Aging Clinical and Experimental Research
https://doi.org/10.1007/s40520-020-01546-8

ORIGINAL ARTICLE

Effects of short- and long-term neurostimulation (tDCS) on Alzheimer's disease patients: two randomized studies

Antonio Gangemi[1] · **Barbara Colombo**[2] · **Rosa Angela Fabio**[3]

Received: 18 December 2019 / Accepted: 30 March 2020

Abstract

Background Non-invasive brain stimulation is an effective treatment for Alzheimer's disease.

Aims The purpose of the two studies presented here is to compare the short- and long-term effects of transcranial direct current stimulation (t-DCS) on two samples of advanced AD patients.

Methods In Study 1 26 patients were involved in a 10-day anodal vs. sham tDCS intervention stimulating the left frontotemporal cortex. A pre–post test assessment was run using two different neurocognitive tests and EEG data. The same protocol was used in Study 2, which involved 18 different patients who underwent the same intervention 10 days a month for 8 months.

Results Results confirmed how the t-DCS intervention was effective both in the short- and the long-term to slow down the progression of AD on specific neurophysiological domains and, to a certain extent, on neurophysiological activity.

Discussion

tDCS appear to be effective and to affect differently neurocognitive and neurophysiological functions when comparing short and long-term outcomes.

Conclusions

Anodal-tDCS is an effective way to slow down the progression of Alzheimer's both in the short and long term. It can also affect the EEG patterns, but this requires a more protracted intervention.

Keywords Alzheimer · tDCS · EEG · Fronto-temporal cortex · Neuromodulation

Introduction

Alzheimer's disease (AD) is the most common form of dementia in the elderly population, characterized by cognitive and behavioral changes that interfere with social relationships and functional activities [1]. It is a progressive neurodegenerative disorder and it causes deficits in cognitive activities and executive functions including cognitive flexibility [2], planning [3], and abstract reasoning [4]. Memory disturbances appear early, at first affecting the ability to learn and retrieve information, and later causing impairments in recognition memory [5] and attention [6].

Some of the most common treatments for AD have limited efficacy, are expensive, sometimes ineffective, and induce side effects [7]. For these reasons, finding alternative or complementary therapeutic strategies is crucial.

Because it has been suggested that AD's behavioral effects result from changes in neuronal activity [8], defined as changes in modulatory transmitter systems and network connectivity—therapies that address these changes from different perspectives have been investigated during the last decade. A promising strategy that emerged from these studies is non-invasive brain stimulation. Non-invasive brain stimulation can be used as a part of specific rehabilitative or preserving interventions for several pathologies [9–11]. Moreover, plasticity mechanisms, triggered by brain stimulation, also play a role in AD, since an increase in the activation of areas involved in memory or the recruitment of new areas has been previously shown [12].

✉ Barbara Colombo
bcolombo@champlain.edu

[1] Department of Cognitive Science and Education, University of Messina, Messina, ME, Italy

[2] Neuroscience Lab, Champlain College, Burlington, VT 05402, USA

[3] Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy

Published online: 16 April 2020

A commonly used technique is transcranial direct current stimulation (tDCS), which modulates cortical excitability and induce neuroplasticity mechanisms [13, 14], that outlast the period of stimulation, due to effects on synaptic long-term potentiation/depression [15]. Patients do not report any side effects or discomfort, and the sham condition is extremely effective.

Several studies have shown a positive effect of tDCS on AD-related symptoms, but protocols are very different and so are the evaluation criteria. Studies report data from case studies or small samples, as well as conflicting results.

Studies that stimulated the left Dorsolateral Prefrontal Cortex (DLPFC) aimed at addressing cognitive functions and memory [16, 17]. Results from case studies [18] and larger samples [19] not always appear to add an additional benefit to other interventions, like individual memory training [20]. A possible explanation for these conflicting results would be hypothesizing that the lDLPFC is not the ideal site to target. As an alternative, other researches target the left temporal and frontotemporal areas of AD patients. They mainly address memory functions or verbal and visual memory. Yet, protocols and size samples are very different and further confirmation is needed. For example, Bystad and colleagues [21] discuss a case study using "accelerated tDCS" (stimulation is administered at short intervals [22]). They examined the effect of 12 anodal stimulations on T3 over six consecutive days. The patient was tested (neuropsychological testing and EEG) before the first tDCS stimulation, 2 days after the last tDCS stimulation and 2 months after the stimulation. The patient improved his verbal memory and his score on the MMSE. No significant changes in the EEG pattern emerged. Interestingly enough, another study using a similar protocol [23] found no positive effects of anodal tDCS in improving verbal memory function on a sample of 25 patients.

Another relevant question concerns the effects of long-term tDCS on AD symptoms. Most of the studies discussed above reported results obtained with one to 10 sessions, with the most typical tDCS paradigm consisting of 30-min sessions conducted for 5 days [22]. To our knowledge, only one single-case study on long-term effects is reported in the literature [24]. The case study reports positive results (improvement in memory functions and stabilization of other cognitive functions) of a—8 months daily anodal tDCS treatment (at 2 mA) over T3. However, these results are based on a single case: variables such as genetic factors, nutrition, medication, or cognitive reserve levels might have influenced the outcome as well.

If anodal tDCS appears to be a promising tool to slow down some of the symptoms related to AD, more evidence is needed using larger samples and exploring long-term effects. The aim of the 2 studies reported in this paper is to address these aspects by testing the short and long-term effects of anodal tDCS on the frontal lobes of two groups of AD patients.

Method: Study 1

The aim of the first study was to explore the effects of a 10-day anodal tDCS protocol over the left frontotemporal cortex (F7) in stabilizing the cognitive decline of AD patients. The study was approved by the local Ethical Committee with protocol number 2016.33.

The primary outcome of this first study the effect of anodal tDCS on MMSE score; secondary outcomes were effect on specific subscales of the MMSE and MODA and effects on EEG bands.

Sample

Based on the clinical sample size commonly reported in the literature and on the estimation of sample size, researchers recruited 26 patients (age between 65 and 74, $F = 16$; see Table 1) diagnosed with mild AD. Patients have been randomly assigned to either the experimental or control group, making sure that the gender distribution was equal in the two groups. The sample size was determined based on the prevalence studies data of Alzheimer's Disease Patients that range from 2.5 to 4.7% and statistical calculation of the number of patients required for significant results [25, 26]. With a 95% confidence limit, and 5% marginal error, and the sample size ranges from 13 (with 2.5%) to 25 (with 4.7%).

Socio-demographic and neuropsychological information are reported in Table 1.

Informed consent was obtained from all the patients.

Inclusion and exclusion criteria

All the patients had been evaluated using an MRI or a CAT scan, a medical evaluation and a neuropsychological evaluation. Their AD diagnose was consistent with the criteria listed in the DSM-V and NINCDS-ADRDA 89 [1]. All selected patients had an MMSE score between 14 and 20

Table 1 Socio-demographic and neuropsychological characteristics of the sample

Variables	Mean score (SD) Experimental group	Mean score (SD) Sham group
Age (years)	67.5 (2.8)	69.01 (3.1)
Education (years)	6.5 (2.0)	6.1 (2.1)
MMSE (score)	14.9 (1.8)	15.3 (1.8)
MODA (score)	73.2 (3.7)	74.1 (1.9)

and a MODA score between 72 and 82. Any other neurodegenerative disease has been excluded.

All the patients included in the study had been on a stable dose of cholinesterase inhibitors with a dosage of 10 mg a day, for at least 1 year prior to the onset of the study.

Advanced AD diagnosis, medical history of neurosurgery, metallic implants, medical history of pace-maker implants or arrhythmias, medical history of epilepsy were used as exclusion criteria.

Two patients of the originally selected sample were excluded, because they did not meet one eligibility criteria.

Neurocognitive and neurophysiological assessment

The patients' level of cognitive impairment was assessed using the Mini-Mental State Exam (MMSE) [27], which includes questions about orientation, attention, recall, and language. They were also assessed using the Milan Overall Dementia Assessment (MODA)—[28], devised using the neuropsychological profile of AD as a model. The MODA is divided into three sections: an autonomy scale (considers aspects of everyday coping ability: walking, dressing, personal hygiene, sphincter control, and eating) and two test sessions: orientation (time, space, personal and family orientation) and cognitive functions (attention, intelligence, memory, language, space cognition, and visual perception).

The neurophysiological assessment has been performed using EEG equipment with 32 acquisition channels. EEG data were recorded in a quiet room, with the subject awake and comfortably seated. Patients were instructed to rest with their eyes closed for most of the session. Patients were also instructed to open their eyes for brief periods of time to record reactivity to the alpha rhythm in the occipital cortex.

Nineteen electrodes were positioned according to the 10–20 International System using an EEG cap. The reference electrode was positioned on FPz, while the ground electrode was positioned behind Fz, mirroring the procedure reported in previous studies [29].

The sampling frequency was 256 Hz with bandpass filtering between 3 and 60 Hz. A notch filter was used to reject the 50 Hz power line noise.

The recording session lasted 20 min for each patient. From each recording, 4 epochs were selected (3 min each and free from artifacts). These epochs have then been analyzed using Mathlab software to evaluate activity and peak EEG frequency for beta and theta rhythms and activity, focusing on central and frontal/temporal channels.

Intervention

The tDCS equipment used in the study was the BRAINDEE transcranial direct current stimulator built by Omicron-t. The stimulation was delivered using two sponge-based electrodes (25 mm each). The anodal electrode was positioned on the left frontotemporal lobe (F7-T3); the reference electrode was positioned on right frontal lobe (Fp2). Electrodes' position was identified through the 10–20 EEG international system.

Stimulation was administered at an intensity of 2 mA (current density: 2.5 mA/cm^2) for 20 min, daily, for 10 days. In the sham condition, electrodes were placed as in the experimental stimulation, but the stimulation automatically ramped down 10 s after the start of the session, which is not enough to deliver any effective stimulation to the brain. To ramp off stimulation allows participants to feel the characteristic tingling sensations in the vicinity of the electrodes and, therefore, makes it possible to keep them blind to the stimulation condition while effectively not receiving stimulation during the control (sham) condition.

Procedure

The patients were recruited from the "Policlinico Madonna della Consolazione" Hospital of Reggio Calabria (Italy).

Participants were randomly assigned (using a computer-generated list of random numbers implemented by an investigator with no clinical involvement in the trial) either to the experimental group (anodal stimulation) or the sham group (sham stimulation), with equal randomization (1:1). It was a double-blind, sham-controlled, parallel-group design. The investigator with no clinical involvement managed the tDCS settings according to the randomization plan, to prevent both the persona administering the tDCS and the patient to be aware of the experimental condition.

Experimental and sham group were equivalent for age, MMSE and MODA scores (Table 1).

An ABA design has been used: pre-test (A), intervention (B), post-test (A′—after the intervention). The intervention was performed daily for 10 days for both the experimental and sham groups.

Patients kept taking their medication through the duration of the study.

Statistical analyses

All statistical analyses were performed using IBM SPSS software version 22. The main aim of the analyses was to explore possible differences between experimental (i.e., anodal stimulation) and control group (i.e., sham stimulation) in task performance as derived by the number of correct responses to the MODA test (and the related subscales). Repeated-measures (RM) ANOVAs have been performed, using the experimental group as a between-subject factor, and the phases—pre-and post-tests—and the subscales as within-subject factors. Moreover, if the RM ANOVAs were significant, we carried out a post hoc analysis by applying Bonferroni's correction to identify which group

show changes between pre and post-test. Post hoc pairwise comparisons were made using the Student paired *t* test. To address the multiple comparisons issue, significance was only ascribed to level $p < 0.005$.

Results are reported as mean (SD) unless otherwise stated.

Results: Study 1

Effects of brain stimulation on neuropsychological performance

Focusing on the patients' MODA score, a 2 × 2 RM GLM MANOVA has been computed, using the group condition (experimental vs. sham) and the two evaluations (pre-test vs. post-test) as a between-subject variable and the MODA scores as dependent variables.

A significant main effect of the variable group emerged ($F_{1,40} = 8.71$; $p < 0.001$, $d = 0.76$) as well as a significant interaction effect between Group and evaluation phase ($F_{1,40} = 11.02$; $p < 0.001$, $d = 0.78$). The scores of the experimental group did not change significantly, while the sham group shows a clear decrease in their cognitive performance (see Table 2).

The same 2 × 2 RM MANOVA was computed focusing on the MMSE scores.

A significant main effect of the variable group emerged ($F_{1;40} = 80.14$; $p < 0.01$, $d = 0.81$), while no significant interaction effect between the group and the evaluation phase emerged ($F_{1;40} = 3.14$; $p < 0.09$, $d = 0.67$). Patients in the experimental group showed almost no change in their score between the and post-test phase, while the sham group shows an average 5 points difference in their scores between the pre- the post-test (Table 2).

The same 2 × 2 RM MANOVA has been computed considering the individual subscales of each test.

Considering temporal orientation, the intervention returned a significant effect both for the MODA ($F_{1;40} = 2.96$; $p < 0.01$, $d = 0.65$) and the MMSE temporal orientation scores ($F_{1;40} = 2.90$; $p < 0.01$, $d = 0.67$). Anodal tDCS apparently helped preserving skills in the experimental group, which were negatively affected in the sham group ($t = 3.11$, $p < 0.005$).

The same trend emerged when considering spatial orientation. Both questionnaires (MODA: $F_{1;40} = 1.02$, $d = 0.56$; $p < 0.001$; MMSE: $F_{1;40} = 1.05$; $p < 0.05$, $d = 0.56$) showed how tDCS was effective in preventing participants to lose spatial orientation skills between the pre- and the post-test, while the opposite was true for the sham group ($t = 4.11$, $p < 0.003$).

Considering the MODA scores for personal orientation, the experimental group showed an actual improvement at the follow-up test, while the sham group scored got significantly worse ($F_{1;40} = 5.55$; $p < 0.05$, $d = 0.87$; paired *t* test for the sham group: $t = 3.65$, $p < 0.004$).

No significant change emerged when considering the MODA subscales for family orientation, autonomy, reversal learning, verbal intelligence, and word production. Similarly, no significant change emerged when considering the MMSE subscales words memory and language.

Focusing on other specific MMSE subscales, a significant positive effect of anodal tDCS emerged for attention and calculation ($F_{1;40} = 4.07$; $p < 0.05$, $d = 0.87$): the experimental group did not get any worse, while the opposite was true for the sham group ($t = 4{,}01$, $p < 0.004$).

The same trend emerged when considering the ability to recall (MMSE) ($F_{1;40} = 3.07$; $p < 0.05$, $d = 0.81$). Data also reported a significant positive effect of tDCS in preventing worsening of apraxia symptoms (MMSE) ($F_{1;40} = 5.72$; $p < 0.01$, $d = 0.88$; paired t test for the sham group: $t = 2.99$, $p < 0.004$).

Effects of brain stimulation on neurophysiological activity

To examine the modifications in broad-band frequency representations of alpha and beta oscillations, these signals were extracted using the following passbands: 4–7 Hz (theta), 9–12 Hz (alpha), and 16–26 Hz (beta). With their respective transition widths, this gave full width at half-maximum responses of 3.5–8 Hz (theta), 7.6–13.7 Hz (alpha), and 14–29.9 Hz (beta). We decided to focus on these specific bands, given the relevance of their oscillations for Alzheimer's patients reported in the literature [30–32]

A 2 × 2 RM GLM MANOVA has been computed, using the group condition (experimental vs. sham) and the two evaluations (pre-test vs. post-test) as a between-subject

Table 2 Mean scores (and standard deviations) for MMSE and MODA tests

Group	MMSE Pre-test	MMSE Post-test	MODA Pre-test	MODA Post-test
Experimental	15.15 (2.49)	14.85 (2.64)	74.00 (8.21)	73.75 (3.78)
Sham	16.00 (1.71)	13.62 (2.96)	74.00 (6.45)	67.12 (4.21)
	$t = 2.98$, $p < 0.005$		$t = 3.6$, $p < 0.005$	

Table 3 Neurophysiological rhythms (alpha, beta, and theta) before and after tDCS intervention

EEG	Experimental group		Sham group	
	Pre-test	Post-test	Pre-test	Post-test
	M (SD)	M (SD)	M (SD)	M (SD)
Alfa rhythm	8.29 (0.31)	8.24 (1.20)	8.11 (2.2)	8.05 (0.17)
Beta rhythm	14.6 (1.1)	14.9 (1.7)	14.6 (1.1)	14.5 (1,1)
Theta rhythm	7.12 (1.6)	6.79 (0.74)	6.9 (0.54)	6.1 (0.59)

Table 4 Socio-demographic and neuropsychological characteristics of the sample

Variables	Mean score (SD) Experimental group	Mean score (SD) Sham group
Age (years)	68.5 (2.8)	68.7 (3.1)
Education (years)	6.7 (2.0)	6.2 (2.7)
MM SE (score)	15.8 (1.8)	15.9 (1.6)
MODA (score)	74.5 (3.7)	74 (2.4)

variable and the alfa, beta and theta frequency bands as dependent variables.

Focusing on alpha, beta and theta bands, no significant main effects of the variable Evaluation emerged as well as no significant interaction effect between Group and Evaluation. Scores did not change significantly, and that was true for both the experimental and sham groups (Table 3).

The aim of the second study was to explore the long-term effects (8 months) in stabilizing the cognitive decline of AD patients of an anodal tDCS intervention, using the same protocol of Study 1.

Method: Study 2

The primary outcome of this second study was the long-term effects of anodal tDCS on the MMSE score; secondary outcomes were effect on specific subscales of the MMSE and MODA and effects on EEG bands.

Sample

Study 2 involved a different sample (for clinical reasons: the second study took place serval months after the first one and several patients included in the first study did not meet the eligibility criteria; a few patients also decided not to join the second study) of 18 patients (age between 69 and 76, $F = 13$; Table 4) diagnosed with mild AD. All the patients had been evaluated using the same protocol of study 1. Patients have been randomly assigned to either the experimental or control group, making sure that the gender distribution was equal in the two groups

Socio-demographic and neuropsychological information are reported in Table 4.

Inclusion and exclusion criteria

All patients selected to be involved in the study had an MMSE score between 14 and 20 and a MODA score between 72 and 82. Any other neurodegenerative disease has been excluded. All patients had been on a stable dose of cholinesterase inhibitors with a dosage of 10 mg a day, for at least 1 year prior to the onset of the study. The same exclusion criteria of the first study were used.

Neurocognitive and neurophysiological assessment

Same as Study 1.

Intervention

The same tDCS equipment used for Study 1 has been used. Anodal tDCS has been administered to patients at an intensity of 2 mA (current density: 2.5 mA/cm^2) for 20 min, daily, for 10 consecutive days each month, for 8 months.

Procedure

Same as Study 1.

Results: Study 2

Effects of brain stimulation on neuropsychological performance

Considering the patients' score in response to the MODA test, a 2 × 2 RM GLM MANOVA has been computed, using the group condition (experimental vs. sham) and the two evaluations (pre-test vs. post-test) as a between-subject variable and the MODA scores as dependent variables.

A significant main effect of the variable Group emerged ($F_{1;32} = 12.71$; $p < 0.01$, $d = 0.76$) as well as a significant interaction effect between Group and Evaluation ($F_{1,32} = 546.83$; $p < 0.001$, $d = 0.98$). Scores for the experimental group did not change significantly, while the sham group shows a clear decrease in their cognitive performance (Table 5).

The same 2 × 2 RM MANOVA was computed for the MMSE scores. Mean scores and Standard deviations are reported in Table 5.

A significant main effect of the variable Group emerged ($F_{1;32} = 14.1$; $p < 0.01$, d = 0.81) as well as a significant

Table 5 Mean scores (and standard deviations) for MMSE and MODA tests

Group	MMSE Pre-test	MMSE Post-test	MODA Pre-test	MODA Post-test
Experimental	16.11 (2.1)	15.83 (2.84)	71.06 (5.92)	70.83 (6.63)
Sham	16.00 (1.71)	11.92 (2.77)	73.80 (7.98)	64.81 (7.61)
	$t=4.22$, $p<0.001$		$t=3.71$, $p<0.005$	

interaction effect between Group and Evaluation ($F_{1;32}=24.14$; $p<0.01$, $d=0.87$). Patients in the experimental group did not score almost any worse at the post-test, while the sham group shows an average 6 points difference in their scores between the pre-test and the post-test (Table 5).

A 2×2 RM MANOVA has been computed considering the individual subscales of each test. Focusing on temporal orientation, the intervention returned a significant effect both for the MODA ($F_{1;32}=2.32$; $p<0.01$, $d=0.65$) and the MMSE scores ($F_{1;32}=3.10$; $p<0.01$, $d=0.67$). Anodal tDCS helped to maintain skills linked to temporal orientation in the experimental group, while the same skills were negatively affected in the sham group ($t=6.11$, $p<0.005$).

The same trend emerged when considering spatial orientation. Both questionnaires (MODA: $F_{1;32}=1.99$, $p<0.01$; $d=0.56$; MMSE: $F_{1;32}=1.88$; $p<0.05$, $d=0.56$) showed a positive effect of tDCS in preventing participants to lose spatial orientation skills between the pre-test and the 8-month post-test, while the opposite was not true for the sham group.

Considering the MODA scores for personal orientation, the experimental group showed no significant change at the follow-up test, while the sham group's scores got significantly worse ($F_{1;32}=2.84$; $p<0.05$, $d=0.87$; paired t test for the sham group: $t=5.11$, $p<0.001$).

No significant change emerged at the 8-month post-test in any of the MODA subscales linked to family orientation, autonomy, reversal learning, verbal intelligence, and word production. Similarly, no significant change emerged for the MMSE subscales for words memory and language.

Considering the other MMSE subscales, a significant positive effect of anodal tDCS emerged for attention and calculation ($F_{1;32}=3.87$; $p<0.05$, $d=0.87$): the experimental group did not lose any of their ability, while the opposite was true for the sham group, $t=5.11$, $p<0.001$. The same trend emerged when considering the ability to recall (MMSE subscale) ($F_{1;32}=2.97$; $p<0.05$, $d=0.81$). Data also highlighted a significant positive effect in preventing worsening of apraxia symptoms (MMSE) after the tDCS treatment ($F_{1;32}=3.99$; $p<0.01$, $d=0.88$; paired t test for the sham group: $t=4.23$, $p<0.001$).

Effects of brain stimulation on neurophysiological activity

To explore possible modifications in the alfa, beta and theta bands, a 2×2 RM GLM MANOVA was computed, using the group condition (experimental vs. sham) and the two evaluations (pre-test vs. post-test) as between subject variables and the alfa, beta and theta frequency bands as dependent variables. We decided to focus on these specific bands, given the relevance of their oscillations for Alzheimer's patients reported in literature [30–32]

Significant main effects of the variable Evaluation emerged for alpha, beta and theta bands (respectively, $F_{1;32}=312.57$; $p<0.001$, $d=0.88$; $F_{1;32}=168.96$; $p<0.001$, $d=0.91$; $F_{1;32}=246,59$; $p<0.001$, $d=0.93$) as well as a significant interaction effect between Group and Evaluation (respectively, $F_{1;32}=168,40$; $p<0.001$, $d=0.88$; $F_{1;32}=167,18$; $p<0.001$, $d=0.91$; $F_{1;32}=156,12$; $p<0.001$, $d=0.93$ ($F_{1;32}=11.02$; $p<0.001$). Scores for experimental group did not change, while the sham group shows a clear decrease in alpha and beta bands, paired t test for the sham group were respectively: $t=3.12$, $p<0.004$ and $t=4.23$, $p<0.002$ (Table 6).

Discussion

This paper presents two studies aimed at assessing the short (Study 1) and long-term (Study 2) effects of anodal tDCS on the left frontotemporal lobe in AD patients. Results confirmed how anodal t-DCS intervention is effective both in the short and the long-term to slow down the progression of AD on specific neurophysiological domains and on neurophysiological activity. Participants in the

Table 6 Neurophysiological rhythms (alpha, beta, and theta) before and after the tDCS intervention

EEG	Experimental Group		Sham Group	
	Pre-test	Post-test	Pre-test	Post-test
	M (SD)	M (SD)	M (SD)	M (SD)
Alfa Rhythm	8.10 (.19)	8.17 (1.2)	7.9 (.21)	7.1 (.28)
Beta Rhythm	14.2 (1.6)	14.3 (1.3)	14.7 (1.0)	10.94 (1.12)
Theta Rhythm	7.04 (1.62)	6.64 (1.7)	6.8 (1.3)	4.8 (1.5)

experimental group were able to maintain the same level of neuropsychological performance, while the participants in the sham group showed a significant decrease. This was true both for the short and the long-term intervention. This first result offers evidence to support previous findings either based only by single case studies [21, 24] or only partially confirmed by data [23]. Moreover, this suggests that if a tDCS based intervention can be effective in the short term by stabilizing neurocognitive functions, this effect can be prolonged over 8 months. No other studies (to our knowledge) explored the effect of the same protocol over short- and long-term intervention; moreover, studies reporting results of long-term interventions were conducted only on single cases. Our two studies had relatively small (if statistically acceptable) samples, but it also worth mentioning that the effect size that we achieved was constantly high. This implies a very strong and clear relationship between our target variables, and add more promises to well-designed tDCS-based interventions to slow down the progression of AD.

Our studies, using two scales that measure different neuropsychological domains, allowed to gain a better understanding of the effects of tDCS on specific cognitive domains. Both studies recorded a positive effect on temporal and personal orientation, attention, calculation, and recall. The intervention was also successful, in both studies, in preventing worsening of apraxia symptoms. The only other study who used MMSE to assess the effect of an anodal tDCS based intervention [19] found an improvement (after 2 months) for the experimental group in specific MMSE subscales: orientation, registration, attention, and language. The partial differences in results could be due to the fact that the stimulation protocol was different: they focused on the DLPFC and their stimulation sessions lasted 25 min instead of 20. Moreover, for their neurocognitive evaluation, they used MMSE and the WAIS—the two tools combined might have influenced participants' performance. The fact that our results (using two similar scales that are less likely affect each other scores) have been confirmed by both assessments and by both studies is encouraging.

Marceglia and colleagues [33] discuss a positive effect of anodal tDCS in modulating in the cortical EEG activity in AD patients and partially reversing the abnormal patterns of EEG activity after one anodal tDCS session. Our results support the fact that tDCS can positively influence EEG patterns, but we found this effect to be significant only after a long-term intervention. This difference could be explained by the fact that the other study [33] involved a small sample of patients with Probable AD (MMSE score > 20), while our sample included patients with confirmed diagnose of AD and an MMSE score between 14 and 20. This comparison also suggests that tDCS might have an immediate effect on modulating EEG patterns with patients in a very early stage of the disease. Working with moderate AD, the treatment has to be prolonged to achieve a significant change.

Future steps include comparing the short- and long-term effects of anodal tDCS over different cerebral locations.

The authors report no conflicts of interest in relation to the work described.

The two studies have been approved by the local Ethical Committee with protocol number 2016.33. Each patient (and/or guardian) signed a consent form.

Compliance with ethical standards

Conflict of interest The authors report no conflicts of interest in relation to the work described.

Ethical approval The two studies have been approved by the local Ethical Committee with protocol number 2016.33. Each patient (and/or guardian) signed a consent form.

Informed consent Informed consent was obtained from all the patients.

References

1. McKhann GM, Knopman DS, Chertkow H et al (2011) 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 Dement 7:263–269. https://doi.org/10.1016/j.jalz.2011.03.005
2. Monsell S (2003) Task switching. Trends Cognit Sci 7:134–140. https://doi.org/10.1016/S1364-6613(03)00028-7
3. Chan R, Shum D, Toulopoulou T et al (2008) Assessment of executive functions: Review of instruments and identification of critical issues. Arch Clin Neuropsychol 23:201–216. https://doi.org/10.1016/j.acn.2007.08.010
4. Altamura C, Scrascia F, Quattrocchi CC et al (2016) Regional MRI diffusion, white-matter hyperintensities, and cognitive function in Alzheimer's disease and vascular dementia. J Clin Neurol 12:201–208. https://doi.org/10.3988/jcn.2016.12.2.201
5. Morris JC, Storandt M, Miller JP et al (2001) Mild cognitive impairment represents early-stage Alzheimer disease. Arch Neurol 58:397–405. https://doi.org/10.1001/archneur.58.3.397
6. Fabio RA, Castriciano C, Rondanini A (2015) ADHD: auditory and visual stimuli in automatic and controlled processes. J Atten Disord 19:771–778
7. Birks JS (2006) Cholinesterase inhibitors for Alzheimer's disease. Cochrane Database of Systematic Reviews. https://doi.org/10.1002/14651858.CD005593
8. Holtzman DM, Morris JC, Goate AM (2011) Alzheimer's disease: the challenge of the second century. Sci Transl Med 3:77sr71. https://doi.org/10.1126/scitranslmed.3002369
9. Fabio RA, Billeci L, Crifaci G et al (2016) Cognitive training modifies frequency EEG bands and neuropsychological measures in Rett syndrome. Res Dev Disabil 53–54:73–85. https://doi.org/10.1016/j.ridd.2016.01.009
10. Fabio RA, Colombo B, Russo S et al (2014) Recent insights into genotype–phenotype relationships in patients with Rett syndrome using a fine grain scale. Res Dev Disabil 35:2976–2986. https://doi.org/10.1016/j.ridd.2014.07.031

11. Cotelli M, Manenti R, Zanetti O et al (2012) Non-pharmacological intervention for memory decline. Front Human Neurosci 6:46. https://doi.org/10.3389/fnhum.2012.00046
12. Backman L, Andersson JLR, Nyberg L et al (1999) Brain regions associated with episodic retrieval in normal aging and Alzheimer's disease. Neurology 52:1861–1861. https://doi.org/10.1212/WNL.52.9.1861
13. Boggio PS, Ferrucci R, Mameli F et al (2012) Prolonged visual memory enhancement after direct current stimulation in Alzheimer's disease. Brain Stimul 5:223–230. https://doi.org/10.1016/j.brs.2011.06.00
14. Gangemi A, Caprì T, Fabio RA et al (2018) Transcranial Direct Current Stimulation (tDCS) and Cognitive Empowerment for the functional recovery of diseases with chronic impairment and genetic etiopathogenesis. Adv Genetic Res 18:179–196
15. Karim AA, Kammer T, Cohen L et al (2004) Effects of TMS and tDCS on the physiological regulation of cortical excitability in a brain-computer interface. Biomed Tech 49:55–57
16. Fabio RA, Caprì T, Mohammadhasani N et al (2018) Frequency bands in seeing and remembering: comparing ADHD and typically developing children. Neuropsychol Trends 24:97–116. https://doi.org/10.7358/neur-2018-024-fabi
17. Fabio RA, Gangemi A, Capri T et al (2018) Neurophysiological and cognitive effects of Transcranial Direct Current Stimulation in three girls with Rett Syndrome with chronic language impairments. Res Dev Disabil 76:76–87. https://doi.org/10.1016/j.ridd.2018.03.008
18. Andrade SM, de Mendonça CTPL, Pereira TCL et al (2016) Adjuvant transcranial direct current stimulation for treating Alzheimer's disease: a case study. Dement Neuropsychol 10:156–159. https://doi.org/10.1590/S1980-5764-2016DN1002013
19. Khedr EM, Gamal NFE, El-Fetoh NA et al (2014) A double-blind randomized clinical trial on the efficacy of cortical direct current stimulation for the treatment of Alzheimer's Disease. Front Aging Neurosci 6:275. https://doi.org/10.3389/fnagi.2014.00275
20. Gangemi A, Fabio RA (2019) Transcranial direct current stimulation for Alzheimer disease with P300. Asian J Gerontol Geriatr. https://doi.org/10.12809/ajgg-2019-344-oa
21. Bystad M, Rasmussen ID, Abeler K et al (2016) Accelerated transcranial direct current stimulation in Alzheimer's disease: a case study. Brain Stimul 9:634–635. https://doi.org/10.1016/j.brs.2016.04.018
22. Brunoni AR, Nitsche MA, Bolognini N et al (2012) Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions. Brain Stimul 5:175–195. https://doi.org/10.1016/j.brs.2011.03.002
23. Bystad M, Grønli O, Rasmussen ID et al (2016) Transcranial direct current stimulation as a memory enhancer in patients with Alzheimer's disease: a randomized, placebo-controlled trial. Alzheimers Res Ther 8:13. https://doi.org/10.1186/s13195-016-0180-3
24. Bystad M, Rasmussen ID, Grønli O et al (2017) Can 8 months of daily tDCS application slow the cognitive decline in Alzheimer's disease? A case study. Neurocase 23:146–148. https://doi.org/10.1080/13554794.2017.1325911
25. Di Fiandra T, Canevelli M, Di Pucchio A et al (2015) The Italian dementia national plan. Annali dell'Istituto Superiore di Sanità 51:261–264
26. Niu H, Álvarez-Álvarez I, Guillén-Grima F et al (2017) Prevalence and incidence of Alzheimer's disease in Europe: a meta-analysis. Neurología (English Edition) 32:523–532
27. Folstein MF, Folstein SE, McHugh PR (1975) Mini-mental state. J Psychiatric Res 12:189–198. https://doi.org/10.1016/0022-3956(75)90026-6
28. Brazzelli M, Capitani E, Della Sala S et al (1994) A neuropsychological instrument adding to the description of patients with suspected cortical dementia: the Milan overall dementia assessment. J Neurol Neurosurg Psychiatry 57:1510–1517. https://doi.org/10.1136/jnnp.1557.1512.1510
29. Storti SF, Formaggio E, Beltramello A et al (2012) Wavelet analysis as a tool for investigating movement-related cortical oscillations in EEG-fMRI coregistration. Brain Topogr 23:46–57
30. Moretti DV, Babiloni C, Binetti G et al (2004) Individual analysis of EEG frequency and band power in mild Alzheimer's disease. Clin Neurophysiol 115:299–308
31. König T, Prichep L, Dierks T et al (2005) Decreased EEG synchronization in Alzheimer's disease and mild cognitive impairment. Neurobiol Aging 26:165–171
32. Simpraga S, Alvarez-Jimenez R, Mansvelder HD et al (2017) EEG machine learning for accurate detection of cholinergic intervention and Alzheimer's disease. Sci Rep 7:5775. https://doi.org/10.1038/s41598-017-06165-4
33. Marceglia S, Mrakic-Sposta S, Rosa M et al (2016) Transcranial direct current stimulation modulates cortical neuronal activity in Alzheimer's Disease. Front Neurosci 10:134. https://doi.org/10.3389/fnins.2016.00134