The Nature and Time Course of Cortical Activation Following Subthalamic Stimulation in Parkinson’s Disease

We studied the time course and nature of interactions between the subthalamic nucleus (STN) and the motor cortex in 8 Parkinson disease (PD) patients with chronically implanted STN deep-brain stimulation (DBS) electrodes. We first identified the cortical evoked potentials following STN stimulation. The most consistent potential was positive wave with peak latency of 22.2 ± 1.2 ms from stimulation of clinically effective contacts. We then stimulated the motor cortex with transcranial magnetic stimulation (TMS) at 2–15 ms and at the latency of the evoked potential (~ 23 ms) following STN DBS. TMS induced currents in 3 directions: lateral– medial (LM) direction activated corticospinal axons directly, posterior– anterior (PA), and anterior–posterior (AP) directions activated corticospinal neurons transynaptically. Motor-evoked potentials (MEPs) elicited by AP and PA TMS were facilitated at short (2–4 ms) and medium latencies (21–24 ms). However, MEPs elicited by LM TMS were not modified by STN DBS. Short-latency antidromic stimulation of the corticosubthalamic projections and medium latency transmission likely through the basal ganglia–thalamocortical circuit led to cortical evoked potentials and increased motor cortex excitability at specific intervals following STN stimulation at clinically effective contacts. Cortical activation may be related to the clinical effects of STN DBS in PD.

Keywords: cortical facilitation, deep-brain stimulation, Parkinson’s disease, subthalamic nucleus, transcranial magnetic stimulation

Introduction

High-frequency stimulation of the subthalamic nucleus (STN) improves motor symptoms in Parkinson’s disease (PD) (Krack et al. 2003; Rodriguez-Oroz et al. 2005; Deuschl et al. 2006). However, its mechanism of action is not fully understood. The STN modulates the activities of basal ganglia output structures. STN activities in PD (Ceballos-Baumann et al. 1999; Magnin et al. 2000; Levy et al. 2002) are characterized by augmented synchrony of neuronal firing, loss of specificity of the receptive fields, and increased firing rates with bursting activities (Hutchison et al. 1998; Magarinos-Ascone et al. 2000; Hamani et al. 2004). This pathological drive from STN is hypothesized to disrupt the activities of the substantia nigra pars reticulata (SNr), globus pallidus pars interna (GPI), globus pallidus pars externa (GPe), pedunculopontine nucleus, thalamus, and various cortical areas (Benazzouz et al. 2000; Dostrovsky and Lozano 2002; Vitek 2002; Hamani et al. 2005). Currently several hypotheses exist to explain the mechanism of action of deep-brain stimulation (DBS) including depolarization blockade (Beurrier and Lozano 2001), synaptic inhibition (Dostrovsky and Lozano 2002), synaptic depression (Wang and Zucker 1998; Zucker and Regehr 2002), and stimulation-induced disruption of the pathological network (Montgomery and Baker 2000; Brown and Eusebio 2008). Recent animal studies suggested that inhibition of the STN is not sufficient to produce motor benefit and STN DBS may work by activation of the motor cortex (Dejean et al. 2009; Gradinaru et al. 2009). STN DBS may act by different mechanisms on the various parkinsonian signs and multiple mechanisms may operate in parallel (Temperli et al. 2003).

The interactions between STN and motor cortex have been studied in animal models (Hazarri et al. 1995; Nambu et al. 1997; Inase et al. 1999; Dejean et al. 2009; Gradinaru et al. 2009) and in patients with STN DBS (Cunic et al. 2002; Strafella et al. 2004; Gaynor et al. 2008; Eusebio et al. 2009). Transcranial magnetic stimulation (TMS) of the motor cortex changed the firing rate of STN neurons (Strafella et al. 2004) and the oscillatory activities of the STN (Gaynor et al. 2008). Several authors reported evoked potentials recorded from scalp electrodes following low frequency STN stimulation at short (2–8 ms), medium (18–25 ms), and long latencies (more than 50 ms) (Ashby et al. 2001; Baker et al. 2002; MacKinnon et al. 2005). A previous study from our group demonstrated that single-pulse STN stimulation facilitated the ipsilateral motor cortex tested with TMS with induced current in the posterior– anterior (PA) current direction at short latencies of 3–4 ms (Hanajima et al. 2004). However, the study was performed shortly after surgery. It was not known if the contacts used were capable of producing clinically effective stimulation and the results could have been influenced by microlesion effects. No study has evaluated the interaction between STN and ipsilateral motor cortex at medium latencies. In the present study, we tested the effects of STN stimulation on cortical excitability at interstimulus intervals (ISIs) corresponding to the short and medium latency–evoked potentials using TMS at different current directions. The different current directions were used to determine whether the changes occurred at the cortical or subcortical levels. TMS with induced currents in the anterior–posterior (AP) and PA directions activate pyramidal neurons transsynaptically through interneurons and are sensitive to changes in cortical excitability, whereas induced current in the lateral–medial (LM) direction directly activates corticospinal axons and is not sensitive to changes in cortical excitability (Kaneko et al. 1996; Sakai et al. 1997; Di Lazzaro et al. 2001). Because animal studies showed that STN DBS activates the motor cortex (Dejean et al. 2009; Gradinaru et al. 2009), we hypothesized that motor cortex will be facilitated at the times of the short and medium latency–evoked potentials from STN DBS.
Materials and Methods

Subjects
We studied 8 PD patients (Table 1) who had bilateral STN DBS for more than 3 months. Patients were recruited from the Movement Disorders Clinic at the Toronto Western Hospital. All patients gave written informed consent, and the protocol was approved by the University Health Network Research Ethics Board.

Magnetic Resonance Imaging (MRI) Localization of STN DBS Electrode Contacts
The methods to assess the location of DBS electrode contacts have been described in detail (Hamani et al. 2008). Briefly, preoperative T2 and postoperative axial 3D inversion recovery images were fused. We then registered the anterior and posterior commissures and established the location of each electrode contact relative to the midcommissural point and the internal anatomy of the subthalamic region. We considered the region extending from 2 mm ventral to 2 mm dorsal to the MR border of the STN as the dorsal STN/zona incerta (ZI) region (dSTN-ZI) (Saint-Cyr et al. 2002).

Experimental Design
The study consisted of 2 experiments performed on separate days. Experiment 1 identified the latencies of cortical evoked potentials from STN stimulation. In Experiment 2, the effects of STN DBS on motor cortex (M1) excitability were examined. Patients continued their usual scheduled dopaminergic medications during the study.

Experiment 1: Recording of Evoked Potentials from STN DBS

DBS Settings
The DBS frequency was changed to 10 Hz with same pulse width as that used in clinical setting (60–90 μs). In our preliminary studies, we recorded evoked potential using 3, 5, and 10 Hz of STN stimulation from 2 patients. Because the potentials recorded were identical, we chose 10 Hz stimulation to reduce the duration of study and to increase the number of epochs for averaging. The stimulation voltage was set at the highest level without adverse effect. All bipolar stimulation montages using adjacent contact pairs were tested (e.g., −0.1, −1, +2, −2 + 3, −1 + 0, −2 + 1, and −3 + 2). Bipolar stimulations were used to reduce the stimulus artifact. Both sides were tested separately, and the contralateral stimulator was switched off.

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Age (years)</th>
<th>Disease duration (years)</th>
<th>Time after surgery (years)</th>
<th>H&amp;Y</th>
<th>DBS parameters</th>
<th>UPDRS*</th>
<th>Medication—levodopa equivalent (mg/day)</th>
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</thead>
<tbody>
<tr>
<td>P1</td>
<td>75</td>
<td>16</td>
<td>11</td>
<td>4</td>
<td>Right: 2.3 V, 60 μs, 130 Hz, 2–C+</td>
<td>47/41</td>
<td>800</td>
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<tr>
<td>P2</td>
<td>58</td>
<td>14</td>
<td>2</td>
<td>3</td>
<td>Left: 2.8 V, 120 μs, 130 Hz, 2–C+</td>
<td>39/30</td>
<td>1500</td>
</tr>
<tr>
<td>P3</td>
<td>67</td>
<td>15</td>
<td>5</td>
<td>2</td>
<td>Left: 2.5 V, 120 μs, 80 Hz, 3–C+</td>
<td>32/20</td>
<td>1000</td>
</tr>
<tr>
<td>P4</td>
<td>57</td>
<td>18</td>
<td>6</td>
<td>2.5</td>
<td>Right: 3.5 V, 60 μs, 185 Hz, 2–C+</td>
<td>21/20</td>
<td>262</td>
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<tr>
<td>P5</td>
<td>59</td>
<td>11</td>
<td>1</td>
<td>2</td>
<td>Left: 3.6 V, 90 μs, 185 Hz, 3–C+</td>
<td>15/8</td>
<td>600</td>
</tr>
<tr>
<td>P6</td>
<td>62</td>
<td>13</td>
<td>8</td>
<td>3</td>
<td>Left: 3.5 V, 60 μs, 185 Hz, 2–C+</td>
<td>49/37</td>
<td>1000</td>
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<tr>
<td>P7</td>
<td>52</td>
<td>13</td>
<td>2</td>
<td>2.5</td>
<td>Right: 3.3 V, 60 μs, 185 Hz, 1–C+</td>
<td>27/16</td>
<td>1000</td>
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<tr>
<td>P8</td>
<td>61</td>
<td>12</td>
<td>6</td>
<td>2</td>
<td>Right: 3.5 V, 90 μs, 185 Hz, 1–C+</td>
<td>24/10</td>
<td>900</td>
</tr>
</tbody>
</table>

Mean ± SD: 61 ± 6.9 years, 14 ± 2.2 years, 5.1 ± 3.3 years, 2.6 ± 0.7 years

Note: All patients are men. H&Y—Hoehn and Yahr staging. UPDRS*—UPDRS motor score off/on stimulation. We calculated Levodopa equivalent dose by the formula: 100 mg of standard levodopa = 133 mg of controlled-release levodopa or 75 mg of levodopa plus entacapone or 1 mg of pramipexole or 5 mg of ropinirole or 10 mg of bromocriptine.

Electroencephalographic (EEG) Recording
Potentials evoked at the scalp from STN DBS were recorded with 5-mm diameter gold-plated cup electrodes at 7 positions (Cz, C3, C4, F1, F2, Fp1, and Fp2) of the international 10–20 system. The reference electrodes were placed on the linked ears and the ground electrode was placed over Fz. Three minutes of EEG was recorded during stimulation with each pair of bipolar contacts.

Data Acquisition and Processing
EEG signals were amplified (gain 10k; band pass filter 5–500 Hz), sampled at 5 kHz using Synamps (Compumedics Neuroscan, Texas, United States) and Scan 4 software (NeuroScan Inc., El Paso, TX), and were stored in a computer for offline analysis. The continuous EEG data were transformed to epochs using the DBS artifacts as triggers. One thousand eight-hundred epochs were averaged. The latencies of evoked potentials from DBS were measured from the averaged signal.

Experiment 2: Effects of STN DBS on Motor Cortex Excitability

Electromyographic Recording
Electromyography (EMG) was recorded from the first dorsal interosseous (FDI) muscle contralateral to the stimulated motor cortex using disposable 9-mm diameter surface electrodes with a belly-tendon montage. EMG was amplified at 1k (Intronix Technologies Corporation Model 2024F, Bolton, Ontario, Canada), filtered (band pass 20 Hz–2.5 kHz), digitized at 5 kHz (Micro 1401, Cambridge Electronics Design, Cambridge, United Kingdom) and stored in a laboratory computer for offline analysis. Subjects were asked to relax throughout the experiment with EMG monitored on a computer screen and via loudspeakers.

DBS Protocol
The DBS frequencies were set to 3 or 30 Hz, at the same pulse width used in the clinical setting (60–90 μs). Stimulation frequencies of 3 and 30 Hz were used to explore the effects of different stimulation frequencies. We could not use frequencies higher than 30 Hz because the time between pulses would be too short for the medium-latency potentials. Monopolar stimulation was used for the study with the implanted programmable pulse generator case as the anode and the DBS electrode contact as the cathode (3–case+, 2–case+, 1–case+, and 0–case+), using the same contacts used in the clinical setting. The side showing greater clinical benefit but without significant rest tremor was chosen for the study. The other stimulator was switched off. The voltage for STN stimulation was set at 0.5 V below the threshold for eliciting motor-evoked potentials (MEP) in contralateral FDI muscle by loudspeakers.
direct current spread to the corticospinal tract. This threshold was estimated by averaging 500 epochs of STN DBS triggered EMG responses from resting contralateral FDI muscle.

Transcranial Magnetic Stimulation

A figure of 8-shaped coil (external diameter was 9.5 cm) connected to a Magstim 200 stimulator (Magstim, Whitchurch, Dyfed, United Kingdom) was used to deliver single-pulse TMS over the M1, ipsilateral to STN stimulated. Three different coil orientations were studied. To induce PA current in the brain, the handle of the coil pointed posteriorly and laterally at about 45 deg from the midsagittal line, which induced current perpendicularly to the central sulcus. In this orientation, pyramidal neurons were activated transsynaptically and produced early indirect (II) waves (Kaneko et al. 1996; Sakai et al. 1997; Di Lazzaro et al. 2001). The coil was rotated by 180 deg to induce AP current in the brain, which recruited later 13 waves. LM current was induced by holding the handle of the coil laterally and perpendicularly to the direction used for PA current. The LM direction preferentially activates corticospinal neurons directly and induces the direct (D) wave (Sakai et al. 1997; Hanajima et al. 1998, 2002). The optimal position for activating the contralateral FDI muscle in each current direction was established by moving the coil in 0.5-cm steps around the presumed hand motor area and was marked on the scalp. TMS intensity to produce MEP of 1 mV (MEP_{max}) in the relaxed contralateral FDI muscle was determined separately for all 3 coil orientations.

**Experimental Design**

STN DBS were used as conditioning stimuli and were paired with ipsilateral TMS over M1. STN stimulation artifact recorded with surface electrodes placed over the chest was used to trigger TMS at the following ISIs: 2, 3, 4, 5, 6, 7, 8, 10, and 15 ms; evoked potential (EP) latency, EP +2 ms, EP −2 ms. EP referred to the peak of the middle latency EP (−22 ms) found in Experiment 1 using the same electrode contact (cathode was considered the active contact) in the same patient. These ISIs were selected based on the results of Experiment 1. The trigger pulses for TMS were delivered from a Micro-I410 interface (Cambridge Electronics Design) controlled by Signal Software (v3.07).

TMS was delivered every 6 s. In Experiment 2.1, TMS over ipsilateral M1 was delivered in the AP direction. STN stimuli were delivered at 3 Hz. Experiment 2.2 was the same as Experiment 2.1 except that STN stimuli were delivered at 30 Hz instead of 3 Hz to test the effects of different background stimulation rates. Experiments 2.3 and 2.4 tested the effects of different current directions of TMS. Experiment 2.3 was the same as Experiment 2.1 except that TMS was delivered in the PA direction, whereas Experiment 2.4 used TMS in the LM direction.

In each experimental run, the 12 ISIs between STN stimulation and TMS over M1 were delivered in random order, and each was repeated 10 times. TMS over M1 was adjusted to produce MEPs of −1-mV amplitude without DBS in the corresponding coil direction. Control responses were obtained by single-pulse TMS over M1 (20 trials) at the same intensity for each coil direction with DBS switched off.

**Data Analysis**

For each ISI, MEP amplitudes were expressed as a ratio to the mean amplitude of the control MEP without DBS. Repeated-measures analysis of variance (rmANOVA) was performed for Experiments 2.1, 2.3, and 2.4 with the TMS current direction and ISI as the within-subject factors, and for Experiments 2.1 and 2.2 with the STN DBS frequency and ISI as the within-subject factors. Separate rmANOVA was also conducted for Experiments 2.3 and 2.4 with the TMS current direction and ISI as the within-subject factors, and with the within-subject factors. Separate rmANOVA was also conducted for Experiments 2.3 and 2.4 with the TMS current direction and ISI as the within-subject factors.

**Results**

The clinical profile and STN DBS stimulation parameters of the 8 PD patients are summarized in Table 1.

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### Table 2

<table>
<thead>
<tr>
<th>Patients</th>
<th>Right side</th>
<th>Left side</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 1 2 3</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>P2</td>
<td>SN STN*</td>
<td>dSTN/zi*</td>
</tr>
<tr>
<td>P3</td>
<td>SN SN/STN</td>
<td>STN* Zi*</td>
</tr>
<tr>
<td>P4</td>
<td>SN STN</td>
<td>STN* Thal</td>
</tr>
<tr>
<td>P5</td>
<td>SN STN*</td>
<td>dSTN/zi*</td>
</tr>
<tr>
<td>P6</td>
<td>SN STN*</td>
<td>Zi Thal</td>
</tr>
<tr>
<td>P7</td>
<td>SN STN*</td>
<td>Zi Thal</td>
</tr>
</tbody>
</table>

Note: ZI—zona incerta, dSTN—dorsal subthalamic nucleus, SN—substantia nigra reticulata, Thal—thalamus, STN—subthalamic nucleus, and 0, 1, 2, 3—electrode contacts.

*Clinically effective electrode contacts, MRI for P1 and P8 was not available.

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### Table 3

<table>
<thead>
<tr>
<th>Patients</th>
<th>Right side</th>
<th>Left side</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>dSTN-ZI</td>
<td>Zi-Thal</td>
</tr>
<tr>
<td></td>
<td>Onset (ms)</td>
<td>Peak (ms)</td>
</tr>
<tr>
<td></td>
<td>Onset (ms)</td>
<td>Peak (ms)</td>
</tr>
<tr>
<td>P2</td>
<td>14.2* 22.3*</td>
<td>11.2 19.5</td>
</tr>
<tr>
<td>P3</td>
<td>16.4* 20.5*</td>
<td>14* 20.8*</td>
</tr>
<tr>
<td>P4</td>
<td>NR NR</td>
<td>NR NR</td>
</tr>
<tr>
<td>P5</td>
<td>14.2* 23.3*</td>
<td>11.5 19.5</td>
</tr>
<tr>
<td>P6</td>
<td>13.3* 22.9*</td>
<td>11.5 19.3</td>
</tr>
<tr>
<td>P7</td>
<td>14.4* 21.5*</td>
<td>11.8 19.2</td>
</tr>
<tr>
<td>EC</td>
<td>1+ 2+</td>
<td>2+ 3+</td>
</tr>
<tr>
<td>P1</td>
<td>14.3* 23.5*</td>
<td>12.5 20.4</td>
</tr>
<tr>
<td>P8</td>
<td>NR NR</td>
<td>NR NR</td>
</tr>
</tbody>
</table>

Note: P4 had no electrode contact points in the ZI or thalamus. ZI—zona incerta, dSTN—dorsal STN, EC—electrode contact, NR—no response, Thal—thalamus. P1 and P8 did not have MRI information of electrode contacts.

*Clinically effective contact points.
latencies of 14.2 ± 0.6 ms and peak latencies of 22.7 ± 1.7 ms (Fig. 1B) in 10 of 12 sides studied in 6 patients. However, stimulation of contacts in the STN proper and SNr did not produce these potentials (Fig. 1C,D). The potentials from stimulation of bipolar contacts in ZI-Thal had significantly shorter onset and peak latencies than potentials from stimulation of contacts in dSTN-ZI (P = 0.0007). The medium latency–evoked potentials were elicited from clinically effective contacts in 11 of 16 sides studied in 8 patients. In patient 7, on the left side, the clinically effective contact was in thalamus. Medium-latency potentials were not elicited in patient 4, in whom no contacts were located in the dSTN, ZI, or thalamus (Table 2). This patient had suboptimal clinical improvement with high frequency STN DBS (Table 1).

Negative potentials at ~3 ms were seen in 5 of 16 sides tested. The onset latency was 3.7 ± 0.6 ms (range 3.1–4.7 ms; Fig. 1D). These potentials had a maximum amplitude over the ipsilateral frontal and central leads. They were seen following stimulation of contact points in ZI, STN, and SNr. In 6 of 16 sides tested, a negative potential ~7 ms was seen with an onset latency of 7.4 ± 0.9 ms (range 6.4–8.9 ms; Fig. 1C). These potentials were most prominent in the ipsilateral frontal leads and were elicited following stimulation of the ZI, STN, and SNr. Both ~3 and ~7-ms negative potentials were elicited from clinically effective as well as ineffective contacts in dorsal and ventral STN area. The short latency–evoked potentials in all patients are summarized in Table 4.

**Experiment 2**

**Recording of MEP from STN Stimulation**

Thresholds for eliciting MEP in the contralateral FDI muscle by monopolar stimulation of the clinically effective STN contacts were 4.57 ± 0.97 V (range 3–6 V) on the side selected for TMS study. The MEP latencies following STN stimulation were 19.7 ± 0.99 ms (range 18–21 ms). Figure 2A and B shows the averaged EMG response recorded from the left FDI muscle with right STN stimulation at 3 and 7 V in patient 1. The thresholds and mean MEP latencies following direct STN stimulation in all patients are given in Table 5.

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### Table 4

<table>
<thead>
<tr>
<th>Patient</th>
<th>Right (ms)</th>
<th>Left (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>SNr-STN</td>
<td>dSTN-ZI</td>
</tr>
<tr>
<td>P2</td>
<td>dSTN-ZI</td>
<td>SNr-STN</td>
</tr>
<tr>
<td>P3</td>
<td>dSTN-ZI</td>
<td>SNr-STN</td>
</tr>
<tr>
<td>P4</td>
<td>6.5*</td>
<td>SNr-STN</td>
</tr>
<tr>
<td>P5</td>
<td>3.5 &amp; 11.4</td>
<td>SNr-STN</td>
</tr>
<tr>
<td>P6</td>
<td>3.1 &amp; 7.5</td>
<td>3.8 &amp; 6.9*</td>
</tr>
<tr>
<td>P7</td>
<td>1+ 2–</td>
<td>2 2+ 3+</td>
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<tr>
<td>EC</td>
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<td>7.43*</td>
</tr>
<tr>
<td>P8</td>
<td>6.34</td>
<td>7.43*</td>
</tr>
</tbody>
</table>

Note: The onset latencies of evoked potentials are shown. ZI—zona incerta, dSTN—dorsal subthalamic nucleus, EC—electrode contact, and NR—no response, SNr—substantia nigra reticulata.

*Clinically effective contact points.

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**Figure 1.** Examples of evoked potentials elicited with bipolar stimulation in different locations in the subthalamic area. (A) Medium latency–evoked potential with onset latency of 11.6 ms and peak latency of 20.3 ms following stimulation of electrode contacts in ZI-thalamus in patient 6. The stimulation parameters were left side, 2–3+, 8 V, 60 μs, 10 Hz. Maximum amplitude was observed in C3 and Cz. Short latency negative-evoked potential was also observed with a peak latency of 3.2 ms in bilateral frontal and central leads. (B) Medium latency–evoked potential with onset latency of 13.7 ms and peak latency of 24.5 ms following stimulation of electrode contacts in dSTN-ZI in the patient 7. The stimulation parameters were right side, 1–2+, 7.5 V, 60 μs, 10 Hz. Maximum amplitude was seen in C4 and Cz. Short latency negative-evoked potential was also seen with a peak latency of 4 ms in bilateral frontal and central leads. (C) Short latency–evoked potential with peak latency of 6.4 ms following stimulation of electrode contacts in SNr-STN patient 4 and was observed in bilateral frontal and central leads, more prominent on left side. The stimulation parameters were left side, 1–2+, 8 V, 60 μs, 10 Hz. (D) Short latency–evoked potentials with peak latency of 3.5 and 11.4 ms following stimulation of electrode contacts in SNr-STN in patient 5 and was observed in bilateral frontal and central leads, more prominent on the right side. The stimulation parameters were right side, 0–1+, 8 V, 60 μs, 10 Hz.

**Figure 2.** Examples of MEPs from the contralateral FDI muscle following STN stimulation and TMS over the motor cortex in Patient 1. Each trace represents the average of 20 trials. (A) STN stimulation at 3 V produced no MEP. (B) STN stimulation at 7 V produced MEP with a latency of 20 ms. (C) LM direction TMS over M1 produced MEP with latency of 22 ms. (D) PA direction TMS produced MEP with latency of 23.5 ms. (E) AP direction TMS produced MEP with a latency of 26.5 ms.
However, for Experiment 2.4, the effect of ISI was not significant (Table 5).

There were no significant interactions of TMS output for AP current direction, 43.1 ± 4.1% for PA direction, and 39.4 ± 4.4% for LM direction. The MEP latencies were 25.9 ± 1.0 ms for AP, 23.2 ± 1 ms for PA, and 21.9 ± 1.4 ms for LM direction. Figure 2 shows the MEP latencies following TMS with LM, PA, and AP current directions in Patient 1. TMS intensities used and the MEP latencies following M1 TMS in all patients are given in Table 5.

**Table 5**

<table>
<thead>
<tr>
<th>Patient</th>
<th>STN stimulation (V)</th>
<th>STN threshold (V)</th>
<th>STN stimulation setting (Exp 2)</th>
<th>TMS intensity (% of output)</th>
<th>Mean MEP latencies (ms)</th>
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<tbody>
<tr>
<td></td>
<td>R</td>
<td>L</td>
<td></td>
<td>AP</td>
<td>PA</td>
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<td>5%</td>
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</table>

Note: Exp 1—Experiment 1; Exp 2—Experiment 2; R—right side, L—left side; STN threshold—lowest stimulation voltage that evoked MEP from the contralateral FDI muscle; TMS intensity—intensity of TMS required to evoke 1 mV MEP in the contralateral FDI muscle; AP—anterior-posterior direction of TMS; PA—posterior-anterior direction of TMS; LM—lateral-medial direction of TMS; and Data were not available for P7 as TMS study was not performed due to worsening of disease.

**Discussion**

STN stimulation at 10 Hz produced evoked potentials recorded from the scalp with onset latencies at about 3, 7, and 13 ms (peak latencies of about 22 ms). Following STN stimulation, increased MEP amplitude was observed after 2-5 and 15–25 ms with TMS in AP and PA current directions but not with TMS in the LM direction over the ipsilateral motor cortex.

**Short Latency–Evoked Potentials from STN Stimulation**

We obtained short latency–evoked potential with onset latencies around 3 and 7 ms following STN stimulation from about one-third of the DBS contacts studied. The evoked potentials were most prominent in the ipsilateral frontal and central areas, consistent with the known anatomical projection of the basal ganglia. Previous studies have reported similar short latency–evoked potentials at 3, 5, and 8 ms in about two-thirds of the sides tested. Based on the short chronaxie and refractory period, these potentials likely arose from stimulation of myelinated axons (Ashby et al. 2001; Baker et al. 2002). One study found that the contacts that evoked short-latency potentials were often located in the ventral STN but could be located in the dorsal STN as well (Ashby et al. 2001). This is consistent with our findings.

**Medium Latency–Evoked Potentials from STN Stimulation**

We found that the most consistent response was a medium latency–evoked potential with an average onset latency of 14 ms and peak latency of 22 ms. It occurred only with stimulation of dorsal STN contact points near the ZI and was most prominent over the ipsilateral central region. This is similar to the findings of previous studies (MacKinnon et al. 2005; Eusebio et al. 2009), although postoperative MRI contact localization was not reported. In our study, the contacts that produced the medium latency–evoked potential were also the contacts that produced clinical benefit with high-frequency stimulation. However, MacKinnon et al. (2005) reported that the contacts used for clinical benefit were often ventral to the contacts that produced the largest medium latency–evoked potentials. The topography of potentials evoked by stimulation through clinically used contacts and contacts with largest medium latency–evoked potential were often different (MacKinnon et al. 2005). The different findings may be because we used electrodes with longer distance between contacts (Medtronic 3387) than those used by MacKinnon et al. (2005) (Medtronic 3389). Moreover, the selection of the clinically...
used contacts not only depends on clinically efficacy but also incorporates the need to avoid side effects. The monopolar stimulation montage used for clinical benefit also produced a larger stimulation volume than the bipolar montage used for the evoked potential studies. Therefore, it is likely that the circuits involved in medium latency-evoked potentials are also activated by the parameters used for chronic DBS. This is consistent with findings of Eusebio et al. (2009) that stimulation of the contacts used for clinical benefits also consistently produced this potential. Our results are similar to recent reports showing that 95% of clinically effective contact points for STN DBS in PD are located near the dorsal border of the STN (Godinho et al. 2006) and structures adjacent to the STN such as the ZI and Forel’s field H2 could mediate some of the clinical benefit from STN DBS (Hamel et al. 2003; Benazzouz et al. 2004).

Medium latency-evoked responses have been reported following Gpi and ventrolateral thalamic stimulation. Gpi stimulation produced an evoked potential with a peak latency of 26.6 ± 1.6 ms (onset latencies were 10.9 ± 0.77 ms; Tisch et al. 2008), whereas ventrolateral thalamic stimulation produced a peak latency of 8–12 ms (onset latencies 4–6 ms; Nishimoto and Matsumoto 1970). The evoked potentials were similar from all 3 sites and were distributed mainly over the ipsilateral hemisphere, maximum centrally. The finding that similar evoked potentials are elicited following stimulation of dorsal STN, Gpi, and ventrolateral thalamus suggest that the basal ganglia thalamocortical circuit are involved, but further work is needed to examine the pathways involved. Interestingly, the medium latency-evoked potentials are enhanced with STN DBS at 20 Hz compared with lower or higher frequencies, possibly related to a resonance frequency of the subthalamo-cortical circuit (Eusebio et al. 2009).

**MEP Facilitation Following STN DBS**

MEP facilitation with AP and PA TMS was observed at 2–5 ms following STN stimulation. These findings suggest STN stimulation increases cortical excitability at short latencies. This is similar to a previous study in which MEP facilitation was observed at 3 ms with AP TMS (Hanajima et al. 2004). However, the clinically effective contacts were not known in that study, whereas we used the clinically effective contacts. In addition, cortical excitability was examined for only 10 ms after DBS. TMS studies that examined cortical excitability at medium...
latency-evoked potentials have not been reported and we found cortical facilitation following STN stimulation at 15–25 ms. Our finding suggests the interaction between STN and motor cortex at medium latencies (15–25 ms) is facilitatory.

We studied patients in the on-medication state because our study was lengthy and DBS was switched to ineffective stimulation rates or switched off during the study. Many of our patients with advanced PD did not tolerate off medication and off stimulation for long periods. We also avoided increased tremor and difficulties in relaxation of muscles in the off-medication state that could have affected our study. However, the clinical effects of STN DBS is greater in the off-medication than in the on-medication state (Deuschl et al. 2006). Therefore, we may have potentially underestimated the effects on STN DBS on cortical excitability.

Several previous studies found that high-frequency STN DBS increased motor cortical inhibition but had no effect on motor threshold or MEP amplitude (Cunic et al. 2002; Dauper et al. 2002; Pierantozi et al. 2002). This is likely because, in these studies, TMS was not time locked to STN DBS and changes in motor cortex excitability only occur at specific time intervals after STN DBS.

It is not possible to study directly cortical effects time locked to clinically effective higher frequency DBS because of the stimulus artifacts and the short time between pulses (~6 ms for 180 Hz). However, we examined STN DBS at 3 Hz (1 pulse every 333 ms) and 30 Hz (1 pulse every 33 ms) and found virtually identical cortical facilitatory effects (Fig. 3A,B). Thus, the facilitatory effects we observed are likely due to STN DBS pulse immediately preceding the TMS rather than the cumulative effects of preceding pulses. High-frequency stimulation likely influences these circuits, but it is not known whether they are activated in the same manner and they may even be inhibited. Previous studies demonstrated that low-frequency STN stimulation (~20 Hz) may exacerbate PD symptoms, especially bradykinesia (Eusebio et al. 2008). However, the effects are subtle and only studies in “off” medication state have been reported. It is possible that at low frequencies, cortical activation may augment pathological oscillations in the basal ganglia-thalamo-cortical network.

**Site of MEP Facilitation Following STN Stimulation**

The neuronal populations activated by TMS depend on the direction of induced currents in brain. AP TMS leads to the late I3 wave, PA TMS leads to the I1 wave, and LM TMS preferentially evokes the earliest D wave (Kaneko et al. 1996; Sakai et al. 1997; Di Lazzaro et al. 2001). As a result, the MEP latencies following AP TMS are ~4.5 ms and PA TMS ~1.5 ms longer than LM TMS, and this is consistent with our findings (Table 5). Therefore, AP TMS and PA TMS activate corticospinal neurons located in layer V of the motor cortex transsynaptically through interneurons and are sensitive to changes in cortical excitability. In contrast, LM TMS directly activates corticospinal axons and is not sensitive to changes in cortical excitability. We observed MEP facilitation following STN stimulation with both AP and PA TMS but not with LM TMS (Fig. 3). These findings suggest that MEP facilitation occurs at the cortical level. Following STN stimulation, significant facilitation was observed only at 2–5 and 15–25 ms with TMS at AP and PA current directions, suggesting that facilitatory interactions between STN and interneurons in the motor cortex responsible for generating the I1 and I3 waves occur at these specific intervals that coincided with the peaks of the evoked potentials. Some previous studies reported that the MEP onset latencies after TMS over the M1 were shorter after DBS surgery in the resting state. They postulated that TMS induced currents in scalp leads underneath the TMS coil leading to induced currents at the DBS electrodes that activated the corticospinal tract (Kuhn et al. 2002; Hidding et al. 2006). However, in our study, the MEP latencies following direct stimulation of STN were significantly shorter than those produced by TMS (Fig. 2), suggesting that in our patients TMS did not cause activation of corticospinal tract by inducing current in the DBS leads. Average MEP latency following STN stimulation was 19.7 ms in our study, which is similar to the results obtained in previous studies (Ashby et al. 1999; Costa et al. 2007). The different MEP latencies with different current directions of TMS also make it unlikely that MEP from TMS can be attributed to induction of currents at the STN electrodes. Because we used subthreshold intensities for STN stimulation, it is unlikely that cortical activation at short latencies was due to the direct effects of the stimuli on corticospinal fibers. However, the possibility that fibers were partially depolarized and became facilitated with a subsequent stimulus cannot be completely excluded. Previous studies found TMS to be safe in patients with implanted STN DBS electrodes (Kumar et al. 1999; Cunic et al. 2002; Dauper et al. 2002; Pierantozi et al. 2002), and the study was conducted in accordance with the guidelines published by the Safety of TMS consensus group (Rossi et al. 2009).

**Possible Pathways for Evoked Potentials and Cortical Facilitation**

Because we used voltage subthreshold for eliciting corticospinal effects to stimulate the STN, it is unlikely that our results are due to antidromic activation of the corticospinal tract to stimulate the motor cortex or orthodromic stimulation to activate the contralateral FDI muscle. A previous study (Hanajima et al. 2004) showed the early cortical facilitation at ~3 ms with STN stimulation below the active motor threshold for corticospinal tract activation. Because inhibition rather than facilitation of EMG activity was observed at ~22 ms after stimulation of corticospinal tract near the STN (Ashby et al. 1999; Costa et al. 2007), subthreshold corticospinal activation cannot account for the evoked potential or MEP facilitation at medium latencies.

Evoked potentials and cortical facilitation provide information regarding the STN-cortical interaction and the mechanism of action of STN DBS. The neurophysiological effects of STN stimulation could be due to activation of axon fibers projecting to STN, activation of efferent fibers projecting from STN, inhibition of neurons within STN, or activation of structures adjacent to STN (McIntyre, Mori, et al. 2004; McIntyre, Savasta, et al. 2004; McIntyre, Savasta, Walter, et al. 2004; Valls-Sole et al. 2008). We will consider these possibilities separately.

**Antidromic Activation of Cortico-Subthalamic Fibers**

Direct projections from the motor cortex, the supplementary motor area, and the premotor cortex to the STN have been reported in monkeys and rats (Kunzle 1978; Monakow et al. 1978; Hazrati et al. 1995; Nambu et al. 1996; Inase et al. 1999). Electrical stimuli are more likely to activate axons than cell
bodies, and the effects obtained with low-intensity stimulation are usually due to activation of axons in long tracts in the vicinity of the electrode (Nowak and Bullier 1998; Ashby et al. 1999). The short latency–evoked potentials and cortical facilitation (~3 ms) observed in our study are most likely due to antidromic stimulation of cortical axons projecting to STN. This is supported by short-latency (2–4 ms) facilitation in STN observed following cortical stimulation in primates (Fujimoto and Kita 1993; Nambu et al. 2000). In addition, intracellular recording in rats revealed antidromic spiking of neurons in deep cortical layers following STN DBS (Maurice, Deniau, Glowinski, and Thierry, 1998; Maurice, Deniau, Menetrey, et al. 1998; Li et al. 2007; Dejean et al. 2009).

Activation of Subthalamo-Cortical Pathway
A subthalmo-cortical pathway has been described in the rat (Degos et al. 2008). Orthodromic activation of this pathway is possible, but we consider it less likely as it projects mainly to the orofacial part of the motor cortex (Degos et al. 2008).

Activation of Pallidosubthalamic Fibers and Subthalamicoral Fibers
Activation of GABAergic GPe fibers projecting to the STN can inhibit the STN (Hashimoto 2000). Similarly, activation of glutaminergic STN projection fibers to GPe can stimulate GPe, which can in turn inhibit STN (Filali et al. 2004). Inhibition of the STN leads to decreased activation of GABAergic GPi efferents, which results in increased thalamocortical activity (Alexander et al. 1990; DeLong 1990). The latencies for these pathways are likely more than 6 ms and may explain the 7 ms evoked potential observed in some patients in our study. Activation of STN fibers projecting to GPi can increase GABAergic output to the thalamus thereby decreasing thalamocortical facilitatory projection (Alexander et al. 1990; DeLong 1990). This pathway can lead to decreased cortical facilitation, but we did not find cortical inhibition following STN stimulation. However, rebound bursting of thalamic neurons is a potential mechanism (see below).

Activation of Neurons within STN
Because we used low-frequency rather than high-frequency stimulation, inhibition of STN neurons observed with high-frequency (100–300 Hz) stimulation cannot explain our results (Filali et al. 2004). Activation of STN neurons would have similar effects to activating STN fibers projecting to GPi.

Activation of Structures Adjacent to STN
STN is surrounded by dense bundles of myelinated fibers (Yelnik and Percheron 1979). Forel’s field H2 and ZI lies along the dorsal border of STN and separates it from ventral thalamus (Schaltenbrand et al. 1971; Parent and Hazrati 1995). Forel’s field H2 contains pallidothalamic GABAergic fibers that inhibit ventral anterior thalamus (Parent et al. 2000). The ZI has rich GABAergic projections to ventrolateral thalamic nucleus (Bartho et al. 2002). Stimulation of dorsal STN contacts can activate adjacent pallidothalamic fibers and ZI (Godinho et al. 2006). Excessive GABAergic inhibition may cause hyperpolarization of thalamocortical neurons followed by rebound burst firing (Jahnsen and Llinas 1984a, 1984b). Because the medium latency–evoked potential seen with peak latency around 22 ms (mean onset 15 ms) was observed with stimulation of contacts located in the dorsal STN and ZI area (Table 3), this potential could be explained by activation of this pathway. Studies using GPi and ventral lateral thalamic stimulation have elicited similar medium latency–evoked potentials (Nishimoto and Matsumoto 1970; Tisch et al. 2008). Moreover, a TMS study showed that thalamic DBS increases motor cortex excitability (Molnar et al. 2005). These findings support our hypothesis that either pallidothalamic fibers or ZI stimulation may be responsible for medium latency–evoked potentials.

Possible Relationship between MEP Facilitation and Clinical Effects of STN DBS
The sensory-motor region of the STN is located in the dorsal STN, which receives afferent input from the supplementary motor area, premotor cortex, motor cortex, and motor portions of pallidum and centromedian nucleus of thalamus (Monakow et al. 1978; Nambu et al. 1996; Hamani et al. 2004).

Several recent animal studies provided direct evidence that STN DBS activates the cortex, and this may be related to the therapeutic effect of STN DBS. High-frequency STN DBS in rats produced short-latency (~2 ms) antidromic spiking of deep-layer cortical neurons, which dampened the oscillation of local field potentials in cortex. The amplitude of antidromic activation correlated with suppression of slow waves and beta band activity during STN DBS (Li et al. 2007). Moreover, in awake animals, the amplitude of this short-latency cortical antidromic activation from STN DBS correlated with the degree of improvement in akinesia produced by dopaminergic blockade (Dejean et al. 2009). An elegant study used opticogenetic and solid-state optics to show that stimulation of inhibition of STN neurons failed to improve parkinsonian rats but stimulation of afferent fibers of the STN produced marked improvement in motor signs (Gradinaru et al. 2009). Afferent fibers stimulated were the cortico-STN fibers rather than the GABAergic projections to the STN. Importantly, the stimulation of STN afferents antidromically activated layer V neurons in the M1 and selective high-frequency stimulation of layer V in the M1 also ameliorated parkinsonian symptoms (Gradinaru et al. 2009). Because MEPs generated by TMS are due to activation of corticospinal neurons in layer V of the M1, our findings are consistent STN DBS activating layer V neurons in the M1 at specific intervals. Therefore, the short latency–evoked potential and excitatory STN–motor cortical interaction at ~3 ms demonstrated in our study could be related to antidromic activation of cortical circuits and desynchronization of abnormal noisy signals in PD. Previous studies showed that this potential can follow stimulation rates up to 100 Hz (Ashby et al. 2001; Baker et al. 2002) and may therefore be activated with high-frequency DBS used in the clinical setting.

We found medium latency STN–motor cortical facilitation following stimulation of clinically effective dorsal STN area contacts. This could be also due to activation of ZI and/or pallidothalamic fibers that lies close to the dorsal border of STN (Godinho et al. 2006). One study suggested that high-frequency stimulation of the ZI produced greater improvement in contralateral motor scores in PD patients than stimulation of the STN itself (Plaha et al. 2006). It has been postulated that in PD, ZI receives abnormal synchronized oscillations from basal ganglia output nuclei and motor cortex (Merello et al. 2006). The ZI is in a position to transmit these abnormal oscillations.
via its efferent connections to the thalamic nuclei (centromedian/parafascicular and ventral intermedius), the brainstem locomotor center and back to the basal ganglia output nuclei (Gpi and Snr) and the cortex (Foffani et al. 2006). High-frequency stimulation of caudal ZI could potentially override these abnormal oscillations and lead to more profound effects in controlling PD symptoms than stimulation of the STN, whose efferents are predominantly confined to the basal ganglia output nuclei (Plaha et al. 2006).

Conclusions
STN DBS led to medium latency–evoked potentials observed mainly following stimulation of clinically effective contacts located near dSTN border. Short latency–evoked potentials were elicited from stimulation of contacts in both dorsal and ventral STN areas. STN stimulation using contacts that produced clinical benefit increased the excitability of the motor cortex at specific short and medium latencies. This is likely due to short-latency antidromic stimulation of cortico-subthalamic projections and the medium-latency facilitatory basal ganglia–thalamo–cortical interactions following dSTN stimulation. These findings support animal studies (Gradinaru et al. 2009) suggesting that cortical activation could be one of the mechanisms mediating the clinical effects of STN DBS in PD.

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Notes
Conflict of Interest: Dr Hamani acted as a consultant for St Jude Medical. Dr Moro received honorarium from Medtronic Inc for lecturing and consulting services. Dr Lozano acted as a consultant for Medtronic Inc. Dr Chen received research grant and acted as a consultant for Medtronic Inc.

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