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Subthalamic stimulation and levodopa modulate cortical reactivity in Parkinson's patients

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ABSTRACT

Background: The effects of deep brain stimulation of the subthalamic nucleus (DBS-STN) and L-dopa (LD) on cortical activity in Parkinson's disease (PD) are poorly understood.
Objectives: By combining transcranial magnetic stimulation (TMS) and electroencephalography (EEG) we explored the effects of STN-DBS, either alone or in combination with L-Dopa (LD), on TMS-evoked cortical activity in a sample of implanted PD patients.
Methods: PD patients were tested in three clinical conditions: i) LD therapy with STN-DBS turned on (ON/ON condition); ii) without LD therapy with STN-DBS turned on (OFF/ON condition); iii) without LD therapy with STN-DBS turned off (OFF/OFF condition). TMS pulses were delivered over left M1 while simultaneously acquiring EEG. Eight age-matched healthy volunteers (HC) were tested as a control group.
Results: STN-DBS enhanced early global TMS-evoked activity (~45–80ms) and high-alpha TMS-evoked oscillations (11–13 Hz) as compared to OFF/OFF condition, independently from concomitant LD therapy. LD intake (ON/ON condition) produced a further increase of late TMS-evoked activity (~80–130ms) and beta TMS-evoked oscillations (13–30 Hz), as compared to OFF/OFF and OFF/ON conditions, that normalized reactivity as compared to HC range of values.
Conclusions: Our data reveal that bilateral STN-DBS and LD therapy induce a modulation of specific cortical components and specific ranges of frequency. These findings demonstrate that STN-DBS and LD therapy may have synergistic effects on motor cortical activity.

1. Introduction

Deep Brain Stimulation (DBS) of the subthalamic nucleus (STN) represents an effective therapy in Parkinson's disease (PD). STN-DBS may exert its control on motor cortical activity through the modulation of basal ganglia-thalamo-cortical pathways, influencing intracortical inhibitory mechanisms. In particular, it is of interest to understand whether STN-DBS determines peculiar effects on motor cortical activity, eventually different from those induced by L-Dopa (LD). It has been proposed that in the motor cortex STN-DBS has profound effect on the activity of specific intracortical circuits. Previous TMS studies showed consistently that STN-DBS restores mainly GABA-A dependent short intracortical inhibition (SICI) circuit closer to normal levels [1,2]. On the other hand, STN-DBS seems less effective in modulating late inhibitory processes such as long intracortical inhibition (LICI) [3] and cortical silent period (CSP) [3,4]. Previous works showed that STN-DBS alone has no effects on SP duration [1,3,4], but increases CSP duration if coupled with LD therapy [2]. This is consistent with previous work in PD patients not treated with STN-DBS showing

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Abbreviations

DBS	deep brain stimulation
STN	subthalamic nucleus
LD	levodopa
PD	Parkinson's disease
TMS	transcranial magnetic stimulation
EEG	electroencephalography
M1	primary motor cortex
HC	healthy volunteers
SICI	short-interval intracortical inhibition
LICI	long-interval intracortical inhibition
CSP	cortical silent period
FDI	first dorsal interosseous
ISI	interstimulus interval
EOG	electrooculography
ICA	independent component analysis
TEP	TMS-evoked potential
GMFP	global mean field power
TRSP	TMS-related spectral perturbation
GABA	gamma-Aminobutyric acid

that CSP duration is reduced in the OFF LD state [5,6] being normalized after LD intake [4,5]. In the current study we took advantage of novel combined TMS/EEG approach to investigate in depth the hypothesis that STN-DBS and LD may modulate differently the activity of separate motor cortical circuits. In contrast with standard TMS methods based on peripheral measurements of corticospinal excitability, the combined use of TMS and EEG allow the direct recording of the post-synaptic potentials produced by the TMS-evoked depolarization. The analysis of the TMS-evoked potentials (TEPs) reveals the neurophysiological state of the stimulated area and of its connections, representing a reliable tool to identify key changes associated with concurrent therapies [7]. We performed TMS/EEG recordings in advanced PD patients treated with STN-DBS in three clinical conditions: during LD therapy with STN-DBS turned on, without LD therapy with STN-DBS turned on and without LD therapy with STN-DBS turned off. As a control condition, we tested a group of age-matched healthy controls to be compared with PD patients.

2. Methods

2.1. Patients

Six advanced akinetic-rigid PD patients with bilaterally implanted DBS electrodes into the STN were enrolled in the study. All patients underwent neurosurgery at least three years before the study. Inclusion criteria were: age <75 years, stable LD dosage and steady electrical parameters over 4 weeks before the study, documented clinical response to STN-DBS and LD, absence of contraindications to TMS, dementia, history psychiatric disorders. Each participant gave written informed consent to the study, which was approved by the local Ethic Committee (PROG. 378-74). Safety studies have shown that TMS can be applied to implanted patients as long as the TMS coil is not triggered in the immediate vicinity of the subcutaneous stimulator [8].

2.2. Control group

Eight healthy controls (HC), age-matched to the PD patients (61.5 ± 11.3 y; four females), were recruited for the study as a control group. They gave written informed consent to the study, which was approved by the local Ethic Committee. All participants were tested for TMS exclusion criteria [8].

2.3. General procedure

Each patient was examined in three experimental conditions on different days, at least 1 week apart, in a randomized order. In ON/ON condition, patients were examined 2 h after the first daily dose of LD therapy, whit the DBS electrodes turned on. In OFF/ON condition, patients were examined after overnight LD therapy withdrawal; therapy with dopamine agonists was suspended 48 h before the examination. OFF/OFF condition was identical to OFF/ON but DBS was turned off 90 min before the examination. Motor performance was assessed in each session by UPDRS-III. During TMS participants were seated on a comfortable armchair in a relaxed position. Control group was tested in a single session. Patients' clinical characteristics are summarized in Table 1.

2.4. Transcranial magnetic stimulation

TMS was carried out using a Magstim 200 stimulator with a 70 mm figure-of-eight coil (Magstim Company Limited, Whitland, UK), which produced a monophasic waveform with a pulse width of ~0.1 ms. The coil was positioned tangentially to the scalp at about 45° angle away from the midline over the hand motor area of left M1, defined as the point where stimulation evoked the largest MEPs from the contralateral FDI muscle. Stimulus intensity was set to 90% of RMT, defined as the lowest TMS intensity which evoked at least five out of ten MEPs with an amplitude >50 μV peak-to-peak in the contralateral FDI at rest [9]. For each condition, 80 TMS single pulses were delivered over left M1 at an inter-stimulus interval (ISI) of 4–6 s, while acquiring EEG. A TMS neuronavigation system (SofTaxic, EMS, Bologna, Italy) was used to ensure a high degree of reproducibility across the sessions [10].

2.5. EEG recordings

EEG was continuously acquired from 19 electrodes positioned according to the 10–20 International System by means of a TMS-compatible EEG equipment (BrainAmp 32MRplus, BrainProducts). The ground electrode was positioned in AFz, while an active reference was positioned on the tip of the nose. Skin/electrode impedance was maintained <5 kΩ. Horizontal electrooculography (EOG) was recorded from electrodes positioned on the outer canthi of both eyes, and vertical EOG from electrodes located beneath the right eye recorded vertical eye movements and blinks. EEG signal was band-pass filtered at 0.1–1000 Hz and digitized at a sampling rate of 5 kHz. To reduce auditory contamination of EEG induced by coil clicks, participants wore earplugs throughout the experiment.

2.6. EEG analysis.

EEG data were off-line analyzed using BrainVision Analyzer 2 and Fieldtrip toolbox, running in a MATLAB environment (Version 7.9.0, MathWorks Inc., Natick, USA). EEG signals were first re-referenced to the average of all electrodes. EEG data from PD patient #2 (see Table 1) were excluded due to excessively artifact movements. Thus, a total of five PD patients were considered for the analysis. In order to remove the TMS artifact, we excluded and subsequently interpolated data from 5 ms before to 10 ms after the

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