Motor cortex stimulation in patients with Parkinson disease: 12-month follow-up in 4 patients

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Object. Since the initial 1991 report by Tsubokawa et al., stimulation of the M1 region of cortex has been used to treat chronic pain conditions and a variety of movement disorders.

Methods. A Medline search of the literature published between 1991 and the beginning of 2007 revealed 459 cases in which motor cortex stimulation (MCS) was used. Of these, 72 were related to a movement disorder. More recently, up to 16 patients specifically with Parkinson disease were treated with MCS, and a variety of results were reported. In this report the authors describe 4 patients who were treated with extradural MCS.

Results. Although there have been benefits seen within the first 6 months in Unified Parkinson's Disease Rating Scale Part III scores (decreased by 60%), tremor was only modestly managed with MCS in this group, and most benefits seen initially were lost by the end of 12 months.

Conclusions. Although there have been some positive findings using MCS for Parkinson disease, a larger study may be needed to better determine if it should be pursued as an alternative surgical treatment to DBS.

(DOI: 10.3171/JNS/2008/109/7/0133)

Key Words • cortical stimulation • deep brain stimulation • motor cortex stimulation • movement disorder • Parkinson disease

During the 1950s, Heath18 stimulated the septal area in the hope that by activating pleasure centers he could alleviate pain. Later, Woolsey et al.56 would show inhibition of tremor and rigidity in patients with PD by precentral stimulation, although permanent implantation of electrodes was not attempted. In 1991, Tsubokawa and colleagues52 reported chronic stimulation of the M1 region to treat posthemorrhage stroke pain. A Medline search conducted in the years between 1991 and 2006 revealed 459 cases of treatment with MCS for either pain (378 cases),3-7, 10,12,14-16,19-25,28-32,36-40,43-47,48-50,52-54 stroke rehabilitation (9 cases),41 or movement disorders (72 cases [22 of these cases were managed with MCS and DBS,21 and some of the studies may have included previously reported cases]).4,4,8,9,11,13, 21,23,26,33-35,42 Since 2004 the largest study has been that of the Italian group who studied 16 patients and found generally positive results.34

The M1 region of cortex is in some sense the final common link between deeper circuitry coordinating movement and the spinal cord itself. It is also one of the few areas where the extrapyramidal and pyramidal systems interact. Movement disorders, such as PD, tremor, or dystonia, may respond to some type of stimulation to cells in this region, particularly in light of the suggestive aforementioned clinical precedent. Because MCS would have advantages over DBS in that it can be performed after induction of general anesthesia, does not require microelectrode recording or a stereotactic frame, and virtually eliminates the risk of an intracerebral hemorrhage, it is important to consider it as an alternative, or preliminary, procedure to DBS in the treatment of PD. We have undertaken a pilot study to examine MCS in patients with medically refractory idiopathic PD, no history of stroke or other degenerative process, and who otherwise were not appropriate for, or did not desire, DBS. This study was approved through the internal institutional review board at Lahey Clinic.

Methods

Four patients with PD were enrolled in an internal institutional review board–approved prospective pilot study to examine the use of bilateral extradural MCS as a treatment option. All patients except 1 then underwent bilateral implantation of a 4-contact Resume lead (model 3587, Medtronic, Inc.) through bilateral small craniotomies and with the intraoperative use of SSEP phase-reversal potential mapping and direct epidural motor stimulation mapping (Fig. 1). One patient instead underwent unilateral implantation. Placement of the electrode was intended to be parallel with and essentially overlying the M1 strip of cortex.

Abbreviations used in this paper: DBS = deep brain stimulation; MCS = motor cortex stimulation; PD = Parkinson disease; SSEP = somatosensory evoked potential; UPDRS = Unified Parkinson's Disease Rating Scale.
and was sutured directly to the dura to avoid movement of the electrode postoperatively. All patients had undergone a complete baseline neurological assessment, including UPDRS measurements, Sinemet challenge test, day clinic videotaping, and MR imaging of the brain in addition to a complete neuropsychological assessment. All patients also had been treated medically by our movement disorders specialist (D.A.) who had concluded that little further benefit could be expected with medical management alone. Three of the patients had decided they did not wish to try DBS first but were otherwise considered candidates for DBS. One patient was believed to exhibit a greater amount of cognitive decline in neuropsychological testing than typical for patients undergoing DBS and MCS was offered to him instead. All patients had at least a 30% improvement in their UPDRS scores when taking Sinemet (Table 1).

Both intraoperative somatosensory and motor mapping was used to determine the course of the central sulcus and the M1 region underlying the dura. Somatosensory testing consisted of placing the 4-contact Resume lead on the dura in a variety of directions, mostly perpendicular to the suspected precentral gyrus. Median and ulnar nerve SSEPs were then run (Cascade EP machine, Cadwell Laboratories, Inc.) using a 20-mA 100-μsec monopolar square pulse at a rate of 4.32 Hz. The SSEPs were recorded from the Resume lead in both a bipolar (Contacts 0–1, 1–2, and 2–3) and monopolar (all referenced to the International 10–20 System location of Fz) recording montage. The central sulcus was determined as the point where the N20 response phase reversed (Fig. 1). This was performed in multiple locations to be able to map out the central sulcus over the complete craniotomy opening. Motor mapping consisted of placing an anodal 5-mm stimulation ball probe (model E1564, Valleylab) over the M1 area referenced to a cathode placed at Fz. Stimulation consisted of trains of 5 stimuli each, at a rate of 5 trains/second, a 500-μsec pulse width, and a 4-msec interspike interval. Stimulation amplitudes were slowly increased at each location starting at 5 mA and increasing to a maximum of 25 mA. Stimulation was stopped when the first response was noted. The electromyography needles were placed in bipolar fashion (separated by 2 cm) in the orbicularis oculi, orbicularis oris, trapezius, deltoid, biceps, triceps, flexor carpi ulnaris, abductor pollicis brevis, first dorsal interosseus, quadriceps, anterior tibialis, and abductor hallucis muscles. Stimulation was performed with a Grass S-88 and 2 SIU-7 constant current stimulus isolators (Astromed-Grass). Responses were recorded on a Cadwell Cascade (Cadwell Laboratories, Inc.). Figure 2 shows an example of the findings in the extensor and abductor pollicis brevis muscles with this technique. In this fashion, 2 types of intraoperative physiological markers were able to be used in locating the precentral gyrus. 

Patient programming was started within 24 hours of electrode implantation. At the initial programming session all contacts were checked in a monopolar setting using 210 μsec and 130 Hz. The voltage was slowly increased to 4.0 V to look for adverse motor movements and sensory changes. As amplitude was slowly increased the patient’s state was evaluated. One primary concern was the possible generation of seizure activity during these tests. No sei-
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TABLE 1
The UPDRS Part III (motor) scores during off medication and on stimulation

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs) at Op</th>
<th>Disease Duration (yrs)</th>
<th>Preop</th>
<th>1 Mo</th>
<th>3 Mos</th>
<th>6 Mos</th>
<th>1 Yr</th>
<th>New 6 Mos*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>72</td>
<td>15</td>
<td>27</td>
<td>17</td>
<td>22</td>
<td>infection</td>
<td>infection</td>
<td>15</td>
</tr>
<tr>
<td>2</td>
<td>67</td>
<td>8</td>
<td>46</td>
<td>11</td>
<td>31</td>
<td>31</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>44</td>
<td>7</td>
<td>41.5</td>
<td>12</td>
<td>10</td>
<td>5</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>66</td>
<td>8</td>
<td>18</td>
<td>10</td>
<td>9</td>
<td>14</td>
<td>—</td>
<td></td>
</tr>
</tbody>
</table>

* This patient’s infection required device removal before the initial 6-month test could be performed. Therefore, this value was obtained 6 months after the second implantation. — = The stimulator was turned off in this patient at 6 months.

Fig. 2. Intraoperative photograph and tracings providing further clarification of the M1 region, particularly in delineating face from arm and hand by testing with the ball-probe stimulus. The signal was measured by performing electromyography of specific muscle groups distally, verifying the subregions of the motor cortex. APB = abductor pollicis brevis; FDI = first dorsal interosseus.

zures were noted at this time or during any later programming sessions in these 4 patients. At this initial session, Contacts 1 and 2 were left in the on position with the stimulator amplitude at 3.0 V, assuming the patient tolerated each of these settings. If the patient felt for whatever reason they could not tolerate these settings, then either Contact 3 or 0 alone was used instead. In all cases, 2 contacts were able to be activated at the initial programming session. The use of cathodal stimulation may seem odd, given that it is known that, with transcranial motor stimulation, anodal stimulation will generate D-waves and motor evoked potentials at a lower intensity than with cathodal stimulation. Due to the design of the present implantable stimulators, however, options are limited to cathodal stimulation only. Also, and more importantly, work by Hanajima et al. have found that cathodal chronic stimulation activated neurons in the motor cortex at levels lower than anodal stimulation.

Additionally, it should be noted that subthreshold stimulation is used, and modeling studies by Manola et al. have shown that cathodal stimulation (if the cathode is located directly over a gyrus) produces activation levels similar to anodal stimulation. Such activation is not necessarily at the same site but within the same fibers. If minimal benefit was noted during later sessions, more contacts were added to the monopolar configuration. If this situation failed, then one contact (either Contact 0 or 3) was placed in the cathodal mode and the other 3 contacts were set as the anode. Other changes that were investigated when stimulation either did not work, or started to lose efficacy was to change the pulse width to 410 μsec, increase the amplitude to 4.0 V, or change the frequency to either 185 Hz or 80 Hz. Table 2 shows the stimulation parameters relative to the surgical implant date.

Comparisons of UPDRS III scores in the stimulation on/
medication off phase were made using paired t-tests (SAS version 8). Baseline UPDRS III values were compared with values obtained at 1, 3, and 6 months, and 1 year for patients with available data.

Results

Overall, all 4 patients tolerated the implantation procedure well. An infection was noted in Case 1 at the 3 month visit requiring explantation of the system. An “ON” UPDRS was recorded prior to removal of the electrode. Additionally, 1 intraoperative seizure was generated during the motor mapping. There were no other complications caused by the device, the implant procedure, or postoperative programming of the device. One patient developed a superficial infection of the extension wire site and required removal of the device. He had improvement of ~ 50% over his baseline condition in dyskinesia, rigidity, and tremor, but it significantly regressed when the device was removed (this was the patient who underwent unilateral implantation). After reimplantation of the device several months later, he again improved over his preoperative baseline status by nearly 50%. Two patients had a 20–30% reduction in medication requirements. One patient, however, had a 37% increased medication requirement. One patient had a return of dyskinesia after 3 months; this patient’s condition had initially improved, but then the amplitude of stimulation was reduced and the benefit was lost. Once the patient’s stimulation amplitude was increased again, dyskinesias were again controlled.

An examination of the UPDRS Part III scores over the initial 12 months of the study is shown in Fig. 3 and detailed in Table 1. By paired t-test, there was a trend toward a significant difference in the UPDRS III scores between the baseline score and the scores at 1, 3, and 6 months. This difference was not evident at 1 year, possibly because of the smaller number of data point observations available for analysis. At 1 month, there was a mean decrease in the UPDRS III score of 21 ± 13 points (p < 0.057) from baseline. At 3 months the mean decrease from baseline was 15 ± 11 points (p < 0.081), and at 6 months it was 18 ± 16 points (p < 0.192). By 1 year there was no significant decrease in the score when compared with baseline (9 ± 9
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points; p < 0.386) for the 2 patients with sufficient follow-up data. Tables 3 and 4 show how the UPDRS scores changed in the on-medication, on-stimulation state for the UPDRS Part III scores and the total UPDRS. Table 5 shows the changes in medication over the study.

### Discussion

Deep brain stimulation has become a standard approach in treating patients with PD whose conditions have become more or less refractory to further medical management. However, many patients would be more comfortable with DBS as an option, and many more neurologists would be more comfortable referring patients for surgery, if the risk of an intracerebral hemorrhage were eliminated. This complication is rare by most accounts. In our program (~200 implants) we have not observed any significant hemorrhages and one questionable minor hemorrhage; most reported series suggest that the risk is 0.2–9.5%. Motor cortex stimulation offers the possibility of a surgical option without this risk. Moreover, the need to perform surgery with the patient awake, typically with microelectrode recording and macrostimulation, is also unnecessary for MCS. If MCS is as effective as DBS in treating the cardinal symptoms of PD and shows itself to have equal or fewer complications or more comfort for the patient overall, then it becomes a preferable option for this type of patient.

Despite several reports suggesting that MCS is beneficial in patients with PD, our results are only consistent with these findings within the first 12 months. More detailed analysis of these earlier studies, however, suggests that patients often benefited early on and then lost those gains over time. In one other preliminary study (J.M. Schwalb et al., unpublished data, 2006), in which subdural electrode placement was performed, a benefit was found only in tremor scores for 1 patient with predominant tremor. Akin-

### Conclusion

Motor cortex stimulation appears to show transient benefit in treating PD. However, different stimulation parameters, or different electrode design, may allow beneficial effects to continue for longer periods of time in these patients. Further studies should be performed to examine these outstanding questions.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>UPDRS Part III (motor) scores during on medication and on stimulation</th>
<th>New</th>
<th>On Meditation</th>
<th>Off Meditation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preop</td>
<td>1 Mo</td>
<td>3 Mos</td>
<td>6 Mos</td>
</tr>
<tr>
<td>1</td>
<td>19</td>
<td>26</td>
<td>25</td>
<td>infection</td>
</tr>
<tr>
<td>2</td>
<td>32</td>
<td>47</td>
<td>13</td>
<td>18</td>
</tr>
<tr>
<td>3</td>
<td>24.5</td>
<td>12</td>
<td>18</td>
<td>27</td>
</tr>
<tr>
<td>4</td>
<td>11</td>
<td>off</td>
<td>off</td>
<td>—</td>
</tr>
</tbody>
</table>

| Table 3 |

<table>
<thead>
<tr>
<th>Case No.</th>
<th>UPDRS Total Preop in Off Phase</th>
<th>Preop</th>
<th>1 Mo</th>
<th>3 Mos</th>
<th>6 Mos</th>
<th>1 Yr</th>
<th>New 6 Mos</th>
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<tbody>
<tr>
<td>1</td>
<td>54</td>
<td>46</td>
<td>52</td>
<td>47</td>
<td>infection</td>
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<td>71</td>
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<td>3</td>
<td>70.5</td>
<td>53.5</td>
<td>23</td>
<td>32</td>
<td>54</td>
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<td>29</td>
<td>22</td>
<td>off</td>
<td>off</td>
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</table>
### TABLE 5

**Levodopa daily milliequivalents**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Preop</th>
<th>1 Mo</th>
<th>3 Mos</th>
<th>6 Mos</th>
<th>1 Yr</th>
<th>New Levodopa (mEq)</th>
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<tr>
<td>1</td>
<td>2140</td>
<td>2140</td>
<td>1874</td>
<td>infection</td>
<td>1044 (pre)</td>
<td>1320 (post)*</td>
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<td>754</td>
<td>654</td>
<td>1054</td>
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<td>850</td>
<td>1000</td>
<td>910</td>
<td>950</td>
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<tr>
<td>4</td>
<td>1090</td>
<td>1320</td>
<td>1090</td>
<td>1090</td>
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</tr>
</tbody>
</table>

* The "pre" value is the medication level prior to placement of the second implant, and the "post" value is the level 1 month after the second implant was placed.

### References


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