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Original research article

Opposite effects of L-dopa and DBS-STN on saccadic eye movements in advanced Parkinson's disease☆

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ABSTRACT

Objective: To assess the effects of L-dopa and deep brain stimulation of the subthalamic nucleus (DBS-STN) on saccadic eye movements in patients with Parkinson's disease (PD).
Methods: Visually and internally guided horizontal saccades were evaluated using a saccadometer in 64 patients with advanced PD and 48 healthy controls. Forty-four pharmacologically treated patients were assessed in their ''med-off'' (OFF) and ''med-on'' (ON) status, whereas 20 DBS-STN treated patients were assessed in their ''med-off, stim-off'' (OFF) and ''med-off, stim-on'' (ON) status.
Results: In all PD patients the saccades in the OFF status were delayed, slower and smaller ($p < 0.01$) than in controls. In pharmacologically treated patients all studied parameters showed tendency to worsen in the ON status as compared to the OFF status. In contrast, activating DBS-STN showed tendency to improve all studied parameters. Comparison of the studied saccade parameters between the ON status of DBS-STN treated patients, ON status of the pharmacologically treated patients and the controls showed that 73% of these parameters in the DBS-STN treated patients were similar as in the controls. While in the pharmacologically treated patients only 26% of these parameters were similar as in the controls.
Conclusion: This prospective study comparing the influence of L-dopa and DBS-STN on saccades in advanced PD showed contrasting results between these two treatments; the majority of the studied parameters in patients on DBS-STN were similar as in the controls.

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1. Introduction

There have been several reports describing abnormalities of eye movements in Parkinson's disease (PD), such as difficulties in stabilizing the image on the retina, or difficulties in redirecting the line of sight to a new object (visually or internally guided saccades). Both difficulties can be affected either by the disease itself or by treatment [1].

Saccades are more easily quantified and less dependent on biomechanical parameters than limb movements, thus, they might be a more appropriate for studying movement control in PD. In this disease, measurements of repetitive saccadic movements, in contrast to measurements of limb movements, can be easily performed even in OFF status [2,3]. Saccadic abnormalities in PD essentially resemble somatomotor symptoms, being characterized by increased reaction time, decreased amplitude and decreased velocity, and consequently may reflect hypometria and bradykinesia [4].

Previous studies on the effects of deep brain stimulation of the subthalamic nucleus (DBS-STN) or L-dopa on saccades have led to varying results and their clinical significance was not clear [2,5–8]. We compared the influence of L-dopa and DBS-STN on saccades in patients with advanced PD, using a prospective protocol.

2. Material and methods

2.1. Study participants

The participants were recruited from the Movement Disorders outpatient clinic of the Department of Neurology. Forty-four of the study patients had advanced PD treated only with L-dopa (Hoehn and Yahr scale off drug, 4.1 ± 0.2) and 20 were additionally treated with bilateral DBS-STN, all implanted using the same surgical protocol (mean follow-up since DBS-STN procedure, 2 years; H&Y off drug, 4.0 ± 0.2) [8,9]. Exclusion criteria were as follows: cognitive dysfunction (<24 points on the Mini-Mental State Examination, MMSE), moderate-to-severe depression (>16 points on the Hamilton Rating Scale for Depression, HRSD) [10], color blindness (score <0.1 at the best corrected visual performance, using a standard Snellen Chart), red color vision impairment using the Ishihara Color Test, and severe eye-movement impairments upon neurological examination.

Forty-eight healthy subjects matched by age and gender (28 males; mean age 60 ± 8) served as controls.

All participants provided written, informed consent. Ethical approval was given by the institutional review board.

2.2. Study design

Social and demographic characteristics, medical history including age at disease onset and course of disease as well as L-dopa equivalent daily dose (LEDD) were recorded from all participants during the initial visit and neurological examination was performed, including visual acuity, color distinction and eye movement assessment. Additionally, study subjects were rated on MDS-UPDRS part III in their best clinical ON state–after intake of 1.5 times the equivalent of their morning medication dose – and filled out the quality of life PDQ-39 questionnaire. PD was staged according to the Hoehn-Yahr scale (H&Y) [8], and PD subtype (tremor-dominant vs. bradykinesia, postural instability and gait difficulty, PIGD) [11] was identified in each patient.

During the study period, PD subjects were examined twice, in their clinically defined L-dopa-OFF and ON status, on 2 consecutive days. Following classical guidelines, the first assessment of pharmacologically treated patients was performed in the clinically defined OFF-status after drug withdrawal for at least 12 h for L-dopa and 48 h for other antiparkinsonian drugs (''med off'') [12,13]. The second assessment was carried out approximately 45–60 min after L-dopa intake (1.5 times the equivalent of morning medication dose) in the best ON status (defined as the status when patient and examiner agreed that the patient's best ON was attained) [14]. The assessment of the DBS-STN patients was performed in the clinically defined OFF-status as in the previous group (''med off''), with the stimulator switched on (''stim on'') and repeated 30 min after switching the neurostimulator off, in the stimulation OFF state (''med off'' and ''stim off'') [12,13]. The assessment of patients in their ON (pharmacologically treated patients: ''med on''; DBS-STN patients: ''med off'' and ''stim on'') and OFF states (pharmacologically treated patients: ''med off''; DBS-STN patients: ''med off'' and ''stim off'') involved both neurological examination (including MDS-UPDRS part III assessment) and saccadic eye-movement recording.

In control subjects, only one saccadic eye-movement recording was performed.

2.3. Saccade assessment

The participants were seated in a comfortable armchair, one meter away from a board with light-emitting diodes along a horizontal line. Saccadic eye movements were recorded using a miniaturized infra-red 1 kHz saccadometer, low pass filtered at 250 Hz with 12 bit resolution (Ober Consulting, Poznan, Poland) [15]. While the device was mounted on the subject's forehead, resting on the bridge of the nose, five built-in low-power lasers projected red 13 cd m^{-2} spots subtending some 0.1 degrees in horizontal line in the midline at ±20 degrees from central vision. As stimuli moved exactly with the head, no head-restraint was necessary, unless desired by the patient.

Participants underwent 3 experimental runs in a random order. Saccades were determined to begin when eye velocity was greater than 20°/s. Of all performed saccades, only centrifugal visually and internally guided saccades were analyzed. Each experimental run was preceded by a number of preliminary saccades (usually 10, toward a 10-deg or 20-deg lateral target that appeared randomly right or left), used to calibrate the device. Each experimental run lasted 10–15 min and participants rested between trials to minimize fatigue.

For visually guided saccades, a test with a gap paradigm was performed. Participants were instructed to initially fixate a central fixation point illuminated for 3.5 s, then to make a saccade toward a 10-deg or 20-deg lateral target that appeared randomly right or left 200 ms (temporal gap) after the disappearance of the fixation point [5]. Participants were cued

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