Brain Stimulation 13 (2020) 1396–1398

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: http://www.journals.elsevier.com/brain-stimulation

Education moderates the effect of tDCS on episodic memory performance in cognitively impaired patients

Keywords:
MCI
AD
Education
Cognitive reserve
tDCS
Moderation

Introduction

Transcranial direct current stimulation (tDCS) can improve episodic memory performance. In healthy aging those with higher education seem to benefit particularly [1]. Whether the same applies to pathological aging remains to be tested. In pathological aging, however, the severity of cognitive impairment, which is influenced by pre-morbid cognition, compensatory processes, and neuropathology, needs to be considered. In this pilot study, we therefore tested whether education moderates the effect of tDCS on memory performance in patients with mild cognitive impairment (MCI) or dementia due to Alzheimer's disease (AD) by also considering the level of cognitive impairment.

Methods

We recruited 28 participants (12 AD/16 MCI) from the University Medical Centre Freiburg. A diagnosis of MCI required impaired cognitive performance, the report of a cognitive complaint, no impairment in activities of daily living, and no dementia [2]. Patients with AD had to fulfil criteria for probable AD [3] and had to report impaired activities of daily living.

In a double-blind, sham-controlled, and between subject design, we randomly assigned participants to a single session of sham or real anodal tDCS during encoding of a verbal episodic memory task. We presented stimuli with Presentation® (Version 18.1, Neurobehavioral Systems, Inc., Berkeley).

Episodic memory task

During encoding, 32 nouns [4] appeared consecutively on a 14-inch computer screen (2s each). The time to the presentation of the next word was pseudo-randomly jittered between 0.5 and 2.5s. After a delay, the participants performed a free recall.

Transcranial direct current stimulation

We applied tDCS with a DC-plus stimulator device (Neuroconn GmbH, Ilmenau, Germany). We used two rubber electrodes (3×5 cm) coated with saline solution-soaked sponges. We placed the anode over the left dorsolateral prefrontal cortex (F3) and the cathode on the contralateral supraorbital region. Real tDCS consisted of 15s ramp-up followed by constant current at 1 mA (20 min) and 15s ramp-down. For sham stimulation, the current was ramped up to 1 mA but immediately ramped down again. At the end of the experiment, side effects and what the participants perceived to be the stimulation condition were captured.

Statistical analysis

In moderated moderations, we tested whether education moderated the effect of tDCS on memory performance and whether this was influenced by a) the categorical variable clinical diagnosis or b) a continuous variable representing memory impairment [5] instead of clinical diagnosis (Fig. 1A). Stimulation served as predictor and delayed recall as the outcome variable. We performed statistical analyses with SPSS (Version 24, IBM Inc., USA) and PROCESS [6], with a statistical significance level set to $p < .05$.

Results

The groups were similar regarding age, gender, education, and perceived side effects. When asked whether they thought they had sham or real tDCS, participants' responses were at chance level.

The effect of tDCS on memory performance depends on an interaction between education and clinical diagnosis

The overall fit of the model was significant [$R^2 = 0.61, F_{(7, 20)} = 4.43$, $p < .01$]. We found a significant three-way interaction such that patients with MCI and higher education benefited significantly from stimulation, while patients with AD benefited only when they were less educated [$F_{(1, 20)} = 4.55$, $p < .05$, $R^2_{\text{change}} = 0.09$, $p < .05$; Fig. 1B].

Replacing clinical diagnosis by memory impairment led to similar results

The overall fit of this model was again significant [$R^2 = 0.83$, $F_{(7, 18)} = 12.287$, $p < .001$]. We found a three-way interaction such that patients with better memory and higher education benefited significantly from stimulation, while patients with worse memory

https://doi.org/10.1016/j.brs.2020.07.008

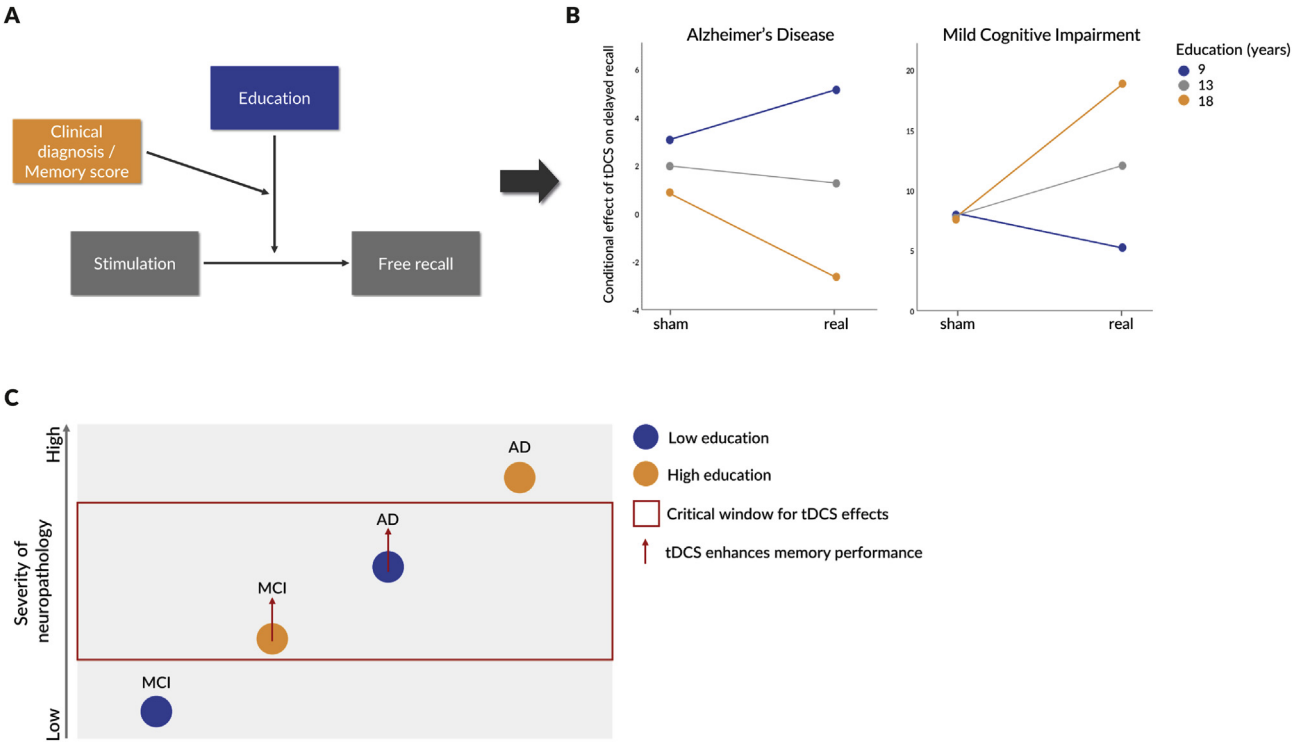

Fig. 1. **A** Schematic of the moderated moderation, **B** Stimulation effects on verbal delayed recall depend on education and clinical diagnosis, **C** Assumed association between neuropathology, education, and stimulation effects on memory performance as well as the critical window of opportunity in which transcranial direct current stimulation may be particularly beneficial.

benefited only when they were less educated [$F_{(1,\ 18)} = 21.56$, $p < .001$, $R^2_{change} = 0.19$].

Discussion

We confirmed that education moderates the effect of tDCS on memory performance. However, the direction of the effect was not consistent in all patients, indicating additional influencing factors.

According to the literature, individuals with higher education show less severe clinical symptoms than those with lower education when both groups exhibit comparable neuropathology [7]. In our sample, highly educated patients with AD retrieved significantly less words than those with lower education ($r_{(12)} = -0.62$, $p < .05$). This may indicate that highly educated AD patients were stronger affected by neuropathology and therefore less able to memorize. Indeed, we suggest that the severity of neuropathology was highest in highly educated patients with AD and least in patients with MCI and lower education (Fig. 1C). This would explain why tDCS was beneficial only for patients with AD and lower education. Highly educated individuals may have already maximally compensated their neuropathology and thus, brain damage has been too severe to allow a beneficial effect of tDCS. The reason is that the weak polarization induced by tDCS is not sufficient to induce plastic changes without ongoing background activity [8]. Thus, the combination of brain polarization induced by tDCS and a priming of brain areas to be responsive to stimulation is important. In areas where neuropathology is very severe, activity may be too low to prime responsiveness to stimulation.

Fig. 1C also suggests why only highly educated patients with MCI benefited from tDCS. Those with low education may have appeared very similar (with regard to neuropathology) to healthy controls. Therefore, and comparable to our previous study in older adults [9], tDCS did not enhance memory performance as they have already reached the maximal cortical excitability during the memory task and no additional tDCS effects were possible.

A limitation of our study is that separating 'late' MCI from 'early' AD is sometimes arbitrary. However, when we repeated our analysis with a continuous variable representing memory impairment rather than diagnosis, we found that our results as well as their interpretation still hold.

To our knowledge, this is the first study investigating whether education moderates tDCS effects on memory performance in pathological aging. While we confirmed such a moderation, the interaction between education and cognitive impairment determined who benefited the most. We suggest a certain window of opportunity for tDCS to work efficiently in pathological aging. Future studies should directly compare groups with similar neuropathology to confirm this.

Declaration of competing interest

We confirm that there are no conflicts of interest.

References

[1] Berryhill ME, Jones KT. tDCS selectively improves working memory in older adults with more education. Neurosci Lett 2012 Jul 19;521(2):148–51.
[2] Petersen RC. Mild cognitive impairment. N Engl J Med 2011 Jun 8;364(23):2227–34.
[3] McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack Jr CR, Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's Dementia 2011 May;7(3):263–9.

[4] Delis DC, Kramer JH, Kaplan E, Ober BA. California verbal learning test —. second ed. San Antonio: Tx: The Psychological Corporation.; 2000.
[5] Paajanen T, Hänninen T, Tunnard C, Hallikainen M, Mecocci P, Sobow T, et al. CERAD neuropsychological compound scores are accurate in detecting prodromal alzheimer's disease: a prospective AddNeuroMed study. J Alzheim Dis 2014;39(3):679–90.
[6] Hayes AF. Introduction to mediation, moderation, and conditional process analysis: a regression-based approach. New York: The Guilford Press; 2013. p. 507 (Methodology in the social sciences).
[7] Roe CM, Xiong C, Miller JP, Morris JC. Education and Alzheimer disease without dementia: support for the cognitive reserve hypothesis. Neurology 2007 Jan 16;68(3):223–8.
[8] Lefaucheur J-P, Wendling F. Mechanisms of action of tDCS: a brief and practical overview. Neurophysiol Clin 2019 Sep;49(4):269–75.
[9] Peter J, Neumann-Dunayevska E, Geugelin F, Ninosu N, Plewnia C, Klöppel S. Reducing negative affect with anodal transcranial direct current stimulation increases memory performance in young-but not in elderly-individuals. Brain Struct Funct 2019 Nov;224(8):2973–82.

Christine Krebs, Stefan Klöppel
University Hospital of Old Age Psychiatry and Psychotherapy, University of Bern, Switzerland

Bernhard Heimbach
Centre for Geriatric Medicine and Gerontology, Faculty of Medicine, University of Freiburg, Germany

Jessica Peter*
University Hospital of Old Age Psychiatry and Psychotherapy, University of Bern, Switzerland

* Corresponding author. University Hospital of Old Age Psychiatry and Psychotherapy, Bolligenstrasse 111, 3000, Bern, 60, Switzerland.
E-mail address: jessica.peter@upd.unibe.ch (J. Peter).

11 July 2020
Available online 23 July 2020