Final Scientific Report

# "Episodic memory enhancement in aging: the role of cognitive training combined with (bilateral) tDCS in the medial-temporal cortex and cerebellum on episodic memory performance in the elderly."

BIAL Project 495/14

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## Aims

The project “Episodic memory enhancement in aging: the role of cognitive training combined with (bilateral) tDCS in the medial-temporal cortex and cerebellum on episodic memory performance in the elderly" (BIAL project 495/14) focused on the combination of tDCS (transcranial direct current stimulation) with cognitive training (CT) to investigate neuroplasticity in older adults and further explore the involvement of the cerebellar cortex in memory processes. In particular, we were interested in understanding whether and how tDCS combined with cognitive training facilitates verbal episodic memory in older adults, compared with sham stimulation. To do this, we proposed to conduct a multi-condition, wait-list, randomized, single-blinded with a third blinded rater, and sham controlled study.

## Methods

### Participants

Fifty-six healthy elderly (≥ 60 years old) were included in the study. Participants were recruited through means of broad-based advertisements in the community (e.g., flyers, websites, public talks) and referral institutions (e.g., senior universities, community health centers, nursing homes). All the participants were Portuguese native speakers, right-handed, had no history of neuropsychiatric disorders (e.g., stroke, epilepsy, dementia, depression) or head injury, had no metallic implants, did not intake concurrent medication likely to affect cognition and had no history of alcohol and drug abuse or dependence. Written informed consent was obtained from all participants prior to the beginning of the study. Participants were each paid €50 upon completion of the study. This study was approved by the Ethics Committee of the Faculty of Psychology and Educational Sciences of the University of Coimbra and performed following the ethical principles of research with human subjects.

### Procedure

Screening for eligibility was performed by phone and in-person before commencement of the study. Upon inclusion in the study, participants were randomly assigned (1:1:1:1) to the following groups: 1) anodal tDCS to the left DLPFC plus cognitive training; 2) anodal tDCS to the right cerebellum plus cognitive training; 3) sham tDCS plus cognitive training; 4) wait list group. Participants allocated to the first three conditions were not informed as to what group they were allocated but were told that they were receiving either active or sham tDCS stimulation. There were 15 study sessions: baseline assessment, 12 stimulation sessions, post-intervention assessment and 4-month follow-up. The 12 stimulation sessions were conducted on consecutive weekdays, at the same time of the day, and comprised 20minutes of anodal tDCS (either to the left DLPFC or to the right cerebellum), followed by 1 hour of computer-based or pen-and-paper cognitive training tasks. Both the participant and the investigator administering the cognitive training were blinded to the experimental condition and only the investigator applying tDCS was aware of the participants’ allocation per group. The assessment sessions (baseline, post-intervention and follow-up) included a neuropsychological assessment protocol, carried out by an external blinded rater, and a MRI. After completion of the intervention sessions (session 12), participants in the tDCS+CT training conditions were asked to guess whether they had received

active or sham tDCS. Participants were unblinded to their condition (i.e. active or sham tDCS+CT) after the follow-up session.

**Cognitive training tasks**

The cognitive training program consisted of 12 sessions of computerized and pen-and-paper exercises focused on memory training. The training was organized in 6 sessions per modality (computer/pen-and-paper), administered in alternate order, to increase the sessions' dynamics and the participants' interest. For the interactive computerized exercises, specific tasks of the RehaCom® cognitive rehabilitation software were used (memory for words and memory for faces; Hasomed, 2012). On the other hand, the pen-and-paper tasks focused on similar exercises, administered in a different format. The pen-and-paper tasks were adapted from a memory training program (Silva, 2016; Silva et al., 2017) and included the following domains: autobiographical memory, attention, semantic memory, verbal and visual episodic memory.

**tDCS**

Anodal tDCS was applied daily for 12 consecutive weekdays in all experimental sessions, using a TCT Stimulator Model 101 (Research Limited, Hong Kong, China). From the four intervention groups mentioned above, two received active and one received sham tDCS. In the active tDCS groups, electric stimulation was given continuously for 20minutes, with 60 second ramping up and down, at an intensity of 2mA. The anode electrode was either placed on the left DLPFC, over the T3 location according to the 10-20 EEG international system, or over the right cerebellar cortex, following the set up proposed by Pope and Mial (Pope & Mial, 2012) – 1cm under and 4cm lateral to the inion. In the sham condition, current was applied for 60 seconds only (30 seconds ram up and 30 seconds down). It should be noted that less than 3 minutes of tDCS induces no effects on cortical excitability (Nitsche & Paulus, 2011) and using 60 seconds of stimulation is a reliable method of blinding, as it induces similar sensations on the scalp as real tDCS. For each montage, the reference electrode (cathode) was applied over the right deltoid muscle. The extra-cephalic reference was used to avoid the possible confounding effects that may be induced by two electrodes with opposite polarities. For all conditions, the anode and cathode rubber electrodes (5 x 5 cm, 25cm2) were placed inside a sponge soaked in saline solution and held in place by cloth straps with velcro. Throughout the duration of each session, the participants were accompanied by an investigator, who continuously monitored the current intensity and impedance. The tDCS device was placed by the investigator behind the participants, to preserve blinding. After every tDCS session, the stimulation sites were checked for side-effects and a questionnaire was filled out.

Still regarding tDCS, we changed the stimulation site proposed in the initial protocol, as we found the medial temporal cortex (proposed in the initial protocol) hard to reach using this non-invasive neuromodulation method. Therefore, we decided to stimulate the dorsolateral prefrontal cortex, which is also a region extremely linked to memory processes, well reported in the literature.

**Neuropsychological Assessment**

The neuropsychological assessments were conducted before, immediately after and 4 months after the intervention to assess its long-term effects. Our protocol for the neuropsychological

assessment included our main outcome (memory domain) and other domains, to assess the possible interference effects of the intervention. The final version of the instruments used is outlined below:

**Screening**

- **Cognitive/Intelectual Global Assessment:** *Montreal Cognitive Assessment* (MoCA; Nasreddine et al., 2005; Simões et al., 2008; Freitas et al., 2011).
- **Cognitive Assessment**: *Alzheimer's Disease Assessment Scale – Cognitive Subscale* (ADAS-Cog; Mohs et al., 1983; Rosen et al., 1984; Guerreiro et al., 2008).
- **Emotional Functioning:** *Geriatric Depression Scale* (GDS-30; Yesavage et al., 1983; Simões, Prieto, Pinho, & Firmino, 2015).
- **Functional Assessment:** *Functional Assessment Inventory of Adult and Elderly* (IAFAI; Sousa et al., 2013).

**Cognitive Assessment – Memory:**

- *Subjective Memory Complaints – SMC* (Schmand et al., 1996; Ginó, Mendes, Mendonça, & Guerreiro, 2015)
- *Free and Cued Selective Reminding Test – FCSRT* (Buschke, 1984; Grober & Buschke, 1987; Lemos et al., 2012)
- *Continuous Visual Memory Test* (CVMT; Trahan & Larrabee, 1988).

**Cognitive Assessment – Attention, Processing speed, Executive Funtion/Language:**

- *Toulouse-Piéron Cancellation test* (Toulouse & Piéron, 1904; Amaral, 1967).
- *"Symbol search"and "Code" – Subtests of the Wechsler Adult Intelligence Scale* (WAIS-III; Wechsler, 1997, 2008).
- *Stroop* (Golden & Freshwater, 1994; Fernandes, 2013).
- *Verbal Fluency test* (Cavaco et al., 2013; Santos, 2009).

**Quality of Life:**

- *World Health Organization Quality of Life-Older Adults Module* – WHOQOL-OLD; Power, Quinn, Schmidt, & WHOQOL-Old Group, 2005; Vilar, Sousa, & Simões, 2015).

**MRI**

Images were acquired using a Siemens TRIO 3-T scanner at the host. The participants lay supine with their heads snugly fixed with foam pads to minimize head movement. The resting-state functional imaging data were comprised of 200 continuous EPI whole-brain functional volumes: 32 axial slices; 4mm thickness; TR= 2000ms; TE= 33ms; FA=73°; matrix size= 64× 64; FOV= 200× 200 mm; voxel size= 3.125× 3.125× 4 mm. During resting-state fMRI scanning, participants were instructed to close their eyes, keep still, and not think about anything systematically or fall asleep. T1-weighted anatomical images were acquired were acquired using a 3D MPRAGE sequence: 144 slices; 1.33mm thickness; TR=2530ms; TE=3.39ms; inversion time=1100ms; FA=7°; FOV=256×256mm; voxel size=1.0×1.0×1.33mm; matrix size=256×256. Diffusion-weighted data were acquired with the following parameters: time repetition (TR)/time echo (TE) 8900 ms/86 ms, image resolution 128 X 128 with 70 slices and voxel size of 2X2X2 mm. Monopolar diffusion weighting was performed along 69 independent directions, with a b-value of 1000 s/mm2. Ten reference images with no diffusion weighting (b = 0) were also obtained for each data set.

**Results and Discussion**

We first wanted to understand if tDCS combined with CT facilitates verbal episodic memory in healthy older adults. Our results show an improvement in verbal episodic memory tasks in the groups receiving CT + tDCS. Interestingly, there is a greater improvement and consistency in the group receiving CT + tDCS in the rCC.

What about at the neuroimaging level? Is it possible that the combination of tDCS with CT could modify the functional connectivity network? In fact, we have neuroimaging data showing that participants receiving excitatory tDCS over the rCC present an increase of the functional connectivity in the left hippocampus. Specifically, the participants of this group show higher functional connectivity between the hippocampus – a main episodic memory area – and the superior temporal gyrus, the middle temporal gyrus, and the posterior cingulate cortex. Other studies also show the coupling between the hippocampus and those areas, reflecting the verbal episodic memory functional network. These results demonstrate an effect of the intervention at the neural level and support the importance of the cerebellum in cognition. Moreover, our neuroimaging data support the results from the neuropsychological assessment, since the group that received tDCS over rCC is also the group that shows enhanced behavioral performance in verbal episodic memory tasks.

We then focused on anatomical connectivity by testing, using DTI, whether white matter tracts around the hippocampus were differently affected by tDCS. For this set of data, we indeed show white matter diffusion differences in the hippocampus for the participants receiving tDCS over rCC, but not for the other groups. These results suggest that tDCS over rCC combined with CT could establish a more direct pathway in promoting hippocampal plasticity.

Overall, these data suggest that CT and neuromodulation hold promise as a means to enhance cognitive functions in healthy elderly. Furthermore, greater light is also shed on the role of the cerebellar cortex in cognitive processing.

Once we had difficulties in recruiting eligible participants, we could only conclude the implementation phase of the project in the end of the year 2017. This fact didn't allow us to have the results ready to submit in a manuscript form. These results and conclusions are now in the process of being written and will be submitted soon.

Importantly, and as can be seen in the list of publications below, this project also allowed us to develop different studies in the topic of aging. Because we had access to an elderly population and because of the extensive assessment protocol that we put in practice, we were able to develop a normative study to the Portuguese population. Specifically, the main goals of that normative study were to demonstrate the validity of ADAS-Cog (Alzheimer's Disease Assessment Scale – cognitive sub-scale) and to establish robust norms to evaluate the performance of the Portuguese population. Attached is a paper (Nogueira et al), which describes these data.

We also perform a review study to analyze the reported effects in the literature of neuromodulation techniques on cognitive abilities in healthy older adults. Attached is a paper (Martins et al), which describes these results.

**Conclusions and recommendations**

We believe this project has been very successful, since we were able to achieve all the scientific goals. Furthermore, we also overcome our main difficulty, which was the recruitment. Although we had a big number of people interested in participating on the project, our stringent eligibility criteria prevented most of these from being included. To circumvent this, we needed a 6-months extra time to conclude the project and the recruitment was a necessary process until the end of

the time. Due to this fact, we were able to conclude the pre and post visits of all participants, but the follow-up visit of four participants will happen until April of the current year.
Moreover, this project grant allowed to expand the research team – a research assistant, and for a short period of time, another research assistant that helped with the final MRI analysis. This was also a project where we had different Master students participating in the collection and the data analysis. In fact, two of our students will finish their Master thesis this year and their work will be related to this project.
For these reasons we would like to thank the BIAL Foundation for having funded our project. We hope that in the future you will consider our research worthy of your support.

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