Motor responses of muscles supplied by cranial nerves to subthalamic nucleus deep brain stimuli

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The distribution of human corticobulbar motor excitatory and inhibitory output is not fully understood. In particular, it is unclear whether the pattern of innervation is the same for upper and lower facial muscles, and what is the motor cortical area giving rise to such innervation. We used electrodes implanted in the subthalamic nucleus (STN) in patients with Parkinson’s disease to activate motor tracts at a subcortical level. We examined the excitatory and inhibitory effects of unilateral single STN deep brain stimulation (sSTN-DBS) in 14 patients by taking recordings from facial, cervical and upper limb muscles on both sides. We measured the latency and amplitude of the motor-evoked potentials (MEPs), and the latency and duration of the silent periods, and compared ipsilateral with contralateral responses and responses obtained in different muscles. Unilateral sSTN-DBS induced strictly contralateral MEPs in the trapezius, deltoid, biceps and thenar muscles. The same stimulus always induced bilateral MEPs in the orbicularis oculi, orbicularis oris, masseter and sternocleidomastoid at a mean latency in the range 6.0–9.1 ms. MEP latencies in the orbicularis oculi and orbicularis oris were significantly longer than in the masseter and sternocleidomastoid (P < 0.01). A short latency small action potential was recorded in the ipsilateral orbicularis oculi that was likely generated by activation of extraocular muscles. During sustained voluntary muscle contraction, a silent period was recorded at similar onset latency on both sides. This period was significantly shorter in orbicularis oculi than in masseter, and in the ipsilateral side for both muscles (P < 0.01). sSTN-DBS is able to activate the descending projecting fibres in the corticobulbar tract eliciting bilateral MEPs and silent periods in facial and cranial muscles. This suggests that fibres to both ipsi- and contralateral motor nuclei descend together at the level of the STN. These findings are relevant in the discussion of the innervation of upper and lower facial muscles in humans and in the interpretation of previous results obtained with transcranial cortical stimulation.

Keywords: cranial nerves; facial muscles; pyramidal tracts; subthalamic nucleus; deep brain stimulation

Abbreviations: MEP = motor-evoked potential; M1 = primary motor cortex; RT = resting motor threshold; STN = subthalamic nucleus; sSTN-DBS = single STN deep brain stimulation; TMS = transcranial magnetic stimulation


Introduction

Since the pioneer work of Penfield and Jasper (1954), which explored systematically the human brain with electrical stimulation during surgery to draw the well-known motor homunculus, the cortical motor representation of muscles of the human body has been a subject of great interest. The development of methods to activate transcranially the motor cortex (Merton and Morton, 1980; Barker et al., 1985) has provided the possibility to assess the cortical representation of muscles in relatively large numbers of subjects. However, our knowledge of the distribution of cortical innervation to muscles innervated by cranial nerves is less accurate than for limb muscles. This may be due to various drawbacks of cortical stimulation such as the generation of large artefacts because of the proximity between stimuli and recording...
electrodes, and the superimposition of responses generated by the stimulation of trigeminal nerve terminals under the stimulating electrode or the cranial nerves in the posterior fossa. Therefore, issues such as the bilaterality of facial and cranial muscle innervation, the site of origin of cortical inputs to facial motoneurons or the existence of a silent period in facial muscles are still a matter of debate.

The classical notion that there is bilateral innervation of cranial nerve nuclei (Kuypers, 1958; Jenny and Saper, 1987; Lepore, 1987) has been confirmed with transcranial magnetic stimulation (TMS) studies of the motor cortex by recording bilateral motor-evoked potentials (MEPs) in muscles supplied by cranial nerves (Benecke et al., 1988; Cruccu et al., 1990a; Benecke and Meyer, 1991; Berardelli et al., 1991; Meyer et al., 1994; Urban et al., 1997; Curra et al., 2000; Desiato et al., 2002; Triggs et al., 2005). However, this is not a general finding since some studies have failed to show bilateral responses in some muscles (Berardelli et al., 1991; Cocito et al., 1993a, b; Odergren and Rimpilainen et al., 1996; Kobayashi et al., 2001). Recent studies show contradictory results regarding the projections of the primary motor cortex (M1) to upper and lower facial muscles (Kobayashi et al., 2001; Sohn et al., 2004; Paradiso et al., 2005; Yildiz et al., 2005). Furthermore, the origin and characteristics of silent periods elicited by TMS in facial and trigeminal muscles are not completely clear. While there are arguments to suggest that it originates solely from cortical inhibitory mechanisms (Leis et al., 1993; Cruccu et al., 1997; Curra et al., 2000), there are also findings that favour a subcortical contribution (Werhahn et al., 1995).

The implantation of electrodes for deep brain stimulation with therapeutic purposes has provided a unique opportunity to carry out physiological studies about the function of deep brain structures in conscious humans, and in particular about central motor pathways (Ashby and Rothwell, 2000). Studies that applied single stimuli through the DBS electrodes inserted either in the ventral intermedial nucleus of the thalamus, the globus pallidus internus, or the subthalamic nucleus (STN) were able to induce an MEP in the contralateral hand muscles, considered to reflect the spread of the electrical current to the neighbouring corticospinal tract (Strafella et al., 1997; Ashby et al., 1999; Hanajima et al., 2004; Khun et al., 2004). In some of those studies, the generation of silent periods in limb muscles has been at least in part attributed to activation of thalamocortical fibres (Strafella et al., 1997; Ashby et al., 1999; Compta et al., 2006).

In this study we used single electrical stimuli applied through the electrodes implanted for single STN deep brain stimulation (sSTN-DBS) in patients with Parkinson’s disease to investigate the characteristics of the MEPs and silent periods induced in muscles supplied by cranial nerves. We considered that such a study could shed light on the distribution of the corticobulbar tract projections to facial and other cranial muscles, and on the physiological mechanisms of the silent period induced in facial and trigeminal muscles during voluntary contraction.

Material and methods

Patients

We studied 14 patients with advanced Parkinson’s disease: 8 males and 6 females, with a mean age of 63.2 ± 7.3 years (range, 51–76), mean Hoehn and Yahr stage of 3.3 ± 0.2 (range, 3–4) and mean disease duration of 14 ± 9 years (range, 8–25). DBS electrodes for long-term stimulation (Medtronic, 3389; Minnesota, USA) were implanted in the STN under stereotactic guidance. The electrodes were left externalized for up to 3 days before programmable pulse generators were implanted in the subclavicular area. Patients were examined during that period and in overnight ‘off medication’ condition. All patients gave their written informed consent for the study, which was approved by the Ethics Committee of our institution.

Surgical placement of electrodes

STN-DBS electrodes were inserted in a postero-medial-caudal direction under neurophysiological guidance targeting the STN (Molinuovo et al., 2003). The tip of the electrode was placed just before the substantia nigra, which separates the STN from the cerebral peduncle. The decision on electrode placement was made after on-site evaluation of the effects of stimulation. At this site stimulation induced optimal therapeutic effects and minimum undesired effects. If activation of the corticospinal tract was noticed, we slightly pulled the electrode backwards, assuming that it could have been activating the cerebral peduncle. If pulling was not effective in suppressing corticospinal tract activation, we considered that the effect was due to activation of tracts of the internal capsule and the electrode was moved to a more lateral trajectory. The final electrode location was assessed using postoperative MRI scans. The anatomical relations between the electrode/STN and the surrounding structures are shown in Fig. 1.

Stimulation

The STN electrodes used in our patients have four platinum-iridium contact poles, numbered 0–3. Each contact-pole measures 1.27 mm in width and 1.50 mm in length, and they are separated by 0.5 mm. Therefore, their centres are separated by 2.0 mm. An adapted Medtronic switch was used to connect all four leads to terminals suitable for the stimulator of an electromyograph (Mystro5Plus, Oxford Instruments, Surrey, UK). The most caudal contact-pole was connected to the electrode-lead 0, and the most rostral one, to the electrode-lead 3. To explore the effects of stimulus polarity we used bipolar stimulation montages between the two extreme electrode leads to allow preferential stimulation from either caudal or rostral poles. Therefore, the assumed distance between cathode and anode in our montages was 7.5 mm. As a default condition, we used electrode-lead 3 as cathode (−). We used unilateral single stimuli with a duration of 0.2 ms of progressively increasing intensity to determine the resting motor threshold (RT) for a MEP in the contralateral thanar muscles. The RT was defined as the lowest stimulus intensity that induced a MEP in the contralateral thanar muscles with a minimum amplitude of 100 μVs in at least 50% of a series of 6 stimuli with the muscles at rest. To explore the effects of stimulus intensity we tested three different stimuli with intensities of 100% RT, 115% RT and 130% RT. All stimuli were delivered through the stimulator system of the electromyograph (Mystro5Plus) and applied to the left STN electrodes.
Cranial motor responses to STN-DBS

Fig. 1 Anatomical relations between the STN electrode and the surrounding structures. (A) Postoperative T1-weighted coronal MRI image showing the position of the electrodes. (B) Anatomic stereotaxic atlas (Schaltenbrand and Wahren, 1977) superimposed to a postoperative CT scan showing the artefact caused by the electrodes. Coronal slice 3.5 mm posterior to mid-comissural plane. The dotted line represents the trajectory of the electrode. STN = subthalamic nucleus; IC = internal capsule; SN = substantia nigra; CP = cerebral peduncle; Th = thalamus; RN = red nucleus; OMr = oculomotor root; GP = globus pallidus internus; OT = optic tract; LV = lateral ventricle; III V = third ventricle.

Recording
The EMG activity of the orbicularis oculi, orbicularis oris, masseter, sternocleidomastoid and thenar muscles of both sides was recorded by means of surface silver/silver chloride 9 mm diameter recording electrodes attached to the skin. The band pass frequency filter was set between 20 and 3000 Hz. For orbicularis oculi, active electrodes were placed 1 cm below the lower eyelid rim and the reference 2 cm lateral. For orbicularis oris, the active electrode was placed 1 cm lateral to the mouth corner, and the reference 2 cm lateral. For masseter, the active electrode was placed over the muscle belly, near the angle of the mandible, and the reference was attached to the ear lobe. For sternocleidomastoid, the active electrode was placed between the upper and the lower two-thirds of the muscle and the reference electrode on the tendon. In two patients, we also recorded from the trapezius, biceps and deltoid muscles.

In three patients we also performed electro-oculographic recordings to document possible eye movements elicited by sSTN-DBS. We set the recording frequencies at 0.5–20 Hz. The active electrode in the horizontal plane was placed 1 cm lateral to the outer canthus and the reference on the lateral wall of the nose. The active electrode in the vertical plane was positioned in the upper orbital rim and the reference in the lower orbital rim (Heide et al., 1999).

General procedure
Patients were lying in the examination bed, relaxed, in a dimly lit room. They were instructed not to speak and to remain calm and relaxed during the experiment. All neurophysiological studies were performed by the same examiner, under the same experimental conditions and with the same equipment.

We connected the leads of the STN electrode to the stimulator of the electromyograph. After determining the RT for contralateral thenar muscles we recorded the MEPs in facial and cervical muscles at rest to five successive stimuli at three different intensities (100, 115 and 130% RT). To explore the effects of stimulus polarity we tested two different bipolar stimulation montages (−3, +0, and +3, −0). The examination of polarity effects was done at a stimulus intensity that was capable of inducing an MEP clearly recognizable above the background activity in at least 50% of a series of six stimuli. Five successive single stimuli at 130% AT and with cathode placed rostrally (−3; +0) were applied to determine the silent periods in muscles of both sides.

Data analysis
All recordings were printed on thermosensitive paper for off-line analysis. In the recordings at rest, we determined the probability of inducing a MEP in orbicularis oculi, orbicularis oris, masseter, sternocleidomastoid and thenar muscles as the per cent number of responses observed with respect to the total number of stimuli. We measured the onset latency (defined in ms as the onset of the first positive or negative deflection component from the start of the stimulus) and peak-to-peak amplitude of the MEP in each of the five trials recorded, and calculated the mean values for each muscle and patient. We also looked at the intraindividual standard deviation of the MEP latency as a measure of the latency variability of the response to successive stimuli.

In the recordings obtained during contraction, we measured onset latency and peak-to-peak amplitude of the MEP, and the onset latency and duration of the silent period. We measured onset latency in ms from the actual onset of EMG suppression. Duration was measured from the end of the excitatory response to the latency at which the EMG activity returned to its pre-stimulus level. For each patient and muscle, we calculated the mean values of these variables in each of the five trials recorded.

For group comparisons of MEP variables we considered the data obtained with a stimulus intensity of 130% RT because at this intensity we have always obtained well-defined bilateral responses.
in all muscles. For both MEP (latency and amplitude) and silent period (latency and duration) analysis, data from all patients were grouped together according to the different muscles studied to calculate the grand mean and the standard deviation for each variable. Comparisons between ipsilateral and contralateral responses were performed with paired Student’s t-test. Comparisons between different muscles were done with two-tailed unpaired t-test. For silent period analysis, we performed non-parametric correlations (Spearman coefficient) between MEP amplitude and duration of the silent period. Results are expressed as mean ± standard deviation. All statistical analyses were done using the SPSS 13.0 for windows. The level of significance was set at $P = 0.01 (0.05/4 = 0.0125)$ to correct for multiple comparisons.

Results

No patient reported any pain or discomfort during or after the experiments. Specifically, no patient reported noticing the sSTN-DBS at the intensities used. Occasional higher intensity sSTN-DBS delivered while assessing the individual’s threshold intensity caused a twitching in facial and upper limb muscles and some patients reported transient blurred vision. Mean RT was 9.5 ± 0.9 mA. Mean AT was 8.4 ± 1.3 mA.

MEPs

Unilateral bipolar single stimuli at an intensity of 130% RT induced strictly contralateral responses in thenar muscles in all individuals, at a mean latency of 20.1 ± 2.0 ms and mean amplitude of 0.64 ± 0.27 mV. The MEPs obtained in the trapezius, deltoid and biceps muscles were also present in only the contralateral side. The same stimulus induced always (i.e. a probability of 100%) bilateral MEPs in all facial muscles studied, as well as in the masseter and sternocleidomastoid, at a mean latency ranging from 6.0 to 9.1 ms. Mean values for latency and amplitude of the MEPs found on ipsi- and contralateral side for all muscles studied are presented in Table 1. Figure 2 shows representative examples of the recordings from one patient.

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**Table 1** Mean values of onset latency and peak-to-peak amplitude of the MEPs found in ipsilateral and contralateral sides for all muscles studied at rest

<table>
<thead>
<tr>
<th>MEP</th>
<th>Latency (ms)</th>
<th>Amplitude (mV)</th>
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<tr>
<td></td>
<td>Ipsilateral</td>
<td>Contralateral</td>
</tr>
<tr>
<td>OOr</td>
<td>3.6 (0.2)</td>
<td>—</td>
</tr>
<tr>
<td>OOr2</td>
<td>8.4 (0.9)</td>
<td>8.7 (1.2)</td>
</tr>
<tr>
<td>OOr</td>
<td>8.6 (1.2)</td>
<td>9.1 (1.5)</td>
</tr>
<tr>
<td>MAS</td>
<td>5.9 (1.1)</td>
<td>6.3 (1.5)</td>
</tr>
<tr>
<td>SCM</td>
<td>5.9 (0.7)</td>
<td>6.8 (0.7)</td>
</tr>
<tr>
<td>Trapezius</td>
<td>—</td>
<td>8.1 (1.1)</td>
</tr>
<tr>
<td>Deltoid</td>
<td>—</td>
<td>9.8 (1.2)</td>
</tr>
<tr>
<td>Biceps</td>
<td>—</td>
<td>10.5 (1.5)</td>
</tr>
<tr>
<td>Thenar</td>
<td>—</td>
<td>20.1 (2)</td>
</tr>
</tbody>
</table>

OOc1 and OOr2 refer to the two action potentials identified in the orbicularis oculi. Values in brackets represent standard deviation.

*Comparisons showing significant differences ($P ≤ 0.01$) between ipsilateral and contralateral side responses for the same muscle.

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![Fig. 2](https://via.placeholder.com/150)

**Fig. 2** MEPs recorded in muscles supplied by cranial nerves, deltoid and thenar muscles after single left STN stimulation (cathode placed caudally) at intensity of 130% RT. OOr = orbicularis oris, OOr = orbicularis oculi, MAS = masseter, SCM = sternocleidomastoid, TRAP = trapezius, DEL = deltoid, RT = resting threshold; Ipsil = ipsilateral; Contral = contralateral. Muscles with bilateral responses are shown on the left side and muscles with only contralateral responses are shown on the right side of the figure. Note the presence of a small short latency action potential in the ipsilateral (left) OOr, the similar latencies of bilateral MEPs in all facial and cranial muscles (except trapezius), and the presence of MEP exclusively on the contralateral side in trapezius, deltoid and thenar muscles. Two traces are superimposed for each muscle.

In all muscles, ipsilateral MEPs had a non-significant shorter onset latencies in comparison to the contralateral ones ($P > 0.05$). The latency in response of the facial-nerve innervated muscles (orbicularis oculi and orbicularis oris) was significantly longer than that of the masseter and sternocleidomastoid ($P < 0.01$). There were no significant
differences when comparing the latencies of the latter or those of the former two muscles. The peak-to-peak amplitude was smaller in ipsilateral MEPs in comparison with contralateral ones ($P < 0.01$ for all muscles). A small amplitude action potential was consistently recorded in the ipsilateral orbicularis oculi at very short latency (3.6 $\pm$ 0.2 ms range 2.5–4.7), which was significantly shorter than that of the bilateral MEPs ($P < 0.01$). This action potential, identified as OOC1 in Table 1, had a rather simple form and was never present in contralateral recordings (see Figs 2 and 3A).

Effects of intensity and polarity changes
Low intensity stimuli (100% RT) induced MEPs with high intra- and inter-individual variability of latency and amplitude. The probability of inducing a MEP at 100% RT ranged from 40 to 100%, with no significant differences between muscles. In some trials, only the contralateral MEPs were present, again with no significant differences between muscles. In each patient, the latency and amplitude variability reduced, and the probability of inducing an MEP increased to 100% in all muscles, with increasing stimulus intensity (Fig. 3A). Latency variability of the action potential recorded in the contralateral orbicularis oculi, measured as the standard deviation of the response latency to five successive stimuli, was 0.8 ms at a stimulus intensity of 100% RT and shortened to 0.3 ms at a stimulus intensity of 130% RT. The behaviour of the short latency action potential recorded in the ipsilateral orbicularis oculi was different from the behaviour of all other action potentials. Its amplitude increased with increasing the stimulus intensity but its latency and shape were not modified (Fig. 3B).

Since some patients reported a sudden blurring of their sight with sSTN-DBS, we considered the possibility that the short latency action potential in the orbicularis oculi was related to activation of extraocular muscles. Therefore, in three patients, we performed electro-oculographic recordings to document possible eye movements elicited by sSTN-DBS of the same intensity and polarity as before. In all three patients, sSTN-DBS induced an action potential in the ipsilateral eye recordings at the same latency (3.5 $\pm$ 0.1 ms) and with similar characteristics as the short latency action potential recorded with EMG electrodes placed on the orbicularis oculi. However, the polarity of this action potential was negative in vertical recordings and positive in horizontal recordings (Fig. 4), suggesting that it was generated by a vector in the direction of the inner and upper electrodes.
In all patients changing the polarity of the stimulation (+3; -0, i.e. cathode placed caudally) did not cause any significant changes in the latency or amplitude of the MEPs recorded, except for a significant increase in the amplitude of the short latency action potential recorded in the ipsilateral orbicularis oculi (24.8 ± 20.2 μV with the cathode placed rostrally and 75.3 ± 18.1 μV with the cathode placed caudally, both at a stimulus intensity of 130% RT) without any change in its latency (Fig. 5). In six patients, low-intensity stimulation with the cathode placed caudally generated only the short latency action potential of the ipsilateral orbicularis oculi. Again, increasing the stimulus intensity did not induce significant changes in the latency of this potential, which intra-individual latency variability was <0.1 ms at intensities ranging from 100 to 130% RT.

Silent periods
Well-defined silent periods to sSTN-DBS were present in both sides of the orbicularis oculi and masseter in all patients. Mean values for latency and amplitude of MEPs obtained during contraction, and for latency and duration of the silent periods, are presented in Table 2. The orbicularis oculi and masseter MEPs had shorter latencies and higher amplitudes during sustained contraction compared with the recordings obtained at rest (P < 0.01 for both muscles and comparisons). There were no significant differences in MEP latency between the ipsi- and contralateral side for both muscles. The amplitude of the MEP was higher in the contralateral side for both muscles (significant for orbicularis oculi). The silent period was significantly longer on the contralateral side (P < 0.01 for both muscles). As at rest, the MEP latencies in the ipsi- and contralateral sides were shorter in masseter compared with orbicularis oculi (P < 0.01 for both comparisons). On the contrary, the duration of the silent period in the ipsi- and contralateral sides was longer in masseter (P < 0.01 for ipsilateral side). In both, the duration of the silent period had no significant correlation with the MEP amplitude, both in the ipsi- and contralateral sides (r < 0.2 for all correlations). Figure 6 shows representative examples of silent periods. In <10% of the recordings a second silent period consisting of an incomplete suppression of EMG activity was identified in the orbicularis oculi and masseter.

Discussion
The most relevant findings of our study are as follows: (i) Single unilateral deep brain electrical stimulus is able to induce short latency MEPs in cranial nerve innervated muscles, compatible with activation of the corticobulbar tract. (ii) The finding of bilateral MEPs and silent periods with similar latencies in ipsi- and contralateral facial and cranial muscles indicates that both ipsi- and contralateral tracts directed towards cranial nerve nuclei descend together at the site where the stimulus was applied and have bilateral projections from there to the nuclei. This brings interesting arguments to discuss on the pathways of the ipsilateral projection to facial and cranial muscles. It also tells us that upper and lower facial muscles of both sides are innervated by fibres from a unilateral tract running at the level of the internal capsule. (iii) MEPs in facial muscles had longer latencies than those of other cranial muscles, an observation that is in agreement with TMS findings and suggests polysynaptic corticobulbar projections to facial muscles. (iv) Although it is believed that facial and cranial silent periods are exclusively due to cortical inhibition, our results suggest the presence of other mechanisms in the genesis of these.

The results of our study were very consistent among all patients. However, we should keep in mind that they were obtained in those with Parkinson’s disease and some of the findings and hypothesized mechanisms may not apply to the general population.

Physiology of the excitatory responses (MEPs)
The most likely physiological mechanism accounting for the generation of the MEPs in facial and cranial muscles is activation of axons of the corticobulbar and corticospinal tracts within the internal capsule, in agreement with the observations of other authors that recorded from hand muscles (Strafella et al., 1997; Ashby et al., 1999; Kuhn et al., 2004; Compta et al., 2006). In fact, the internal capsule is located at a mean distance of about 4.5 mm in the
mediolateral plane and 2 mm in the anteroposterior plane from the tip of the electrode implanted in the STN (Schaltenbrand and Wahren, 1977; Voges et al., 2002; Molinuevo et al., 2003). According to the general principles of the effects of stimulation of the neuropil (Nowak and Bullier, 1998; Ashby et al., 1999), electrical stimuli are more likely to activate axons than cell bodies, fibres near the cathode than those near the anode and fibre tracts that run parallel rather than those that run perpendicular to the electrode.

Activation of axons of the corticospinal and corticobulbar tracts by sSTN-DBS is most likely to generate a single axonal depolarization volley, propagated orthodromically and antidromically. The orthodromic volley would be responsible for inducing an excitatory post-synaptic potential in a number of alpha motoneurons of the cranial nerve nuclei and eventually lead to their synchronized firing, inducing the MEP. Cortical neuronal activation would have required a certain time for the antidromic volley to travel back and induce cortical neuronal firing that would show in the latency of the MEP.

In our subjects, the latency of the MEP at rest in hand muscles and in muscles supplied by cranial nerves was 3–4 ms shorter than the figures reported for electrical or magnetic cortical stimulation of M1 (Benecke et al., 1988; Cruccu et al., 1990b; Benecke et al., 1991; Berardelli et al., 1991; Rothwell et al., 1991; Ghezzi et al., 1992; Meyer et al., 1994; Urban et al., 1997; Curra et al., 2000; Triggs et al., 2005). Such latency difference between TMS and sSTN-DBS-induced MEPs is probably explained by cortico-cortical synaptic connections and the temporal summation needed for cortical motoneuronal activation plus the conduction time from the motor cortex to the internal capsule. The delay of the MEPs obtained in facial muscles compared with other cranial innervated muscles may reflect the polysynaptic nature of the corticobulbar connections to the facial nuclei (Jenny and Saper, 1987; Cruccu et al., 1990b). The fact that the MEPs elicited in upper and lower facial muscles had similar latencies supports previous findings of TMS studies using needle electrodes to avoid electrical cross-talk, and is another argument against the possibility that MEPs in orbicularis oculi were blink reflexes to activation of the trigeminal nerve because lower facial muscles would not have been activated. The latencies of the MEP in orbicularis oculi and masseter were shorter during voluntary contraction compared with rest, a phenomenon that is possibly due to the descending volley being more effective in causing the primed motoneurons to fire. In fact, MEP latency shortening in our study was within the range of the period of increased firing probability of a single motor unit to DBS (0.9 ± 0.2 ms), defined with post-stimulus time histograms (Kuhn et al., 2004).

Table 2: Mean values of onset latency and peak-to-peak amplitude of the MEPs, and onset latency and duration of the silent period (SP) found in ipsilateral and contralateral sides for OOc and MAS muscles at sustained contraction (20% of pre-activation)

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<tr>
<th></th>
<th>MEP Latency (ms)</th>
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<td>Ipsilateral</td>
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<tr>
<td>OOc</td>
<td>7.8 (0.8)</td>
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<td>307.5 (149.0)</td>
<td>523.2 (235.9)*</td>
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<tr>
<td>MAS</td>
<td>5.2 (0.6)</td>
<td>5.4 (0.7)†</td>
<td>397.2 (128.7)</td>
<td>492.2 (182.7)</td>
</tr>
</tbody>
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Values in brackets represent standard deviation. *Comparisons showing significant differences (P < 0.01) between ipsilateral and contralateral side responses for the same muscle. †Comparisons showing significant differences (P < 0.01) between OOc and MAS muscle responses on ipsilateral and contralateral sides.

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</tr>
<tr>
<td>MAS</td>
<td>5.2 (0.6)</td>
<td>5.4 (0.7)†</td>
<td>397.2 (128.7)</td>
<td>492.2 (182.7)</td>
</tr>
</tbody>
</table>

Values in brackets represent standard deviation. *Comparisons showing significant differences (P < 0.01) between ipsilateral and contralateral side responses for the same muscle. †Comparisons showing significant differences (P < 0.01) between OOc and MAS muscle responses on ipsilateral and contralateral sides.

Activation of axons of the corticospinal and corticobulbar tracts by sSTN-DBS is most likely to generate a single axonal depolarization volley, propagated orthodromically and antidromically. The orthodromic volley would be responsible for inducing an excitatory post-synaptic potential in a number of alpha motoneurons of the cranial nerve nuclei and eventually lead to their synchronized firing, inducing the MEP. Cortical neuronal activation would have required a certain time for the antidromic volley to travel back and induce cortical neuronal firing that would show in the latency of the MEP.

In our subjects, the latency of the MEP at rest in hand muscles and in muscles supplied by cranial nerves was 3–4 ms shorter than the figures reported for electrical or magnetic cortical stimulation of M1 (Benecke et al., 1988; Cruccu et al., 1990b; Benecke et al., 1991; Berardelli et al., 1991; Rothwell et al., 1991; Ghezzi et al., 1992; Meyer et al., 1994; Urban et al., 1997; Curra et al., 2000; Triggs et al., 2005). Such latency difference between TMS and sSTN-DBS-induced MEPs is probably explained by cortico-cortical synaptic connections and the temporal summation needed for cortical motoneuronal activation plus the conduction time from the motor cortex to the internal capsule. The delay of the MEPs obtained in facial muscles compared with other cranial innervated muscles may reflect the polysynaptic nature of the corticobulbar connections to the facial nuclei (Jenny and Saper, 1987; Cruccu et al., 1990b). The fact that the MEPs elicited in upper and lower facial muscles had similar latencies supports previous findings of TMS studies using needle electrodes to avoid electrical cross-talk, and is another argument against the possibility that MEPs in orbicularis oculi were blink reflexes to activation of the trigeminal nerve because lower facial muscles would not have been activated. The latencies of the MEP in orbicularis oculi and masseter were shorter during voluntary contraction compared with rest, a phenomenon that is possibly due to the descending volley being more effective in causing the primed motoneurons to fire. In fact, MEP latency shortening in our study was within the range of the period of increased firing probability of a single motor unit to DBS (0.9 ± 0.2 ms), defined with post-stimulus time histograms (Kuhn et al., 2004).
One difference between TMS and STN-DBS in eliciting MEPs in facial and masseter muscles is that with TMS some pre-innervation is required to evoke a motor response. On the contrary, sSTN-DBS was able to evoke MEPs in muscles at rest probably due to the direct activation of descending motor axons that secondarily activate facial and masseter motoneurons.

**Projections of the corticospinal and corticobulbar tract**
MEPs were consistently elicited in only the contralateral side in the thenar, biceps, deltoid and trapezius muscles, and in both sides in orbicularis oculi, orbicularis oris, masseter and sternocleidomastoid. This is in agreement with previous works in which the authors recorded from hand muscles (Strafella et al., 1997; Ashby et al., 1999; Kuhn et al., 2004), and fits well with known anatomical concepts on the distribution of the corticospinal tract. According to Carr et al. (1994) a common drive to muscles of both sides in the corticospinal or corticobulbar tracts takes place only in muscles that are normally co-activated and cannot be activated independently. Although the corticospinal tract is known to have ipsilateral projections (Brinkman and Kuypers, 1973), ipsilateral MEPs to TMS in hand and arm muscles can be obtained only during facilitation with voluntary contraction (Wassermann et al., 1991; Wassermann et al., 1994; Ziemann et al., 1999). In these instances, the ipsilateral MEP latency is significantly longer than the contralateral one. However, this is not the case with muscles supplied by cranial nerves. Similar to the findings with TMS studies (Benecke et al., 1988; Cruccu et al., 1990a; Benecke et al., 1991; Berardelli et al., 1991; Carr et al., 1994; Meyer et al., 1994), we found that sSTN-DBS at an intensity of 115 and 130% RT induced bilateral MEPs of similar latency in facial and cranial muscles of both sides. At low intensity (100% RT) the MEPs in these muscles were sometimes limited to the contralateral side. This could be due to a higher threshold, a smaller density, or a deeper location of ipsilateral fibres with respect to the contralateral fibres. However, these aspects were not further investigated. Taken together, our findings indicate that both ipsilateral and contralateral fibres directed towards cranial nerve nuclei travel together from the internal capsule to the motor nuclei. Whether they come from the same hemisphere, as suggested by Muellerbacher et al. (1998, 1999), cannot be revealed from our study because fibres to the ipsilateral muscles could actually have already joined the corticobulbar tract via the corpus callosum at the point in which our sSTN-DBS activated them.

**Stimulation of corticofugal fibres from motor cortex**
The corticobulbar tract at the internal capsule is likely to gather corticofugal fibres from different areas of the motor cortex, including rostral cingulate (M3), supplementary (M2), ventral lateral pre-motor cortex (LPMCv), dorsolateral premotor cortex (LPMCd), caudal cingulate (M4) and the primary motor area (M1). Theoretically, the MEPs we obtained in facial and neck muscles could have been due to activation of one or several descending projection systems. However, a few arguments favour the possibility that the MEPs that we obtained resulted from activation of corticofugal fibres from M1. (i) Fibres generated in M1 are always located more posterior in the internal capsule (Fries et al., 1993; Morecraft et al., 2002; Newton et al., 2006) than other motor corticofugal projections, and therefore closer to the electrical field generated by our electrode. (ii) We have always recorded MEPs in hand muscles to the same stimulus generating MEPs in facial and neck muscles. (iii) Fibres from M1 are more numerous and excitable than those from the supplementary motor area (Maier et al., 2002). (iv) According to tractography studies (Ramnani et al., 2006), the human cerebral peduncles receive relatively reduced contribution of the premotor cortex, and increased contribution of the prefrontal cortex, in comparison to macaques. (v) Taking into account the cortico-subcortical delay of ~3–4 ms, the facial MEP latencies found in our subjects (8–9 ms) are more likely to result from activating the same fibres that are activated with TMS over M1 (Paradiso et al., 2005) than those that are activated with TMS targeting the mesial frontal cortex (Sohn et al., 2004).

Therefore, we believe that M1 projects bilaterally to upper and lower facial muscles through polysynaptic connections (reticular neurons and/or cortico-tegmento-nuclear circuits). However, the density of projections to facial nuclei is likely to be higher for contralateral than for ipsilateral muscles, as suggested by tracer studies done in non-human primates (Jenny and Saper, 1987; Morecraft et al., 2001; Gong et al., 2005) and by the fact that, at low intensity stimulation (100% RT), we obtained MEPs limited to the contralateral facial muscles in some trials. In addition, at higher intensity stimulation, contralateral MEPs were of higher amplitude (Table 1). The relatively higher density of contralateral versus ipsilateral projections from both lateral (M1, LPMC) and medial (M2, M3 and M4) cortical motor areas to upper and lower facial motoneurons, and the fact that integrated facial movements may be heavily mediated at the cortical level through reciprocal corticocortical projections may explain the deficits in the contralateral lower facial muscles and the sparing of the upper musculature following unilateral damage to the lateral motor cortices (LPMC and M1).

Taken together, our results do not exclude in any way the existence of other cortical descending pathways to facial muscles as suggested by the dissociation between voluntary and emotional movements in patients with supranuclear lesions (Lees, 1988; Hopf et al., 1992, 2000). In fact, at least five major cortical motor areas (M1, lateral pre-motor cortex, M2, M3 and M4) have descending projections to subsectors of the facial nucleus (Morecraft et al., 2001; Gong et al., 2005). Therefore, facial motoneurons are likely to receive...
inputs from multiple cortical motor areas. Activation of just one of the projections from motor areas to the facial motor nuclei would be enough to elicit MEPs. Even though our results suggest the existence of a corticobulbar projection to the facial nucleus, this does not necessarily mean that facial movements in humans are controlled solely by M1. Our results do not imply a functional correlate.

**Ipsilateral short latency action potential in orbicularis oculi**

A short latency action potential was recorded in the ipsilateral orbicularis oculi and in no other muscle. Therefore, its source was likely different from that of the bilateral MEPs. This potential had a different behaviour from all other action potentials to changes in stimulus intensity and polarity. As a difference with respect to bilateral MEPs, the short latency action potential of the ipsilateral orbicularis oculi did not show significant changes in latency with changes in stimulus intensity, and its amplitude was larger when the cathode was placed caudally and thus closest to the upper part of the brainstem.

This action potential could have been generated by activation of the underlying muscle. The most excitable site of the facial motor pathway is the facial nerve root (Rosler et al., 1989). Activation of the facial nerve root was hypothesized by Sohn et al. (2004) to account for their shortest latency responses (4.1 ± 0.3 ms). However, stimuli applied near the STN would have had to travel a relatively long distance to reach the facial nerve nuclei and would have probably generated other responses along the path. We think that the most likely possibility is that the short latency action potential recorded with the electrodes over the lower eyelid is generated after activation of deep muscles and is picked up in the surface as volume-conducted. The sSTN-DBS could have produced depolarization of the efferent fibres from upper brainstem oculomotor subnuclei, and activated extraocular muscles. This hypothesis is favoured by the close proximity of the stimulus applied caudally to the oculomotor axons exiting mesencephalic nuclei. Electrocorticographic recordings showed an action potential in the ipsilateral eye at the same latency as the one recorded with surface EMG electrodes attached to the orbicularis oculi. This does not fit with the idea of this potential being induced by changes in the orientation of the corneo-retinal electrical axis related to eye movements, as it would be expected from electro-oculographic recordings. Instead, it is more likely that this action potential is actually a volume-conducted activity generated in deeper muscles and therefore recorded by whichever electrode is in the periorbital region. One finding from electro-oculographic recordings helps in interpreting what may be the source of this potential. In fact, the reversed polarity between horizontal (positive) and vertical (negative) recordings with the electro-oculographic electrodes indicates an electrical vector towards the inner and upper walls of the orbit, and suggests the possibility that the source of this potential is activation of superior rectus, internal rectus or both.

**Inhibitory responses (silent periods)**

In our study we observed bilateral silent periods of short duration and similar latencies in orbicularis oculi and masseter. Bilateral silent periods in facial and cranial muscles have been reported in some TMS studies (Werhahn et al., 1995; Odergren and Rimpilainen et al., 1996; Cruccu et al., 1997; Curra et al., 2000; Kobayashi et al., 2001; Desiato et al., 2002), and attributed exclusively to cortical inhibition (Leis et al., 1993; Werhahn et al., 1995; Cruccu et al., 1997; Curra et al., 2000). Facial muscles do not act on joints, have few or no proprioceptors, and their motoneurons neither undergo reciprocal inhibition nor possess axonal collaterals for recurrent inhibition (Lorente, 1933; Crosby et al., 1962; Folkins and Larson, 1978; Poppele, 1993). These characteristics make unlikely the participation of segmental factors as a source of inhibitory inputs. A clear difference between the silent periods found in our study and those reported with TMS is their markedly shorter duration. This cannot be due to low sSTN-DBS intensity because our stimulus generated a MEP of similar size as the one reported with TMS. It has been suggested that the duration of the silent period is related to the intensity of the stimulus rather than to the size of the preceding MEP (Triggs et al., 1992; Inghilleri et al., 1993; Brasil-Neto et al., 1995). In agreement with that, our study also failed to show significant correlations between MEP size and silent period duration. However, the silent period duration was longer in the side contralateral to the stimulus, where there was also an MEP of a larger size. The shortened silent period is unlikely to arise from a relatively low level of background contraction because previous experiments testing the effects of varying the level of muscle activation in normal individuals have shown that, despite increasing levels of EMG activity, the silent period in limb muscles remains fairly constant (Inghilleri et al., 1993; Roick et al., 1993).

We think the silent period induced by sSTN-DBS is mainly due to two effects of the excitatory volley generated in the corticobulbar tract. The orthodromically propagated volley generates the synchronized firing of quiescent motoneurons, which then undergo afterhyperpolarization (Ashby, 1995). The antidromically propagated volley collides with the excitatory inputs travelling down at that specific moment and transiently blocks their arrival at motoneurons. In a few recordings we observed the presence of two silent periods separated by a burst of EMG activity, suggesting that relatively complex circuits may occasionally be involved (Compta et al., 2006). Other possible partly contributory mechanisms observed in our subjects include the activation of thalamocortical inhibitory projections (Strafella et al., 1997; Ashby et al., 1999; Compta et al., 2006) having similar effects on bilateral muscles or descending inhibitory systems (Fuhr et al., 1991), although these are not known to be
bilateral. The relatively shorter duration of the silent period in orbicularis oculi than in masseter is compatible with a weaker excitatory projection from M1 to facial in comparison to trigeminal motoneurons. On the other hand, masticatory muscles do not share the same peculiar functional organization of facial muscles and thus additional segmental inhibitory mechanisms resulting from proprioceptive influences or recurrent inhibition may contribute to the entire silent period (Cruccu et al., 1989).

Our results are not in disagreement with previous observations of facial and trigeminal silent periods with TMS, nor with the idea that facial and cranial silent periods induced by TMS result from cortical inhibitory mechanisms. As discussed above in relation to the corticobulbar tract projections to facial motoneurons, we shall take into account that sSTN-DBS could just be activating a relatively small M1 projection, whereas many other cortical projections could be simultaneously activated by TMS.

One intriguing issue is the fact that silent periods of the same onset latency were generated on both sides to a unilateral stimulus. This suggests that they are indeed induced by a single structure with bilateral projections to facial and trigeminal motoneurons and speaks against a cortical source of the silent period found in our subjects. If the silent period was generated by cortical inputs, it would have been impossible for a unilateral subcortical stimulus to inhibit the activity from the contralateral hemisphere and some EMG activity would have remained.

In conclusion, sSTN-DBS is able to activate the corticobulbar tract eliciting bilateral excitatory and inhibitory motor responses in facial and cervical muscles indicating that both ipsi- and contralateral tracts descend together at the level of the STN and have bilateral projections from there to the nuclei. These findings are of particular importance in the discussion of the innervation of upper and lower facial muscles in humans and in the interpretation of previous results from TMS studies.

References


