Activation of the anterior cingulate cortex by thalamic stimulation in patients with chronic pain: a positron emission tomography study

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Object. Deep brain stimulation (DBS) of the sensory thalamus has been used to treat chronic, intractable pain. The goal of this study was to investigate the thalamocortical pathways activated during thalamic DBS.

Methods. The authors compared positron emission tomography (PET) images obtained before, during, and after DBS in five patients with chronic pain. Two of the five patients reported significant DBS-induced pain relief during PET scanning, and the remaining three patients did not report any analgesic effect of DBS during scanning. The most robust effect associated with DBS was activation of the anterior cingulate cortex (ACC). An anterior ACC activation was sustained throughout the 40 minutes of DBS, whereas a more posteriorly located ACC activation occurred at a delay after onset of DBS, although these activations were not dependent on the degree of pain relief reported during DBS. However, implications specific to the analgesic effect of DBS require further study of a larger, more homogeneous patient population. Additional effects of thalamic DBS were detected in motor-related regions (the globus pallidus, cortical area 4, and the cerebellum) and visual and association cortical areas.

Conclusions. The authors demonstrate that the ACC is activated during thalamic DBS in patients with chronic pain.

Key Words • thalamus • pain • positron emission tomography scanning • cingulate cortex

Analgesia and inhibition of nociceptive neuronal activity in experimental animals can be induced by electrical stimulation of several brain regions including the periaqueductal gray matter, the nucleus raphe magnus, and the sensory thalamus.1,18,24 These findings motivated the development of DBS for pain control in humans. Although rates of clinical success vary widely across studies,20,31 chronic stimulation of the thalamic ventral caudal nucleus or the medial lemniscus has been shown to be effective in reducing chronic pain in some patient groups.25,26,31,42 The mechanism underlying the analgesic effect of thalamic DBS is unknown; however, it probably involves activation of thalamocortical pathways and changes in cortical activity. Classic targets of thalamocortical pathways associated with nonnociceptive somatosensory processes include the SI and SII. Recent brain imaging studies have revealed pain-related activations in the anterior insula, SI, SII, and ACC,1,4,6,7,11,13,14,16,17,29,36,39,41,44 although there is notable variability among specific activation sites within these regions. Thalamic stimulation that evokes paresthesias and produces analgesia might, therefore, be expected to lead to activity changes in tactile and pain-related cortical regions.

Our lack of understanding of the brain structures activated during thalamic stimulation and DBS-induced analgesia in humans is due, in part, to the limited applicability of invasive experimental techniques. Positron emission tomography is a relatively noninvasive imaging technique that is sensitive to changes in rCBF and can be used as an indirect measure of neuronal activity in humans.34 Positron emission tomography scanning has recently been used to reveal cortical effects during stimulation of the thalamus, globus pallidus, and subthalamic nucleus in patients with Parkinson’s disease8,12,15,30 and in patients suffering from pain.21 These studies have provided important insights into the mechanisms underlying the clinical effects of DBS. Therefore, PET imaging may be a useful tool for an examination of the effects of DBS in patients with chronic pain. The aim of the present study was to use PET imaging to determine which cortical areas are modulated during thalamic stimulation in patients with pain. We predicted that one or more of the cortical regions associated with sensory processing and/or pain—SI, SII, insula, and ACC—would be affected by thalamic DBS. A brief report of these findings has been presented previously in abstract form.8

Abbreviations used in this paper: ACC = anterior cingulate cortex; DBS = deep brain stimulation; PET = positron emission tomography; rCBF = regional cerebral blood flow; SI = primary somatosensory cortex; SII = secondary somatosensory cortex.
Thalamic stimulation activates anterior cingulate cortex

Table 1: Characteristics of five patients undergoing DBS during PET scanning*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Diagnosis &amp; Pain Location</th>
<th>DBS Duration (mos)</th>
<th>DBS Laterality</th>
<th>Analgesics on Day of Scan</th>
<th>Analgesia During DBS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>64, F</td>
<td></td>
<td>anesthesia dolorosa/facial pain</td>
<td>18</td>
<td>rt</td>
<td>none</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>40, M</td>
<td></td>
<td>paraplegia/leg pain</td>
<td>9</td>
<td>lt</td>
<td>oxycodone, baclofen, valium, amitriptyline</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>50, F</td>
<td></td>
<td>lower limb amputation/stump pain</td>
<td>4</td>
<td>rt</td>
<td>SR oral morphine, amitriptyline, diazepam</td>
<td>60–45</td>
</tr>
<tr>
<td>4</td>
<td>42, F</td>
<td></td>
<td>atypical facial pain</td>
<td>16</td>
<td>rt</td>
<td>SR oral morphine, carbamazepine, baclofen, amitriptyline</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>49, F</td>
<td></td>
<td>spinal AVM/deafferentation leg pain</td>
<td>16</td>
<td>lt</td>
<td>none</td>
<td>0</td>
</tr>
</tbody>
</table>

* AVM = arteriovenous malformation; SR = sustained release.
† Time between DBS implantation and PET scanning.

Clinical Material and Methods

Patient Population and DBS

Five right-handed patients (four men and one woman) aged 40 to 64 years, in whom thalamic DBS electrodes had been implanted, gave informed consent to undergo procedures approved by the University of Toronto Human Subjects Review Committee. The DBS electrodes had been implanted to treat the patients’ intractable chronic pain, which involved the face (anesthesia dolorosa or atypical facial pain) or a lower limb (stump pain or deafferentation pain) (Table 1). All patients had undergone stereotactic functional surgery at our center. The surgery had included microelectrode thalamic mapping and implantation of thalamic DBS electrodes (Medtronic, Inc., Minneapolis, MN) in the ventral caudal nucleus and the nearby medial lemniscus. Positron emission tomography scans were obtained 4 to 18 months after electrode implantation. Before PET scanning, a test of the effects of DBS at stimulus parameters used clinically and for the PET study (94 ± 62 Hz, 0.2 msec, and 0.2–3 V) revealed that thalamic stimulation elicited tingling sensations referred to the distribution of each patient’s pain. However, the tingling was strongest at the onset of stimulation and often diminished or completely subsided as the stimulation continued. All patients had significant DBS-induced pain relief immediately after surgery. However, at the time the PET study was performed, three of the patients were no longer obtaining good pain relief during thalamic DBS. On the day of scanning, three patients were taking their usual analgesic medications, whereas the other two patients had not taken any analgesic medications within 12 hours before scanning (Table 1).

Positron Emission Tomography Scanning

A PET scanner (Scanditronix GEMS-2048; Medical AB, Uppsala, Sweden) was used to obtain all brain images. Before scanning, procedures and risks were explained to each patient. The patients were instructed to keep their eyes closed and count silently during all scanning procedures. Verbal ratings of pain intensity based on a scale ranging from 0 (no pain) to 10 (most intense pain imaginable) were obtained immediately before each of six 60-second scans following a 40-mCi intravenous bolus injection of [15O]H2O. During each scan, images were obtained simultaneously from 15 axial brain slices, parallel to the anterior–posterior commissure line, from the superrior aspect of the cerebral cortex to the level of the cerebellum with an interslice spacing of 6.5 mm. The total field of view of the scanner in the vertical axis (z plane) was 10 cm. Head motion was limited using a thermoplastic mask individually molded to the patient’s face. Scans were obtained two times before DBS was initiated (pre1 and pre2), at the beginning and after 30 minutes of DBS (stm1 and stm2, respectively), and two times after DBS ceased (post1 and post2). The timing of DBS in relation to the sequence of PET scans is shown in Fig. 1.

Statistical Analysis

All data were analyzed and visualized using the statistical parametric mapping technique (SPM95 or SPM96; Wellcome Department of Cognitive Neurology [1996]) implemented with Matlab software (Mathworks, Inc., Sherborn, MA). The number of scans obtained in each patient was limited by the maximum allowable dosage of [15O]H2O. Therefore, to enhance the relatively low statistical power inherent in individual patient data, a group analysis was performed to assess DBS-associated changes in rCBF. Raw data were reconstructed using transmission-attenuation correction. To facilitate pooling of data across patients, the data obtained from patients receiving left-sided stimulation were flipped from the left to the right side and pooled with data obtained from those receiving right-sided stimulation. Thus all group data are presented as right thalamic stimulation. Images were aligned, transformed into Talairach standard space, and normalized to the global blood flow (average = 50). Voxels were spatially smoothed using a 15-mm gaussian filter. A t statistic was used to compare each pixel under the six scan conditions (pre1 and pre2, stm1 and stm2, and post1 and post2) and was converted to a z score by using a probability cutoff value less than 0.05. Comparisons were made to inspect differences between each pair of scan conditions (for

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FIG. 1. Scanning protocol. The time line indicates the time at which each PET scan was obtained before (pre1 and pre2), during (stm1 and stm2), and after (post1 and post2) DBS.
example, by subtracting pre2 from stm1) and for each general DBS state (by subtracting all pre from all stm, and so forth).

Results

Before PET scanning commenced and with stimulators turned off, all patients reported a significant level of pain ranging from 5.5 to 8 on the 10-point scale. This level of pain remained relatively constant throughout the first 20 minutes of the experiment, during which time pre-DBS scans were acquired (Fig. 2). Three of the five patients did not report any change in their ongoing pain during DBS, despite experiencing paresthesias within the distribution of their pain. However, during the period of DBS, two patients reported a large reduction in their ongoing pain. In both cases, pain was reduced by approximately 50% within the first 2 minutes of DBS and complete pain relief was achieved in one of these patients after 30 minutes of stimulation. This analgesic effect disappeared immediately after cessation of DBS. Figure 2 shows the time course of pain reports for each patient.

A group analysis of changes in rCBF during thalamic DBS revealed stimulation-related increases within the ACC, the globus pallidus (likely the external portion), and a region lateral to the thalamus identified as the internal capsule (Table 2). This latter activation likely represents stimulation sites that varied somewhat across patients and, hence, the location became blurred due to population averaging and the spatial smoothing and transformation into Talairach space. The most pronounced activation observed during DBS was located in the ACC. Increased rCBF within two separate regions of the ACC could be distinguished. A rostral region of the contralateral ACC (Area 32) was activated throughout the 40-minute thalamic stimulation and a more posterior region of the ipsilateral ACC (Area 24) was activated at a delay after onset of thalamic stimulation. This more posterior ACC region demonstrated some recovery immediately after cessation of DBS and a pronounced decrease in rCBF 12 minutes after DBS ended. Figure 3a and c shows the locations of these regions within the ACC. The time course and magnitudes of changes within these regions are shown in Fig. 3b and d, indicating that there was no clear relationship between the degree of stimulation-evoked pain relief and the magnitude of rCBF change in either region of the ACC.

A number of regions demonstrated decreased rCBF associated with the period of DBS, including the visual and motor cortices, the cerebellum, and other parietal and temporal areas (Table 2).

Discussion

The main finding of this study is that thalamic DBS in patients with chronic pain activates the ACC. The ACC receives nociceptive input from the thalamus and contains neurons that are modulated by painful stimuli. In experimental animals, an analgesic effect has been reported during either lidocaine block or electrical stimulation of the ACC. In humans, surgical lesioning of the ACC can attenuate intractable cancer pain and alter the perception of noxious thermal stimuli. Positron emission tomography studies have demonstrated this region’s involvement in pain processes.

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**TABLE 2**

Deep brain stimulation–related changes in rCBF in a group of five patients

<table>
<thead>
<tr>
<th>Region of Activation</th>
<th>Side</th>
<th>Location (x, y, z)</th>
<th>Z Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>increases in rCBF throughout thalamic DBS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>anterior ACC (Area 32)</td>
<td>contralat</td>
<td>–12, 30, 16</td>
<td>3.50†</td>
</tr>
<tr>
<td>globus pallidus</td>
<td>ipsilat</td>
<td>16, –2, 4</td>
<td>2.90‡</td>
</tr>
<tr>
<td>internal capsule</td>
<td>ipsilat</td>
<td>26, –24, 16</td>
<td>2.79‡</td>
</tr>
<tr>
<td>decreases in rCBF throughout thalamic DBS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>visual cortex</td>
<td>ipsilat</td>
<td>6, –94, 0</td>
<td>3.75†</td>
</tr>
<tr>
<td>inferior parietal lobule</td>
<td>ipsilat</td>
<td>52, –36, 36</td>
<td>3.72†</td>
</tr>
<tr>
<td>inferior temporal gyrus</td>
<td>ipsilat</td>
<td>42, –10, –28</td>
<td>3.51†</td>
</tr>
<tr>
<td>visual cortex</td>
<td>ipsilat</td>
<td>44, –74, –16</td>
<td>3.41‡</td>
</tr>
<tr>
<td>motor cortex</td>
<td>ipsilat</td>
<td>56, 2, 12</td>
<td>3.36‡</td>
</tr>
<tr>
<td>inferior parietal lobule</td>
<td>contralat</td>
<td>–56, –48, 28</td>
<td>3.27‡</td>
</tr>
<tr>
<td>auditory–visual association area</td>
<td>contralat</td>
<td>–58, –48, –12</td>
<td>3.26‡</td>
</tr>
<tr>
<td>cerebellum</td>
<td>contralat</td>
<td>–38, –48, –28</td>
<td>3.25‡</td>
</tr>
<tr>
<td>increases in rCBF 30 mins after thalamic DBS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>posterior ACC (Area 24)</td>
<td>ipsilat</td>
<td>4, –14, 32</td>
<td>2.52‡</td>
</tr>
<tr>
<td>anterior ACC</td>
<td>contralat</td>
<td>–12, 24, 20</td>
<td>2.32‡</td>
</tr>
<tr>
<td>globus pallidus</td>
<td>ipsilat</td>
<td>16, –4, 4</td>
<td>2.53‡</td>
</tr>
<tr>
<td>globus pallidus</td>
<td>contralat</td>
<td>–16, –8, –4</td>
<td>2.26‡</td>
</tr>
</tbody>
</table>

* Peak activations or deactivations are localized according to the left–right (x), anterior–posterior (y), and superior–inferior (z) coordinates of the atlas by Talairach and Tournoux. The side of activation or deactivation is defined by its relation to the side stimulated. The most statistically significant and relevant activations are listed.

† p < 0.001.
‡ p < 0.05.

**Fig. 2.** Graph showing the analgesic effect of DBS based on pain intensity ratings obtained from five patients before, during, and after DBS. Pain was significantly reduced during DBS in only two patients (one patient who was an amputee and another who was paraplegic; filled circles), both of whom experienced lower leg pain.
and its sensitivity to the behavioral state.36 In the present study, there were two distinct ACC areas activated, one in the anterior and the other in the posterior portion of the ACC. The locations of these two regions correspond to the posterior pain region described earlier and an anterior attention/general alerting region described in recent imaging studies.10,13 Interestingly, in recent human electrophysiological studies, neurons responsive to noxious stimuli were identified in the posterior ACC28 and neurons modulated during performance of attention-demanding tasks were found slightly more anterior in the ACC (unpublished data). The increased rCBF in the posterior ACC reported in this study indicates that thalamic DBS may alter pain processing and/or the descending inhibition of pain by affecting this region. In contrast, anterior ACC activation may be related to patients’ awareness of the DBS-evoked paresthesias. Interestingly, activation of the posterior ACC was detected after 30 minutes of DBS but not at the onset of stimulation, in contrast to the anterior ACC, which was activated throughout the period of DBS. Therefore, the processes underlying activation of these two regions differ; the former presumably is not related to direct

Fig. 3. Positron emission tomography scans and graphs depicting sustained and delayed ACC activations. The locations and time courses of activations in the contralateral anterior ACC (aACC; A and B) and ipsilateral posterior ACC (pACC; C and D) are shown. The SPM maps were derived from the following computations: all STM – all pre (A) and STM – pre2 (C) across all patients. Time-course data within the aACC and pACC are shown for each patient. The analgesic effect of DBS during PET scanning in each patient is indicated by open or closed circles.
activation from the thalamus but, rather, is dependent on additional neuronal processing that probably involves other structures. Duncan, et al., also noted that some of their DBS-induced activations were stronger after 30 minutes of DBS than at DBS onset.

In a study similar to ours, Duncan, et al., reported some ACC activation in patients with pain that was just subthreshold for statistical significance. This weaker activation may be due to somewhat different electrode placements or stimulation parameters. Duncan, et al., also reported DBS-evoked activation of the insula. However, the patients in their study, in contrast to those in our study, experienced thermal sensations during DBS. The insula has been shown to be activated by cold and warm stimuli. Thus the lack of an insula activation in the present study may be caused by the fact that DBS in our patients did not evoke cold or warmth.

We had expected that several other cortical regions associated with tactile sensations and pain would be affected by thalamic DBS. The lack of strong, detectable activations in the thalamocortical targets SI and SII was surprising. However, methodological issues may have precluded detection of these other activations. For instance, we studied a small, heterogeneous patient population in which DBS was used to treat pain in different body regions. Therefore, in each patient, paresthesias were evoked in a different body region, thus activating different portions of the SI and SII, which would not be detected in the pooled data. Furthermore, the paresthesias often diminished throughout the duration of stimulation and, in some instances, were absent at the time of late DBS “on” scans. Another possible problem might have been that the baseline rCBF and excitability of cortical regions were differentially affected by the various drug regimens. Also, only two patients reported pain relief during PET scanning. Therefore in our study, a separate analysis of those patients with and those without pain relief was hampered by a low statistical power. Because all the patients did obtain some relief of pain from DBS, at least initially, it is possible that the loss of efficacy in some patients was due to changes over time in neural processing in other centers downstream from the ACC. Therefore, activation of the posterior ACC may relate to analgesia, even though it no longer corresponded well to the actual analgesia experienced by the patients during the PET scanning.

In addition to activation of the ACC, in the present study we have identified several cortical and subcortical activations associated with DBS, the implications of which are somewhat unclear. For instance, basal ganglia activation may be related to this area’s involvement in pain. Alternatively, changes in motor areas (the globus pallidus, motor cortex, and cerebellum) during DBS may reflect a motor reaction to the ongoing paresthesias evoked by DBS. Other deactivations in the visual cortex and in Areas 40, 20, and 37 are not easily accounted for by direct connectivity but may reflect higher cognitive activity triggered by thalamic DBS. It is interesting that in the treatment of tremor in parkinsonian patients, DBS of the motor thalamus at sites only a few millimeters anterior to those in the present study also led to changes in blood flow in similar regions of the visual and association cortices but did not produce changes in the ACC.

In conclusion, these data demonstrate that the ACC is activated during thalamic stimulation in patients with chronic pain. Although the locations of posterior and anterior ACC activation sites correspond to previously reported pain- and attention-related regions, respectively, further investigation into the role of the ACC in the analgesic effect of DBS requires a larger and more homogeneous population of patients with pain.

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