Single pulse stimulation of the human subthalamic nucleus facilitates the motor cortex at short intervals

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ABSTRACT

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an effective treatment for Parkinson’s disease (PD). The mechanism is poorly understood. High frequency STN DBS has been reported to affect motor cortex excitability in a complex way but the timing between STN stimuli and changes in motor cortical (M1) excitability has not been investigated. We examined the time course of changes in motor cortical excitability following single pulse STN DBS. We studied 14 PD patients with implanted DBS electrodes in the STN, two patients with electrodes in internal globus pallidus (GPi) and one patient with an electrode in the sensory thalamus. Transcranial magnetic stimulation (TMS) was delivered to the M1 ipsilateral to the DBS with induced currents either in the anterior-posterior direction in the brain to evoke indirect (I) waves, or in the lateral-medial direction to activate corticospinal axons directly. Single pulse stimulation through the DBS contacts preceded the TMS by 0 to 10 ms. Surface EMG was recorded from the contralateral first dorsal interosseous muscle. Three milliseconds after STN stimulation, the motor evoked potential (MEP) amplitudes produced by anterior-posterior current were significantly larger than control responses, while the responses to lateral-medial currents were unchanged. Similar facilitation also occurred after GPi stimulation, but not with thalamic stimulation. Single pulse STN stimulation facilitates the M1 at short latencies. The possible mechanisms include antidromic excitation of the cortico-STN fibers or transmission through the basal ganglia-thalamocortical pathway.
INTRODUCTION

High frequency stimulation of the subthalamic nucleus (STN) can alleviate the symptoms of Parkinson’s disease (PD) (Limousin et al. 1998; Krack et al. 2003; Kumar et al. 1998, Molinuevo et al. 2000), but the mechanism of action of deep brain stimulation (DBS) remains poorly understood. Although it has been hypothesized that high frequency stimulation decreases the effective output of the STN, some studies found that DBS increases the activities of the STN (Hershey et al. 2003) or results in increased glutamate release in the globus pallidus suggesting an excitatory effect (Windel et al. 2003). Single STN stimuli produce a series of cortical evoked potentials in the frontal and central regions, beginning at latencies as short as 2 to 3 ms (Ashby et al., 2001; Baker et al., 2002). The short latency potentials have refractory periods in the order of 0.5 to 2 ms and therefore can be carried at high frequencies (Ashby et al., 2001; Baker et al., 2002). Whether these potentials are associated with changes in cortical excitability is not known. The motor cortex plays a pivotal role in mediating voluntary movement. PET studies showed changes in blood flow in the motor cortex with STN stimulation (Ceballos-Bauman et al. 1999, Hershey et al. 2003).

Transcranial magnetic stimulation (TMS) studies also have detected changes in motor cortical excitability during DBS. High frequency STN stimulation in PD patients was found to normalize short-interval intracortical inhibition, but did not change motor evoked potential (MEP) amplitude or the motor threshold (Cunic et al. 2002, Pierantozzi et al. 2002). High frequency internal globus pallidus (GPI) stimulation in PD patients shortened the silent period, but did not change MEP amplitude or the motor threshold.
(Chen et al 2001). However, in patients with dystonia high frequency GPi stimulation was reported to reduce motor threshold and increase MEP amplitude (Kühn et al 2003). In these studies, TMS was not time locked to the DBS pulses. Ashby et al. (1999) reported that single pulse STN DBS reduced motor cortex excitability 30 to 80 ms later. However, the time between clinically effective STN stimuli is between 5 and 8 ms (130 to 185 Hz) and the effect of STN stimulus on the motor cortex at interstimulus intervals (ISIs) less than 20 ms has not been investigated. We studied how STN stimulation affects motor cortex excitability at short ISIs.
METHODS

Subjects

The subjects were 14 patients with PD (37 - 63 years old, 7 men and 7 women) undergoing chronic bilateral STN DBS. For comparison, one patient with pain who had an electrode in the sensory thalamus (a 40 year old man) and two patients with dystonia (37 and 66 years old, 1 man and 1 woman) who had electrodes in internal globus pallidus (GPI) were investigated. The patients remained on their usual medications during the study. All patients gave free and informed consent to procedures approved by the University Health Network Research Ethics Board.

Surgical procedures

The targets were identified by MRI and located stereotactically (Davis et al. 1998, Tasker 1998). After the target was determined by stimulating and recording with microelectrodes, a quadripolar DBS electrode (model 3387, Medtronic, USA) was implanted. The DBS electrode had four contacts spaced at a distance of 1.5 mm, and named 0, 1, 2, 3 from the tip of the electrode. For 3 to 7 days after this procedure, the wires from each of the four contacts were led out though the scalp and could be connected to external stimulators. At a subsequent second surgery, the leads were connected to an implanted programmable stimulator.
Magnetic resonance imaging (MRI)

Twelve patients had postoperative 3D MRI of the brain to identify the location of each DBS contact using a high-resolution T2-weighted fast spin echo sequence developed to reduce magnetic susceptibility artifacts and minimize noise (Saint-Cyr et al. 2002). The position of the contacts in relation to the midpoint of the anterior commissure (AC) and posterior commissure (PC) (midcomissural point, MCP) and the vertical distance from the AC-PC line was determined.

EMG recording

Surface electromyogram (EMG) was recorded from the first dorsal interosseous (FDI) muscles with 9mm Ag-AgCl surface cup electrodes. The active electrode was placed over the muscle belly and the reference electrode over the metacarpophalangeal joint of the index finger. Responses were amplified (2004F Signal conditioner, Intronix Technologies Corporation) with a band pass of 2 Hz to 1 kHz and digitized at 2 kHz. During the experiments the subjects maintained slight contraction of the FDI (10 - 20 % of the maximum voluntary contraction) with the aid of an oscilloscope monitor.

Stimulation through the DBS electrodes

Stimuli were generated with an isolated, constant-current stimulator (model A360D-B; World Precision Instruments, Sarasota, FL., USA). Pulse widths of 100 µs and currents up to 10 mA were used (usually below 5 mA).
We first determined the contact pair to be used for TMS studies. For STN, we tried to choose the contact pair located closest to the STN and to avoid direct corticospinal activation. We looked first for short-latency motor effects by delivering single stimuli (~1 Hz) through adjacent pairs of STN contacts (1+0-, 0+1-, 1+2-, 2+3-) while averaging 100 trials of rectified EMG from the active contralateral FDI. Contact 0 was the most inferior and most posterior electrode. Short latency facilitation, presumed to be due to current spread to the corticospinal pathway, usually occurs with the lowest threshold at the lowest pair of contacts (1+0-) (Ashby et al 1999). The threshold for this effect was noted for each contact pair. For TMS studies, we used the contact pair just above the highest pair that produced short latency EMG response (Fig 1). In most cases, the pair was 1+2-. In each patient, we confirmed that the conditioning stimulus intensity used did not activate the pyramidal tract. In the two patients with DBS electrodes in GPi, a similar approach was used. In one patient with thalamic DBS electrodes, we chose the pair of contacts from which we recorded the largest amplitude of sensory evoked potentials in response to contralateral median nerve stimulation in order to study the effect of stimulation on the sensory thalamus. This pair of contact is likely located closest to the sensory tract (Hanajima et al. 2003).

The intensity through the DBS contacts for the TMS studies was set just below the threshold for current spread to the corticospinal pathway (Fig. 1).

**Magnetic stimulation**

Transcranial magnetic stimulation (TMS) was applied to the primary motor cortex
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Ipsilateral to DBS electrodes with a 7 cm figure-of-eight shaped coil connected to a Magstim 200 stimulator (The Magstim Company, UK). We placed the coil to induce currents in the anterior-posterior (AP) direction in the brain, in order to preferentially generate I3-waves (Sakai et al. 1997; Hanajima et al. 1998; Di Lazzaro 2001). We confirmed that the onset latencies of the motor evoked potentials (MEPs) were 4 - 4.5 ms later than the responses produced by currents induced in a lateral-medial (LM) direction and about 6 ms later than the short latency response evoked by strong stimulation through the lower STN contacts. In order to examine whether the effect occurred at the cortical level, in four patients we also used induced currents in the LM direction in the brain which preferentially induce the direct (D) corticospinal wave by activating the axons of the corticospinal neurons directly (Sakai et al. 1997; Hanajima et al. 1998, Di Lazzaro et al. 1998, 2001).

Deep brain conditioning stimuli (STN, GPi and Thalamus) were followed by the transcranial magnetic stimulation over the primary motor cortex (test stimuli). Interstimulus intervals (ISIs) between 0 to 10 ms were used (0, 1, 2, 3, 4, 5, 6, 8 and 10 ms). The test stimulus intensity was adjusted to evoke responses with approximately 0.5 mV peak-to-peak amplitude in the active contralateral FDI. For each ISI, conditioning stimulus alone and test stimulus alone, 15 to 20 trials were averaged. Because of the restriction of time and patient condition, not all ISIs were tested in all patients (ISI 0 ms, n = 9; 1 ms, n = 11; 2 ms, n = 12; 3 ms, n = 14; 4 and 5 ms, n = 13; 6 ms, n = 7; 8 and 10 ms, n = 5).
Analysis

We calculated the ratio of the amplitude of the conditioned TMS responses to the mean amplitude of the control TMS response (test stimulus alone) for each ISI in each subject. The paired t-test with Bonferroni’s correction for multiple comparisons was used to compare the ratio at each ISI to the test stimulus alone.
RESULTS

The location of the STN DBS cathode contact used for the conditioning stimulus, identified on postoperative MRIs, was between 3 mm anterior and 4 mm posterior to the MCP and between 0 mm and 8 mm below the AC-PC line. These locations were close to the STN.

The optimal contacts for high frequency STN stimulation for improving parkinsonism and avoidance of side effects was not known as the time of the study and were determined in the subsequent stimulator programming period. Most patients used monopolar stimulation (one contact negative, case positive). The negative contacts used in the present study were also the negative contact used for clinical benefit in 10 of the 14 STN patients. In two patients they differed by one contact and in two other patients they differed by two contacts.

Figure 2 shows an example of the effect of STN stimulation on the responses evoked by TMS with the induced current in the AP direction. DBS alone did not elicit any EMG responses in the active contralateral FDI muscle (top). TMS alone produced MEPs of about 0.3 mV (middle). When both stimuli were given at an ISI of 3 ms, the response to TMS was facilitated (bottom).

Figure 3A shows the time course of the effect of STN stimulation on MEP produced by TMS with the induced current in the AP direction for all patients tested. Significant facilitation occurred at an ISI of 3 ms (ISI 3 ms, p = 0.02; ISI 4 ms, p=0.09; paired t-test corrected for multiple comparisons). When the magnetic stimulation was rotated to induced current in the LM direction, no significant facilitation occurred (Figure
Figure 4 shows the effects of the similar conditioning stimuli delivered to the DBS contacts in the GPi (n = 2) and the sensory thalamus (n = 1). The GPi stimulation caused a similar facilitation of the response to the TMS with induced currents in the AP direction at ISIs of 3 – 4 ms. No facilitation occurred with the stimulation of the sensory thalamus, while inhibition occurred at conditioning-test intervals between 4 and 10 ms.
DISCUSSION

Site of MEP facilitation following STN stimulus

The neuronal population activated by TMS depends on the direction of the induced currents. TMS produces a series of descending volleys and they are numbered according to their latencies (I1, I2, I3 etc). We stimulated the motor cortex using AP current which activates corticospinal neurons indirectly through several interneurons in the cortex and preferentially produce I3-waves (Sakai et al. 1997, Hanajima et al. 1998, DiLazzaro et al. 1998, 2001) (Figure 5) because this current direction may be more sensitive than the conventional posterior-anterior current direction (inducing I1-wave) for detecting changes in cortical excitability and some cortical effects are detected only by responses produced by I3-waves (Sakai et al. 1997, Hanajima et al. 1998, DiLazzaro et al. 1998).

The facilitation from STN stimulation occurred with TMS inducing AP currents in the brain but no facilitation occurred with TMS inducing LM currents in the brain, which activates corticospinal axons directly. These finding suggest that the facilitation occurs in the cortex. Similar effects on the motor cortex were evoked by single pulse GPi stimulation. On the other hand, the thalamic stimulation induced inhibition in the motor cortex. This inhibition is may be similar to the suppression of motor cortex excitability by the median nerve stimulation at ISIs of about 20 ms (Delwaide and Olivier 1990, Bertolasi et al 1998, Tokimura et al 2000).

The optimal ISI between STN stimulation and TMS to evoke I3-wave is about 3 ms. When TMS evokes I3-waves, the corticospinal neurons are activated 4 to 4.5 ms
after the stimulus is given, probably through a polysynaptic pathway (Figure 5). If the impulses evoked by the STN stimulation take 2 ms to reach the cortex and allowing 1 ms for synaptic transmission, the most effective conditioning–test interval of 3 ms can be explained by facilitation at the neurons responsible for initiating the I3 response to TMS. If the convergence occurred at other interneurons between the neuron initiating the I3 response and the corticospinal neuron or the corticospinal neuron itself, the input from the conditioning STN stimulus would have up to about 7.5 ms to reach the motor cortex (Figure 5).

Possible mechanism of the facilitation by STN and GPi stimulation

We obtained MEP facilitation with both STN and GPi stimulation. It is possible the underlying disease could affect the results, even though the patients with PD were taking their regular medications. Since the patients were studied shortly after surgery, micro-lesion effect could also affect the findings. Moreover, the patients with STN DBS and GPi DBS had different diseases. Because of this, we cannot directly compare the results with GPi stimulation with those with STN stimulation. Based on these considerations, we suggest the mechanism of the facilitation evoked by the DBS stimulation.

The facilitation could be evoked by pulses of short duration (100 µs), suggesting that it resulted from the activation of large axons rather than small axons or neurons in the STN (Ranck 1975, 1981). Myelinated fibers close to or within the STN are the likely candidates. The duration of the facilitation was brief (1 to 2 ms). This suggested that
there are few synapses between the neuronal elements activated by STN stimulation and the neurons in the motor cortex upon which the convergence occurs. Ashby et al (2001) recorded negative potentials at the scalp at short latencies (3, 5 and 8 ms) following STN stimulation. The short chronaxie and refractory period of these responses suggested that they arose from the activation of large, myelinated fibers. Thus, the cortical facilitation we observed here may be mediated by similar fibers as these short latency evoked potentials.

There are many fiber systems in the region of the STN contacts (Hamani et al. 2004) (Figure 6). The STN projects to the globus pallidus externa (GPe) and GPi, the striatum and the substantia nigra pars compacta. It receives projections from the GPe, the centro-medial thalamus, peduncular pontine nucleus, the substantia nigra pars compacta and from the motor, supplementary motor and premotor cortices. Any or all of these fiber systems could potentially be activated by STN stimulation. Moreover, fibers of passage such as those in the internal capsule, ansa lenticularis or fasciculus lenticularis could be activated.

One possibility is that STN stimulation causes antidromic activation of the cortico-STN facilitatory pathway (A, Figure 6). There are direct projections to the STN from the motor cortex, the supplementary motor area and the premotor cortex in monkeys and rats (Kunzle et al. 1977, Kunzle 1978, Hartman-von Monakow et al 1978; Nambu et al 1996, 1997; Inase et al 1999; Parent and Hazrati 1995). In primates, cortical stimulation results in a strong facilitation of STN neurons (Fujimoto and Kita 1993, Nambu et al 2000). The latency of this facilitation was generally short (2 – 4 ms) (Nambu et al 2000),
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implying that a fast conducting myelinated fiber system was involved. If the cortico-STN system was activated antidromically by STN stimulation, the motor cortex might be excited through collaterals to other cortical neurons. The latency is certainly appropriate. However, this mechanism cannot explain facilitation from GPi stimulation because there is no direct cortico-GPi pathway.

A second possibility is that GPe fibers projecting to the STN are activated by STN stimulation (B, Figure 6). This is known to inhibit STN neurons (Alexander et al. 1990 DeLong 1990). This decreases the activity of inhibitory GPi neurons resulting in increased thalamocortical neuronal activities. This pathway may take longer than 3 ms, but 6 ms or 7.5 ms might be enough for this mechanism. If the GPi stimulation activates the GPe projecting fibers to GPi, a similar mechanism could explain facilitation with GPi stimulation.

A third possibility is that both STN and GPi stimulation activates STN projections to GPi (C, Figure 6). This pathway facilitates GPi neurons which inhibit the thalamus (Alexander et al. 1990; DeLong et al. 1990) and the cortex. The expected findings were opposite to the results reported here. However, if activating the pallido-thalamic pathway or thalamo-cortical pathway also activates inhibitory neurons in the thalamus or the motor cortex, activation of the STN projections to GPi could evoke facilitation of the motor cortex.

A fourth possibility is that the STN stimulation activates STN projection fibers to GPe (D, Figure 6). This pathway facilitates the GPe neurons and caused disinhibition of the thalamocortical pathway. This could increase of motor cortical excitability.
It is also possible that STN or GPi stimulation activated the corticospinal tract (E, Figure 6). The contacts of the DBS for both the STN and the GPi are close to the internal capsule. We used stimulus intensity below the threshold for facilitation of FDI motoneurons and for obvious contraction of other muscles. Since intrinsic hand muscles have stronger corticospinal projections than other muscles, the activation of corticospinal axons is unlikely but cannot be entirely excluded. Antidromic activation of corticospinal fibers might excite cortical cells through collaterals.

It should be noted that the possibilities listed (Figure 6) are not mutually exclusive and may operate concurrently. In addition, STN or GPi stimulation may reset and synchronize the oscillations in the basal ganglia – thalamocortical system, leading to facilitation at certain intervals.

*Differences between single pulse and high frequency STN stimulation*

The likely reason why MEP facilitation by STN stimulation was undetected in previous studies is that the short duration of facilitation was averaged out during continuous stimulation that was not time locked to TMS. Whether the clinical effect of STN DBS is related to facilitation of the motor cortex by the STN stimulation is unclear. For therapeutic benefit, DBS is usually set at frequencies between 130 to 180 Hz, resulting in 5 to 8 ms between stimuli. Therefore, the effect at ISI of 3 ms that we have demonstrated is potentially relevant to the clinical effect of DBS if the same circuits or neural high frequency stimulation. Our findings are consistent with human (Molnar et al. 2004; Perlmutter et al. 2002; Hershey et al. 2003) and animal studies (Hashimoto et al.)
2003; Windels et al. 2003) suggesting that DBS may have an activating effect in the target area.
ACKNOWLEDGEMENTS

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FIGURE LEGENDS

**Figure 1.** EMG responses produced by STN stimulation alone through different pairs of DBS contacts at 5 mA (left) and 6 mA (right) in one patient.

Each trace represents the average of 100 sweeps of rectified EMG recorded with surface electrodes from the voluntarily activated FDI muscle. Single stimuli at 1 Hz were given through adjacent pairs of contralateral STN electrodes (1+0-, 0+1–, 1+2– or 2+3–) at the dotted lines of each sweep. Stimulation through 1+0- and 0+1– produced short latency facilitation of FDI motoneurons probably representing current spread to the corticospinal pathway. With contact pair (1+2–), a small long latency response was elicited with a stimulus intensity of 6 mA (right) but not with an intensity of 5 mA (left). We used this contact pair (1+2-) with an intensity of 5 mA as the conditioning stimuli in this patient.

**Figure 2.** Effect of single pulse STN stimulation on the responses elicited by TMS over the M1 with induced current in the anterior-posterior direction.

Each trace is an average of 20 sweeps of rectified EMG recorded from the active contralateral FDI muscle. The top trace shows the response to STN stimulation alone. The middle trace shows the response to TMS alone (control response). The latency of the response is 23 ms which is compatible with responses evoked by I3-waves. The bottom trace shows the response was larger when the STN stimulation preceded the TMS stimulus by 3 ms.
Figure 3.

A. The time-course of the facilitation of the response to TMS with anterior-posterior current in the brain by a preceding STN stimulus from all 14 patients

The abscissa indicates the interstimulus interval and the ordinate indicate the amplitude ratio STN+TMS/TMS alone. Each point represents the average of the amplitude ratios from all the patients (± SE). The ratio was significantly larger than the control at the 3 ms interstimulus interval (p<0.02).

B. Effect of the STN stimulation on the responses evoked by the transcranial stimulation with induced current in the lateral-medial direction.

The responses evoked by TMS with lateral-medial currents in the brain were not significantly changed at any ISIs.

Figure 4.

Effects of GPi stimulation in two patients (squares) or the sensory thalamus in one patient (triangles) on the responses to TMS with anterior-posterior directed currents

The abscissa and ordinate are the same as those in Figure 3. With GPi stimulation, both patients show facilitation at ISI of 4 ms similar to STN stimulation (squares). There is no facilitation caused by thalamic stimulation around 3 to 5 ms and inhibition occurred between ISIs of 4 and 10 ms (triangles).

Figure 5. Interstimulus intervals for convergence to different neurons in the motor cortex
The diagram illustrates the STN-cortex conduction times necessary to explain convergence on each of the postulated interneurons implicated in the I3 responses. TMS inducing current in the anterior-posterior directions (evoking I3-waves) is postulated to discharge the corticospinal neuron (triangle) indirectly, taking about 4.5 ms in the motor cortex. TMS inducing current in the lateral-medial direction (evoking D-waves) is postulated to directly activate the axons of the corticospinal neurons. An effect observed with the responses produced by I3-waves but not with D-waves likely occurs in the motor cortex.

Although the optimal interstimulus intervals between STN stimulation and motor cortical stimulation is about 3 ms (Figure 3A), the time available for the STN stimulus to reach the motor cortex thorough some pathways (either direct or indirect) depends on where the interaction between STN stimulation and TMS occurs.

If the effect occurred at the interneuron that produces the I3-wave, STN stimulation should take about 3 ms to reach the motor cortex. If the corticospinal neuron was directly affected by the conditioning stimulus, the STN stimulus could take up to 7.5 ms to reach the motor cortex. If the interaction occurred at interneurons between the I3 neuron and the corticospinal neuron, the latency of the facilitation after the STN stimulation could be between 3 to 7.5 ms.

**Figure 6.** Possible mechanisms of facilitation of the motor cortex by STN and GPi stimulation
Solid lines indicate facilitatory pathways and dotted lines indicate inhibitory pathways.
The arrows indicate possible sites stimulated.
A. STN stimulation causes antidromic activation of the cortico - STN facilitatory pathway.
B. STN stimulation activates the GPe - STN inhibitory pathway and GPi stimulation activates the GPe - GPi inhibitory pathway.
C. STN stimulation activates the STN - GPi pathway.
D. STN stimulation activates the STN - GPe pathway
E. STN and GPi stimulation activates the corticospinal tract.
In the table, the up arrow indicates facilitation and the down arrow indicates inhibition.
Figure 2

- **STN alone**
- **TMS alone**
- **STN+TMS ISI=3ms**

STN stim

TMS over M1

1mV

20ms
Figure 4

Intervals between deep nuclear stimulus and TMS (ms)

Size ratio

(Gpi or Sensory thalamus + TMS/TMS alone)

Intervals between deep nuclear stimulus and TMS (ms)
Figure 5

AP TMS for I3-wave

Primary Motor Cortex

Corticospinal neuron

LM TMS for D-wave

STN stim

3 ms

7.5 ms
Figure 6

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