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Dear Editor

Following our previous article submission and revisions (BRS-D-15-00084R1), and in line with your suggestion we have now formatted our article as letter. It is entitled "**Double-blind randomized trial of t-DCS versus sham in Parkinson patients with mild cognitive impairment receiving cognitive training".**

We found a trend for a delayed effect of t-DCS over the DLPFC combined with cognitive training on learning processes when adopted as cognitive rehabilitation strategy than cognitive training alone. Our study will provide useful data to design future studies evaluating the role of t-DCS in extending the benefit of cognitive treatment.

The study was approved by the ethic committee at "San Camillo" Hospital (N: 2011.05).

Best Regards

Roberta Biundo

Letter to the Editor: Double-blind randomized trial of t-DCS versus sham in Parkinson patients with mild cognitive impairment receiving cognitive training.

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To the Editor: The effect of computer-based cognitive training (CT) alone or in association with non-invasive brain stimulation (t-DCS) over the left dorsolateral prefrontal cortex (l-DLPFC) in Parkinson disease patients with Mild Cognitive Impairments (PD-MCI) is debated. The efficacy of acute t-DCS has been confirmed in AD and PD,[1,2]. By contrast, randomized t-DCS controlled trials in AD and PD have reported variable effects on cognition possibly due to protocol heterogeneity (hemisphere side, electrode montage, duration of stimulation, number of session per day etc),. Recently a double-blind randomized study, reported the beneficial effect of 2-week t-DCS over the DLPFC on executive functions but the follow-up was only one month,[3]. To our knowledge, a blinded intervention trial of CT in PD patients comparing repeated (over 4-week) real vs. sham t-DCS with long-term follow-up (12-week post-treatment completion) has never been conducted. Given the characteristics of cognitive abnormalities in PD-MCI and the critical role of DLPFC in fronto-striatal networks, in this pilot study we tested the hypothesis that repeated anodal t-DCS over l-DLPFC administered during the execution of cognitive task might enhance and extend the effect of computer-based CT on specific cognitive functions.

Methods

Patients

We recruited PD-MCI patients among those admitted for rehabilitation at our Parkinson and Movement Disorders Unit in Venice, (Italy) from 2013 to 2014. All patients underwent an extensive clinical and neuropsychological examination [4] to allow MCI and dementia status categorization according to MDS-Task Force published criteria,[5,6]. We excluded PD with dementia. Drug therapy for patients enrolled in the study was maintained stable during the treatment. All patients signed written consent. Approval from the Local Research Ethics Committee was obtained (N: 2011.05).

Study design

Twenty-four PD-MCI were randomly allocated to receive 4-week CT plus real t-DCS (N=12, 6 men and 1 female, age 69.1±7.6 and education 9±3.4) or sham t-DCS (N=12, 8 men and 1 female, age 72.3±4.1 and education 8.8±4.1), and 16 patients completed the 16-week follow-up session. The

study was double-blinded and consisted of 30 minutes CT plus real or sham t-DCS, 4 days a week for 4 weeks. T-DCS was delivered between 10am and 12 am.

t-DCS and cognitive training protocol

The direct current was initially increased over several seconds (0-10 seconds) until reaching 2 mA, 20 min/session. Anodal electrode was placed over the left DLPFC, cathodal over the contralateral supraorbital region. We identified DLPFC using a infrared-guided neuro-navigation system. In the sham stimulation group, the electrodes were placed in the same position as the real t-DCS stimulations. We used the Rehacom® software, a computer-based CT which provides objective advantages compared with pen and pencil CT (http://www.hasomed.de). Clinical and cognitive assessment at baseline, after 4-week treatment and at 16-week follow-up was made by blinded experts. To avoid learning effect we used the two parallel versions of the Repeatable Battery Assessment of Neuropsychological Status (RBANS) (http://www.rbans.com/testcontent.html).

Results

At the end of 4-week treatment, we observed a significant decrement performance for the real t-DCS compared to sham group in attention/executive skills [Written coding test: -4.6(5.2) vs. 1.6(2.5) difference change for real vs. sham t-DCS, $p<0.01$, Cohen's $d=1.52$]. At week 16, we observed a strong trend for better performance in the real t-DCS compared with sham stimulation arm in the story learning test [3.7(5.7) vs. -0.4(3.4) difference change for real vs. sham t-DCS, $p<0.07$, Cohen's $d=0.9$] and immediate memory index [12.6 (20) vs. 0.3(13.17) difference change for real vs. sham t-DCS, $p<0.07$, Cohen's $d=0.7$] . No significant increment was found for the sham compared to real arm in any of the administered tests. It is worth to underlie that the significant increment in the delayed memory index initially observed for the sham group during the treatment period returned to baseline at follow up. No significant UPDRS-III motor changes were observed between groups at 4 and 16-week follow-up (see Table 1).

Discussion

Our study is the first to use a double-blind randomized design to test the effect of repeated t-DCS

against sham in PD-MCI undergoing CT and to evaluate its long-term effectiveness. We found a strong trend (p=0.07) for increased performance in immediate memory skills (story learning test) with a moderate effect size (d'>0.7) in the real t-DCS cohort only at 16-week follow-up. No increased performance was observed during the treatment (0-4 weeks) for the same PD subgroup in any of the abilities investigated. These findings of delayed effect of t-DCS over the DLPFC on learning processes corroborate recent data from literature in healthy subject[7] and in PD [3], and support studies showing the impact of anodal t-DCS over the prefrontal cortex on enhanced declarative and long term memory consolidation[8]. By contrast, "real t-DCS plus CT" strategy seems to temporary affect performance in specific abilities during the active treatment period (0-4 weeks). Namely we observed a significant decrement in writing coding test score for the real t-DCS group. These scores showed a trend to decrease transiently during the treatment period and to return to baseline levels at the end of follow-up. Reasons explaining these results could be various. Firstly, although task specific effects of t-DCS have been shown, its mechanistic substrate remains poorly explained. Electric field induced by conventional t-DCS montage is widespread and heterogeneous making very hard to predict the behavioral impact of t-DCS. Secondly, it is reasonable that stimulation of multi-tasking complex brain region (such as the DLPFC) may produce unspecific functional changes. Thirdly, it has been supposed that altered network function secondary to a brain neurodegenerative or vascular diseases may alter the susceptibility of t-DCS[9]. It may be that in the context of altered cognitive networks (PD-MCI) repeated left anodal DLPFC and cathodal orbitofrontal cortex stimulation temporarily perturb cognitive networks, breaking down PD "vulnerable" cognitive abilities in brain areas functional to these tasks[10].

Finally our study will provide useful data to design future studies evaluating the role of t-DCS in extending the benefit of cognitive treatment, possibly using different protocol design t-DCS stimulation paradigms.

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Competing interests:

The authors have no competing interest to declare.

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The information of this letter and the letter itself has never been published either electronically or in print. All authors gave final approval of this version of the letter to be published. We can assure that there is no one else who fulfils the criteria but has not been included as an author.

Table 1

Table 1. Within group mean delta changes (d') differences (SD) of each single corrected score and between groups delta changes comparison (p value) at 4-week and after 16-week follow up.

	0-4 weeks				0-16 weeks			
	Real t-DCS	**Sham t-DCS**		**Cohen's effect size**	**Real t-DCS**	**Sham t-DCS**		**Cohen's effect size**
	mean d' (SD)	**mean d'(SD)**	**p value #**	**d**	**mean d' (SD)**	**mean d'(SD)**	**p value #**	**d**
UPDRS-III	-8.00 (9.57)	-0.30 (24.25)	0.707	0.182	0.17 (11.44)	13.83(14.20)	0.275	0.154
STAI-Y	7.56 (15.74)	0.09 (14.08)	0.636	0.5	5.44 (7.92)	0.40 (13.15)	0.513	0.464
PDQ-8	15.5 (8.35)	8.00 (7.62)	0.327	0.938	17.00 (9.85)	10.00 (8.58)	0.594	0.758
BDI-II	-7.00 (8.44)	-6.36 (7.13)	0.647	0.082	-4.22 (13.13)	-3.4 (8.59)	0.932	0.074
MOCA	2.33 (2.24)	1.36 (1.36)	0.272	0.524	0.33 (2.45)	0.70 (1.7)	0.681	0.175
RBANS Tot.	3.11 (8.19)	2.46 (13.2)	0.890	0.05	4.29 (12.74)	0.00 (11)	0.251	0.36
List learning	0.33 (5.15)	2.36 (4.72)	0.488	0.411	1.71 (5.41)	0.56 (5.25)	0.794	0.216
Story learning	1.22 (4.49)	-0.73 (3.93)	0.168	0.462	3.71 (5.74)	-0.44 (3.4)	**0.077**	**0.879**
Immed. Memory index	2.67 (16.55)	2.09 (12.49)	0.395	0.039	12.57 (19.96)	0.33 (13.17)	**0.075**	**0.724**
Complex figure Copy	0.78 (2.44)	0.82 (2.82)	0.453	0.015	-0.71 (3.15)	-0.44 (3.88)	0.583	0.076
Orientantion Line	0.89 (4.04)	-0.09 (2.88)	0.638	0.279	2.57 (2.82)	-0.56 (3.91)	0.115	0.918
Visuo-spatial index	5.44 (18.28)	6.36 (20.22)	0.691	0.047	2.78 (17.25)	3.10 (15.81)	0.987	0.019
Naming	0.33 (0.71)	0.27 (0.47)	0.828	0.099	-0.29 (0.49)	-0.22 (0.44)	0.636	0.15
Semantic Fluency	-5.11 (3.62)	-3.73 (4.1)	0.871	0.357	-1.57 (3.99)	0.33 (2.5)	0.884	0.57
Language index	-1.56 (9.84)	-0.46 (6.82)	0.940	0.1299	-5.29 (5.59)	-0.78 (6.63)	0.284	0.735
Digit Span	1.33 (2.92)	0.09 (1.22)	0.150	0.5541	0.57 (3.6)	-0.78 (1.56)	0.248	0.486
Written coding test	-4.56 (5.2)	1.64 (2.46)	**0.001**	**1.52**	-2.00 (4.51)	2.11 (4.96)	0.383	0.867
Attention index	1.78 (9.44)	2.00 (6.48)	0.796	0.027	-0.86 (16.64)	-1.56 (10.93)	0.342	0.049
List recall	-1.33 (2.74)	1.00 (2.19)	0.040*	0.9394	0.57 (2.51)	0.89 (1.83)	0.396	0.146
List recognition	-1.11 (2.37)	0.55 (3.14)	0.168	0.5967	0.29 (2.29)	-0.56 (1.74)	0.641	0.418
Story recall	1.56 (2.74)	-0.18 (1.72)	0.307	0.76	2.71 (3.5)	-0.22 (2.17)	0.105	1.00
Figure recall	4.00 (3.28)	4.46 (2.58)	0.658	0.156	3.14 (3.63)	3.22 (2.99)	0.917	0.024
Delayed Memory index	0.44 (11.13)	10.27 (11.65)	0.027*	0.863	6.86 (11.61)	6.22 (9.95)	0.447	0.059

Note:* Uncorrected values; d'= difference between baseline and follow up at patient level; #=Mann Whitney U-Test to evaluate between groups delta changes comparison with exact significance (2*1-tailed Significance) $p<0.05$ after 2-tailed Monte Carlo correction (10000 simulation) in order to reduce false positive in statistical estimation.We corrected for Bonferroni multiple comparisons.In the between-group analyses, the effect sizes of changes between real vs. sham t-DCS treatment groups were assessed with Cohen's *d*, an index of the magnitude of treatment effect. We considered only large ($d \geq 0.7$) effect sizes.