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Time up and go task performance improves after transcranial direct current stimulation in patient affected by Parkinson's disease

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HIGHLIGHTS

- Anodal transcranial direct current stimulation (AtDCS) could enhance motor performance.
- Locomotor disturbances represent one of the major distress in Parkinson's disease.
- AtDCS can be a relevant tool to modulate walking abilities in PD.
- tDCS should be considered a useful tool for patients with neurodegenerative diseases.

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ABSTRACT

Locomotor disturbances represent one of the major distress in everyday life in people with Parkinson's disease (PD). Timed up and go test (TUG) has been advocated a useful and reliable tool for quantifying locomotor performance. The aim of this study was to assess the effect of anodal transcranial direct current stimulation (tDCS) applied over the dorsolateral prefrontal cortex (DLPFC) during timed up and go test (TUG) in a group of patients with PD. Ten participants underwent two sessions of anodal tDCS (left and right) and one session of placebo tDCS. TUG was performed before and after each tDCS session (anodal or placebo). A significant motor improvement after right DLPFC stimulation vs. placebo stimulation was observed. These results suggest that anodal tDCS can be a relevant tool to modulate walking abilities in PD.

1. Introduction

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation tool that is now being widely used in neuroscientific and clinical research in humans [8]. One hypothesis is that non-invasive brain stimulation modifies cortical plasticity and that its effects may outlast the stimulation period. In animal models, tDCS has been shown to increase extracellular striatum dopamine levels [18], which might ameliorate both motor and cognitive symptoms in Parkinson's disease (PD) [2,9,14,20].

One of the most distressing symptoms in PD is bradykinesia and deficits in motor performance, which eventually respond less to dopaminergic treatment and thus pose a therapeutic challenge [2].

In the present pilot study, we evaluated whether anodal tDCS (vs. placebo) applied over the dorsolateral prefrontal cortex (DLPFC) has specific beneficial effects on motor performance in PD patients. To test this hypothesis, we used the timed up and go (TUG) test, a simple, quantitative, and objective method for the assessment of locomotor disturbances in PD. The TUG test has been used to monitor the response to treatments in therapeutic trials, and it correlates well with measures of objective functions in PD [10].

2. Methods

2.1. Participants

Ten patients who fulfilled the UK Parkinson's Disease Brain Bank criteria for the diagnosis of idiopathic PD were recruited [12].

We administered the Italian version of the Unified Parkinson's Disease Rating Scale (UPDRS) and the Hoehn and Yahr Scale [1]. Patients were always tested in the *on* phase.

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Table 1
Demographic, clinical features and neuropsychological assessment of the sample of patients with Parkinson's disease.

	Raw score	Adjusted score	Cut-off[a]
Age (years)	67.1 ± 7.2		
Gender (male/female)	6/4		
Education (years)	10.0 ± 4.2		
Duration of disease (years)	8.1 ± 3.5		
More affected body side (right/left)	2/8		
Levodopa dosage (total, mg/die)	749.2 ±445.5		
Unified Parkinson disease rating scale (UPDRS-III)	13.3 ± 5.7		
Hoehn–Yahr	1.3 ± 1.1		
Beck depression inventory-II (BDI-II)	11.1 ± 7.5		
Screening for dementia			
Mini mental state examination (MMSE)	28.5 ± 1.8	27.5 ± 2.4	>24
Mini mental Parkinson (MMP)	27.5 ± 3.2	27.9 ± 3.4	>25.42
Language			
Fluency-phonemic	29.3 ± 8.6	31.8 ± 10.4	>16
Fluency-semantic	32.6 ± 7.8	36 ± 7.9	>24
International picture naming project task			
Object naming (accuracy, %)	92.7 ± 7.9		
Action naming (accuracy, %)	78.9 ± 14.5		
Attentional and executive functions			
Frontal assessment battery (FAB)	15 ± 2.3	15.3 ± 2.3	≥13.5
Reaction time (RTI) – CANTAB			
Movement time, ms	480.7 ± 227.8		
Reaction time, ms	376.3 ± 71.4		

[a] Cut-off scores according to Italian normative data are reported. Values are mean ± SD.

Baseline cognitive and clinical assessments were performed (see Table 1).

Patients with potentially confounding neurological and psychiatric disorders, clinically known hearing or vision impairment, a past history of alcohol abuse, psychosis, major depression, or dementia were excluded. The presence of metal objects or stimulators in the head was considered additional exclusion criteria. All participants were made fully aware of the aims of the research, and informed consent was obtained from all subjects. The work was conducted in accordance with local clinical research regulations and conformed to the Helsinki Declaration.

2.2. tDCS procedure

tDCS was administered at the beginning of the *on* period after the participant had taken the levo-dopa dosage (120 min after medication assumption). Patients were blinded to the treatment. Different researchers performed tDCS and complete baseline evaluation.

The stimulation was delivered by a battery-driven, constant current stimulator (BrainStim, EMS, Bologna, Italy) through a pair of saline-soaked sponge electrodes (7 cm × 5 cm). A constant current of 2 mA was applied for 7 minutes (with a ramping period of 10 s at the beginning and end of the stimulation). The current density (0.057 mA/cm^2) was maintained below safety limits [16]. The electrodes were secured using elastic bands, and an electroconductive gel was applied under the electrodes before the montage to reduce contact impedance. We positioned tDCS electrodes according to the international 10–20 system [11]. The active electrode was placed on the left or right DLPFC, 8 cm frontally and 6 cm laterally with respect to the scalp vertex; the reference electrode was fixed on the contralateral supraorbital area. In the placebo stimulation, the tDCS montage was the same, but the current was turned off 10 s after the stimulation began and turned on for the last 10 s of the stimulation period (the duration of the fade-in and fade-out periods = 10 s), making this condition indistinguishable from the experimental stimulation. Potential tDCS side effects were assessed with a questionnaire at the end of each session. The active stimulations (i.e., anodal left and anodal right) were executed on two different days to minimize the likelihood of interference effects. The placebo stimulation was always performed before the active stimulation on either the first or second day to randomize the order of the stimulation conditions.

2.3. Timed up and go (TUG) test

The TUG test was measured in milliseconds using a professional chronometer [15]. Subjects were instructed to stand up from the sitting position on the examiner's signal, walk a distance of 3 m at a comfortable place, turn around, walk back to the chair and sit down again.

The TUG test was performed before and at the end of each stimulation condition (anodal left, anodal right). Recordings were made by two independent research assistants blinded to the type of stimulation to test for inter-rater reliability (see Fig. 1A). The mean of the recordings taken by the two independent reviewers was used for subsequent analysis.

2.4. Data analyses

Statistical analyses were performed using SPSS software (version 21.0 IBM Statistics, IBM Corp) and R language and environment v.3.0.2 (R Development Core Team, 2012).

First, we investigated the possible effects of participant cognitive status on motor performance, performing a correlation analysis between motor performance achieved at TUG test baseline and neuropsychological tests.

To test tDCS effects for the TUG test, we calculated differences in performance between post- and pre-tDCS scores following active and placebo intervention (anodal left DLPFC, anodal right DLPFC, and placebo tDCS). We performed the Friedman Test to test whether there was an overall effect of the intervention (comparing the three stimulation conditions). Posthoc comparisons were performed by adjusting for multiple tests. Statistical significance refers to a P value of 0.05.

3. Results

We inferred that all of the subjects tolerated the stimulation well by interpreting the spontaneous reports and the questionnaires completed by each subject at the end of the experiment [7].

First, to investigate the possible effects of cognitive status on motor performance, a correlation analysis between motor performance achieved at the TUG test at baseline and neuropsychological test scores was performed.

Significant Pearson correlation coefficients were observed between TUG performance and (a) the CANTAB RTI scores (RTI movement: $R = 0.87$, $p < 0.001$; RTI reaction times: $R = 0.74$, $p < 0.02$), (b) the FAB ($R = -0.64$, $p = 0.04$) and (c) the phonemic verbal fluency test ($R = -0.63$, $p = 0.04$). These results suggest that a progressive decrease in motor abilities is linked to executive functions.

Moreover we found a significant correlation between TUG performance and (d) action naming accuracy ($R = 0.45$, $p = 0.02$) and (e) object naming accuracy ($R = 0.49$, $p = 0.04$).

This finding appears in line with neuropsychological and neuroimaging studies that suggest a common network for motor and language abilities. We didn't find other significant correlations.