ELSEVIER

Journal of the Neurological Sciences 249 (2006) 31 – 38

Journal of the Neurological Sciences

www.elsevier.com/locate/jns

Effects of transcranial direct current stimulation on working memory in patients with Parkinson's disease

Paulo S. Boggio [b,c], Roberta Ferrucci [a,e], Sergio P. Rigonatti [b], Priscila Covre [c], Michael Nitsche [d], Alvaro Pascual-Leone [a], Felipe Fregni [a,*]

[a] *Center for Noninvasive Brain Stimulation, Beth Israel Deaconess Medical Center, Harvard Medical School, 330 Brookline Ave-KS 452, Boston, MA 02215, USA*

[b] *Department of Experimental Psychology and Department of Psychiatry, University of Sao Paulo, Sao Paulo, Brazil*

[c] *Núcleo de Neurociências, Mackenzie University, Sao Paulo, Brazil*

[d] *Department of Clinical Neurophysiology, Georg-August-University, Goettingen, Germany*

[e] *Department of Neurological Sciences, IRCCS Ospedale Maggiore Policlinico, Milan, Italy*

Received 20 February 2006; received in revised form 24 April 2006; accepted 26 May 2006
Available online 14 July 2006

Abstract

Objectives: Cognitive impairment is a common feature in Parkinson's disease (PD) and is an important predictor of quality of life. Past studies showed that some aspects of cognition, such as working memory, can be enhanced following dopaminergic therapy and transcranial magnetic stimulation. The aim of our study was to investigate whether another form of noninvasive brain stimulation, anodal transcranial direct current stimulation (tDCS), which increases cortical excitability, is associated with a change in a working memory task performance in PD patients.
Methods: We studied 18 patients (12 men and 6 women) with idiopathic PD. The patients performed a three-back working memory task during active anodal tDCS of the left dorsolateral prefrontal cortex (LDLPFC), anodal tDCS of the primary motor cortex (M1) or sham tDCS. In addition, patients underwent two different types of stimulation with different intensities: 1 and 2 mA.
Results: The results of this study show a significant improvement in working memory as indexed by task accuracy, after active anodal tDCS of the LDLPFC with 2 mA. The other conditions of stimulation: sham tDCS, anodal tDCS of LDLPFC with 1 mA or anodal tDCS of M1 did not result in a significant task performance change.
Conclusion: tDCS may exert a beneficial effect on working memory in PD patients that depends on the intensity and site of stimulation. This effect might be explained by the local increase in the excitability of the dorsolateral prefrontal cortex.

Keywords: Parkinson's disease; Working memory; Anodal transcranial direct current stimulation; tDCS; Brain stimulation; Brain polarization

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder that causes motor symptoms characterized by resting tremor, rigidity, bradykinesia and postural instability. As the disease progresses, cognitive deficits become another hallmark of this disease. Cognitive capacity declines with age and severity of the disease [1]. The characteristics of the cognitive impairment observed in PD patients resemble those observed following frontal-lobe damage and include deficits of executive functions, such as planning and working memory [2,3].

Past studies have shown that some of these cognitive deficits can be reversed by dopaminergic therapy [4–6]. Recently, we showed that transcranial magnetic stimulation (TMS) improves working memory in PD, perhaps via modulation of dopaminergic activity [7]. We hypothesized that another technique of non-invasive brain stimulation, transcranial direct current stimulation (tDCS), might also

* Corresponding author. Tel.: +1 617 667 5272; fax: +1 617 975 5322.
E-mail address: ffregni@bidmc.harvard.edu (F. Fregni).

0022-510X/$ - see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.jns.2006.05.062

result in an improvement in the working memory performance. Transcranial DC stimulation can modulate brain activity in a manner similar to rTMS [8–12], but has the advantages of being easily applied, extremely safe and reliably blinded by sham tDCS in the setting of clinical trials [13].

Transcranial DC stimulation induces a polarity-dependent excitability shift of the stimulated areas, which is initially induced by a subthreshold membrane potential shift, followed by prolonged after-effects that depend on modification of the strength of NMDA receptors [14]. These excitability shifts are comparable to those achieved by the above-mentioned rTMS protocols. Thus, similar to rTMS, tDCS might be suited to improve cognitive symptoms in PD. Only two studies evaluated the effects of tDCS in working memory thus far; however, these two studies were conducted in healthy subjects [15,16]. Although the results of these studies at the first glance might seem paradoxical, they employed different methodology: whereas Fregni's study [15] evaluated unilateral continuous anodal tDCS, Marshall's study [16] investigated the effects of bilateral and intermittent tDCS. Moreover, electrode size, position and current density differed relevantly in both studies. Finally, different cognitive paradigms were applied, which might be relevant, since the effects of tDCS on performance are task-dependent [12]. Because our previous study [15] showed a positive result on working memory, we used the same methodology for the present study.

In summary, we sought to investigate whether anodal tDCS of left dorsolateral prefrontal cortex (LDLPFC) is associated with a change in a working memory task performance (three-back letter task) when compared to an active control condition (stimulation of the primary motor cortex (M1)) and sham tDCS, and, in addition, using different intensities of stimulation (1 mA or 2 mA).

2. Methods

2.1. Subjects

We studied 18 patients (12 men and 6 women) aged 45 to 71 years (mean 61.1 years) with idiopathic PD who fulfilled the UK Parkinson's disease brain bank criteria [17]. Patients were excluded if they had other neuropsychiatric diseases, were being treated with deep brain stimulation, or could not be withdrawn from antiparkinsonian drugs for 12 h. Furthermore, patients were excluded if they had dementia —we used the criteria suggested by Almeida [18] in which the Mini-Mental State Examination (MMSE) is adjusted to the level of education—we used the cut-off of 20 for patients with no former (or less than 4 years) education and 24 for patients with more than 4 years of formal education [18]. Written informed consent was obtained from all participants prior to inclusion in the study, which was approved by the local ethics committee (Institute of Psychiatry, University of Sao Paulo, Sao Paulo, Brazil). The study was performed in accordance to the ethical standards of the 1964 Declaration of Helsinki.

2.2. Direct current stimulation

Direct current was transferred by a saline-soaked pair of surface sponge electrodes (35 cm^2) and delivered by a specially developed, battery-driven, constant current stimulator (Schneider Electronic, Gleichen, Germany) with a maximum output of 10 mA. To stimulate the LDLPFC, the anode electrode was placed over F3 according to the 10–20 international system for EEG electrodes placement. This method of DLPFC localization was used before in TMS studies [19,20] and has been confirmed as a relatively accurate method of localization by neuronavigation techniques [21]. The cathode was placed over the contralateral right orbit. Although neuroimaging [22,23] and TMS studies [24] have demonstrated that right and left DLPFC are involved in working memory paradigms, we decided to focus our investigation on the left DLPFC as the modulation of this area by rapid rTMS (off-line rTMS) can cause an improvement in some aspects of the cognitive function in patients with major depression [25–27] and Parkinson's disease [7]. In addition, previous neuroimaging studies have shown that activity in the dorsolateral prefrontal cortex is associated with working memory performance in PD patients [28,29].

In order to test if the effects of LDLPFC stimulation were specific, we stimulated the primary motor cortex (M1) in another session. Therefore, subjects underwent the identical protocol design; however, the anode electrode was placed over the primary motor cortex (M1) rather than LDLPFC. The cathode electrode was maintained on the right supraorbital area. In addition, we tested whether the effects depended on the intensity of stimulation and thus performed stimulation with different intensities: a constant current of 1 mA (for experiment 1) or 2 mA (for experiment 2) that was applied for 20 min. Subjects felt the current as an itching sensation at both electrodes for just a few seconds at the beginning of the stimulation. Finally, we also performed sham stimulation. For such condition, the electrodes were placed at the same position as the LDLPFC stimulation; however, the current intensity was gradually decreased after 20 s, being then turned off after 30 s (ramp down of 10 s) as previously described [30]. Therefore, during sham stimulation, the subjects felt the initial itching sensation in the beginning, but received no current for the rest of the stimulation period. This procedure allowed to blind subjects for the respective stimulation condition [8] and has been described as reliable by a recent double-blind tDCS study [13].

2.3. Working memory assessment

We used the three-back letter working memory paradigm described elsewhere [15,31]; however, with longer exposure time and larger size of the stimuli. Subjects were presented

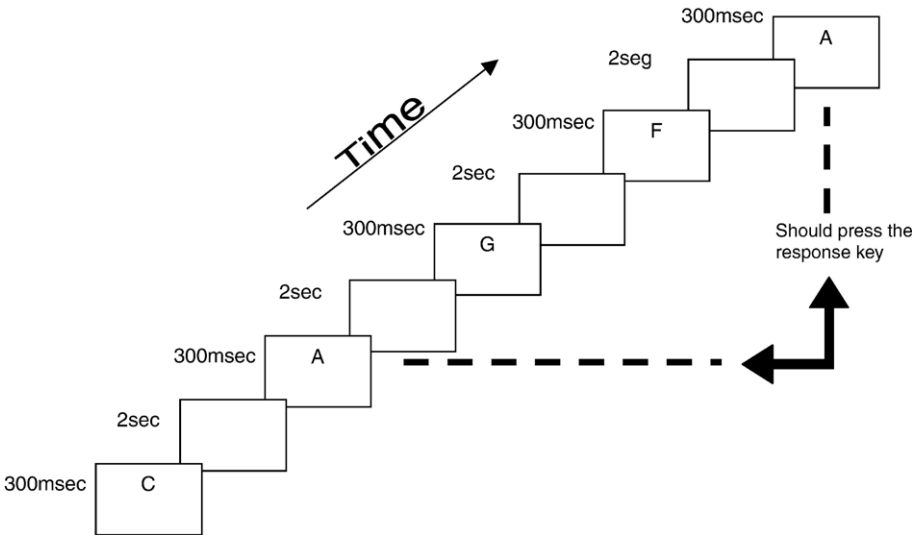

Fig. 1. The sequence of the three-back letter working memory paradigm. The subjects were required to respond (key press) if the presented letter was the same as the letter presented three stimuli previously.

with a pseudo-random set of 11 letters (A to J). The stimuli were generated using the Superlab pro v2.0 software (Cedrus Corporation, San Pedro, Ca). Each letter was displayed on computer monitor for 300 ms. A different letter was displayed every 2 s. Black letters were presented on a white background and subtended 6.2 cm (when viewed at 50 cm). Subjects were required to respond (key press) if the presented letter was the same as the letter presented three stimuli previously (Fig. 1). In this test, a total of 30 correct responses were possible. In each set of this task, the targets could be separated by three to five letters. Subjects were allowed to practice until they reach a stable plateau as defined by less then 10% change in the last two trials. Furthermore, patients with a response rate less than 30% of correct responses were excluded.

2.4. Experimental protocol

Following a first practice run, subjects were tested during each one of the stimulation conditions. Since the test run lasted for about 5 min, it was conducted during the last 5 min of LDLPFC, M1 or sham stimulation (see Fig. 2 below). The three test runs differed in the order of the letters and were randomized across subjects to avoid difficulty bias. To control for possible carryover effects, the order of stimulation (LDLPFC, M1 or sham) was fully counterbalanced across subjects. In addition, each condition was separated by at least 48 h to washout the effects of the previous run. Subjects could not distinguish between real and sham stimulation as they felt the initial itching in both conditions. We performed two experiments—nine subjects participated in each experiment. Both experiments had the same design with only one difference: in experiment 1, we used 1 mA and, in experiment 2, we used 2 mA.

Importantly, antiparkinsonian medications (levodopa or dopaminergic agonist) were held for approximately 12 h prior to the experiment, which was conducted at the same time of the day (morning) in all patients to avoid circadian influences—similar to our previous study that evaluated the cognitive effects of rTMS [7].

2.5. Data analysis

The primary outcomes for this study were number of correct responses, false alarms (errors) and response time during active compared to sham stimulation. Analyses were done with Stata statistical software (version 8.0, Stata Corporation, College Station, Texas). Initially, for each outcome, we calculated the difference between post- and pre-treatment outcome scores following each condition

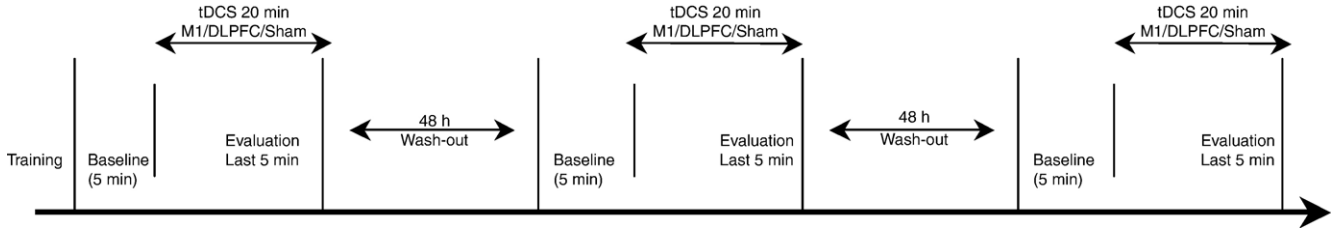

Fig. 2. The experimental protocol design. Each subject was tested before and during sham, active and LDLPFC stimulation.

(anodal LDLPFC, M1 or sham stimulation). We performed a two-way analysis of variance (ANOVA) to test whether there was an overall effect of the intervention (stimulation condition) and experiment (1 mA vs. 2 mA) on each primary outcome measure. We then performed separate ANOVAs for each experiment to test whether there was a main effect of intervention (stimulation condition). When appropriate, we performed post-hoc paired comparisons using Bonferroni correction for multiple comparisons. Finally. we performed a one-way ANOVA to assess the learning effect—we compared the results of the three baseline tests for each experiment. Statistical significance refers to a two-tailed p-value <0.05.

3. Results

Table 1 summarizes demographic and clinical characteristics at baseline. The 18 patients were moderately to severely affected by PD. There were no significant differences in clinical and demographic characteristics across the two groups of patients (experiment 1—1 mA and experiment 2—2 mA) (see Table 1). All patients tolerated the tDCS well without experiencing any adverse effects, and all completed the entire experiment. Importantly, when explicitly asked, none of the patients could tell whether the stimulation was active or sham. In order to assess learning effect, we compared baseline of the three conditions for experiments 1 and 2. These analyses showed that there was no significant difference ($F<2$ and $p>0.18$ for all these tests) across the first, second and third baseline conditions for experiments 1 and 2, therefore ruling out learning and carry-over effect.

3.1. Overall comparison—experiment 1 versus experiment 2

In order to investigate whether 1 mA of tDCS resulted in a differential outcome compared to 2 mA of tDCS, we compared the task performance of the two experiments in a mixed ANOVA with two factors: *condition* (anodal LDLPFC, anodal M1 and sham tDCS) and *experiment* (1 mA versus 2 mA) in which the dependent variable was task performance change (difference between pre- and during tDCS) in the correct responses, errors and reaction time. For the correct responses and errors ANOVA, there was a trend towards a significant effect of the interaction term *condition* × *experiment* ($p=0.07$ for both ANOVAs) and a significant effect of *condition* ($p<0.05$). For the reaction time ANOVA, the interaction term *condition* × *experiment* was not significant ($p=0.64$); however, the term *condition* was significant ($p<0.05$). As shown by the post-hoc analysis, this indicated that reaction time was significantly decreased during anodal stimulation of M1 ($p<0.05$) when combining the results of experiments 1 and 2, but not during stimulation of either LDLPFC or sham stimulation. This overall analysis suggests a trend towards a differential effect in the working memory accuracy, but not speed, between the treatments with 1 mA and 2 mA—i.e., treatment with 2 mA induced a differential, larger effect compared with 1 mA. Next, we performed an individual analysis for each experiment (Table 2 shows the data for each patient).

Table 1
Clinical and demographic characteristics

	Experiment 1		Experiment 2aps		p-value [a]
	Mean	S.D.	Mean	S.D.	
Number of subjects	9		9		
Age (years)	59.2	9.9	61.0	12.1	ns
Gender (male %)	56		78		ns
Years of education	4.7	4.4	5.3	4.7	ns
Disease duration (years)	13.7	8.2	12.7	8.1	ns
HY (mean)	2.3	0.9	2.4	0.7	ns
MMSE (mean)	24.4	3.1	24.9	3.5	ns
UPDRS (mean)	36.8	18.5	43.0	13.7	ns

S.D.—standard deviation; HY—Hoehn & Yahr; MMSE—Mini-Mental State Examination; UPDRS—Unified Parkinson Disease Rating Scale.
[a] Student's t-test for the comparison of continuous variables and Fisher's exact test for the comparison of categorical variables.

3.2. Experiment 1: working memory performance after stimulation with 1 mA

For experiment 1, we performed a mixed ANOVA, but with only one factor (*stimulation:* sham, M1 and LDLPFC). This analysis showed that the main effect of stimulation was not significant for any of the outcomes: correct responses ($p=0.61$), errors ($p=0.29$) and reaction time ($p=0.29$). Indeed, the working memory performance change after LDLPFC stimulation was small and not significant even when compared with baseline for these three outcomes: correct responses (increase by 4.34%, $p=0.31$), errors (decrease by 6.56%, $p=0.12$) and reaction time (decrease by 3.15%, $p=0.56$) (Fig. 3).

3.3. Experiment 2: working memory performance after stimulation with 2 mA

Performing a similar analysis, stimulation with 2 mA showed different results than that of 1 mA. One-way ANOVA showed that the main effect of stimulation (sham, LDLPFC and M1) was significant when the dependent variable was correct responses ($p<0.05$) and errors ($p<0.05$), but not when the outcome was reaction time ($p=0.08$). Post-hoc comparisons showed that the number of correct responses was significantly higher than baseline (20.1%, $p=<0.05$) and significantly different than sham stimulation ($p<0.05$) and M1 stimulation ($p<0.05$). Similar results were obtained for errors frequency: it was significantly decreased compared with baseline (35.3%, $p<0.05$), sham stimulation ($p<0.05$) and a trend towards a significant differential effect between LDLPFC and M1 stimulation ($p=0.07$) could be observed. Interestingly, although M1 stimulation was associated with an increase in the correct responses (by 3.6%) and a decrease in the errors (by 6.7%), it

Table 2
Individual values throughout the experiment

Exp.	Patient	Correct responses						Errors						Reaction time					
		Sham		DLPFC		M1		Sham		DLPFC		M1		Sham		DLPFC		M1	
		Baseline	During	Baseline	During	Baseline	During	Baseline	During	Baseline	During	Baseline	During	Baseline	During	Baseline	During	Baseline	During
1	P1	21	19	22	26	22	22	5	5	5	4	5	5	431	431	444	421	444	537
1	P2	19	17	21	19	18	19	6	5	5	4	6	6	561	523	599	506	432	408
1	P3	27	28	25	27	28	26	2	3	2	3	1	1	478	448	453	411	432	421
1	P4	24	23	25	27	23	25	7	6	7	6	5	5	544	624	585	555	686	532
1	P5	20	28	22	20	20	22	11	10	10	10	11	10	578	609	523	690	543	476
1	P6	25	23	21	25	23	21	9	8	8	9	9	8	432	451	487	434	439	359
1	P7	22	17	24	27	24	27	10	11	13	11	10	11	468	556	405	456	405	377
1	P8	24	24	23	23	19	21	10	10	9	8	9	7	576	690	543	465	621	535
1	P9	21	21	22	21	21	21	9	11	8	8	6	6	421	401	497	434	515	487
2	P1	23	22	21	24	22	20	7	7	5	2	7	7	640	471	598	422	510	355
2	P2	21	20	20	23	20	19	5	5	4	0	9	7	401	316	354	230	527	574
2	P3	24	24	23	29	23	25	6	7	5	2	5	6	383	429	319	278	317	314
2	P4	21	21	20	27	21	24	9	9	8	6	11	12	550	571	500	511	540	478
2	P5	25	25	24	30	26	28	7	9	9	10	6	6	424	443	388	313	356	353
2	P6	28	24	26	30	25	25	9	11	12	9	7	5	424	626	486	370	412	339
2	P7	24	26	20	21	22	21	7	5	8	5	6	6	520	539	545	503	494	456
2	P8	19	19	21	27	20	23	8	7	9	7	8	7	403	452	432	532	460	215
2	P9	18	19	20	24	21	22	9	8	8	8	6	4	605	778	734	795	778	674

Exp.—experiment (1 indicates 1 mA tDCS and 2 indicates 2mA); Sham—sham tDCS; DLPFC—DLPFC (dorsolateral prefrontal cortex) stimulation; M1—M1 (primary motor cortex) stimulation.
Reaction time—in miliseconds.

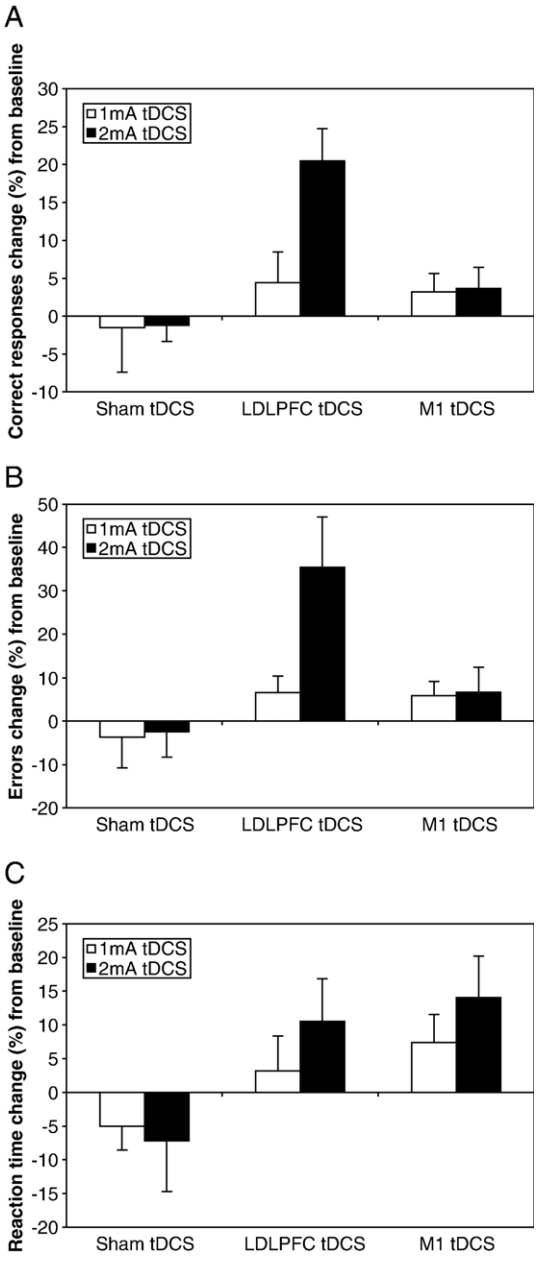

Fig. 3. Working memory performance during stimulation of left dorsolateral prefrontal cortex (LDLPFC), primary motor cortex (M1) and sham stimulation with 1 mA (experiment 1—white columns) and 2 mA (experiment 2—black columns) as indexed by correct responses (A), errors (B) and reaction time (C). Note that a positive change indicates performance improvement (increase in the correct responses, decrease in errors and decrease in reaction time). Columns represent mean performance change and error bars represent standard error of the mean (S.E.M.).

was not significantly different when compared with baseline ($p=0.22$ and $p=0.28$, respectively) and sham stimulation ($p=0.14$ and $p=0.28$, respectively).

4. Discussion

The results of this study show a beneficial effect of anodal tDCS on working memory. Hereby, the improvement in the working memory was specific to the site (LDLPC vs. M1) and intensity of stimulation (1 mA vs. 2 mA). Selectively, anodal tDCS of the LDLPFC with a current strength of 2 mA, but not 1 mA, improved accuracy, but not speed of performance.

This result is in line with our previous experiment in which we showed that tDCS of LDLPFC in healthy subjects induces an enhancement in the working memory performance and that this effect depends on the stimulation site and polarity. In that study, we proposed that the observed effects were due to an enhancement of the local cortical excitability of the left dorsolateral prefrontal cortex since (i) anodal tDCS induces a membrane effect in the neuron characterized by a neuron depolarization [32] and therefore can increase local excitability as shown by previous study in the human motor cortex [10]; and (ii) the LDLPFC is critical to working memory formation as shown by past neuroimaging and rTMS studies [24,31].

One interesting difference between our previous study with healthy subjects and this study is that 1 mA did not induce significant effects in this population of patients. Two reasons might explain this difference. First, age might be an important predictor of tDCS effects; in other words, older subjects might respond less to tDCS. This speculation is based on a recent study that analyzed the effects of rTMS in 195 subjects and showed that older subjects have a smaller behavioural effect when compared to younger subjects [33]. Another possibility is the dopamine depletion and its effects on working memory. It could be speculated that an increase in the local excitability of the frontal cortex resulted in an increase in the dopamine release—this speculation is based on past TMS study that showed such effect after prefrontal cortical stimulation using high-frequency rTMS [34,35]. In such scenario, perhaps 1mA would not be as strong as 2 mA to induce this change in the dopaminergic system.

Indeed, dopamine has an important role in working memory generation and formation. A recent neuroimaging study showed an increased dopamine release in prefrontal and subcortical areas during a working memory task that was correlated to the task performance [36]. Dopaminergic stimulation might be critical to maintain the activity of the prefrontal cortex at an adequate level that is necessary for working memory processes. It has been hypothesized that the loss of nerve cells in the substantia nigra and a subsequent depletion of dopamine levels in the striatum can affect a widespread neural network including the prefrontal structures via mesolimbic-frontal fibres [37] that can contribute to the working memory deficit.

In our study, we showed that tDCS might be viewed as a tool that can significantly impact some aspects of the cognition. This effect might be induced by or independent of the effects of dopamine. Thus far and also based on extensive literature [38–40], we can conclude that a change in the prefrontal excitability by 2 mA can change working memory performance without adverse effects and results in a behavioural improvement. Another evidence linking the

increase in the prefrontal cortex excitability and working memory enhancement comes from a study showing that amphetamine in healthy subjects enhances working memory and increases brain activity in the prefrontal cortex [41]. By the modulation action of tDCS on the local cortical excitability, which has a focusing impact, as shown in previous studies [12], it might additionally to some extent change excitability on an extensive neuronal network [42] associated with working memory.

An interesting parallel can be made with the study of Iyer et al. [43]. In this study, in healthy subjects, the authors showed that, whereas anodal tDCS with an intensity of 1 mA (0.04 mA cm^{-2}) induces no effect on verbal fluency performance, anodal 2 mA tDCS (0.08 mA cm^{-2}) improves verbal fluency significantly [43]. Although the tasks and the current density (i.e., 0.03 mA cm^{-2} and 0.06 mA cm^{-2} for 1 mA and 2 mA, respectively, in our study) are different, the results of this previous and our study underscore that stimulation with a higher intensity (2 mA in both studies) might yield a greater beneficial effect on some aspects of cognition.

This study has some potential limitations that warrant discussion. First, a tDCS-independent learning effect can be viewed as a potential limitation as the task was given repeatedly and a learning curve could have distorted the results. However, all patients underwent a training period until they reached a plateau of performance. In addition, we randomized and counterbalanced the order of stimulation and we waited at least 48 h between two sessions of tDCS. Finally, different implementations of the task were used in each session and we showed that baseline performances were not different throughout this study. Second, we decided not to test different working memory loads (as in the traditional Sternberg paradigm) as our pilot data showed that the three-back task was adequate for this population and we wanted to compare this study with our previous study that employed similar methodology. This however might limit the comparability of the results of this study with those of Marshall's study [16]. Third, because of the important role of the dopamine on working memory, we assessed the patients in the valley of their dopaminergic drugs (withdrawal of dopaminergic drugs for at least 12 h) to avoid this confounding effect. Finally, although tDCS is a technique that has a reliable sham condition, a relatively high intensity (such as 2 mA in comparison to 1 mA) could induce a stronger skin sensation that could theoretically unblind some patients. However, we did not notice any difference in subject's perceptions when comparing stimulation with 1 mA and 2 mA and, in addition, M1 stimulation served as an active control. The main strengths of this study are the reliable sham method that tDCS can provide as recently demonstrated [13] and the dose–effect response for the tDCS treatment as we showed no significant findings using a small intensity of stimulation.

In conclusion, we found that left dorsolateral prefrontal cortex anodal stimulation with 2 mA has a potential positive impact on working memory in patients with PD. Future studies should address the durability of this effect when repeated sessions of tDCS are administered.

Acknowledgements

This work was partially supported by a grant from the Harvard Medical School Scholars in Clinical Science Program (NIH K30 HL04095) to F.F. and a grant from the National Institutes of Health (K24 RR01887) to A.P.-L. The authors are thankful to Barbara Bonetti for the assistance in patient's recruitment.

References

[1] Parrao-Diaz T, Chana-Cuevas P, Juri-Claverias C, Kunstmann C, Tapia-Nunez J. Evaluation of cognitive impairment in a population of patients with Parkinson's disease by means of the mini mental Parkinson test. Rev Neurol 2005;40(6):339–44.
[2] Lees AJ, Smith E. Cognitive deficits in the early stages of Parkinson's disease. Brain 1983;106(Pt 2):257–70.
[3] Taylor AE, Saint-Cyr JA, Lang AE. Frontal lobe dysfunction in Parkinson's disease. The cortical focus of neostriatal outflow. Brain 1986;109(Pt 5):845–83.
[4] Lewis SJ, Slabosz A, Robbins TW, Barker RA, Owen AM. Dopaminergic basis for deficits in working memory but not attentional set-shifting in Parkinson's disease. Neuropsychologia 2005;43 (6):823–32.
[5] Kulisevsky J. Role of dopamine in learning and memory: implications for the treatment of cognitive dysfunction in patients with Parkinson's disease. Drugs Aging 2000;16(5):365–79.
[6] Marini P, Ramat S, Ginestroni A, Paganini M. Deficit of short-term memory in newly diagnosed untreated parkinsonian patients: reversal after L-dopa therapy. Neurol Sci 2003;24(3):184–5.
[7] Boggio PS, Fregni F, Bermpohl F, Mansur CG, Rosa M, Rumi DO, et al. Effect of repetitive TMS and fluoxetine on cognitive function in patients with Parkinson's disease and concurrent depression. Mov Disord 2005;20(9):1178–84.
[8] Nitsche MA, Liebetanz D, Lang N, Antal A, Tergau F, Paulus W. Safety criteria for transcranial direct current stimulation (tDCS) in humans. Clin Neurophysiol 2003;114(11):2220–2 [author reply 2–3].
[9] Lang N, Nitsche MA, Paulus W, Rothwell JC, Lemon RN. Effects of transcranial direct current stimulation over the human motor cortex on corticospinal and transcallosal excitability. Exp Brain Res 2004;156 (4):439–43.
[10] Nitsche MA, Paulus W. Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. Neurology 2001;57(10):1899–901.
[11] Nitsche MA, Grundey J, Liebetanz D, Lang N, Tergau F, Paulus W. Catecholaminergic consolidation of motor cortical neuroplasticity in humans. Cereb Cortex 2004;14(11):1240–5.
[12] Antal A, Kincses TZ, Nitsche MA, Bartfai O, Paulus W. Excitability changes induced in the human primary visual cortex by transcranial direct current stimulation: direct electrophysiological evidence. Invest Ophthalmol Vis Sci 2004;45(2):702–7.
[13] Gandiga P, Hummel F, Cohen L. Transcranial DC stimulation (tDCS): a tool for double-blind sham-controlled clinical studies in brain stimulation. Clin Neurophysiol 2006;117(4):845–50.
[14] Nitsche MA, Seeber A, Frommann K, Klein CC, Rochford C, Nitsche MS, et al. Modulating parameters of excitability during and after transcranial direct current stimulation of the human motor cortex. J Physiol 2005;568(Pt 1):291–303.

[15] Fregni F, Boggio PS, Nitsche M, Bermpohl F, Antal A, Feredoes E, et al. Anodal transcranial direct current stimulation of prefrontal cortex enhances working memory. Exp Brain Res 2005;166(1):23–30.
[16] Marshall L, Molle M, Siebner HR, Born J. Bifrontal transcranial direct current stimulation slows reaction time in a working memory task. BMC Neurosci 2005;6(1):23.
[17] Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992;55(3):181–4.
[18] Almeida OP. Mini mental state examination and the diagnosis of dementia in Brazil. Arq Neuropsiquiatr 1998;56(3B):605–12.
[19] Gerloff C, Corwell B, Chen R, Hallett M, Cohen LG. Stimulation over the human supplementary motor area interferes with the organization of future elements in complex motor sequences. Brain 1997;120(Pt 9):1587–602.
[20] Rossi S, Cappa SF, Babiloni C, Pasqualetti P, Miniussi C, Carducci F, et al. Prefrontal [correction of prefontal] cortex in long-term memory: an "interference" approach using magnetic stimulation. Nat Neurosci 2001;4(9):948–52.
[21] Herwig U, Satrapi P, Schonfeldt-Lecuona C. Using the international 10–20 EEG system for positioning of transcranial magnetic stimulation. Brain Topogr 2003;16(2):95–9.
[22] D'Esposito M, Postle BR, Jonides J, Smith EE. The neural substrate and temporal dynamics of interference effects in working memory as revealed by event-related functional MRI. Proc Natl Acad Sci U S A 1999;96(13):7514–9.
[23] Smith EE, Jonides J. Storage and executive processes in the frontal lobes. Science 1999;283(5408):1657–61.
[24] Mottaghy FM, Krause BJ, Kemna LJ, Topper R, Tellmann L, Beu M, et al. Modulation of the neuronal circuitry subserving working memory in healthy human subjects by repetitive transcranial magnetic stimulation. Neurosci Lett 2000;280(3):167–70.
[25] Martis B, Alam D, Dowd SM, Hill SK, Sharma RP, Rosen C, et al. Neurocognitive effects of repetitive transcranial magnetic stimulation in severe major depression. Clin Neurophysiol 2003;114(6):1125–32.
[26] Moser DJ, Jorge RE, Manes F, Paradiso S, Benjamin ML, Robinson RG. Improved executive functioning following repetitive transcranial magnetic stimulation. Neurology 2002;58(8):1288–90.
[27] Padberg F, Zwanzger P, Thoma H, Kathmann N, Haag C, Greenberg BD, et al. Repetitive transcranial magnetic stimulation (rTMS) in pharmacotherapy-refractory major depression: comparative study of fast, slow and sham rTMS. Psychiatry Res 1999;88(3):163–71.
[28] Cools R, Stefanova E, Barker RA, Robbins TW, Owen AM. Dopaminergic modulation of high-level cognition in Parkinson's disease: the role of the prefrontal cortex revealed by PET. Brain 2002;125(Pt 3):584–94.
[29] Kikuchi A, Takeda A, Kimpara T, Nakagawa M, Kawashima R, Sugiura M, et al. Hypoperfusion in the supplementary motor area, dorsolateral prefrontal cortex and insular cortex in Parkinson's disease. J Neurol Sci 2001;193(1):29–36.
[30] Fregni F, Boggio PS, Mansur CG, Wagner T, Ferreira MJ, Lima MC, et al. Transcranial direct current stimulation of the unaffected hemisphere in stroke patients. NeuroReport 2005;16(14):1551–5.
[31] Mull BR, Seyal M. Transcranial magnetic stimulation of left prefrontal cortex impairs working memory. Clin Neurophysiol 2001;112 (9):1672–5.
[32] Purpura DP, McMurtry JG. Intracellular activities and evoked potential changes during polarization of motor cortex. J Neurophysiol 1965; 28:166–85.
[33] Fregni F, Marcolin MA, Myczkowski ML, Amiaz R, Hasey G, Rumi D, et al. Predictors of antidepressant response in clinical trials of transcranial magnetic stimulation. Int J Neuropsychopharmacol in press, doi:10.1017/S1461145705006280.
[34] Strafella AP, Paus T, Barrett J, Dagher A. Repetitive transcranial magnetic stimulation of the human prefrontal cortex induces dopamine release in the caudate nucleus. J Neurosci 2001;21(15):RC157.
[35] Keck ME, Sillaber I, Ebner K, Welt T, Toschi N, Kaehler ST, et al. Acute transcranial magnetic stimulation of frontal brain regions selectively modulates the release of vasopressin, biogenic amines and amino acids in the rat brain. Eur J Neurosci 2000;12(10):3713–20.
[36] Aalto S, Bruck A, Laine M, Nagren K, Rinne JO. Frontal and temporal dopamine release during working memory and attention tasks in healthy humans: a positron emission tomography study using the high-affinity dopamine D2 receptor ligand [11C]FLB 457. J Neurosci 2005;25(10):2471–7.
[37] Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu Rev Neurosci 1986;9:357–81.
[38] Bindman LJ, Lippold OC, Redfearn JW. The action of brief polarizing currents on the cerebral cortex of the rat (1) during current flow and (2) in the production of long-lasting after-effects. J Physiol 1964;172: 369–82.
[39] Nitsche MA, Liebetanz D, Antal A, Lang N, Tergau F, Paulus W. Modulation of cortical excitability by weak direct current stimulation-technical, safety and functional aspects. Suppl Clin Neurophysiol 2003;56:255–76.
[40] Priori A. Brain polarization in humans: a reappraisal of an old tool for prolonged non-invasive modulation of brain excitability. Clin Neurophysiol 2003;114(4):589–95.
[41] Tipper CM, Cairo TA, Woodward TS, Phillips AG, Liddle PF, Ngan ET. Processing efficiency of a verbal working memory system is modulated by amphetamine: an fMRI investigation. Psychopharmacology (Berl) 2005;180(4):634–43.
[42] Seamans JK, Yang CR. The principal features and mechanisms of dopamine modulation in the prefrontal cortex. Prog Neurobiol 2004;74 (1):1–58.
[43] Iyer MB, Mattu U, Grafman J, Lomarev M, Sato S, Wassermann EM. Safety and cognitive effect of frontal DC brain polarization in healthy individuals. Neurology 2005;64(5):872–5.