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Stimulation-Induced Dyskinesia in the Early Stage after Subthalamic Deep Brain Stimulation

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Key Words
Deep brain stimulation · Dyskinesia · Subthalamic nucleus · Parkinson's disease

Abstract
Background: Deep brain stimulation of the subthalamic nucleus (STN-DBS) is a very effective surgical procedure for Parkinson's disease. It significantly improves cardinal parkinsonian symptoms as well as levodopa-induced dyskinesia. Interestingly, STN-DBS can also provoke or exacerbate dyskinesia. In the present study, stimulation-induced dyskinesia (SID) was found in the early stage (less than 1 month) after STN-DBS in some patients. The aim was to discuss this interesting phenomenon. ***Methods:*** Side effects of each electrode contact were tested at 9.0 ± 3.8 days (range, 3–16 days) after STN-DBS, and 40 contacts of 16 electrodes (15 patients) were found to induce dyskinesia. The location of these contacts was calculated in the postoperative magnetic resonance imaging, and was compared to the positions of active contacts and dorsal margin of the subthalamic nucleus (STN). ***Results:*** Most SID at the threshold manifested as repetitively dystonic involuntary movement, and the most common site was the contralateral lower limb (27/40, 67.5%). The mean location of the 40 contacts with SID was 11.9 ± 0.9 mm lateral, 0.4 ± 1.7 mm anterior, and 1.8 ± 1.9 mm inferior to the midcommissural point. The point was located inferior to the dorsal margin of the STN ($p = 0.01$, t tests), and no significant difference was found between this point and the location of active contacts ($p > 0.05$, t tests). ***Conclusion:*** In the early stage after STN-DBS, dyskinesia is easily induced by high-frequency stimulation of the upper portion of the STN, which may predict the best site for chronic stimulation.

Introduction

There are 4 subcortical targets for the surgical interventions of patients with Parkinson's disease: thalamus, pallidum, subthalamic nucleus (STN), and pedunculopontine nucleus [1, 2]. The STN has become the preferred target because deep brain stimulation of the STN (STN-DBS) could significantly improve cardinal parkinsonian symptoms (tremor, rigidity, bradykinesia) as well as levodopa-induced dyskinesia, and also reduce the daily levodopa dose [3, 4]. However, STN-DBS has also been demonstrated to provoke or exacerbate dyskinesia [3, 5, 6]. The appearance of stimulation-induced dyskinesia (SID) during the operation is considered as a favorable sign predicting beneficial postoperative outcome [7]. In the present study, we would like to discuss SID in the early stage after STN-DBS.

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Patients and Methods

Patients

Fifty-six consecutive patients (74 electrodes) with Parkinson's disease underwent STN-DBS at the Beijing Institute of Functional Neurosurgery between December 2007 and June 2008. For our purpose, only SID in the early stage (less than 1 month) after the surgery was included in this study. The excluding criteria were as follows: ipsilateral thalamotomy or pallidotomy which may inhibit the induction of dyskinesia; severe brain deformation due to pneumocephalus demonstrated by postoperative magnetic resonance imaging (MRI); no satisfactory benefit from the surgery. Overall, 16 electrodes (15 patients) were included in the analysis. Of the 15 patients, 9 were female and 6 were male. Their mean age was 45.5 ± 12.1 years. The mean duration of disease before the operation was 8.5 ± 2.4 years. The preoperative mean Hoehn and Yahr stage was 3.2 ± 1.0 in the 'off-medication' state. Nine patients had preoperative on-period dyskinesia (diphasic and peak-dose dyskinesia).

Surgical Procedure

A Cosman-Roberts-Wells stereotactic frame (Radionics, Burlington, Mass., USA) was applied. Magnetization-prepared rapid acquisition gradient echo sequences were obtained on a 1.5-tesla machine (Siemens, Germany). After the images were reconstructed, the anterior commissure (AC) and posterior commissure (PC) were detected, and the AC-PC distance was calculated by using the most anterior point in the PC and the most posterior point in the AC. The STN target was indirectly defined as 12 mm lateral, 1 mm posterior, and 4 mm inferior to the midcommissural point. The anteroposterior and lateromedial angle was defined as 60° and 12°, respectively.

Single-track microrecording was performed and cell activity was recorded starting from 10 mm above the STN target. Signal amplification and control of the microdrive were performed by a dedicated physiology system (Alpha Omega Engineering, Nazareth, Israel). The neurophysiologist described the dorsal and ventral margins of the STN, which were determined by the significant change in neuronal activity. Then we implanted the quadripolar electrode (model 3389; Medtronic, Inc., Minneapolis, Minn., USA) instead and evaluated the efficacy and side effects (frequency 185 Hz, pulse width 90 μs). In general, the distal tip of the electrode was implanted at the ventral margin of the STN. If the microrecording did not show a long enough (more than 3 mm) STN, and the macrostimulation displayed satisfactory efficacy without side effects up to 5 V, no adjustment was done. If side effects appeared when the voltage was less than 5, we adjusted the position of the quadripolar electrode on the basis of the characteristics of these side effects. After a satisfactory outcome of the macrostimulation was obtained, the subcutaneous implantable pulse generator (Soletra or Kinetra; Medtronic, Inc.) was placed at the subclavicular region or abdomen.

Postoperative MRI and Position of Electrodes

Postoperative MRI (magnetization-prepared rapid acquisition gradient echo sequences) was performed 4.6 ± 1.7 days after the surgery. The exact position of each contact was not visible in the postoperative MRI because of the artifacts. We calculated the coordinates of each contact relative to the most reliable distal tip of the electrode. The distance from the distal tip to the center of each contact (distal to proximal: contact 0, contact 1, contact 2, and contact 3) was 2.15, 4.15, 6.15, and 8.15 mm, respectively [8]. The anteroposterior angle of the electrode, and the anteroposterior and vertical coordinates of the distal tip were calculated on the sagittal planes. The lateromedial angle of the electrode and the lateral coordinate of the distal tip were obtained on the coronal planes. With the following information known including the position of the tip, the trajectory angle, and the distance from the distal tip to the center of each contact, coordinates of each contact could be derived relative to the midcommissural point [9].

Position of the Dorsal Margin of the STN

The length of the STN determined by electrophysiological mapping was recorded. In the postoperative MRI, the coordinates of the dorsal margin of the STN were obtained by calculating the anterior and lateral coordinates of the implanted electrode at the vertical plane of the implantation trajectory (related to the target) corresponding to the most proximal point at which the typical pattern of the STN firing neurons was observed [9]. Three cases were excluded in this series because the length of the STN was less than 3 mm or new microrecording was not performed after positional adjustment.

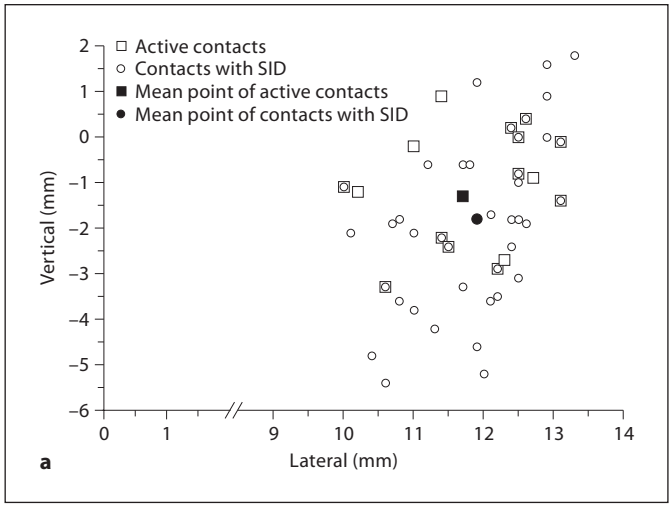
Side Effect Test and Determination of the Active Contact

There was no patient with dyskinesia due to microlesion effect. Side effects of each contact were tested 9.0 ± 3.8 days (range, 3–16 days) after the surgery when the patients were in the off-medication state. The test was delayed if the patient was not in a good state which would result in poor cooperation. The test was performed with monopolar stimulation (frequency 130 Hz, pulse width 60 μs). Voltage was increased by 0.1–0.3 V each time (about 2 s) until side effects appeared. The upper limit of the voltage tested was 5 V. The test of one contact lasted about a quarter of a minute to 2 min. The next contact was not tested until the side effects were completely gone. SID was defined as involuntary movement of the limbs, head or trunk when stimulation was on during the test; when stimulation was switched off, the involuntary movement immediately disappeared. Discomfort sensation or the feeling of 'intending to move body or limbs' was not considered as SID, because the patients may be confused about their feelings. It was also found that in several patients dyskinesia appeared after the stimulation was on for several hours. In these cases, other contacts are hardly tested for a long enough time. It would have been difficult for patients to cooperate for a whole day in the off-medication state if we tested each contact for several hours. Thus, these contacts were excluded from this analysis.

The efficacy test was performed about 1 week after the surgery. Over the next 3–4 weeks, the contact and stimulation parameters were optimized to obtain maximum clinical benefit and minimal side effects. We assumed the best contact to be the one providing the best alleviation of rigidity with the lowest voltage and without side effects, but we found that the variable clinical manifestations of patients, side effects and the microlesion effect may have some influence on the accuracy of this method, so the best contact was considered to be the active contact.

Table 1. Position of the electrode (n = 16)

Anteroposterior angle, degree	58.1 ± 5.7
Lateromedial angle, degree	10.6 ± 3.8
Coordinates of distal tip, mm	
Lateral (x-axis)	10.9 ± 0.9
Anteroposterior (y-axis)	–2.4 ± 1.4
Vertical (z-axis)	–5.9 ± 1.2
Coordinates of contact 0, mm	
Lateral (x-axis)	11.3 ± 0.9
Anteroposterior (y-axis)	–1.2 ± 1.3
Vertical (z-axis)	–4.0 ± 1.3
Coordinates of contact 1, mm	
Lateral (x-axis)	11.6 ± 1.0
Anteroposterior (y-axis)	–0.2 ± 1.2
Vertical (z-axis)	–2.4 ± 1.3
Coordinates of contact 2, mm	
Lateral (x-axis)	11.9 ± 1.0
Anteroposterior (y-axis)	0.9 ± 1.2
Vertical (z-axis)	–0.7 ± 1.4
Coordinates of contact 3, mm	
Lateral (x-axis)	12.2 ± 1.1
Anteroposterior (y-axis)	1.9 ± 1.2
Vertical (z-axis)	1.0 ± 1.4



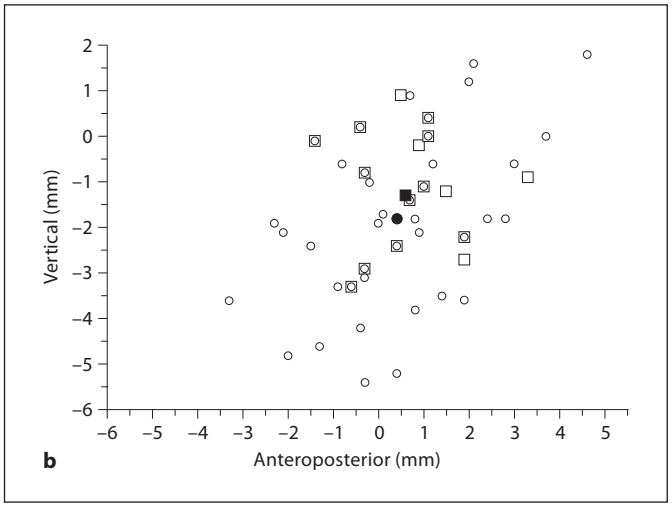


Fig. 1. Positions of 40 contacts with SID and 16 active contacts (in 3 active contacts, the midpoint of 2 negative contacts in 1 electrode was considered as the active contact). Most (11/16) active contacts were contacts with SID, and there was no significant difference between the positions of active contacts and contacts with SID ($p > 0.05$, t tests). **a** Coronal plane. **b** Sagittal plane.

Results

Neurophysiological Mapping of the STN

The mean length of the STN was 5.0 ± 0.9 mm (range, 3.5–7 mm). The dorsal margin of the STN was located 11.8 ± 1.0 mm lateral, 0.5 ± 1.3 mm anterior, and 0.8 ± 0.8 mm inferior to the midcommissural point.

Positions of the Electrode and Active Contacts

Table 1 shows the position of the electrode. There were 12 electrodes with monopolar stimulation and 4 electrodes with bipolar stimulation. When there were 2 negative contacts on 1 electrode, the midpoint was considered as the position of the active contact; there were 3 electrodes with this stimulation mode. In the electrodes with bipolar stimulation, the cathode was considered as the active contact. After a mean follow-up of 9.9 ± 2.8 months (range, 5–14 months), the mean coordinates of the active contacts were 11.7 ± 1.0 mm lateral, 0.6 ± 1.0 mm anterior, and 1.3 ± 1.3 mm inferior to the midcommissural point. When compared to the coordinates of the dorsal margin of the STN, no significant difference was found ($p > 0.05$, t tests).

Stimulation-Induced Dyskinesia

There were 40 contacts with SID during the side effect test. The mean coordinates were 11.9 ± 0.9 mm lateral, 0.4 ± 1.7 mm anterior, and 1.8 ± 1.9 mm inferior to the midcommissural point. The point was located ventrally to the dorsal margin of the STN ($p = 0.01$, t tests), and there was no significant difference in the lateral or anteroposterior direction ($p > 0.05$, t tests). When compared to the site of active contacts, there was no significant difference between them ($p > 0.05$, t tests) (fig. 1). The mean voltage threshold was 1.8 ± 0.7 V (table 2), and mostly (72.5%) it was no more than 2.0 V. Of the 40 contacts, contact 2 was the most common (32.5%), followed by contact 1 (27.5%), contact 0 (25%) and contact 3 (15%). When

there was only 1 contact with SID in an electrode, this contact or the contact superior to it was usually selected as the active contact. When there were 2 contacts with SID in an electrode, mostly (75%) the contact more proximal was selected as the active contact. When there were 3 or 4 contacts with SID in an electrode, the active contact may be variable, however, the contact most distal was rarely used as the active contact. At the last follow-up, no patient experienced dyskinesia in the off-medication state.

Most patients had mild dyskinesia at the threshold. Dyskinesia occurred mostly in the contralateral lower limb (27/40, 67.5%), less frequently in the contralateral upper limb (6/40, 15%), and in the contralateral upper and lower limbs (6/40, 15%), and the least frequently in the trunk (1/40, 2.5%). Most cases of SID at the threshold manifested as repetitive dystonic involuntary movements. When limbs were involved, dyskinesia usually existed in the distal part. The site of arm-related dyskinesia was 12.4 ± 0.6 mm lateral, 1.0 ± 0.8 mm posterior, and 1.6 ± 1.6 mm inferior to the midcommissural point. The site of leg-related dyskinesia was 11.7 ± 0.9 mm lateral, 0.6 ± 1.8 mm anterior, 2.1 ± 2.0 mm inferior to the midcommissural point. The site of arm-related dyskinesia was situated posteriorly relative to the site of leg-related dyskinesia ($p = 0.039$, t tests); there was no difference in the dorsoventral ($p = 0.573$, t tests) or lateromedial ($p = 0.090$, t tests) direction.

The Stimulation Parameters

Table 3 shows the stimulation parameters at the last follow-up. Monopolar stimulation with 1 active contact (56.3%) was the most common stimulation mode.

Table 2. Contacts with SID

Contact 0	10
Contact 1	11
Contact 2	13
Contact 3	6
Stimulation threshold, V	1.8 ± 0.7

Table 3. Stimulation parameters at the last follow-up

Stimulation parameters	Stimulation mode		
	monopolar stimulation with 1 cathode (n = 9)	monopolar stimulation with 2 cathodes (n = 3)	bipolar stimulation with 1 anode and 1 cathode (n = 4)
Voltage, V	2.6 ± 0.4	3.3 ± 0.3	2.2 ± 0.8
Pulse width, μs	76.7 ± 15.8	70.0 ± 17.3	82.5 ± 15.0
Frequency, Hz	148.3 ± 14.6	175.0 ± 13.2	152.5 ± 8.7

Discussion

Our results demonstrate that the position of SID in the early stage after STN-DBS is in the upper portion of the STN, close to the dorsal margin, which may predict the best site for chronic stimulation. After a mean follow-up of 9.9 ± 2.8 months, most active contacts were related to SID, and the others were located more dorsally. This finding can be used to facilitate programming.

Stimulation-Induced Dyskinesia

According to the current model of basal ganglia [10], lesions of the STN should theoretically induce dyskinesia. Disabling dyskinesia has been reported after lesions within the STN in parkinsonian [11] and nonparkinsonian patients [12]. As we know, high-frequency stimulation mimics some lesion-like effects. Our result is consistent with a previous study reporting that dyskinesia is induced by high-frequency stimulation of the STN [13].

In our study, the contralateral lower limb was the most commonly involved in SID, which may be explained by one of the following two reasons: (1) initially after STN-DBS, low stimulation parameters could induce repetitive dystonic dyskinesia, mimicking diphasic levodopa-induced dyskinesia which usually begins distally in the lower limbs [14]; (2) there is a somatotopic organization in the sensorimotor region of the STN [15–17]. Romenalli et al. [16] also found out that leg-related cells tended to be situated anteriorly relative to arm-related cells. Our data showed that leg-related dyskinesia may more easily be induced when the electrode is located more anteriorly, but the small sample size in our study may have influenced the accuracy of this conclusion.

Programming

In these patients of our study, the programming was difficult in the early stage after the surgery because the threshold of SID was low. As the microlesion effect and brain edema were gone and/or the stimulation was tolerable, the stimulation parameters increased and no patient experienced dyskinesia in the off-medication state. How-

Table 4. Optimal site for STN-DBS in the past studies

Author	Year	Optimal site, mm		
		lateral (x-axis)	anteroposterior (y-axis)	vertical (z-axis)
Lanotte et al. [20]	2002	12.3 ± 0.9	–1.7 ± 0.9	–1.7 ± 1.5
Saint-Cyr et al. [21]	2002	11.72 ± 1.5	–1.62 ± 1.98	–2.47 ± 1.76
Hamel et al. [22]	2003	12.8 ± 1.0	–1.9 ± 1.4	–1.6 ± 2.1
Herzog et al. [23]	2004	12.7 ± 0.7	–2.3 ± 1.1	–2.1 ± 1.4
Yokoyama et al. [24]	2006	12.3 ± 1.4	–0.5 ± 1.7	–1.2 ± 1.3
Pollo et al. [9]	2007	12.04 ± 1.62	–2.34 ± 1.63	–2.57 ± 1.68

ever, in a few patients the stimulated therapeutic window is still extremely narrow between the 'off' and 'on' state with dyskinesia. In these cases, we had to select some particular stimulation methods or choose the contacts dorsal to the contact with SID as the active contacts to reach suboptimal effects. It has been reported that high-frequency stimulation of the area including the zona incerta and Forel's field H could directly alleviate dyskinesia [13, 18]. Thus, in our experience, we would like to try Katayama's [19] or the following method: the contact with SID as a cathode, plus 1 negative contact dorsal to the STN which has an antidyskinetic effect.

Best Site for STN-DBS

The best site for STN-DBS varies in the past studies. The different preoperative STN target selection, approaches of surgery, and different methods of evaluating the best contact may have influenced the outcome (table 4) [9, 20–24]. It seems that the best site for stimulation in our study is more anterior. It should be noted that our target was more anterior and single-track microrecording was used in our study, which may explain the difference. It is still not clear whether the best site is in the STN proper or just outside. Herzog et al. [23] indicated that the best site for stimulation was in the lateral and dorsal portion of the STN. In our study, the average position of active contacts was located in the dorsal margin of the STN, which compared well to some previous studies [9, 22, 24].

It may take seconds, minutes or hours to induce dyskinesia. Thus, during the side effect test it is possible that the threshold recorded may be higher than the actual one in some patients. In this study, the exclusion of contacts with SID after the test and the microlesion effect may have influenced the exact site related to SID. Further study is needed in the future.

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