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The effects of unilateral versus bilateral subthalamic nucleus deep brain stimulation on prosaccades and antisaccades in Parkinson's disease

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Abstract

Unilateral deep brain stimulation (DBS) of the subthalamic nucleus (STN) in patients with Parkinson's disease improves skeletomotor function assessed clinically, and bilateral STN DBS improves motor function to a significantly greater extent. It is unknown whether unilateral STN DBS improves oculomotor function and whether bilateral STN DBS improves it to a greater

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extent. Further, it has also been shown that bilateral, but not unilateral, STN DBS is associated with some impaired cognitive-motor functions. The current study compared the effect of unilateral and bilateral STN DBS on sensorimotor and cognitive aspects of oculomotor control. Patients performed prosaccade and antisaccade tasks during no stimulation, unilateral stimulation, and bilateral stimulation. There were three sets of findings. First, for the prosaccade task, unilateral STN DBS had no effect on prosaccade latency and it reduced prosaccade gain; bilateral STN DBS reduced prosaccade latency and increased prosaccade gain. Second, for the antisaccade task, neither unilateral nor bilateral stimulation had an effect on antisaccade latency, unilateral STN DBS increased antisaccade gain, and bilateral STN DBS increased antisaccade gain to a greater extent. Third, bilateral STN DBS induced an increase in prosaccade errors in the antisaccade task. These findings suggest that while bilateral STN DBS benefits spatiotemporal aspects of oculomotor control, it may not be as beneficial for more complex cognitive aspects of oculomotor control. Our findings are discussed considering the strategic role the STN plays in modulating information in the basal ganglia oculomotor circuit.

Keywords

STN DBS; Parkinson disease; Saccade; Subthalamic nucleus; Deep brain stimulation

Introduction

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an effective treatment for improving several aspects of motor function for many patients with advanced stage Parkinson's disease (PD). Tremor is markedly reduced (Sturman et al. 2004), bradykinesia of upper and lower limb is improved (Tabbal et al. 2008), rigidity is lessened (Shapiro et al. 2007), and clinical scores on the Unified Parkinson's Disease Rating Scale are significantly lowered (Castritto et al. 2011; Krack et al. 2003). It is known that unilateral stimulation improves skeletomotor function (Vaillancourt et al. 2004), and that bilateral stimulation can provide greater improvements in motor function than unilateral stimulation (Bastian et al. 2003; Kumar et al. 1999). However, the relative effects of unilateral and bilateral stimulation on eye movement are currently unknown. As such, it is unknown whether unilateral and bilateral stimulation provide differential beneficial or adverse effects on eye movement control.

Both the oculomotor and skeletomotor circuits are modulated by activity within the basal ganglia. The STN is strategically located in the functional organization of the basal ganglia and has been shown to have saccade-related neurons that discharge mainly after saccade onset (Fawcett et al. 2005; Matsumura et al. 1992). The STN has excitatory glutamatergic outputs to globus pallidus internus and substantia nigra pars reticulata, the two major output nuclei of the basal ganglia (Hikosaka et al. 2000). Studies on non-human primates have shown that the dorsal portion of the STN receives somatotopically organized input from the primary motor cortex and the supplementary motor area, while the ventral portion receives input from supplementary eye fields, prefrontal cortex, and frontal eye fields (Monakow et al. 1978; Nambu 2011; Nambu et al. 2002). Consequently, it is ideally situated to modify basal ganglia processing for both limb and eye control.

Considering the role of the STN in oculomotor function, it follows that altering the activity of the STN via high-frequency stimulation should affect saccade generation. This premise has been previously tested implementing the prosaccade and the antisaccade task. The prosaccade task is primarily a reflexive task that requires the participant to make a saccade toward a visual target. The antisaccade task requires the participant to first inhibit a reflexive saccade to a visual target (prosaccade) and then internally generate a saccade in the opposite direction from the target (antisaccade). Thus, the antisaccade task requires responses based on internal plans rather than sensory cues and requires more cognitive processing than visually guided prosaccades to suddenly appearing targets. Three studies have investigated the effect of bilateral subthalamic nucleus deep brain stimulation (STN DBS) on the prosaccade and antisaccade task (Fawcett et al. 2010; Rivaud-Péchoux et al. 2000; Yugeta et al. 2010). Fawcett et al. (2010) tested the effects of bilateral stimulation compared to no stimulation on prosaccade and antisaccade task performance while patients were off their anti-Parkinsonian medication. They found that bilateral STN stimulation reduced latency in the prosaccade task and increased gain in the antisaccade task. They did not report the prosaccade error rates on the antisaccade task, but two other studies have shown that bilateral STN DBS had no effect on prosaccade error rates (Rivaud-Péchoux et al. 2000; Yugeta et al. 2010). A possible reason for this is that participants in both of these studies were on anti-Parkinsonian medication during testing, which has been shown to reduce prosaccade error rates during the antisaccade task (Hood et al. 2007). Thus, it is unclear how bilateral STN stimulation affects prosaccade error rates in an antisaccade task. Additionally, no previous studies have investigated the effects of unilateral stimulation on saccade tasks, nor has the effect of stimulation been compared to healthy controls.

Furthermore, despite the effectiveness of bilateral STN stimulation on motor function, there is evidence to suggest that bilateral stimulation of the STN may be associated with cognitive decline including mild impairments in nonverbal recall (Williams et al. 2011), verbal fluency (Williams et al. 2011; York et al. 2008), and inhibition of dominant verbal responses (as measured by the Stroop test) (York et al. 2008). When comparing the effects of unilateral STN stimulation to bilateral STN stimulation on a cognitive-motor dual-task, Alberts et al. (2008) found cognitive performance to be significantly worse with bilateral stimulation compared to no stimulation and unilateral stimulation. This was attributed to possible disruption of prefrontal function during bilateral stimulation.

The current experiments studied the effects of unilateral and bilateral STN DBS on oculomotor tasks with varying cognitive demands while patients were off anti-Parkinsonian medication. We used a prosaccade task to investigate the effects of STN DBS on sensorimotor control and an antisaccade task to investigate the effects of STN DBS on cognitive-oculomotor control. We tested three sets of hypotheses. First, with respect to the prosaccade task, we hypothesized that: (a) unilateral stimulation would reduce prosaccade latency, (b) bilateral stimulation would reduce prosaccade latency to a greater extent, and (c) neither unilateral nor bilateral stimulation would affect prosaccade gain. Further, we predicted the STN DBS would bring prosaccade latency closer to control values. The first set of hypotheses was based on the following two facts: (1) unilateral STN DBS improves limb movement, and bilateral STN DBS improves limb movement to a greater extent, and (2) bilateral STN DBS reduces prosaccade latency but has no effect on prosaccade gain.

Second, with respect to the antisaccade task, we hypothesized that: (a) neither unilateral nor bilateral stimulation would affect antisaccade latency, (b) unilateral stimulation would increase antisaccade gain, and (c) bilateral stimulation would increase antisaccade gain to a greater extent. Further, we predicted that STN DBS would bring antisaccade gain closer to control values. The second set of hypotheses was based on that fact bilateral STN DBS does not affect antisaccade latency but does increase antisaccade gain. Third, we hypothesized that the prosaccade error rate during the antisaccade task would be greatest during bilateral STN DBS. The third hypothesis was based on previous findings, showing impaired performance on cognitive tasks involving prefrontal processes during bilateral STN DBS.

Methods

Subjects

Twenty subjects were recruited for this study, 10 of whom had advanced PD (7 males, 3 females; mean age 58 years $\pm$ SD 6.8) and bilaterally implanted STN stimulators (Medtronic Inc., Minneapolis, MN, USA), and 10 who were healthy age- and sex-matched controls (57 years $\pm$ 8.2). All patients and controls were right-hand dominant as confirmed by the Edinburgh Handedness Inventory (Oldfield 1971). Patients were examined by a movement disorders neurologist and included in the study if they: (1) met UK Parkinson's disease Society Brain bank diagnostic criteria for PD (Hughes et al. 1992), (2) had a successful response to bilateral STN DBS surgery, (3) scored 25 or greater on the mini-mental state examination (Folstein et al. 1975), and (4) exhibited no eyelid opening apraxia or other clinically evident eye movement abnormalities. Additionally, the presence of multiple kinesthetic cells during microelectrode recording in each patient confirmed that the electrodes were placed in the sensory motor area of the STN. With the exception of PD, the patients had no other known neurological disorders. All subjects gave informed consent to all experimental procedures, which were approved by the Institutional Review Board at the University of Illinois at Chicago. Table 1 shows patient demographics, Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) motor scores, and stimulator parameters. All patients were tested using stimulator parameters that were clinically optimal. Patient 9 was unable to perform testing for the OFF stimulation condition due to excessive rigidity and distress.

Experimental procedures

Patients completed 4 separate testing sessions on 4 consecutive days (one stimulation condition per day) as illustrated in Fig. 1a. Patients arrived the day before testing while on stimulation and anti-Parkinsonian medication. They were consented and acclimatized to the laboratory and practiced saccade tasks. Patients were checked into a nearby hotel and were instructed to have their last dose of anti-Parkinsonian medication no later than 9:00 pm. The next morning, LCG or FJD arrived at the hotel at 6:00 am to set the experimental condition for the day. Each testing session began at 9:00 am; 3 h after, the appropriate stimulators were turned off for the condition of that day to minimize recent stimulator effects (Temperli et al. 2003). This was repeated every morning. Thus, each day, the patients were tested after a 12-h over-night withdrawal from anti-Parkinsonian medication under 1 of 4 stimulator conditions: off stimulation (OFF), left unilateral stimulation on (LEFT), right unilateral

stimulation on (RIGHT), or both stimulators on (BOTH). The order of stimulation conditions was randomized for the first five patients and counterbalanced for the last five patients. Patients were administered the MDS-UPDRS by a certified rater, followed by the prosaccade and antisaccade tasks. The order of the two saccade tasks was randomized. Each saccade task lasted approximately 15 min. Breaks were provided as needed between and within tasks. Each session occurred between 9 am and 11 am. Healthy, age-matched control subjects completed testing in one session to provide an index of normative performance on the eye movement tasks.

Instrumentation

Eye movement tasks were performed in a completely darkened room. Patients sat upright in a height-adjustable chair with armrests so that visual stimuli could be presented at eye level. In order to control for head movement, patients placed their chin on a stationary chin rest, and head movements were recorded using a 3D motion capture system (Optotrak 3020, Northern Digital, Inc.). Horizontal eye movements were collected using an eye-tracking system consisting of two miniature cameras mounted on a comfortable padded headband (Eyelink II, SR Research Ltd, 2002). Direction of gaze was sampled at 500 Hz. Visual stimuli (LEDs) were presented at eye level, along the horizontal plane at a distance of 47 cm from the chin rest. Eye and head movement data were synchronized and stored using the Motion Monitor software (Innovative Sports Training, Inc. 2011).

Eye movement tasks

Prosaccade task—Each trial began with the subject fixating a central LED (0° visual angle) for 3000 ms. Next, the central fixation cue disappeared, and after a 200-ms gap, a target was presented at 20° of visual angle to the left or right of center. The subjects were instructed to “look at the target location as quickly and accurately as possible.” This is illustrated in Fig. 1b. Intertrial intervals were constant (2000 ms), and target locations were presented in random order with each target presented 25 times. The prosaccade task was completed in a single block of 50 trials.

Antisaccade task—For the antisaccade task, the sequence of events and target locations were identical to those used in the prosaccade task. Subjects were instructed to “look to the mirror-image location in the opposite direction as quickly and accurately as possible.” This is shown in Fig. 1c. Each target was presented 25 times. The antisaccade task was completed in a single block of 50 trials.

Data processing

Clinical data—An unblinded certified rater performed the MDS-UPDRS prior to saccade testing for all 4 stimulation conditions. Each MDS-UPDRS session was video-taped and subsequently rated by another certified rater blinded to stimulation condition. It should be noted that scoring rigidity requires assessing the resistance to passive motion of the neck and limbs. It is not possible to score rigidity on a video recording, and it was not included in this blinded rating. The intra-class correlation coefficient between the unblinded and blinded ratings was 0.96 (95% CI 0.93–0.98). Consequently, the MDS-UPDRS ratings conducted with direct clinical observation of the patient are reported below.

Eye movement data—The data were analyzed using a custom MATLAB script (The MathWorks, Natick, MA). A 100-Hz low-pass second-order Butterworth filter was applied to the position data of the right and left eyes. Peak saccade velocity was calculated from the filtered eye position data. We determined saccade onset using an algorithm that first determined peak velocity and then searched backward to detect the first time point when eye velocity was below 5% of peak velocity. Every trial was visually inspected, and saccade onsets and offsets were visually edited if needed. Trials were rejected and omitted from analyses if the subject blinked, failed to perform the task, and/or made an anticipatory saccade (latency <90 ms) (Munoz et al. 1998). From these data, latency and gain were calculated for the prosaccade and antisaccade tasks. In addition, for the antisaccade task, the prosaccade error rate was determined. Prosaccade errors in the antisaccade task (looking toward the peripheral target despite instruction to look away) were used to calculate prosaccade error rate. Antisaccade latency and gain calculations were made only with correctly performed trials. Latency was the time between target presentation and saccade onset. Gain was the ratio of primary saccade amplitude to target displacement (Hood et al. 2007). Prosaccade error rate was the percentage of prosaccades made to the target during the antisaccade task.

Statistical analyses

LEFT unilateral stimulation and RIGHT unilateral stimulation were collapsed into a UNI stimulation condition as our initial analyses revealed no significant differences between LEFT and RIGHT unilateral stimulation. Additionally, left and right target presentation were also collapsed for the following reasons: (1) our initial analyses revealed no systematic lateralization patterns as a consequence of the interaction between stimulation side and target presentation side and (2) it simplified our presentation of the results without changing our main findings. The initial analyses in which LEFT and RIGHT stimulation conditions and left and right target presentations were not collapsed are included as electronic supplement (Online resource 1).

MDS-UPDRS—A mixed-effects regression model was used to analyze the MDS-UPDRS scores. Subject was considered a random effect. The fixed effect was stimulation condition (OFF, UNI, and BOTH). In the event of a significant effect of condition, pairwise comparisons between stimulation conditions were evaluated using *t* tests. Critical alpha was 0.05, and *p* values associated with pairwise comparisons were corrected using the Bonferroni method. A residual analysis was performed to confirm that distributional assumptions for parametric testing were not violated.

Prosaccade and antisaccade task—For latency and gain during the prosaccade and antisaccade tasks, we used mixed-effects regression models. This method was preferred over repeated measures analysis of variance because mixed-effects regression models allow retaining cases with missing data, while repeated measures analysis of variance does not (Hedeker and Gibbons 2006). For the prosaccade error rates in the antisaccade task, a mixed-effects logistic regression model was used. For both of these mixed models, subject was the random effect, and the fixed effect was stimulation condition (OFF, UNI, and BOTH). In the event of a significant effect of condition, pairwise comparisons between

stimulation conditions were evaluated using *t* tests. In addition, for each outcome variable in the prosaccade and antisaccade task, we present independent *t* tests comparing each stimulation condition to age- and sex-matched healthy controls. All tests were two-tailed, critical alpha was 0.05, and *p* values associated with pairwise comparisons were corrected using the Bonferroni method. SAS 9.4 was used for all statistical analyses.

Results

Clinical measures: MDS-UPDRS

Table 1 presents the MDS-UPDRS scores for each individual patient for the OFF, UNI, and BOTH stimulation conditions. There was a main effect of stimulation condition for MDS-UPDRS ($F_{2, 27} = 11.84$, $p < 0.001$). Compared to OFF, UNI (mean difference estimate, 12.7; 95% CI 0.4–25.1; $p = 0.04$) and BOTH (26.7; 12.7–40.8; $p < 0.001$) improved MDS-UPDRS motor scores. BOTH improved scores more than UNI (14; 2.2–25.8; $p = 0.02$) stimulation.

The effect of stimulation on prosaccade latency and gain

Prosaccade latency—We observed a main effect of stimulation condition ($F_{2, 1488} = 24.3$, $p < 0.001$) for prosaccade latency (Fig. 2a; Table 2). Pairwise comparisons between stimulation conditions revealed that latency during the UNI condition did not differ from OFF and that latency during BOTH was significantly reduced compared to OFF (35 ms; 18–53 ms; $p < 0.001$) and UNI (41 ms; 27–55 ms; $p < 0.001$) stimulation. Even though BOTH brought the mean prosaccade latency below that of the healthy controls, this was not statistically significant ($p = 0.22$).

Prosaccade gain—There was a significant effect of stimulation condition ($F_{2, 1488} = 24.5$, $p < 0.001$, see Table 2) for gain (Fig. 2b). Gain was significantly lower during UNI stimulation compared to OFF (−0.03; −0.06 to −0.008; $p = 0.006$). Gain was significantly greater during BOTH stimulation compared to OFF (0.04; 0.007–0.07; $p = 0.006$) and UNI stimulation (0.07; 0.05–0.1; $p < 0.001$). Prosaccade gain during all stimulation conditions was significantly less than the mean gain of the healthy controls (see Table 2 for all *p* values).

The effect of stimulation on antisaccade latency and gain

Antisaccade latency—No differences were observed between stimulation conditions, nor were there any differences between stimulation conditions and healthy controls (Fig. 3a; Table 2).

Antisaccade gain—There was a significant effect of stimulation condition ($F_{2, 1115} = 17.8$, $p < 0.001$; see Table 2). Gain in the UNI condition was greater than during OFF (0.1; 0.04–0.14; $p < 0.001$) stimulation. Gain in the BOTH condition increased gain compared to the OFF (0.16; 0.1–0.22; $p < 0.001$) and UNI (0.07; 0.02–0.13; $p = 0.006$). Despite increases in gain during stimulation, gain remained significantly lower than the gain of healthy controls (see Fig. 3b; Table 2).

The effect of stimulation on prosaccade error rates

There was a main effect of stimulation condition ($F_{2, 1115} = 12.4$, $p < 0.001$; Fig. 4; Table 2). There were no differences in prosaccade error rates between UNI and OFF stimulation ($p = 0.62$). Prosaccade error rates were significantly higher during BOTH stimulation compared to OFF ($p < 0.001$) and UNI ($p < 0.001$) stimulation. There were no differences between OFF and healthy controls ($p = 0.35$) and UNI and healthy controls ($p = 0.08$), but prosaccade error rate during BOTH was greater than the healthy controls ($p = 0.02$).

Discussion

This study investigated the effects of unilateral and bilateral deep brain stimulation of the STN on oculomotor control. We implemented a prosaccade task to investigate the effect of stimulation on sensorimotor control of the eyes and an antisaccade task to investigate the effect of stimulation on eye movements with a greater cognitive demand. We found that stimulation had both beneficial and deleterious effects on saccade performance. With respect to our first set of hypotheses related to the prosaccade task, we found that unilateral STN DBS did not affect prosaccade latency relative to no stimulation, but bilateral STN DBS did in fact reduce prosaccade latency. In contrast to our prediction that stimulation would have no effect on prosaccade gain, we found that unilateral STN DBS reduced gain and bilateral STN DBS increased gain. Thus, for the prosaccade task, unilateral STN DBS had no effect on prosaccade latency and reduced prosaccade gain; bilateral STN DBS reduced prosaccade latency and increased prosaccade gain. There were no differences in prosaccade latency between any of the stimulation conditions and healthy controls, and prosaccade gain during all stimulation conditions remained significantly lower than controls.

With respect to our second set of hypotheses related to the antisaccade task, we correctly predicted that (1) stimulation would have no effect on antisaccade latency, (2) unilateral STN DBS would increase antisaccade gain, and (3) bilateral STN DBS would increase antisaccade gain to a greater extent. There were no differences in antisaccade latency between any of the stimulation conditions and healthy controls, and antisaccade gain during all stimulation conditions remained significantly lower than controls. And, finally, in regard to our third hypothesis, we correctly predicted that bilateral STN DBS would induce a greater percentage of prosaccade errors in the antisaccade task, an observation not seen with unilateral stimulation. We discuss these findings in the context of different mechanisms that may facilitate and impair the control of eye movements.

Mechanisms that facilitate eye movement

The pathophysiology underlying the deficit in prosaccade and antisaccade gain in the current study is presumably related to basal ganglia dysfunction. In the healthy state, the substantia nigra pars reticulata (SNr) tonically inhibits saccade generating cells of the superior colliculus during rest and releases its inhibitory activity before and during saccade execution (Hikosaka et al. 2000). In PD, dopamine depletion of the basal ganglia results in a weakened direct pathway and a pathologically enhanced indirect pathway, which increases inhibitory output of the SNr and impairs activation of saccade cells in the superior colliculus (Bergman et al. 1998). The STN, a key structure of the indirect pathway that sends excitatory

glutamatergic projections to the SNr, exhibits abnormal firing patterns in PD that result in the excitation of the SNr and downstream inhibition of the superior colliculus (Hamani et al. 2004; Magill et al. 2001). This could underlie our finding of reduced gain in the prosaccade and antisaccade task while OFF stimulation, which parallel some previous findings (Sauleau et al. 2008; Yugeta et al. 2010).

Many hypotheses have been proposed to explain the mechanism of action of STN DBS including depolarization blockade, synaptic inhibition, synaptic depression, and stimulation-induced modulation (McIntyre et al. 2004). It is likely that these mechanisms act in parallel to modulate pathological basal ganglia–cortical network activity. It is possible that bilateral STN DBS reduces the excessive inhibitory output of the SNr (Benazzouz et al. 1995), thereby allowing the superior colliculus to more effectively and quickly activate brain stem saccade generators resulting in improved saccadic gain and faster response latencies that might contribute to increases in antisaccade error rates.

It has been shown that STN DBS reduces STN firing rate (Toleikis et al. 2012; Welter et al. 2004) in patients with PD. It has also been shown that STN DBS can modify both the excitatory signals from the STN to the SNr as well as the inhibitory signals from the globus pallidus externus to the SNr via antidromic stimulation (Chiken and Nambu 2014; Maurice et al. 2003). Consequently, the superior colliculus is released from the inhibitory effect of the SNr culminating in excitation of the superior colliculus. This increased excitation of the superior colliculus could underlie our findings of reduced prosaccade latency and increased prosaccade gain during bilateral STN DBS, as well as the increase in antisaccadic gain during unilateral and bilateral STN DBS.

Mechanisms that impair eye movement

The prosaccade error rate during OFF and unilateral STN DBS was no different from healthy controls. Bilateral STN DBS, however, significantly increased the prosaccade error rate. The antisaccade task in our study, as well as the cognitive task implemented in the Alberts' study, is dependent in part on dorsal prefrontal networks (Alberts et al. 2008). Three possible mechanisms by which prosaccade error rate may be increased are discussed below. One is disrupted processing in the dorsolateral prefrontal cortex (DLPFC) due to bilateral STN DBS. The second is that due to bilateral STN DBS, the STN's effect on the superior colliculus is so influential that the modulatory capacity of the DLPFC on the superior colliculus is no longer as effective, resulting in an easily excitable superior colliculus. The third possibility is that STN DBS interacts with compensatory mechanisms that could diminish proactive inhibitory processes. These potential mechanisms are not mutually exclusive and may together account for observed findings.

With respect to the first proposed mechanism, i.e., disrupted processing in the DLPFC due to bilateral STN DBS, lesion and functional neuroimaging studies provide strong evidence that the DLPFC plays a crucial role in voluntary saccade inhibition in the antisaccade task (Condy et al. 2004; Everling and Johnston 2013; Pierrot-Deseilligny et al. 2003; Sweeney et al. 1996). Further, Everling and Johnston (2013) proposed that damage to the prefrontal cortex (or disruption of neural processing) leads to a failure to maintain and implement the correct task set. Bilateral STN DBS may be disrupting prefrontal processes that facilitate

context-relevant goal-directed behavior. It has been argued that bilateral STN DBS causes a functional lesion that disrupts information processing in the DLPFC (Limousin et al. 1997; Thobois et al. 2002). Additionally, it has been shown that STN DBS increases regional cerebral blood flow (rCBF) to the DLPFC (Campbell et al. 2008; Limousin et al. 1997). It is possible that high-frequency stimulation of the STN may alter DLPFC activity via basal ganglia–thalamo–cortical projections. Alternatively, given the direct projection from the DLPFC to the STN (Benarroch 2008), it is also possible that high-frequency stimulation of the STN antidromically disrupts DLPFC information processing. This disruption manifests itself most when bilateral STN DBS is used. The fact that bilateral, and not unilateral, STN DBS resulted in increased prosaccade error rates in the antisaccade task could indicate that during unilateral stimulation, the non-stimulated side can compensate or maintain behavioral control.

With respect to the second proposed mechanism, i.e., that prosaccade error rate may increase during bilateral STN DBS because the influence of the STN on the superior colliculus is altered such that the modulatory capacity of the DLPFC is less effective, previous work has shown that untreated schizophrenic patients showed an increase in prosaccade error rate in the antisaccade task which was related to a significant reduction in prosaccade latency in the prosaccade task (Harris et al. 2006). Further, the increase in prosaccade error rate in the antisaccade task was significantly correlated with prosaccade latency in the prosaccade task, suggesting that the increased speed of motor response may have compounded prefrontal deficits associated with inhibition of reflexive saccades (Harris et al. 2006). The current study shows that bilateral STN DBS significantly reduces prosaccade latency in the prosaccade task (Fig. 2a) and significantly increases prosaccade error rate in the antisaccade task (Fig. 4) compared to no stimulation; therefore, it is possible that both increased speed of motor response time and DLPFC disruption are factors involved with the increase in prosaccade error rate observed during the antisaccade task.

With respect to the third proposed mechanism, i.e., STN DBS interacts with compensatory mechanisms that could diminish proactive inhibitory processes, the deleterious effect of bilateral STN DBS on response inhibition has previously been reported (Ballanger et al. 2009). Similar to our findings, Ballanger et al. (2009) found that bilateral STN DBS reduced reaction time of a simple “Go” task and impaired response inhibition in a “Go/No Go” task. This parallels our findings of reduced latency during the prosaccade task and increased errors during the antisaccade task. In healthy individuals, adaptive generation of motor responses in varying situations depends on tonic, proactive inhibition of automatic sensorimotor responses to external stimuli (Jaffard et al. 2008). In PD, this ability to flexibly shift between automatic and controlled responding may be impaired (Redgrave et al. 2010; Torres et al. 2011). Patients with PD may rely more on externally guided sensorimotor control to facilitate movement initiation due to difficulty initiating voluntary movement (Ballanger et al. 2009). Because of the highly reflexive nature of prosaccades, this might account for the relative preservation of prosaccade performance in PD. It should be noted that our findings and that of Ballanger et al. are in contrast to Swann et al. (2011). Swann et al. (2011), found that bilateral STN DBS improved response inhibition. One reason for this difference in results is likely due to the fact that the subjects in Swann et al. (2011) were on medication, while the subjects in the Ballanger et al. (2009) and our study were off

medication. Anti-Parkinsonian medication is known to improve response inhibition by reducing the prosaccade error rates in the antisaccade task (Hood et al. 2007). The findings from the current study and those of Ballanger et al. (2009) suggest that bilateral STN DBS may interfere with proactive inhibition, via effects on DLPFC or superior colliculus, and therefore, lead to automatic sensorimotor responses (prosaccade errors) happening more frequently after DBS.

Interestingly, unilateral STN DBS further reduced prosaccade gain (Fig. 2b). It is not clear why unilateral stimulation reduced prosaccade gain. One possibility is that unilateral STN DBS disrupts activity between crossed and uncrossed nigro-collicular fibers (Sauleau et al. 2008). Uncrossed nigro-collicular fibers project from the SNr to the ipsilateral superior colliculus and facilitate visuomotor activity, while crossing fibers projecting to the contralateral superior colliculus inhibit visuomotor activity (Jiang et al. 2003). It is possible that unilateral stimulation disrupts the synchrony of the activity between these crossed and uncrossed fibers, resulting in ineffective input to the superior colliculus. However, unilateral STN DBS improved gain in the antisaccade task. Thus, the effects of unilateral STN DBS on saccadic gain may depend on whether the saccade is externally (prosaccade) or internally (antisaccade) generated. Alternatively, the results of unilateral stimulation may have been due to confounds such as asymmetric disease progression and/or asymmetric stimulation parameters within and across subjects.

Conclusion

Clinically, optimized high-frequency stimulation of the STN improves MDS-UPDRS motor scores. Whereas it has been shown that unilateral STN DBS improves limb motor function (Tabbal et al. 2008; Vaillancourt et al. 2004), the effects on eye movement control are more complex. We now show that unilateral STN DBS optimized for clinical motor function has differential effects on prosaccades compared to antisaccades. Bilateral STN DBS improves gain of prosaccades and antisaccades, but it also weakens inhibitory cognitive control as reflected by the increased prosaccade error rate in the antisaccade task. Given the influence that the STN has on both the motor and oculomotor circuits, it appears that bilateral STN DBS may improve aspects of general motor control such as latency and amplitude, but may also impair specific aspects that rely more heavily on cognitive processes. The mechanisms underlying the differential effect of unilateral versus bilateral STN DBS on oculomotor and limb movement remain to be clarified by future work directly comparing eye and limb responses on parallel automatic and voluntary tasks. Future work needs to address these differences mechanistically and to study their broader impact using studies of real-world goal-directed movement that integrates and parses visuomotor, cognitive, and skeletomotor control systems.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

BOTH Bilateral stimulation condition

DBS	Deep brain stimulation
DLPFC	Dorsolateral prefrontal cortex
LEFT	Left unilateral stimulation on condition
MDS-UPDRS	Movement Disorder Society-Unified Parkinson's Disease Rating Scale
OFF	Stimulators off condition
PD	Parkinson's disease
RIGHT	Right unilateral stimulation on condition
SNr	Substantia nigra pars reticulata
STN	Subthalamic nucleus
UNI	Unilateral stimulation

Fig. 1.

a Participant's schedule from the day of arrival through the 4 days of experimental testing is shown. It shows overnight withdrawal from anti-Parkinsonian medication. Every morning at 6 am, the stimulation settings for that day were set. Each session occurred between 9 am and 11 am. Medication and stimulation were resumed as prescribed after the testing session. The order of experimental stimulation conditions and the order of the prosaccade and antisaccade tasks were randomized. Panel **b** top row shows the prosaccade task. The target amplitude was 20°. *Middle row* shows the timing of onset and offset of fixation (*gray line*) and target (*black line*) LEDs. A 200-ms gap was employed between the offset of fixation LED and the onset of target LED. *Bottom row* shows the sample corresponding eye position. Panel **c** top row shows the antisaccade task. The target amplitude was 20°. *Middle row* shows the timing of onset and offset of fixation (*gray line*) and target (*black line*) LEDs. A 200-ms gap was employed between the offset of fixation LED and the onset of target LED. *Bottom row* shows the sample corresponding eye position for a correct antisaccade response (*black solid line*) and an incorrect prosaccade error (*black dashed line*). Modified, with permission, from Munoz and Everling (2004)

Fig. 2.

These plots show the mean ($\pm$ standard error) prosaccade latency (**a**) and gain (**b**) for all stimulation conditions (*dark bars*) and the control group (*light bars*). *Significant differences between stimulation conditions. ‡Significant differences between control and all stimulation conditions

Fig. 3.

These plots show the mean ($\pm$ standard error) antisaccade latency (**a**) and gain (**b**) for all stimulation conditions (*dark bars*) and the control group (*light bars*). *Significant differences between stimulation conditions. ‡Significant differences between control and all stimulation conditions

Fig. 4.

This plot shows the mean ($\pm$ standard error) percentage of prosaccade errors in the antisaccade task for all stimulation conditions (*dark bars*) and the control group (*light bars*). *Significant differences between stimulation conditions. †Significant differences between control and BOTH stimulation condition

Table 1

Patient characteristics, MDS-UPDRS motor scores, and stimulator settings

ID	Sex	Age (years)	Date of surgery		Disease duration at time of surgery (years)	MDS-UPDRS motor score				Left stimulator			Right stimulator		
			Left electrode	Right electrode		OFF	UNI	BOTH	Voltage (v)	Frequency (Hz)	Pulse Width (µs)	Voltage (v)	Frequency (Hz)	Pulse Width (µs)	
															Left
1	F	50	7/10/2001	1/11/2002	8	34	40	36	40	2.2	185	120	2.0	185	120
2	M	59	6/6/2006	6/6/2006	13	74	48	51	50	4.1	185	80	4.5	185	100
3	M	50	4/14/2006	4/14/2006	24	55	47	51	31	2.9	185	60	2.6	185	60
4	M	58	4/14/2009	4/14/2009	7	53	43	49	37	2.6	185	90	4.0	185	60
5	M	58	12/20/2011	12/20/2011	14	97	45	73	12	4.1	140	120	3.5	140	210
6	M	63	3/19/2010	3/19/2010	8	38	26	34	13	2.3	130	60	2.2	130	450
7	M	59	6/28/2002	6/1/2001	11	56	74	36	31	3.1	160	60	3.1	160	60
8	M	73	10/8/2007	10/8/2007	4	53	27	40	25	5.5	185	120	4.0	185	120
9	F	61	3/28/2006	3/28/2006	5	X	42	29	30	2.9	185	60	3.7	125	80
10	F	53	6/8/2004	10/18/2002	6	65	52	61	43	2.5	130	60	2.6	180	60

Table 2

Statistical comparisons for the prosaccade and antisaccade tasks

	Prosaccade		Antisaccade	
	Latency (ms)	Gain	Latency (ms)	Gain
DBS condition	$F_{2,1488} = 24.3$ $p < 0.0001$	$F_{2,1488} = 24.5$ $p < 0.0001$	$F_{2,1115} = 0.8$ $p = 0.46$	$F_{2,1115} = 17.8$ $p < 0.0001$
				$F_{2,1115} = 12.4$ $p < 0.0001$
Pairwise comparisons				
OFF-UNI	Diff = -6	Diff = 0.03	Diff = 7	Diff = -0.09
	$t = -0.9$	$t = 3.1$	$t = 0.9$	$t = -4.0$
	$p = 1.00$	$p = 0.006$	$p = 1.00$	$p = 0.0002$
OFF-BOTH	Diff = 35	Diff = -0.04	Diff = 11	Diff = -0.16
	$t = 4.8$	$t = -2.9$	$t = 1.2$	$t = -5.9$
	$p < 0.0001$	$p = 0.01$	$p = 0.68$	$p < 0.0001$
UNI-BOTH	Diff = 41	Diff = -0.07	Diff = 5	Diff = -0.07
	$t = 6.9$	$t = -6.9$	$t = 0.6$	$t = -3.1$
	$p < 0.0001$	$p < 0.0001$	$p = 1.00$	$p = 0.006$
Stimulation condition versus control				
OFF-CONTROL	Diff = -20	Diff = -0.1	Diff = 53	Diff = -0.63
	$t = -0.6$	$t = -2.4$	$t = 1.2$	$t = -4.03$
	$p = 1.00$	$p = 0.04$	$p = 0.73$	$p = 0.0003$
UNI-CONTROL	Diff = -10	Diff = -0.16	Diff = 52	Diff = -0.58
	$t = -0.4$	$t = -3.6$	$t = 1.2$	$t = -3.7$
	$p = 1.00$	$p = 0.001$	$p = 0.66$	$p = 0.0006$
BOTH-CONTROL	Diff = -47	Diff = -0.1	Diff = 34	Diff = -0.46
	$t = -1.8$	$t = -2.5$	$t = 0.8$	$t = -2.4$
	$p = 0.22$	$p = 0.03$	$p = 1.00$	$p = 0.05$