Unilateral subdural motor cortex stimulation improves essential tremor but not Parkinson’s disease

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Epidural motor cortex stimulation has been reported to be effective in treating some movement disorders. Nevertheless, clinical results have been variable and no double-blinded evaluations have been reported. The aim of this study was to investigate efficacy and safety of unilateral subdural motor cortex stimulation in patients with essential tremor and Parkinson’s disease. Six patients with essential tremor and five parkinsonian patients were selected. Craniotomy was performed under local anaesthesia with conscious sedation. A four contact electrode (Resume II model 3587, Medtronic, Inc) was positioned on the motor cortex, after identification of the area with direct monopolar cortical stimulation. Soon after surgery, a variety of different settings of stimulation were assessed using standard rating scales to select the optimal stimulation parameters. The effects of chronic stimulation were evaluated in both groups of patients after 3 months (double-blinded fashion) and 1 year (open fashion). In essential tremor, contralateral hand tremor scores significantly improved (P = 0.04) with stimulation during the double-blinded study, whereas in Parkinson’s disease, there were no changes in the OFF medication/on stimulation motor scores compared with off stimulation. At 1 year, tremor was improved by stimulation in two out of three patients with essential tremor available at follow-up, whereas no improvement was observed in the five parkinsonian patients. One parkinsonian patient had a cortical venous infarct. Three other patients had self-limiting seizures with aggressive trials of stimulation in the period of dosage selection. These findings suggest that unilateral subdural motor cortex stimulation may be useful for contralateral hand tremor in selected patients with essential tremor but was not effective in improving parkinsonian signs in our series.

Keywords: essential tremor; motor cortex stimulation; Parkinson’s disease

Abbreviations: OFF = OFF medication; ON = ON medication; UPDRS = Unified Parkinson’s Disease Rating Scale

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Introduction

Chronic extradural motor cortex stimulation was first introduced to relieve refractory deafferentation pain in the late 1980s (Tsubokawa et al., 1991, 1993). Subsequently, motor cortex stimulation was reported to improve post-stroke involuntary movements such as hemichoreaathetosis and resting tremor in patients receiving motor cortex stimulation for pain relief (Katayama et al., 1998, 2003). Others described improvements in action tremors (Nguyen et al., 1998), dystonia and intention myoclonus (Franzini et al., 2003). As early as 1979, electrical stimulation of the primary motor cortex was reported to reduce rigidity and tremor in patients with Parkinson’s disease (Woolsey et al., 1979). On this basis, Canavero et al. (2002, 2003) performed motor cortex stimulation in three patients with Parkinson’s disease, who were considered poor candidates for subthalamic nucleus deep-brain stimulation because of advanced age (>70 years), abnormal neuroimaging or neuropsychological deficits. Unblinded assessments demonstrated improvement in the three Parkinson’s disease cardinal signs bilaterally in all patients using low-frequency unilateral motor cortex stimulation. One patient with multiple system atrophy also showed a clinical improvement, especially in gait and bradykinesia. In contrast, our group found no benefit in five patients with multiple system atrophy after unilateral motor cortex stimulation (Kleiner-Fisman et al., 2003), using higher frequencies than those applied by Canavero et al. (2003). Other small case series of patients with Parkinson’s disease treated with motor cortex stimulation have been reported (Pagni et al., 2005; Benvenuti et al., 2006; Cilia et al., 2007; Cioni, 2007; Arle et al., 2008; Fasano et al., 2008; Gutiérrez et al., 2009). In all cases, the evaluations were conducted in an open-label fashion. Only one small study has reported data in two patients with essential tremor, who underwent unilateral motor cortex stimulation (Lyons et al., 2006).

Most previous studies of chronically applied motor cortex stimulation have used epidural implants without direct visualization of the motor cortex. There are several problems with this approach. First, the exact placement of the electrodes can be imprecise, as it is not always possible to obtain anatomically validated placement of the stimulators over the primary motor cortex. In addition, given the variable volume of cerebrospinal fluid within the subarachnoid space due to the sometimes long distance between the dura and the underlying cortex, particularly in patients of advanced age or with atrophy, it is unclear how much current, if any, actually reaches the cerebral cortex with the stimulation parameters that have been used previously. For these reasons, our approach was to open the dura, physiologically map the cortex and place stimulating electrodes subdurally. The potential advantage of cortical stimulation versus deep-brain stimulation is that it is, at least in theory, less complex to perform and should be associated with a lower incidence of cerebral haemorrhage because the brain is not penetrated. The objectives of the present study were to determine the acute and long-term safety and efficacy of unilateral subdural motor cortex stimulation in patients with essential tremor and Parkinson’s disease using blinded and open assessments.

Patients and methods

Patients

Six patients with essential tremor and five patients with Parkinson’s disease underwent unilateral subdural motor cortex stimulation between May 2004 and May 2006 at the Toronto Western Hospital. The main clinical characteristics of the patients are summarized in Table 1.

Patients with essential tremor

Inclusion criteria for patients with essential tremor were: (i) diagnosis of essential tremor (Bain et al., 2000); (ii) insufficient benefit from adequate trials with common medical treatments for essential tremor (i.e. propranolol, primidone, gabapentin); (iii) no evidence of dementia (Saint-Cyr and Trépanier, 2000); (iv) no evidence of active major psychiatric issues (i.e. major depression, psychosis); (v) age between 30 and 80 years; (vi) brain MRI showing no contraindications for surgery (i.e. brain tumours); (vii) no significant or unstable medical or neurological disorders (coagulopathies, severe pulmonary or heart diseases, uncontrolled hypertension or diabetes, etc. or history of epilepsy); (viii) no previous neurosurgical treatments; (ix) availability to come to the clinic for many study assessments; (x) not suitable for deep-brain stimulation surgery (for age limits, intracranial issues and personal preferences); and (xi) signed informed consent for the research protocol.

Patients with Parkinson’s disease

Patients with Parkinson’s disease met the same criteria as essential tremor patient for points (iii–xii), and additionally: (i) idiopathic Parkinson’s disease (Hughes et al., 1992) with at least 5-year duration; (ii) good clinical response to levodopa (Defer et al., 1999); and (iii) severe motor fluctuations (i.e. disabling and prolonged off periods).

The University Health Network Research Ethics Board approved the study protocol.

Procedures

Preoperative assessments

All patients with essential tremor underwent neuropsychological assessment (Saint-Cyr and Trépanier, 2000), videotaped tremor assessment using the Fahn–Tolosa–Marin Tremor Rating Scale (Fahn et al., 1993), brain MRI, neurological, psychiatric and neurosurgical assessments.

All patients with Parkinson’s disease underwent neuropsychological assessment (Saint-Cyr and Trépanier, 2000), videotaped acute levodopa challenge (Defer et al., 1999), brain MRI, neurological, psychiatric and neurosurgical assessments. Anti-Parkinson’s disease medications were not changed during the month before surgery and patients were instructed to fill daily symptom diaries starting the week before surgery.

Surgical procedure

The motor cortex contralateral to the most affected side was targeted. All but one patient (with Parkinson’s disease) had left motor cortex surgery. Cranietomy was performed using a standard procedure, under local anaesthesia with conscious sedation, with patients positioned comfortably on one side (Kleiner-Fisman et al., 2003). Monopolar current was used to stimulate the motor cortex after opening the dura, in order to map the central area and identify the motor and sensory cortex. A strip containing four electrode contacts (Resume II model...
Table 1 Characteristics of the six patients with essential tremor and the five patients with Parkinson’s disease at time of surgery

<table>
<thead>
<tr>
<th></th>
<th>Sex</th>
<th>Age (years) at time of surgery, mean ± SD</th>
<th>Age (years) at time of disease onset, mean ± SD</th>
<th>Clinical scores at time of surgery, mean ± SD</th>
<th>Medications at time of surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Essential tremor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 1</td>
<td>Female</td>
<td>65</td>
<td>25</td>
<td>20/10.5</td>
<td>Primidone 375 mg</td>
</tr>
<tr>
<td>Patient 2</td>
<td>Male</td>
<td>67</td>
<td>17</td>
<td>52/28</td>
<td>None</td>
</tr>
<tr>
<td>Patient 3</td>
<td>Female</td>
<td>67</td>
<td>22</td>
<td>25/13</td>
<td>Propranolol 360 mg</td>
</tr>
<tr>
<td>Patient 4</td>
<td>Male</td>
<td>72</td>
<td>10</td>
<td>43.5/21</td>
<td>Propranolol 20 mg</td>
</tr>
<tr>
<td>Patient 5</td>
<td>Female</td>
<td>75</td>
<td>20</td>
<td>41/20</td>
<td>None</td>
</tr>
<tr>
<td>Patient 6</td>
<td>Male</td>
<td>76</td>
<td>16</td>
<td>25.5/18</td>
<td>Gabapentin 2400 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>70.3 ± 4.6</td>
<td>18.3 ± 5.2</td>
<td>34.3 ± 11.8/18.4 ± 6.2</td>
<td></td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 1</td>
<td>Male</td>
<td>73</td>
<td>60</td>
<td>38.5/8</td>
<td>850</td>
</tr>
<tr>
<td>Patient 2</td>
<td>Male</td>
<td>77</td>
<td>71</td>
<td>29.5/8.5</td>
<td>1200</td>
</tr>
<tr>
<td>Patient 3</td>
<td>Male</td>
<td>71</td>
<td>53</td>
<td>42/14.5</td>
<td>950</td>
</tr>
<tr>
<td>Patient 4</td>
<td>Male</td>
<td>72</td>
<td>54</td>
<td>39/21</td>
<td>1400</td>
</tr>
<tr>
<td>Patient 5</td>
<td>Male</td>
<td>70</td>
<td>57</td>
<td>37/15.5</td>
<td>1000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>72.6 ± 2.7</td>
<td>59.0 ± 7.2</td>
<td>37.2 ± 4.7/13.5 ± 5.4</td>
<td>1069.6 ± 174.4</td>
</tr>
</tbody>
</table>

LEDD = levodopa equivalent daily dose.

Postoperative assessments

Postoperative brain MRI and neurophysiological studies (see Supplementary Data) to verify the position of the electrodes were performed in all patients the day after surgery and between 6 and 12 months after surgery. T1 axial images were transferred to a workstation (Stealth Station; Medtronic) for a 3D reconstruction of the brain. Using the FrameLink 4.1 software (Mach 4.1), electrode contacts were visualized in all three planes and the centre of the corresponding magnetic resonance artefact was targeted. For the purpose of our study, we considered the centre of the sphere-shaped artefacts as the electrode contacts. This was based on the deep-brain stimulation literature, in which the centre of the artefact has been shown to represent the centre of the contact (Pollo et al., 2004). As electrode arrays were parallel to the motor strip, most contacts in our series were either on the precentral gyrus or within the immediate vicinity (Fig. 1).

Clinical effects of stimulation were assessed using three different paradigms: acute, intermediate and chronic stimulation.

Acute stimulation

After the Soletra implant, the acute effect of each setting on tremor was assessed using spiral drawing after 2 min of continuous stimulation. A subsequent washout period of 2 min off-stimulation followed each assessment. If 2 min off-stimulation were not enough to reach the baseline condition, stimulation was kept off until clinical signs returned to baseline agreed by both examiner and patient.

Patients with Parkinson’s disease were studied in the defined OFF medications (OFF) condition (Defer et al., 1999). Selected Unified Parkinson’s Disease Rating Scale (UPDRS) Part III items (Fahn et al., 1987), such as bilateral resting and postural tremor, rigidity, gait and Bradykinesia contralateral and ipsilateral to stimulation were used to score the acute benefits of stimulation. Each setting was tested after 5 min of continuous stimulation and after a subsequent period of 2 min off-stimulation washout.

Intermediate duration stimulation

After the acute stimulation assessments, settings that had shown any benefit on the clinical signs were set for a longer period of time without changing medications, and assessed with the Fahn–Tolosa–Marin Tremor Rating Scale or with the UPDRS(III) score in OFF/on-stimulation condition after at least 1 week of continuous stimulation. Patients with Parkinson’s disease were also asked to complete clinical diaries.

Chronic stimulation

The most efficacious settings (according to the clinical evaluations and the clinical diaries) were chosen and left as chronic settings. Patients with essential tremor were allowed to test whether they noted clinical differences between keeping the stimulation on for 24 h/day and stimulation only during the daytime hours (patients with Parkinson’s disease maintained stimulation on for 24 h/day). Modification of the medical treatment was allowed only when necessary. After 3 months...
of continuous stimulation with the best stimulation setting, patients underwent a double-blind assessment of stimulation efficacy. Patients with essential tremor were studied in randomized double-blind fashion after 30 min of on-stimulation and then off-stimulation or the reverse. Patients with Parkinson’s disease were randomized to be assessed first with the stimulation on or off and then the opposite 2 weeks later; on both occasions, they were evaluated with the motor UPDRS before and after an acute levodopa challenge (using the same dose they received during the preoperative assessments). During this 4-week period of assessments, patients were also required to complete clinical diaries.

Subsequently, further adjustments in the settings of stimulation were done again when needed.

After 1 year of motor cortex stimulation, patients with essential tremor had an open assessment with stimulation on and after 30 min off stimulation. An open assessment was performed in patients with Parkinson’s disease in the following order: OFF/on stimulation; after 2 h off stimulation (in OFF), after an acute levodopa challenge with the same preoperative dose of levodopa (off stimulation/ON), and after 2 h on stimulation (ON).

**Statistical analysis**

For patients with essential tremor, primary outcome measures were changes in the tremor scores in the on stimulation versus off-stimulation conditions during the double-blinded assessment at 3 months. Secondary outcome measures were changes in tremor induced by acute stimulation during the programming (compared with off stimulation), and in tremor and the activities of daily living at 1 year of chronic stimulation compared with before surgery. Due to the small number of patients with essential tremor (three) who completed the 1-year end-point assessment, data concerning tremor, activities of daily living and medication changes are presented as mean ± SD and percentage of change, and compared between ‘on stimulation’ and before surgery. Spirals were scored using an analogue scale (Bain and Findley, 1993). All the spirals collected during acute stimulation were scored by two independent raters and analysed with a series of ANOVAs and t-tests, to assess the effects of contact combinations, frequency, pulse-width, voltage and tremor side on patient scores. The total tremor score was calculated from the sum of resting, postural and action tremor, drawings and pouring water for the upper limbs, handwriting, and tremor in the lower limbs, voice and head. Contralateral and ipsilateral hand tremor subscores were also analysed. The Wilcoxon signed rank test was used to compare tremor scores and activities of daily living scores in the off stimulation and on stimulation condition during the double-blinded assessment.

For patients with Parkinson’s disease, primary outcome measures were changes in the UPDRS motor scores in OFF/on stimulation versus OFF/off stimulation condition and ON/off stimulation versus ON/on stimulation condition during the double-blinded assessment at 3 months. Secondary outcome measures were changes in the motor scores during acute stimulation programming and during the 1-year open assessment (on stimulation/Off condition compared with OFF condition before surgery), and changes in the activities of daily living UPDRS (Part II), complications of anti-Parkinson’s disease medication treatment (UPDRS Part IV), dose of anti-Parkinson’s disease medications and clinical diaries at 3 and 12 months of continuous chronic stimulation compared with before surgery. Of the UPDRS III,
Results

All patients with essential tremor had the electrode positioned over the left motor cortex. Contralateral acute hand tremor suppression was seen in four patients (Patients 1–4) in response to direct motor cortex stimulation during surgery. There was a profound insertion-related effect with improvement in the contralateral tremor and to a lesser extent ipsilateral tremor after surgery, even before the initiation of stimulation. The degree of improvement was variable and lasted an average of 4 weeks. The acute tremor improvement was scored between 15% and 70% compared with before surgery.

Four patients with Parkinson’s disease had the electrode positioned over the left motor cortex, and one patient over the right motor cortex. Acute tremor suppression was seen in one patient with Parkinson’s disease during direct motor cortex stimulation during surgery. No changes in Parkinson’s disease signs were observed in the patients soon after surgery, with the exception of tremor disappearance in the patient suffering a venous infarct (see below).

Acute stimulation

Patients with essential tremor

In the patients who had acute tremor reduction during surgery, stimulation testing was begun when tremor returned to the preoperative state (see Supplementary Data). As also noted in the patients with Parkinson’s disease, when tremor was acutely suppressed by a particular stimulation setting, the benefit persisted for several minutes (up to several hours in Patient 1) after switching off the stimulator. These findings made the clinical assessment more challenging. A significant acute improvement in the contralateral action tremor of the hand was seen with several settings in four patients (Patients 1, 3, 4 and 5). Polarity and contact effects varied between patients; in three patients bipolar stimulation was better than monopolar. Frequencies between 70 and 185 Hz and voltages between 1 and 3 V were more effective. Pulse-width changes did not significantly affect the scores.

Patients with Parkinson’s disease

No significant differences in tremor, rigidity, akinesia and gait scores were found between off- and acute on-stimulation with different settings tested on the same day (see Supplementary Data). Mild differences in contralateral rigidity and tapping test scores were noted with some settings. In one patient with severe tremor (Patient 5), selected settings at contact 0, 1 and 2 showed a significant improvement in hand tremor at 20, 130 and 185 Hz, without noticeable impact of pulse-width changes (although there was a trend towards more efficacy with wider pulse-widths).

Intermediate and chronic stimulation

Settings that significantly improved tremor during the acute testing were selected in random order for 1–2 weeks of continuous stimulation (intermediate stimulation).

Patients with essential tremor

In the two patients without overt clinical improvement, the settings were selected based on minor improvement in drawing spirals (see Supplementary Data).

Patients with Parkinson’s disease

The motor UPDRS in on stimulation/OFF conditions during the intermediate component of the study did not show any improvement compared with the preoperative score (see Supplementary Data).

The choice of the optimal setting for chronic stimulation was directed by the clinical diaries and by the clinical assessments at each follow-up visit, taking into account any objective and subjective clinical changes.

Double-blinded assessment at three months

Patients with essential tremor

The main results of the evaluations are shown in Table 2 (see Supplementary Data). There was a significant improvement in the total tremor score of the contralateral hand. Some other specific scores (action tremor, drawing, ipsilateral total and total tremor) improved, but not significantly.

Table 2 Essential tremor: main clinical results of the double-blinded study in six patients (2 h on stimulation and 2 h off stimulation, randomized) following 3 months of continuous motor cortex stimulation

<table>
<thead>
<tr>
<th></th>
<th>Stimulation off</th>
<th>Stimulation on</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total tremor score (0–72)</td>
<td>36.7 ± 14.1</td>
<td>34.8 ± 15.9</td>
<td>0.10</td>
</tr>
<tr>
<td>Contralateral hand tremor total score (0–32)</td>
<td>19.1 ± 8.7</td>
<td>17.7 ± 9.1</td>
<td>0.04</td>
</tr>
<tr>
<td>Resting tremor (0–4)</td>
<td>0.5 ± 0.5</td>
<td>0.5 ± 0.5</td>
<td>1.00</td>
</tr>
<tr>
<td>Postural tremor (0–4)</td>
<td>2.0 ± 0.7</td>
<td>1.7 ± 1.0</td>
<td>0.17</td>
</tr>
<tr>
<td>Action tremor (0–4)</td>
<td>2.7 ± 1.2</td>
<td>2.3 ± 1.4</td>
<td>0.10</td>
</tr>
<tr>
<td>Handwriting (0–4)</td>
<td>2.5 ± 1.7</td>
<td>2.5 ± 1.7</td>
<td>1.00</td>
</tr>
<tr>
<td>Drawing (0–12)</td>
<td>8.3 ± 3.5</td>
<td>7.8 ± 3.2</td>
<td>0.17</td>
</tr>
<tr>
<td>Pouring water (0–4)</td>
<td>3.0 ± 1.5</td>
<td>2.8 ± 1.8</td>
<td>0.70</td>
</tr>
<tr>
<td>Ipsilateral hand tremor total score (0–28)</td>
<td>14.7 ± 6.4</td>
<td>13.6 ± 8.8</td>
<td>0.06</td>
</tr>
<tr>
<td>Head tremor (0–8)</td>
<td>0.7 ± 1.0</td>
<td>0.7 ± 0.8</td>
<td>0.89</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD. Total tremor score: total tremor score for resting, postural and action tremor, handwriting and pouring water for both the upper limbs, and tremor in the lower limbs, voice and head.
The Fahn–Tolosa–Marin Tremor Rating Scale activities of daily living (0–27) scores did not change following 3 months of continuous stimulation (13.8 ± 6.9) compared with before surgery (13.3 ± 3.5; \( P = 0.78 \)). The main parameters of stimulation are reported in Table 3. Figure 2A shows contralateral hand results in each patient.

### Patients with Parkinson’s disease

Table 4 shows the main results of the evaluations (see Supplementary Data). Even excluding Patient 4 who suffered the venous infarct, there was virtually no difference (1.9%) between the total motor UPDRS scores in on stimulation and the scores in off stimulation in the OFF condition in the five patients with Parkinson’s disease. Some contralateral items, such as tremor and rigidity, slightly worsened in on stimulation, whereas some axial signs, such as gait and balance, were unchanged or slightly improved (Table 4). In the ON condition, the on stimulation total motor scores were mildly better (19.2%) than the off stimulation scores. Similarly, several contralateral items also mildly improved with stimulation. The total UPDRS-II in OFF was unchanged, whereas there was a mild improvement in the ON condition (Table 4). The UPDRS-IV did not vary between the off- and on-stimulation conditions (Table 4). Clinical diaries were available only for four patients, and no differences were found between the off- and on stimulation conditions. The main parameters of stimulation are reported in Table 3. Figure 2B shows the contralateral hand results in the three patients with Parkinson’s disease who had tremor at time of the assessments.

### Open assessment at 1 year

#### Patients with essential tremor

The 1-year assessment was available in only three patients (Patients 1, 3 and 6) at 11.3 ± 4.2 months after surgery (see Supplementary Data). Patient 2 died 10 months after the motor cortex stimulation surgery from metastatic prostate cancer. Patient 4 had left thalamic ventralis intermedius nucleus deep-brain stimulation surgery 10 months after motor cortex stimulation surgery (with remarkable tremor improvement) and Patient 5 had left \( \gamma \)-knife thalamotomy 9 months after motor cortex stimulation surgery (with no benefit at any time-point up to 30 months). Table 5 illustrates the main clinical results in the three patients. At 1 year, two patients showed some benefit in the total and contralateral hand tremor scores compared with before surgery. Two patients showed tremor improvement with stimulation on versus stimulation off. Medication changes are also shown in Table 5. Parameters of stimulation are shown in Table 3.

### Long-term follow-up

#### Patients with essential tremor

Both Patients 1 and 3 continued to obtain similar benefit at 5-year follow-up as reported at 1 year. Patient 1 underwent right subdural motor cortex stimulation surgery 4 years after the left surgery with modest improvement in the left hand tremor. Patient 5 had left thalamic deep-brain stimulation surgery 40 months after motor cortex stimulation surgery, and 30 months post-unsuccessful \( \gamma \)-knife thalamotomy with remarkable tremor improvement. Patient 6 died of cardiac arrest 18 months after motor cortex stimulation surgery.

#### Patients with Parkinson’s disease

Patient 1 continued to worsen cognitively and met the criteria for dementia 3 years after surgery. His last follow-up at 5 years in open fashion showed 10.0% improvement of the total motor UPDRS in OFF/on stimulation versus OFF/off stimulation conditions (47/108 versus 53/108). In Patient 2, the pulse generator expired 3 years after motor cortex stimulation surgery and was not replaced because of lack of benefit. He subsequently died 2 years after surgery.
Figure 2  Contralateral hand tremor score in six patients with essential tremor (ET) (A) and three patients with Parkinson’s disease (B) with and without motor cortex stimulation (stim) during the double-blinded study at 3 months. Only three patients with Parkinson’s disease had hand tremor at time of the assessments.

Table 4  Parkinson’s disease: main clinical results of the double-blinded study in five patients (2 weeks on stimulation and 2 weeks off stimulation, randomized) following 3 months of continuous motor cortex stimulation

<table>
<thead>
<tr>
<th></th>
<th>Medication OFF</th>
<th>Medication ON</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stimulation off</td>
<td>Stimulation on</td>
</tr>
<tr>
<td>UPDRS-II total</td>
<td>19.6 ± 4.8</td>
<td>19.6 ± 5.1</td>
</tr>
<tr>
<td>UPDRS-III total</td>
<td>41.0 ± 6.7</td>
<td>41.8 ± 10.8</td>
</tr>
<tr>
<td>Contralateral tremor (items 20, 21)</td>
<td>1.6 ± 2.1</td>
<td>2.5 ± 3.4</td>
</tr>
<tr>
<td>Contralateral rigidity (item 22)</td>
<td>3.3 ± 2.3</td>
<td>3.4 ± 1.8</td>
</tr>
<tr>
<td>Contralateral bradykinesia (items 23–26)</td>
<td>6.6 ± 2.1</td>
<td>6.6 ± 3.0</td>
</tr>
<tr>
<td>Gait (item 29)</td>
<td>2.3 ± 1.5</td>
<td>1.9 ± 1.2</td>
</tr>
<tr>
<td>Balance (item 30)</td>
<td>1.9 ± 1.0</td>
<td>1.8 ± 1.1</td>
</tr>
<tr>
<td>UPDRS-IV total</td>
<td>5.8 ± 1.3</td>
<td>5.8 ± 2.3</td>
</tr>
<tr>
<td>Dyskinesia duration (item 32)</td>
<td>0.4 ± 0.5</td>
<td>0.4 ± 0.5</td>
</tr>
</tbody>
</table>

Data are presented in mean ± SD. Difference = a positive value means a clinical worsening.
later from pneumonia. Patient 3 continued to experience motor deterioration and died of pneumonia 4 years after motor cortex stimulation surgery. Patient 4, who did not have the stimulation reactivated after the 1-year assessment, continued to deteriorate cognitively, meeting the criteria for dementia 1.5 years after surgery. Patient 5 had right thalamic deep-brain stimulation surgery 4 years after the right motor cortex stimulation surgery (which was then discontinued), with marked tremor improvement.

### Adverse events and other effects

#### Patients with essential tremor

Patient 1 noted an improvement in both restless leg syndrome and generalized arthritic pain soon after surgery. Patient 3 also noted a marked improvement of arthritic pain in both knees after surgery. Both patients continued to experience these benefits in the long-term follow-up. Two patients (Patients 1 and 2) had simple partial motor seizures during the acute testing period. Patient 2 also had one secondary generalized tonic–clonic seizure during the stimulation and was started on oral phenytoin. Other side effects were the induction of contraction of the contralateral fingers (five patients), and sensory effects (two patients) (see Supplementary Data).

#### Patients with Parkinson’s disease

One patient (Patient 4) had a cortical venous infarction during surgery, with consequent right hemiparesis and aphasia. In this patient, stimulation was started ~2 months after surgery, when he had obtained ~70% recovery in his motor functional disability, which allowed reliable testing. However, this patient experienced low-voltage threshold induced motor seizures. Due to his poor compliance with anti-epileptic medications, the motor cortex stimulation programming was not fully explored. Two patients spontaneously reported a marked improvement of bilateral knee arthritic pain since motor cortex stimulation surgery. In the immediate postoperative period, one patient had a generalized tonic–clonic seizure, whereas another patient had transient aphasia. Three patients had simple partial motor seizures restricted to the acute testing period and were started on oral phenytoin or carbamazepine. These drugs were discontinued at the end of the acute stimulation period, without recurrence of seizures afterwards. Induction of contraction and paraesthesiae of the fingers was observed during the acute testing in three patients (see Supplementary Data).

### Discussion

This is the first study reporting double-blinded outcomes from unilateral subdural motor cortex stimulation in patients with essential tremor and Parkinson’s disease. After 3 months of optimal stimulation, unilateral subdural motor cortex stimulation significantly improved contralateral hand tremor in six patients with essential tremor, but was not effective in improving motor signs in five patients with advanced Parkinson’s disease.

In contrast with a previous open study describing no clinical benefit in two patients with essential tremor with unilateral epidural motor cortex stimulation (Lyons et al., 2006), our patients with essential tremor showed contralateral tremor improvement at 3 months of chronic stimulation. Two of the three patients available for the long-term follow-up still had clinical benefit.

In patients with Parkinson’s disease, our results confirm the overall negative outcomes found in two previous open studies (Cilia et al., 2007; Gutierrez et al., 2009) and are in contrast to other open data showing motor improvement after unilateral...
epidural motor cortex stimulation (Canavero et al., 2002, 2003; Pagni et al., 2005; Benvenuti et al., 2006; Cioni, 2007; Arle et al., 2008). There was a progressive worsening of motor signs and activities of daily living regardless of stimulation on or off. In particular, the ON-medications condition was markedly worse at 1 year compared with before surgery. These observations, together with the progressive worsening of the cognitive performance in two patients, could be evidence for a negative impact of motor cortex stimulation in patients with Parkinson’s disease.

Several explanations could account for the differences between our results and those of previous studies, including the double-blinded design of our study, the different type of electrode and its epidural location (Canavero et al., 2002; Pagni et al., 2005; Cioni, 2007; Arle et al., 2008; Gutiérrez et al., 2009), more patients with essential tremor assessed in our study, and the multiple settings of stimulation that we used in acute and chronic fashion.

Unfortunately, long-term follow-up (5 years) was available only in two patients with essential tremor and one patient with Parkinson’s disease. Although any conclusion is very speculative considering this small number of subjects, the two patients with essential tremor maintained the same tremor control in the long term.

Unlike the consistently negative effects in the Parkinson’s disease group, there was variability in the clinical outcome in the essential tremor group. Two patients had notable and overall stable tremor improvement. The other four did not show satisfactory benefit at 3 months (Fig. 2). The reasons for these different outcomes are unclear. The position of the electrodes and the neurophysiology testing did not differ in the patients, suggesting that other factors are involved in the different responses to motor cortex stimulation observed in the patients with essential tremor.

Acute stimulation using a wide range of settings improved tremor in patients with essential tremor, but the benefit was transient with many of these. No specific parameters of stimulation were more effective than others, but voltages between 1 and 3 V and frequencies >50 Hz were initially more effective. However, frequencies <50 Hz seemed to be more useful for tremor improvement in the long-term follow-up. This is an intriguing point, since it supports the concept that there is virtually no ideal frequency of stimulation to suppress tremor using motor cortex stimulation, as instead seen with thalamic or subthalamic deep-brain stimulation (where high frequencies are clearly more effective on tremor than lower frequencies). Thus, the role of frequency and the other electrical parameters of stimulation on the real mechanism of action of motor cortex stimulation are largely unknown and require further investigation. Monopolar stimulation was not more effective than bipolar stimulation.

It is interesting to note that there was a prolonged benefit on tremor after switching off motor cortex stimulation, in contrast to the almost immediate tremor reoccurrence seen after stopping thalamic deep-brain stimulation. This different behaviour implies different mechanisms of action. Tentative postulated mechanisms of action of motor cortex stimulation in patients with essential tremor need to take into account possible distal neuromodulatory effects at various levels. Motor cortex stimulation might activate axons of inhibitory interneurons surrounding the electrode or efferent fibres connected with several cortical and subcortical structures (Priori and Lafaucheur, 2007).

A major adverse event occurred during the surgical procedure (a venous infarct related to injury of a bridging cortical vein) and caused permanent spastic right hemiparesis in one patient with Parkinson’s disease. Side effects induced by stimulation were transient (finger contraction), but the induction of simple partial motor seizures in five of 11 patients and one secondary generalized tonic-clonic seizure in one patient with essential tremor mandates the need for caution during the programming period.

Four patients (two with essential tremor and two with Parkinson’s disease) reported marked improvement in their arthritic pain after motor cortex stimulation surgery, one of them also in restless leg syndrome, and the patients with essential tremor experienced pain reoccurrence several hours after the stimulation was turned off. The beneficial effect on neuropathic pain from motor cortex stimulation is well-known (Tsubokawa et al., 1991, 1993), but not much has been reported about motor cortex stimulation effects on bilateral nociceptive pain or restless leg syndrome. These anecdotal observations might deserve further investigation.

In contrast to their negative response to motor cortex stimulation, one patient with essential tremor and one patient with Parkinson’s disease obtained marked benefit with thalamic deep-brain stimulation while another patient with essential tremor had unsuccessful γ-knife thalamotomy.

Conclusion

Unilateral subdural motor cortex stimulation may improve essential tremor, although the clinical benefit seems to be variable and generally modest at best. Both with double-blind assessment at 3 months and unblinded assessment at 1 year, there was no significant clinical benefit in Parkinson’s disease. More studies are needed to assess the clinical response and better understand possible predictive factors of benefit.

Acknowledgements

The authors thank Dr Janis Miyasaki for the concurrent care of some of the patients with Parkinson’s disease.

Funding

Parkinson Society Canada (New Investigator Award Program) (partial).

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