli G (2015) tDCS in post-stroke aphasia: the role of stimulation parameters, behavioral treatment and patient characteristics. Cortex. 63:296–316. https://doi.org/10.1016/j.cortex.2014.08.015

59. Elsner B, Kugler J, Pohl M, Mehrholz J (2015) Transcranial direct current stimulation (tDCS) for improving aphasia in patients with aphasia after stroke. Cochrane Database Syst Rev 5:CD009760. https://doi.org/10.1002/14651858.CD009760.pub3