Effects of STN stimulation on the initiation and inhibition of saccade in Parkinson disease

ABSTRACT

Objectives: The basal ganglia (BG) play an important role in controlling saccades. Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is widely used as a treatment of Parkinson disease (PD) by altering the function of the BG. Nevertheless, the effects of STN DBS on saccade performance are not fully clarified in a systematic manner. In this study, we examined the effects of bilateral STN DBS on both the initiation and inhibition of saccades in PD.

Methods: Thirty-two patients with PD performed 4 oculomotor tasks. Two tasks (visually guided saccades and gap saccades) were reflexive and 2 (memory-guided saccades [MGS] and antisaccades) were volitional. While taking their regular doses of antiparkinsonian drugs, patients performed these tasks under 2 conditions: during DBS (DBS-on condition) and without DBS (DBS-off condition). Fifty-one age-matched subjects served as controls.

Results: In the DBS-on condition, parameters of saccade initiation were improved in all tasks, with shorter latencies and increased amplitudes, except for MGS latency. STN DBS improved the ability to suppress unwanted saccades to the cue stimulus in the MGS task. However, it did not suppress prosaccades during the antisaccade task.

Conclusions: These results suggest that deep brain stimulation (DBS) of the subthalamic nucleus (STN) affects the neural pathway common to both reflexive and volitional saccades, possibly by acting on the STN–substantia nigra pars reticulata–superior colliculi pathway. STN DBS may set the functional level of the superior colliculi appropriate for both saccade initiation and inhibition through this pathway. These findings provide novel insights into the pathophysiology of Parkinson disease and may yield better treatment strategies.

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GLOSSARY

AS = antisaccades; BG = basal ganglia; DBS = deep brain stimulation; EOG = electro-oculography; GS = gap saccade; MGS = memory-guided saccades; PD = Parkinson disease; RT = reaction time; SC = superior colliculus; SNr = substantia nigra pars reticulata; STN = subthalamic nucleus; UPDRS = Unified Parkinson’s Disease Rating Scale; VGS = visually guided saccades.

The basal ganglia (BG) have 2 output pathways implicated in the control of movements: the thalamocortical parallel pathways1 and the brainstem motor networks.2 The oculomotor circuit of the former projects back to the frontal eye field and supplementary eye field, although little is known about its physiologic and pharmacologic aspects. The role of the latter on saccadic eye movement has been demonstrated not only anatomically but also physiologically and pharmacologically.2,3 Through the BG–superior colliculus (SC) pathway and the corticotectal pathways, the SC is the common terminal for controlling saccadic eye movements. Therefore, saccades reflect the output of the BG, and can be a good indicator of BG function.

From the Department of Neurology (A.Y., Y.T., R.H.), Graduate School of Medicine, The University of Tokyo, Tokyo; National Institute of Occupational Safety and Health Japan (H.F.), Kanagawa, Japan; Laboratory of Sensorimotor Research (O.H.), National Eye Institute, National Institutes of Health, Bethesda, MD; Tokyo Metropolitan Neurological Hospital (F.Y., R.O., M.T., H.T.), Tokyo; Tokyo Metropolitan Institute of Neuroscience (I.H.), Tokyo; and Department of Neurology (Y.U.), School of Medicine, Fukushima Medical University, Fukushima, Japan.

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Parkinson disease (PD) impairs not only somatomotor functions but also oculomotor functions. Patients with PD have difficulty in initiating voluntary saccades. Memory-guided saccades (MGS) are hypometric, and laten-initiating voluntary saccades. Memory-guided saccades (MGS) are hypometric, and laten-initiating voluntary saccades. Memory-guided saccades (MGS) are hypometric, and laten-initiating voluntary saccades. Memory-guided saccades (MGS) are hypometric, and laten-initiating voluntary saccades. Memory-guided saccades (MGS) are hypometric, and laten-initiating voluntary saccades.

In contrast, reflexive saccades to visual targets such as visually guided saccades (VGS) are relatively spared. 

The preferential impairment of voluntary saccades as compared with reflexive saccades has been explained by the fact that the BG are more involved in voluntary saccades such as MGS. In addition to the difficulty in initiating saccades, patients with PD have difficulty in suppressing unwanted saccades to cues in the MGS task. Nevertheless, it remains unclear how the impairment of initiation and inhibition of saccades can coexist.

Today, deep brain stimulation (DBS) of the subthalamic nucleus (STN) has become a common treatment for advanced PD. DBS is believed to interfere with increased output from the BG and improve the functions of its target structures including the thalamus, a component of the BG-thalamocortical circuits, and the SC, which is the output center of ocular movement. Based on these observations, we considered that STN DBS will affect saccade performance as well as motor functions in PD, and we predicted that voluntary saccades would be more improved by STN DBS than reflexive saccades.

There are some recent reports on the effects of STN stimulation on saccades in patients with PD. STN DBS decreases latencies of reflexive saccades, increases amplitudes of reflexive saccades, and increases gains of memory-guided saccades. In addition, it reduces interruptive saccades during fixation. However, the pathophysiology underlying effects of STN DBS on saccade performance are not fully clarified. Our study was designed to investigate the effect of STN DBS on the performance of several kinds of saccades in a large group of patients with PD. Our results show that performances of both reflexive and voluntary saccades are affected by STN DBS. Along with the effect of STN DBS on initiation and inhibition of saccades, our findings provide novel insights into the function of the BG and the pathophysiology of PD.

**METHODS Subjects.** The subjects were 32 patients with PD undergoing bilateral STN DBS (15 men and 17 women; age 58.3 ± 7.9 [mean ± SD]; Hoehn & Yahr stage 2–4 [while medicated, but with DBS off]) (table e-1 on the Neurology® Web site at www.neurology.org). Their Unified Parkinson’s Disease Rating Scale (UPDRS) part III scores were 6–44 in the DBS-off condition. Their mean levodopa equivalent dose 7.9 [SD] (mean ± SD) was 528.4 ± 397.2 mg. For ethical reasons, subjects continued to take their antiparkinsonian drugs as usual. We also collected control data from 51 age-matched normal subjects (20 men and 31 women; age 57.1 ± 8.3) for comparison with the patients’ results (table e-1).

The study was approved by the Ethics Committee of Tokyo Metropolitan Neurological Hospital and the University of Tokyo. A written informed consent was obtained from all participants in the study. The experiments were conducted in accordance with the ethical standards of the Declaration of Helsinki.

**Experimental setup.** We used the experimental system developed by Kato et al. and Hikosaka et al. The head was immobilized and DC electro-oculography (EOG) was recorded with 5 Ag–AgCl gel electrodes (bilateral outer canthi for horizontal eye movement, upper and lower edges of the right eye for vertical eye movements, and one ground on the forehead), with low-pass filtering at 20 Hz and digitizing at a sampling rate of 500 Hz. The calibration of EOG gain was adjusted to a target point at 20 degrees left or right. The subjects held a microswitch button and could start and terminate a trial by pressing and releasing it.

**Experimental procedures.** Four oculomotor tasks—the VGS, gap saccade (GS), MGS, and AS tasks—and the visual detection task surveying the manual reaction time (RT) were performed in the DBS-on state. Two hours after turning off DBS, the same tasks were performed in the DBS-off state in 26 of the 32 subjects. To exclude order effects, the on and off experiments were reversed in the remainder of the subjects. UPDRS part III was also measured in the DBS-on and DBS-off states. All experiments were performed 90–120 minutes after the intake of antiparkinsonian drugs.

**Visually guided saccade task.** A fixation point was turned on, and the subjects had to fixate on this point. It was turned off after an arbitrary period of 1,500–2,000 msec, and simultaneously the target point was turned on at 5, 10, 20, or 30 degrees to the left or right randomly, and the subjects had to make a saccade quickly to the new position (figure e-1A). The gap saccade task. The GS task was identical to that of the VGS, except that the target was turned on 200 msec after the fixation point was turned off (figure e-1B). During the GS task, we occasionally noted inappropriate saccades in the opposite direction of the target immediately before initiating a correctly directed saccade. We termed such saccades premature saccades.

**Memory-guided saccade task.** A fixation point was turned on and while the subject gazed at it a cue was flashed for 50 msec at the future location of the saccade target. The subject had to memorize the position of the cue while looking at the fixation point without making a saccade toward the flash. After 2,000–3,000 msec, the fixation point was turned off and the subject had to quickly make a saccade to the remembered location of the target. The target point was turned on again 600 msec after the fixation point was turned off (figure e-1C). Saccades erroneously
made to the flash cue stimulus during fixation were termed saccades to cue.

Antisaccade task. A fixation point and a cue point were turned on and off in the same way as in the VGS task, but the subject had to make a saccade toward the opposite location of the cue point (figure e-1D). In other words, the actual target point for the saccade was a point opposite to where the cue stimuli appeared. Saccades erroneously made toward the cue point were termed prosaccades.

Visual detection task. This is not an eye movement task but a kind of attention and hand movement task. A central fixation point was turned on and left on throughout each trial. After an arbitrary period of 2,000–2,500 msec, a target point was turned on randomly 5, 10, 20, or 30 degrees to the left or right. The subject had to release the button as soon as the target appeared, without making a saccade toward it.

In all the tasks, subjects were asked to alternate between the left and right hands in consecutive sessions to exclude possible effects of response hand.

Data analysis and statistical assessment. We judged that an eye movement (candidate of a saccade) occurred if velocity and acceleration exceeded threshold values (28 deg/s and 90 deg/s² respectively). Eye movement was assessed as a saccade based on its velocity and duration: after the onset, the velocity had to exceed 88 deg/s, and the total duration time had to be more than 30 msec. However, EOG signals could contain a significant amount of noise. Small, slow saccades could be omitted whereas large fluctuations due to body movements could be judged to be a saccade. The final judgment was made by visually inspecting whether the eye movement was a saccade or not. Saccades with latency of less than 60 msec were classified as anticipatory and were excluded from analyses. Saccades with onset latency greater than 660 msec in the MGS task were classified as a kind of visually guided saccade which directed to the target after a time lag. These were excluded from the analysis of MGS.

The saccade accuracy was calculated as the ratio of the amplitude of the first saccade to the target presented at 20 and 30 degrees. We counted the frequency of premature saccades in the GS task, saccades to cue in the MGS task, and prosaccades in the AS task.

To assess the effect of STN DBS, the patients’ performance on the individual task, the results on the tasks were compared using the 2-tailed paired Student’s t test. Furthermore, the results of 3 groups (the control subjects, patients with PD in DBS-on state, and patients with PD in DBS-off state) were compared using the Tukey-Kramer multiple comparison test.

RESULTS Saccade traces of one patient in the DBS-on and DBS-off states (figure e-2) shows that saccades were often hypometric without DBS, but became less hypometric during DBS. Their latencies became shorter and varied less during DBS. Saccades to the cue in the MGS task were less common during DBS. Similar changes were detected in other patients (table e-2), which we describe in the following sections.

Effects on saccade initiation. With or without DBS, the latencies of saccades in the patients were longer than those in the control subjects (Tukey-Kramer multiple comparison test; p < 0.001 for VGS, GS, and AS, p < 0.006 for MGS) (table e-2). DBS significantly reduced the latencies in all types of saccade except MGS (figure, A).

Without DBS, saccades of all types were more hypometric in the patients than in the controls. The accuracies of these saccades were improved significantly by DBS (figure, B), but the accuracy was still more hypometric than that of the controls, with the exception of the AS task (p < 0.001 for VGS, GS, and MGS; p = 0.280 for AS).

The improvement of UPDRS part III score correlated with the improvement of VGS accuracy (r = 0.483, p = 0.005) and GS latency (r = −0.407, p = 0.021) (figure e-3).

Effects on saccade inhibition. Without DBS, the patients made saccades to cues in the MGS task more often than the controls (p < 0.001). DBS made such saccades significantly less frequent (figure, C).

Without DBS, the patients made prosaccades in the AS task more often than the controls (p < 0.001). The frequency of such prosaccades was not affected by DBS (figure, C).

Without DBS, the patients with PD made premature saccades in the GS task as often as the control subjects (p > 0.980 both for DBS). The premature saccades were not influenced by DBS (table e-2).

No parameters of saccade inhibition correlated with the improvement of UPDRS part III score (figure e-3).

Effects on the visual detection task. Without DBS, RT was longer in the patients than in the controls (p < 0.001). RT was significantly shortened by DBS in almost all the patients (figure, D). The UPDRS part III scores were significantly improved by DBS in all the patients (figure, D). The improvement of RT significantly correlated with the improvement of UPDRS part III score (r = 0.595, p < 0.001) (figure e-3).

DISCUSSION In this study, we found that in patients with PD undergoing levodopa therapy, STN DBS improves performances of volitional saccades; memory-guided saccades and antisaccades, as well as those of reflexive saccades; visually guided saccades; and gap saccades. In addition, STN DBS improved the inhibitory control of saccades; STN DBS decreased the saccades to cue in MGS, but did not affect the frequency of prosaccades in AS. The improvement of the accuracy of VGS amplitude, the latency of GS, and the RT correlated with the improvement of UPDRS part III score.

The BG are thought to play an important role in the inhibitory control of saccades.20 In PD, both the initia-
tion and the inhibition of nontarget saccades are impaired. In a previous study, the frequency of saccades to cue in MGS was found to be increased in patients with PD, suggesting impaired inhibitory control of unwanted saccades. Excessive inhibition of the SC, as postulated in the rate model of the BG circuit, would actually prevent direct visuomotor execution in response to the cue stimulus. This would be expected to decrease the frequency of saccades to cue, which conflicts with the results of the present study.

STN DBS decreased the frequency of saccades to cue, suggesting that DBS restored the inhibitory control of reflexive saccades. This restorative effect indicates that STN DBS normalizes the inhibitory function of the BG, setting the excitability of SC at an appropriate level, both for initiating and inhibiting saccades. This result seems consistent with the suggestion that the STN plays an important role in keeping the eye position fixed. Our results are better explained by the oscillation model of the BG circuit than by the rate

Figure Saccade results with deep brain stimulation (DBS) on and off

The figures show how the saccade latency (A), saccade amplitude (B), and frequency of saccade errors (C) changed when DBS was turned on. The horizontal axis shows the DBS-off condition and the vertical axis shows the DBS-on condition. The plot falls on a line of unison, as indicated by the dashed line running through the origin, if the saccade parameter is identical under subthalamic nucleus (STN) DBS-on and DBS-off conditions. Plots under this line show that the parameter under the DBS-off condition is larger than that under the DBS-on condition, and vice versa. Reaction time (RT) was significantly shortened by DBS in almost all the patients (D). Unified Parkinson’s Disease Rating Scale (UPDRS) part III scores were significantly improved by DBS in all the patients.

AS – antisaccades; GS – gap saccade; MGS – memory-guided saccades; VGS – visually guided saccades.
model of the BG circuit. The rate model predicts that if DBS simply restored the firing rate of STN and reduced the excessive inhibitory output through the STN-substantia nigra pars reticulata (SNr) circuit, STN DBS would not only facilitate initiation of saccades but also increase the frequency of unwanted saccades to cue in MGS task. In fact, STN DBS improved saccade initiation but reduced unwanted saccade to cue. Recent studies take into account the oscillation in the BG,29-32 Beta band oscillations in BG are abnormally enhanced in PD, and the desynchronization in beta band is required to fulfill motor commands to override the elevated threshold for saccade generation. STN DBS would decrease the pathologic oscillations and facilitate motor commands in PD by decreasing the beta band and enhancing the gamma band, while reducing the BG output and lowering the threshold. Reduction in the oscillatory activities by DBS would help maintain the appropriate SC excitability required for saccade initiation and inhibition by normalizing the “leaky” suppression exerted by the BG and decrease the emergence of unwanted saccades to cue. Therefore, STN DBS facilitates the initiation commands and also normalizes inhibition commands. Furthermore, such oscillatory activities might also spread “noisy input” throughout the BG-thalamocortical pathway33 and disrupt processing involved in saccade inhibition at the cortical and subcortical regions. STN DBS would occlude this noisy input and enable the effective function of neural processing to be issued within the relevant neural structures.

Our results indicate that STN DBS (in addition to levodopa) causes a decrease in saccades to cue. A candidate locus explaining the improvement of inhibitory control is the STN-SNr-SC circuit. This direct projection to the SC appears to play a more important role in suppressing unwanted saccades than the BG-thalamocortical pathway. STN DBS may thus improve the function not only of the BG-thalamocortical pathway, but also of the STN-SNr-SC circuit, although we have to admit the limitation of this study; since we investigated the effects of STN DBS while the patients were taking levodopa, the effects of levodopa may be included in the baseline DBS-off state.

To date, inhibitory control of saccades has been studied mostly using the AS task. In our study, the frequency of prosaccades in the AS task was higher in patients with PD than in controls, which is consistent with previous reports.8-10 On the other hand, STN DBS caused no change in the frequency of directional errors in the AS task, suggesting that the inhibitory mechanism involved in the AS task may be distinct from that for inhibiting saccades to cue. The occurrence of prosaccades in the AS task has been explained by the failure of the prefrontal cortex to inhibit the SC directly via the descending pathway16,17,34 although some involvement of the BG (i.e., the caudate nucleus) has also been suggested for AS.35-37 Therefore, STN DBS might specifically affect the inhibitory mechanism of saccades mediated by the STN-SNr circuit rather than that mediated by the frontal cortex, leaving the frequency of prosaccades unaffected.

The present results showed that both reflexive and voluntary saccades are impaired in PD, consistent with results of our previous study.38 As mentioned in the Introduction, we predicted that MGS would be more improved by STN DBS than VGS; however, we found that saccades of both types were improved by STN DBS. This suggests that STN DBS improves the function of the neural structures involved in saccades of both types. The simplest explanation is that STN DBS improves the function of the SC. If STN DBS works by interfering with the overactivity of the STN-SNr circuit and reversing the excessive inhibition of the SC, it would engender decreased latency and increased saccade amplitude for both reflexive and voluntary saccades. This is because SC comprises the final common pathway for saccades of both types.

An alternative explanation, but not a mutually exclusive one, is that STN DBS normalizes the activity of the BG-thalamocortical circuits including the motor and oculomotor loops. STN comprises part of this circuit. Therefore, STN DBS might induce functional changes in the entire loop. Both volitional and reflexive saccades would be affected by such functional changes because the oculomotor cortical regions are directly or indirectly connected with this circuit.

DISCLOSURE
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