Deep brain stimulation of the subthalamic nucleus in Parkinson's disease: similar improvements in saccadic and manual responses

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The purpose of this study was to determine whether the very large effects of saccadic latency distribution, generated by deep brain stimulation of the subthalamic nuclei are reflected in quantitatively corresponding changes for manual responses, rather than representing a reflection of the specific role of the subthalamus in controlling saccades. Saccadic and manual reaction times were measured under as nearly identical conditions as possible in six patients with implanted subthalamic electrodes and in six age-matched controls with the stimulation either on or off. Median latency was found to be reduced by stimulation in a similar way to saccadic latency; in neither case was there a significant change in the Linear Approach to Threshold with Ergotic Rate parameter σ. For both types of response, the effect is to move the responses proportionately in the direction of average of responses in the control group. We therefore conclude that the previously described effects of stimulation on latency are not a phenomenon peculiar to saccades, increasing confidence in using saccadic latency measurements as a surrogate for more general responses when determining the efficacy of deep brain stimulation. ***NeuroReport*** **23:179–183 © 2012 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

To date, thousands of patients with advanced Parkinson's disease (PD) have undergone deep brain stimulation [DBS: bilateral high frequency stimulation of the subthalamic nucleus (STN)] at centres throughout the world. Long-term follow-up studies have consistently shown that DBS has striking therapeutic effects on their motor disabilities [1–3], and may be regarded as the therapy of choice in the surgical management of such cases [4,5].

Despite this success, the mechanism by which it works is essentially unknown. What has been lacking so far are robust, quantitative ways of assessing these effects. From a clinical point of view, conventional assessments using standard rating scales such as the Unified Parkinson's Disease Rating Scale (UPDRS) [6], are convenient and quite reliable when carried out by experienced clinicians. But they are necessarily subjective, and may not be sensitive enough to provide the kinds of quantitative measures that are required. One possible alternative is to use saccades, in effect as a surrogate for more general motor impairment. One measure that is quick and easy to obtain noninvasively and is increasingly used to provide information about impairment of the decision mechanisms that precede movement initiation is to record saccadic latency. As the decision of where to look next is one we all make two or three times each second, some 200 saccades can be measured in approximately 10 min without fatigue; with a modern device worn on the head this can be done noninvasively, using targets projected from the device, so that there is no need for stabilization of the head. The same recording system can also be used to measure sets of manual reaction times, the patient pressing buttons in response to the appearance of target light emitting diodes.

In the case of saccades, earlier work has demonstrated that DBS of the STN has very large effects on saccadic latency distributions, with a very substantial decrease in latency [7,8]. However, it could be argued that rather than being a behavioural effect that can be regarded as a surrogate for more general motor impairment, these very large effects on saccades are more of a consequence of the particular role played by the STN in saccadic control. The STN sends an important glutamatergic projection to substantia nigra pars reticulata (SNr), so that modulation of STN activity by DBS has immediate consequences for SNr firing [9]. The SNr, in turn, sends inhibitory connections to the superior colliculus, and contains saccade-related neurons [10–13], which decrease their activity when a saccadic movement is made [14].

Thus, it is clear that the STN is strategically placed to control saccadic initiation. Consequently, the demonstration

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that DBS in this region has dramatic effects on saccadic latency does not necessarily mean that they reflect the amelioration of the underlying Parkinsonian pathology; they might only represent a parallel process due to the special relationship that the STN enjoys with saccadic control system. For this reason, it is important to check that the effects previously observed for saccades also occur with manual rather than saccadic responses, and this is what the experiments that we have described were intended to do.

Materials and methods

Patients

Patients were selected for STN stimulation if they had clinical findings consistent with idiopathic PD and severe response fluctuations and/or dyskinesias, despite optimal pharmacological treatment. Good initial levodopa response was an absolute criterion. Exclusion criteria consisted of significant atrophy, multiple white matter lesions, or other focal brain abnormalities on MRI, Hoehn and Yahr stage 5 at the best moment of the day, a score of less than 24 on the mini-mental state examination, psychosis, and general contraindications for surgery, such as severe hypertension or blood coagulation disorders. Six patients with PD with bilateral STN DBS were included, and together with six age-matched controls underwent evaluations; their characteristics are listed in Table 1. Informed consent was obtained from all patients and controls and the study was approved by the local ethics committee.

Table 1 Characterization of the Parkinson's group and controls

	Parkinson's disease ($n=6$)	Controls ($n=6$)
Age in years	55.17 ± 3.40	57.21 ± 4.10
Male:female ratio	2 : 4	3 : 3
Disease duration till surgery (years)	12.83 ± 2.62	
Unified Parkinson's Disease Rating Scale part III		
Preoperative medication off	48.00 ± 5.55	
Postoperative stimulation on medication off	21.33 ± 2.09	
Saccadic reaction times		
μ (s^{-1})		5.35 ± 0.32
Stimulation on/medication on	3.83 ± 0.45	
Stimulation off/medication on	2.96 ± 0.27	
σ (s^{-1})		1.45 ± 0.21
Stimulation on/medication on	1.21 ± 0.20	
Stimulation off/medication on	1.49 ± 0.29	
Manual reaction times		
μ (s^{-1})		2.77 ± 0.15
Stimulation on/medication on	2.47 ± 0.23	
Stimulation off/medication on	2.09 ± 0.14	
σ (s^{-1})		0.71 ± 0.08
Stimulation on/medication on	0.64 ± 0.09	
Stimulation off/medication on	0.69 ± 0.09	

Except where stated, all figures are mean ± 1 standard error.

Surgery

The surgical procedure has been described previously [15]. In brief, the stereotactic procedure was performed using the Cosman-Roberts-Wells stereotactic frame, under local anesthetic, after 36-h withdrawal of antiparkinsonian drugs. The target was determined on fused computed tomography/MRI-images (Neuroplan, Radionics, Ghent, Belgium). Special attention was paid to the trajectory planning in all patients, to avoid blood vessels during the installation of the electrodes. After making a precoronal burr hole, recording electrodes were introduced. A single semi-microelectrode (Model RAD SME-E; Radionics) was introduced 10 mm above the presumed target for electrophysiological recordings (Neuromap, Radionics). Recordings were taken and the STN was characterized by a neuronal firing pattern consisting of an increased baseline activity and a strong increase of high-voltage spikes, which were usually present over a length of 4–5 mm. Subsequently, the electrode was withdrawn, another electrode for test stimulation was introduced (Model TC 112, Radionics) and macrostimulation to test for the clinical effects was initiated. At each point of test stimulation the clinical effect was evaluated by the neurologist. The following clinical parameters using the UPDRS [6] were scored: tremor (if present) and rigidity in all four extremities, finger taps, hand movements/handgrips, and leg agility]. When a good effect was found in the absence of side effects, the test electrode was replaced by the final quadripolar electrode (Medtronic Model 3389; Medtronic, Minneapolis, Minnesota, USA). On the second postoperative day, a computed tomography scan was performed to evaluate the positions of the electrodes. Usually, 1 week later a second operation was performed under general anesthesia, to implant the pulse generator infraclavicularly or abdominally (Itrell III or Kinetra, Medtronic, Minneapolis).

Evaluation of motor effects using the Unified Parkinson Disease Rating Scale

In this study, we focused on the change in the UPDRS part III score (motor score) due to STN high-frequency stimulation and dopaminergic medication and the correlation of this score with saccadometric parameters. Evaluations were performed with medication on and stimulators on or off for 12 h as previously described [15], resulting in two experimental conditions. All data were collected by the same investigators in the same sequence, and the patient as well as the investigator was necessarily aware of the status of the medication and stimulation. Medication intake was defined by the levodopa equivalent dose [15].

Saccadic reaction times

A head-mounted saccadometer was used to record horizontal saccadic eye movements (Ober Consulting, Poznan, Poland [16]). The saccadometer is worn on the forehead, resting on the bridge of the nose, and there are three lasers mounted on it, generating projected red visual targets 10° apart, of luminance exceeding

$1000\,\text{cd m}^{-2}$ and subtending some 5-min arc. As the targets move exactly with the head, there is no need for a bite bar or other form of stabilization, and the patient can therefore sit comfortably. We used a standard saccadic step task, with randomized target direction and time of appearance, for which the protocol has previously been published [8,17].

Manual reaction times

The manual measurements were acquired by using the same saccadometer device but switching to the manual mode; the protocol was otherwise identical. The participants held the control box in both hands with their thumbs resting on buttons on the left and right. They were instructed to respond to the appearance (random in direction and timing) of the left or right LED by pressing the corresponding button. In the case of the visual recording, 300 trials were used over a period of 10–15 min.

Analysis of latency data

In general, both manual and saccadic reaction times vary randomly from trial to trial, creating skewed latency histograms with an extended tail toward longer latencies [18]. However, the reciprocal of latency generally follows a normal distribution, implying that is the rate of the underlying decision process that is the fundamental stochastic variable. Consequently, just two parameters, μ and σ (mean and standard deviation of the distribution of reciprocal latency) together provide a succinct quantitative summary of observed latency distribution; they have the further advantage of being closely related to a well-supported model [Linear Approach to Threshold with Ergodic Rate (LATER)] of the underlying neural decision mechanisms [18,19].

We downloaded data for both the saccadic and manual reaction times to a computer and used the LatencyMeter software [16] for automatic elimination of any trials whose profiles were contaminated by blinks, undue head movement, incorrect direction or amplitude, or other irregularities, and calculation of latencies using a criterion based on instantaneous velocity and acceleration. Latency data were then exported to the SPIC program [20] for distribution analysis, determining the best-fit values of the LATER parameters by minimization of the Kolmogorov–Smirnov one-sample statistic.

Results

Unified Parkinson Disease Rating Scale part III

The total UPDRS III score was consistently reduced ($P < 0.05$) in the stimulation-on condition in all patients, by an average of 26.7 across all patients (Table 1). In addition, in the stimulation-off condition, suprathreshold medication reduced the UPDRS III score significantly as well ($P < 0.05$).

Latencies

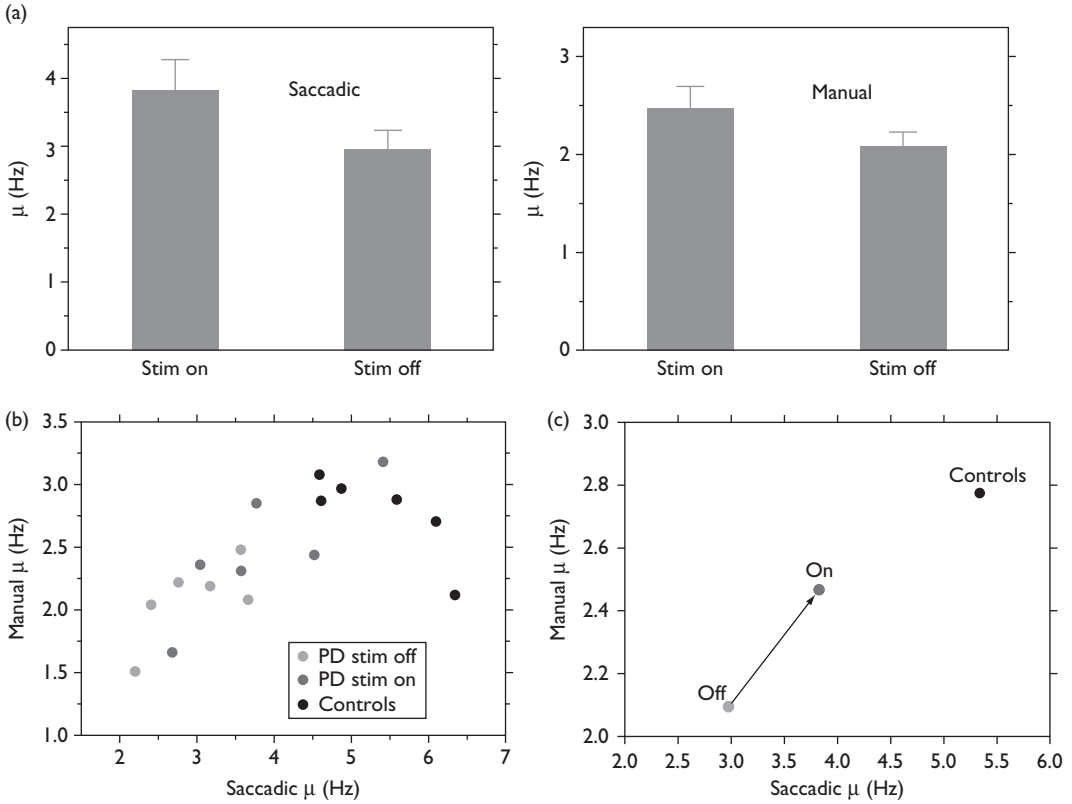
Table 1 shows the means and standard errors of μ and σ for both saccadic reaction times and manual-evoked responses under the following conditions (a) with both stimulation and medication on and (b) with the stimulator switched off but with the medication on. For saccades, stimulation increased μ (corresponding to an increased speed of response) by an average of 0.87/s, or 29.4% (equivalent to a reduction of average median latency from 338 to 261 ms). Stimulation also increased μ for manual responses, by an average of 0.38/s, or 18.2% (average median latency falling from 478 to 405 ms). All these comparisons are shown graphically in Fig. 1a. Paired *t*-tests (having first established normality with the Shapiro–Wilks test) demonstrated that both these differences were significant [saccadic $P = 0.03$, manual $P = 0.02$, 5 degree of freedom (d.f.)]. No significant differences were observed for σ either for manual or saccadic responses ($P = 0.46$, 0.4, 5 d.f.). Comparison with the control population showed that – even with the stimulation on – patients' responses are significantly slower (unpaired *t*-test, saccadic $P = 0.02$, manual $P = 0.03$, DF = 5). Comparisons of σ between stimulation on and stimulation off, and between both patient groups and controls showed no significant difference in any of the cases ($P > 0.05$ for all).

Figure 1b shows the individual data points for each patient and control, and demonstrates first that the disease appears to reduce μ in a proportionate manner for both manual and saccadic responses, and also that the effect of stimulation is in general to undo this influence, by shifting the data points back along the same line in the direction of the controls. This can be seen more clearly in Fig. 1c, which plots just the averages for each group.

Discussion

These results demonstrate two features of reaction time in Parkinson patients undergoing DBS. First, that the effect of the stimulation is both qualitatively and quantitatively similar for saccades and manual responses; there is an increase in μ, with no concomitant change in σ and the effect is in general to shift responses along a proportional line in the direction of the controls. Second, the effect of the disease itself appears roughly to move patients along the same line in the opposite direction. In terms of the LATER model [18], this change in μ, while σ remains constant, implies a change in the rate of processing of information rather than, for example, an alteration in excitability. It is similar to what has been reported earlier as a result of sedation by low doses of anaesthetic [21]. This again suggests that the dramatic effects of DBS of the STN on saccadic latency are not simply because of the involvement of this area in saccadic initiation, but are due to a more general mechanism that affects manual as well as oculomotor responses.

Fig. 1



The effect of stimulation. (a) Comparison of the effect of stimulation (while on medication) on μ for saccadic and manual responses. (b) Comparison of effects on manual and saccadic movements, and compared with the controls (black): medium grey shows stimulation on, light grey is off. Left shows individuals, right shows averages for each group. PD, Parkinson's disease; Stim on/off, stimulation on/off.

The magnitude of the effects seen here is very similar to what was reported in an earlier study [7,8]. These findings strengthen one's confidence in the use of saccadometry as a measure of DBS efficacy, and point in particular at its potential use as a possible guide to the intraoperative placement of the electrodes, as well as in providing a quantitative measure of alleviation that may be of some benefit in these patients.

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Conflicts of interest

There are no conflicts of interest.

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