This was elegantly demonstrated in single frontal cortical neurons, which frequently harbor somatic CNVs. 1,8,12 Both SNCA and PARK2 may be particularly susceptible to somatic CNV generation, because they are in chromosomal fragile sites.4,20 The concept of widespread mosaicism is gaining ground, 8,21,22 and a substantial proportion of the risk of sporadic diseases may be explained by nonheritable somatic genomic variation, possibly in genes involved in Mendelian forms of the same disease. 8 Another common sporadic disease with complex genetics, hypertension can be attributable to somatic mutations in genes involved in aldosterone production, with a more severe phenotype in inherited cases.23-25 Because most PD risk remains unexplained, further analysis for somatic mutations could advance our understanding of sporadic PD pathogenesis, but evidence has yet to be provided to support this hypothesis, and we must acknowledge the potential that this concept is not relevant to PD. ●

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References


Supporting Data

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Transcranial Direct Current Stimulation for Treatment of Freezing of Gait: A cross-over Study

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ABSTRACT

Background and objective: Progression of Parkinson’s disease (PD) is frequently characterized by the occurrence of freezing of gait (FOG) representing a disabling motor complication. We aim to investigate safety and efficacy of transcranial direct current stimulation of the primary motor cortex of PD patients with FOG.

Methods: In this cross-over, double-blind, sham-controlled study, 10 PD patients with FOG persisting in...
Freezing of gait (FOG) is a disabling clinical phenomenon characterized by brief episodes of inability to generate effective stepping. FOG significantly impairs mobility and causes falls, representing one of the most important challenges in the treatment of Parkinson’s disease (PD). Indeed, although an increase in levodopa dosage may help in reducing frequency and duration of “off”-related FOG, some patients still present freezing in “on” state. Along with the dopaminergic deficit, several other pathogenetic mechanisms might underlie FOG. Recently, it has been hypothesized that FOG could be triggered by a breakdown in the normal symmetry and bilateral coordination of gait. Accordingly, restoration of a more physiological interhemispheric functional balance by deep brain stimulation (DBS) has proved to reduce FOG frequency and severity. The aim of this study was to investigate the efficacy and safety of transcranial direct current stimulation (tDCS) for treatment of FOG persisting in “on” state in PD patients. Transcranial direct current stimulation is a method of noninvasive brain stimulation modulating cortical activity and inducing synaptic plastic changes that outlast the end of the stimulation. We hypothesized that anodal tDCS, which increases cortical excitability, could improve FOG in PD patients by modulating corticostriatal interactions and abnormal patterns of cortical activation related to gait planning.

Patients and Methods

Patients

Patients with PD in a Hoehn and Yahr stage of 2 to 4 while “off” medication, scoring 3 or more on item 3 of the Freezing of Gait Questionnaire (FOG-Q), were included in the study (see Supplemental Data, Materials and Methods). The PD diagnosis was made according to UK PD Brain Bank criteria. Each patient was examined in the “off” state (12 hours after last medication intake) and “on” state (peak effect of usual medication). Only PD patients with FOG persisting in the “on” state, that is, FOG unresponsive to or only slightly ameliorated by the dopaminergic therapy, were enrolled. Patients with only “off” FOG (i.e., relieved by dopaminergic medication) and “on” FOG (i.e., induced by the dopaminergic medication) were not included in the study. Before enrollment, all of the subjects were checked for contraindications to tDCS. The study was approved by the local ethics committee, and written informed consent to participate was obtained from all subjects before the experiment according to the Declaration of Helsinki.

Study Design and tDCS Intervention

The study followed a double-blind, cross-over, randomized, and sham-controlled design. All subjects underwent a preliminary clinical assessment (see “Clinical Assessment”) before randomization to sham or anodal stimulations. Both anodal and sham tDCS were applied for 5 consecutive days. Patients who underwent anodal tDCS as first treatment were then switched to sham stimulation, and vice versa. A 3-month wash-out was carried out to prevent bias related to carryover effects from the first session. The anode was positioned with anteroposterior orientation over the primary motor cortex (M1) corresponding to the leg with which the patient usually started walking after a FOG episode. The cathode was positioned over the contralateral orbitofrontal cortex. Currents were given for 20 minutes at an intensity of 2 mA, and they were ramped up or down over the first and last 8 seconds of stimulation. For the sham condition, the intensity was set to 2 mA, as for anodal tDCS, but the DC stimulator was turned off after 30 seconds of stimulation, and again switched on for 30 seconds at the end of the stimulation period (see Supplemental Data, Materials and Methods).

Clinical Assessment

Disease severity was assessed by the Italian validated Movement Disorder Society revision of the Unified Parkinson and Movement Disorder Society revision of the Unified Parkinson Disease Rating Scale score, with reduction in the Unified Parkinson’s Disease Rating Scale score, were observed after anodal stimulation. Beneficial effects were more evident after the entire 5-day stimulation session, and persisted until the end of the observation period.

Conclusions: Anodal transcranial direct current stimulation of the motor cortex is safe and has therapeutic potential in PD patients with FOG.
Parkinson’s Disease Rating Scale (MDS-UPDRS). The Stand Walk Sit (SWS) test was used to evaluate gait and occurrence of FOG episodes in different contexts, such as start hesitation/destination or freezing while turning (see Supplemental Data, Materials and Methods). Patients underwent MDS-UPDRS and SWS test at baseline, immediately after the 1st and 5th tDCS interventions (Monday and Friday), 2 days, and 2 and 4 weeks after the end of the tDCS session. All clinical evaluations, both in baseline and after the experimental procedures, were performed each day at the same hour during the “on” state. To assess gait, falls, and FOG episodes, the FOG-Q, Gait and Falls Questionnaire were administered to patients at baseline, 2 days, and 2 and 4 weeks after the end of the tDCS session.

### Statistical Analysis

Data were analyzed by two-way repeated-measures analyses of variance followed by Duncan post hoc test for multiple comparisons (see Supplemental Data, Materials and Methods). Primary outcome measures were changes in parameters evaluated by the SWS test. For all analyses, the level of statistical significance was set at $P < 0.05$.

### Results

Ten patients (5 men and 5 women; mean age, $72.3 \pm 3.60$ standard deviation) were enrolled and completed the entire study evaluations (Table 1). No dropouts occurred during the study. In all patients, the dopaminergic treatment was not modified throughout the entire duration of the study. The experimental procedures were well tolerated, and no adverse effects were observed.

Measurements of all of the parameters evaluated by the SWS test significantly improved in the anodal compared with the sham condition (Fig.1). We observed a significant effect of “Time” for both number of steps ($F_{3,31} = 6.42; P < 0.002$) and duration of FOG episodes ($F_{4,32} = 3.68; P < 0.02$); a significant interaction between “Condition” and “Time” was found for number of steps ($F_{5,42} = 4.52; P < 0.005$), number ($F_{3,34} = 4.75; P < 0.005$), and duration ($F_{3,22} = 3.19; P < 0.05$) of FOG episodes. Significant effect of “Time” ($F_{1,12} = 5.32; P < 0.05$) and significant interaction between “Condition” and “Time” ($F_{3,25} = 3.54; P < 0.05$) were observed when evaluating the time needed to perform the SWS test (Fig.1).

The analysis of variance showed that total and motor (part III) MDS-UPDRS scores, as well as FOG-Q and Gait and Falls Questionnaire scores, significantly ameliorated after anodal tDCS (see Supplemental Data, Results).

### Discussion

The present study shows that anodal tDCS of the primary motor cortex significantly improves motor performances and gait in PD patients with FOG. The therapeutic potential of noninvasive cortical stimulation techniques for adjunctive treatment of PD has been widely assessed, with promising results. However, this is the first study that primarily evaluates the potential therapeutic effect of tDCS in PD complicated by moderate to severe FOG persisting in the “on” state. In a pilot study, Rektorova et al. have found no effect of “facilitatory” high-frequency repetitive transcranial magnetic stimulation (rTMS) of M1 in PD patients with FOG. However, rTMS and tDCS are not strictly comparable, and, in contrast with the results of our study, the primary outcome measure was improvement of “off”-related FOG in patients “off”-medication. Thus, lack of enduring effects with rTMS could be partly attributed to deficient induction of long-term potentiation–like changes in the absence of dopamine.

Two main mechanisms may be taken into account to explain our results. First, we could hypothesize that anodal tDCS might have induced dopamine release in the basal ganglia by activation of glutamatergic...
corticostriatal fibers. This hypothesis is supported by evidence that 1) dopamine can be released under direct control of glutamatergic corticostriatal projections \(^{25,26}\); 2) tDCS modulates functional connectivity of the cortico-striatal and thalamo-cortical circuits \(^{27}\); 3) other “facilitatory” methods of noninvasive brain stimulation, such as high-frequency rTMS, may induce ipsilateral dopamine release in the striatum when applied to the frontal cortex. \(^{28-30}\) However, mechanisms by which tDCS and rTMS induce cortical excitability changes are different. Whereas tDCS induces only changes in the spontaneous cell firing, rTMS causes the neuron’s action potentials to fire, possibly resulting in a stronger effect. \(^{21}\)

The second possible mechanism refers to the modulation of cortical excitability and neural network activity. Functional imaging, positron-emission tomography and transcranial magnetic stimulation (TMS) studies of PD subjects with and without FOG have demonstrated increased bilateral activation in the M1 and supplementary motor area (SMA), \(^{31-33}\) which has been supposed to represent a beneficial attempt to compensate for the underactive pallido-thalamo-cortical drive. \(^{34}\) Thus, in our patients, in agreement with previous reports, \(^{35}\) anodal stimulation could have enhanced this compensatory mechanism, possibly acting not only on the targeted M1 but also on the neighboring SMA. This could be attributable to the relatively large stimulation area of tDCS, even if further studies will need to clarify to which extent the modulation of SMA activity could have affected the present results. In addition, some authors have suggested that an uncoordinated bilateral control of gait could lead, once the level of asymmetrical gait exceeds a certain threshold, to FOG episodes. \(^{36,37}\) In particular, a recent study showed that, in PD patients with subthalamic DBS, the reduction of the stimulation voltage in the side contralateral to the leg with longer step length (“less affected” hemisphere) improved frequency and duration of FOG through the normalization of gait symmetry and coordination. Based on these considerations, facilitatory anodal tDCS, when applied over the M1 contralateral to the leg with which the first movement after FOG was usually executed (“more affected” hemisphere), might improve the functional balance between cortical areas responsible for gait coordination.

Some methodological considerations should be made regarding the design of the study. Cross-over studies are characterized by reduced influence of confounding factors and require fewer subjects as compared with non-cross-over longitudinal studies to reach higher statistical efficacy. The main
disadvantage is the possibility of the carry-over effect. However, it is unlikely that the effect of a 5-day session of tDCS would last up to 3 months, given that baseline evaluations in each patient, before sham and anodal stimulation, were not significantly different. Another aspect worth mentioning refers to the minimal, not significant placebo effects seen after sham stimulation. This is in line with evidence that placebo effects may be short-lived, without cumulative benefit after repeated treatment sessions, and may be mainly associated with a benefit for subjective outcomes.38 In addition, given that various clinical manifestations of PD may be differently influenced by placebo effects,39,40 we cannot exclude that in our patients gait and FOG were not significantly affected by placebo effects, possibly because of specific underlying pathophysiological mechanisms.

Finally, a limitation of the study refers to the possibility that a complete blinding was not achieved with 2 mA stimulation intensity. Indeed, at the higher stimulation intensity of 2 mA there could be, at least theoretically, the possibility that patients continue to perceive an itching skin sensation throughout the entire period of real tDCS stimulation. All patients reported a tingling or itching sensation over the electrodes placement area only at the beginning and at the end of the stimulation, without differences between sham and anodal tDCS. In conclusion, this study suggests that tDCS improves gait and FOG in PD patients, and supports the concept that FOG might be a manifestation of asymmetrical and uncoordinated bilateral motor performance of gait. If corroborated by clinical trials involving larger numbers of patients, this approach might become a viable option to relieve otherwise intractable FOG in advanced PD patients.

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Supporting Data

Additional supporting information may be found in the online version of this article at the publisher’s web-site.

History of Smoking and Olfaction in Parkinson’s Disease

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ABSTRACT

Objective: Olfactory dysfunction is the most common pre-motor symptom in Parkinson’s disease (PD), and smoking is known to be associated with lower risk of PD. This study tested the hypothesis that smoking is associated with better olfaction in PD.

Methods: Smoking history was obtained from 76 PD subjects (22 with a history of smoking [smokers], 54 who never smoked [nonsmokers]), and 70 controls (17 smokers, 53 nonsmokers). Olfaction was assessed using the 40-item University of Pennsylvania Smell Identification Test (UPSIT). The olfactory scores between groups and subgroups were compared using analysis of covariance with adjustment for age, gender, and monoamine oxidase B (MAO-B) inhibitor usage.

Results: Overall the olfactory score was lower in PD compared with controls (olfactory scores: 21.5 vs. 33.5, P<0.0001). Among controls, there was no significant difference in olfaction between smokers and nonsmokers (olfactory scores, 33.2 vs. 34.2; P = 0.95). Among PD subjects, however, smokers scored significantly better regarding olfaction compared with nonsmokers (olfactory scores: 24.4 vs. 19.9, P = 0.02).

Conclusions: These data suggest that a history of smoking is associated with better olfaction among PD patients. The finding may be related to why smoking may be protective against PD. Further studies are needed to confirm this finding and investigate the underlying mechanisms. © 2014 International Parkinson and Movement Disorder Society

Key Words: smoking; Parkinson’s disease; olfactory; cigarette

Parkinson’s disease (PD) is a progressive neurodegenerative disorder marked pathologically by loss of dopamine neurons in the substantia nigra of the basal ganglia. Although the cardinal clinical signs are defined by motor disabilities, many nonmotor symptoms such as olfactory, gastrointestinal, and cognitive dysfunction are also recognized to be associated with PD. Some of this nonmotor dysfunction, such as hyposmia and constipation, may develop during the prodromal stage of PD and precede PD diagnosis by years.1 Because the nasopharynx and gastrointestinal (GI) tract have direct contact with the environment, these areas can be the port-of-entry for neurotoxins.2,3 Thus, there is an emerging concept that pre-motor symptoms represent intermediate phenotypes before overt PD and may offer a vehicle to understand the role of genetics and the environment in the early stages of PD development.4 As such, a detailed understanding of these nonmotor features and...