Assessing the microlesion effect of subthalamic deep brain stimulation surgery with FDG PET

Clinical article

MICHAEL POURFAR, M.D.,1 CHENGKE TANG, M.D.,2 TANYA LIN, M.D.,1,3 VIJAY DHAWAN, PH.D.,1,2 MICHAEL G. KAPLITT, M.D.,4 AND DAVID EIDELBERG, M.D.1,2

1Departments of Neurology and Medicine, North Shore University Hospital, Manhasset; 2Center for Neurosciences, The Feinstein Institute for Medical Research, North Shore-Long Island Jewish Health System, Manhasset; 3Albert Einstein College of Medicine, Bronx; and 4Department of Neurological Surgery, Weill Medical College of Cornell University, New York, New York

Object. The authors investigated whether the insertion of deep brain stimulation electrodes into the subthalamic nucleus can alter regional brain metabolism in the absence of stimulation.

Methods. Six patients with Parkinson disease (PD) underwent preoperative FDG PET scanning, and again after STN electrode implantation with stimulation turned off.

Results. Compared with baseline values, glucose utilization was reduced in the postoperative off-stimulation scans in the putamen/globus pallidus and in the ventral thalamus (p < 0.01), and there was increased metabolism in the sensorimotor cortex and cerebellum (p < 0.005). The expression of a specific PD-related spatial covariance pattern measured in the FDG PET data did not change after electrode implantation (p = 0.36), nor was there a significant change in clinical motor ratings (p = 0.44). Differences in PD-related spatial covariance pattern expression among the patients after electrode implantation did, however, correlate with the number of microelectrode recording trajectories placed during surgery (r = –0.82, p < 0.05).

Conclusions. These findings suggest that electrode implantation can impart a microlesion effect on regional brain function. Nonetheless, these local changes did not cross the threshold of network modulation needed to achieve clinical benefit. (DOI: 10.3171/2008.12.JNS08991)

KEY WORDS • deep brain stimulation • microlesion • Parkinson disease

Abbreviations used in this paper: BA = Brodmann area; DBS = deep brain stimulation; GP = globus pallidus; MER = microelectrode recording; PD = Parkinson disease; PDRP = Parkinson disease–related pattern; RMANOVA = repeated measures analysis of variance; STN = subthalamic nucleus; UPDRS = Unified Parkinson’s Disease Rating Scale; VOI = volume of interest.
Metabolic microlesion after STN DBS electrode placement

Methods

Patients and Procedures

Six patients with PD were included in this study: 5 men, and 1 woman with a mean age 61.7 ± 8.0 years (± SD). The mean UPDRS motor rating in these patients was 26.8 ± 6.9, and they experienced an effective 24 ± 4% improvement (p < 0.001) after bilateral STN DBS implantation. The surgical procedures used MER and were performed in accordance with previous studies.12 The minimum number of MER trajectories was used with ≥ 4 mm of STN recording plus the presence of movement-responsive cells constituting an acceptable trajectory. One patient received a total of 2 trajectories (1 per side), 2 patients received a total of 3 trajectories, and 3 patients received 4 trajectories. Microelectrode recording was followed by confirmatory macroelectrode testing prior to implantation of DBS electrodes.

Scanning with FDG PET was performed preoperatively (within 3 months of surgery) and again at an average of 20 months postoperatively. In both imaging sessions, antiparkinsonian medications were discontinued for at least 12 hours before scanning, and DBS was turned off ~ 1 hour before the postoperative PET session. Positron emission tomographic imaging was performed as described previously2 with the GE Advance tomography (General Electric Medical Systems) at the North Shore University Hospital. Ethical permission for these studies was obtained from the Institutional Review Board of North Shore University Hospital, Manhasset, New York. All patients received a detailed explanation of the procedures and provided written consent for their participation.

Statistical Parametric Mapping

Image preprocessing and analysis were performed using SPM99 (Institute of Neurology, London) implemented in MATLAB 6.1 (Mathworks). To test for a microlesion effect caused by electrode implantation surgery, FDG PET scans obtained before and after surgery were compared on a voxel basis using the paired t-test option in SPM. To account for differences in the between-scan intervals, this value was entered as a nuisance variable in the analysis of STN DBS scan data.

We also compared these changes to those occurring 12 months after therapeutic STN lesioning.14 Because the subthalamicotomies were unilateral, images from the left-sided subthalamotomies were flipped such that the lesioned hemispheres appeared on the right. Likewise, the left hemispheres of the STN DBS patients were flipped to the right and averaged prior to the between-group comparison. We used conjunction analysis to identify regions in which the STN interventions gave rise to similar metabolic changes, for example areas where both procedures led to either increases or decreases in regional glucose utilization.

For both the within- and between-group contrasts, the results were thresholded at p = 0.001, uncorrected at the voxel-level, and considered significant at an extent threshold of p < 0.05. In the between-group comparison, significant regions were further analyzed using a VOI approach in which a 4-mm sphere was centered on each peak voxel.2,15 The VOI values for each region were compared across the 2 STN surgical groups using 2 × 2 RMANOVA with posthoc Bonferroni tests. The results were considered significant at p < 0.05.

Network Assessment

Parkinson disease–related pattern expression was quantified on an individual case basis using an automated voxel-based algorithm.2,9,15 To assess network changes before and after STN electrode implantation, we computed PDRP expression for the whole brain in the pre- and postoperative scans. We correlated the changes in PDRP expression with microlesioning with the total number of MER trajectories placed during electrode implantation, the interscan interval, and the UPDRS motor ratings using Pearson's product-moment correlations. Additionally, changes in PDRP scores for the STN DBS microlesion group were compared with those for the subthalamotomy group using 2 × 2 RMANOVA with posthoc testing as described above. The results were considered significant at p < 0.05.

Results

Metabolic Changes After STN DBS Electrode Implantation

Voxel-based comparison of metabolic scans acquired preoperatively and after STN electrode implantation revealed changes in several regions (Fig. 1; Table 1). Even without stimulation, the DBS cohort exhibited significant metabolic reductions in the putamen extending into the adjacent GP, and in the ventrolateral and mediodorsal thalamic regions, extending caudally into the region of the STN. Significant metabolic increases were noted in the left occipital cortex (BA 19), the right sensorimotor cortex (BA 3, 4) and in the right cerebellar hemisphere (lobule VI).

On average, there was no difference in PDRP expression in the baseline and postoperative scans (p = 0.36). When analyzed on an individual case basis, the changes in PDRP expression after STN electrode implantation were found to be variable. Two patients exhibited a postoperative increase in network activity while a postoperative reduction in this measure was shown in the other 4. These changes correlated with the total number of microelectrode passes that were performed (r = −0.82, p < 0.05), and did not correlate with changes in the motor UPDRS ratings (p = 0.44) or with the interscan interval (p = 0.2).

Comparison With Metabolic Changes Following Therapeutic STN Lesioning

Conjunction analysis revealed that both the STN microlesion and the therapeutic lesioning groups demonstrated postoperative metabolic reductions in the GP (16, −2, 8; Zmax = 4.45, p = 0.016; false discover rate corrected) and the mediodorsal and ventrolateral thalamic nuclei (8, −16, 10; Zmax = 5.38, p = 0.004, false discovery rate corrected). However, the magnitude of metabolic reductions in both regions (Fig. 2) differed for the 2 groups (GP: F(1,10) = 15.8, p < 0.005; thalamus: F(1,10) = 6.8, p < 0.05; RMANOVA). In each region, these metabolic re-
ductions were greater in the subthalamotomy group (GP: p < 0.001 for subthalamotomy, p < 0.005 for microlesion; thalamus: p < 0.001 for subthalamotomy, p < 0.005 for microlesion; posthoc Bonferroni tests).

The PDRP changes with surgery differed (F_{(1,10)} = 6.2, p < 0.05; RMANOVA) across the 2 groups (Fig. 3) in that a significant reduction in PDRP expression was present only in the subthalamotomy group (p = 0.001), but not in the microlesion group (p = 0.42). Similarly, there was a disparity in changes in motor ratings across the 2 groups (F_{(1,9)} = 22.3, p < 0.005; RMANOVA), with significant improvement only in the subthalamotomy group (p < 0.001).

Discussion

Changes in Regional Glucose Metabolism

Subthalamic nucleus DBS procedures have repeatedly been demonstrated to modulate metabolic activity at both the regional and network level. In this PET study, we found that electrode implantation itself imparted a microlesion effect on regional metabolism in the STN, GP, and ventral thalamus. These changes differed in degree, rather than in localization, from those observed during actual stimulation. The regions most impacted by the microlesion effect were those associated both directly and indirectly with STN activity. Indeed, we have recently demonstrated with FDG PET that individual patient differences in regional metabolism in the putamen/GP, thalamus, and sensorimotor cortex correlated with intraoperatively recorded STN firing rates in patients with PD. It was therefore not surprising that the same regions were found to be involved in the STN microlesion effect. Similarly, in a recent FDG PET study, the metabolic effects of microlesioning were observed in the STN and GP; functional changes in other brain regions were not assessed.

Also anticipated was the finding that the degree of local metabolic change in these areas was smaller in the off relative to the on stimulation state. The relatively weaker changes off stimulation may have reflected a waning of the microlesion effect over time, as has been reported in the GP of patients undergoing therapeutic STN lesioning. Evidence for a small but measurable microlesion effect can also be inferred from past reports. Comparing postoperative SPECT scans acquired in the on versus off stimulation condition, Sestini et al. identified cortical regions in which measures of regional perfusion off-stimulation were closer to the on-stimulation condition than the preoperative state. In contrast to our previous findings that STN stimulation further reduced pallidal metabolism, the authors of a recent study suggested that stimulation increases GP metabolic activity from the microlesion level to that of the preoperative baseline state. The observed pallidal increases in metabolism with stimulation may relate in part to the targeting of the zona incerta in one third of their patients. Stimulation of adjacent white matter pathways may have led to the metabolic increases that were observed in the GP and thalamus. More studies will be needed to clarify the effect of STN stimulation on pallidal metabolism in humans. It is however likely that the clinical effects of STN DBS relate to functional changes occurring in the thalamus and cortical motor areas as well as other downstream nodes of the spatially distributed metabolic network that mediates PD motor symptoms.
Changes in Metabolic Network Activity

The pallidum and thalamus are key nodes of the PDRP network. Nonetheless, despite the observed metabolic decline in these regions relative to baseline, there was no network-level change in PDRP expression. This disparity implies the presence of a threshold for the degree of regional change that is needed to affect overall network activity and clinical outcome. Although the UP-DRS will probably remain the gold standard for assessing the outcome of surgical interventions for PD, metabolic imaging can provide objective ancillary information regarding treatment response.

Interestingly, differences in network modulation among the patients correlated with the number of MER trajectories: individuals with a discernible network effect received more surgical passes through the STN during surgery. While the number of patients was small, this observation suggests that procedural variations can affect functional outcome. This source of variation may be relevant

**TABLE 1:** Brain regions with significant changes in metabolic activity following STN DBS electrode insertion

<table>
<thead>
<tr>
<th>Brain Region</th>
<th>Coordinates</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>Zmax</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreases (DBS off &lt; preop)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VL thalamus, left</td>
<td>−12 −18 2</td>
<td>4.73</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MD thalamus, right</td>
<td>8 −18 4</td>
<td>4.44</td>
<td>0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lateral putamen, right</td>
<td>24 6 −8</td>
<td>4.40</td>
<td>0.002</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Putamen/GP, right</td>
<td>20 10 2</td>
<td>4.09</td>
<td>0.008</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increases (DBS off &gt; preop)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occipital association cortex</td>
<td>−36 −84 20</td>
<td>4.52</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postcentral gyrus (BA 3,4),</td>
<td>48 −18 20</td>
<td>4.24</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebellum, lobule VI‡</td>
<td>34 −48 −24</td>
<td>3.70</td>
<td>0.004</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Precuneus (BA 31), left</td>
<td>−6 −68 20</td>
<td>3.59</td>
<td>0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Coordinates were assessed using the Montreal Neurological Institute standard space. Abbreviations: MD = mediodorsal; VL = ventrolateral.
† Thresholded at uncorrected voxel-level of p < 0.001 followed by extent correction.

**FIG. 2.** Bar histogram comparing the magnitude of the metabolic reductions that occur with both interventions. In both the thalamus and the GP, the degree of metabolic reduction is greater (p < 0.05, arrows) in the subthalamotomy group relative to the microlesion cohort (p < 0.005; **p < 0.001; postoperative versus preoperative metabolic values are compared using posthoc Bonferroni tests).

**FIG. 3.** Bar histogram demonstrating microlesion versus therapeutic lesioning (subthalamotomy) effect on PDRP expression. A significant reduction in PDRP is observed only in the subthalamotomy cohort (p = 0.001), but not in the microlesion group (p = 0.42).
in comparing imaging results from patients with DBS to those from patients undergoing newer surgical techniques that involve a greater degree of local intervention.

Our findings do not exclude the possibility that the procedure initially impacted network metabolism, and that this effect waned by the time of the follow-up scan. Clinical reports suggest that a microlesion benefit is sometimes appreciable for 2 months after surgery. The effect of long-term stimulation on brain metabolism at the regional and network levels is also not known. The cardinal motor features of PD typically reemerge within minutes of turning off the stimulation. The authors of previous publications have suggested that the metabolic effects of DBS also wane quickly following the cessation of stimulation. Nevertheless, a low level of residual benefit from stimulation may persist and influence neuroimaging findings. Assessing the influence of microlesion on cerebral function prior to the initiation of stimulation will be a way to determine the true magnitude of this effect.

Conclusions

Following the implantation of DBS electrodes into the STN, we found a significant reduction in glucose metabolism (the microlesion effect) in the putamen/GP and thalamus, even in the absence of stimulation. These metabolic reductions colocalized with but were less dramatic than the changes observed in PD patients who had undergone therapeutic STN lesioning (subthalamotomy). Furthermore, there were no significant changes in motor UPDRS ratings or in PD network activity, suggesting that the functional effects of microlesioning did not reach the threshold needed for clinical benefit. These findings imply that the surgery itself can affect cerebral metabolism independent of stimulation condition. Such changes should be taken into account when assessing the impact of DBS or other stereotactic procedures on brain function.

Disclaimer

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Acknowledgments

The authors thank Ms. Toni Flanagan for manuscript preparation and Mr. Claude Margouleff for technical support.

References


Manuscript submitted August 7, 2008.
Accepted December 8, 2008.

Please include this information when citing this paper: published online March 20, 2009; DOI: 10.3171/2008.12.JNS08991.

Address correspondence to: David Eidelberg, M.D., Center for Neurosciences, The Feinstein Institute for Medical Research, North Shore-LIJ Health System, 350 Community Drive, Manhasset, New York 11030. email: david1@nshs.edu.