Is the Target for Thalamic Deep Brain Stimulation the Same as for Thalamotomy?

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Abstract: Deep brain stimulation (DBS) has virtually replaced thalamotomy for the treatment of essential tremor. It is thought that the site for DBS is the same as the optimal lesion site; however, this match has not been investigated previously. We sought to determine whether the location of thalamic DBS matched the site at which thalamotomy would be performed. Eleven patients who had detailed microelectrode recording and stimulation for placement of DBS electrodes and subsequent successful tremor control were analysed. An experienced surgeon, blinded to outcome and final electrode position, selected the ideal thalamotomy site based on the reconstructed maps obtained intraoperatively. When the site of long-term clinically used DBS and theoretical thalamotomy location was calculated in three-dimensional space and compared for each of the \( x \), \( y \), and \( z \) axes in stereotactic space, there was no significant difference in the mediolateral location of DBS and theoretical lesion site. There was also no difference between the theoretical lesion site and the placement of the tip of the electrode; however, the active electrodes used for chronic stimulation were significantly more anterior (\( P = 0.005 \)) and dorsal (\( P = 0.034 \)) to the ideal thalamotomy target. This mismatch may reflect the compromise required between adverse and beneficial effects with chronic stimulation, but it also suggests different mechanisms of effect of DBS and thalamotomy. © 2003 Movement Disorder Society

Key words: thalamus; microelectrode recording; deep brain stimulation; tremor

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Tremor, both parkinsonian and essential tremor, is effectively treated with both thalamotomy and thalamic deep brain stimulation (DBS). However, the reversibility, ability to adjust stimulus parameters, and the fewer adverse effects of DBS have led to its popularity in developed countries. In fact, thalamic stimulation has virtually replaced lesioning for tremor over the past 5 years.

Experience with thalamotomy stretches over the past 40 years. The best target for thalamotomy was known by the 1980s and further refined with the addition of microelectrode recording to intraoperative mapping. Whereas some debate remains about targets for other movement disorders, the ideal lesioning site for tremor is well accepted as being the ventral intermedius nucleus (Vim) of the thalamus, where movement-related and tremor cells coexist. It is presumed that the ideal DBS target is the same as the ideal thalamotomy target, because one of the methods used to determine the correct lesion site is that of tremor suppression with intraoperative acute electrical stimulation. Yet the electrode most commonly used for thalamic DBS (lead 3387; Medtronic, Minneapolis, MN) has four possible electrode poles, each 1.5 mm long and spaced 1.5 mm apart. This electrode could span three thalamic nuclei and the electrical fields produced may extend for up to a 2.5 mm radial distance at the usual stimulation amplitudes. Therefore, the actual effective stimulation site may be distant from the intended target. The primary aim of this study was to determine whether the thalamic site of chronic stimulation for tremor is the same as the site that would have been selected for lesioning. In addition, knowledge of the true stimulation site may provide clues to the mechanism of action of this treatment.

PATIENTS AND METHODS

All patients undergoing thalamic DBS surgery for essential tremor and at least 6 months follow-up were included in analysis. Each of these patients had detailed awake microelectrode recording and stimulation performed intraoperatively, which allowed the surgeon to select the site of DBS placement. Postoperative testing with the temporary external lead confirmed adequate stimulation effects (if the patient did not have a microthalamotomy effect) and tolerable side effects. A second surgical procedure then removed the external lead and connected the DBS electrode to the implantable pulse generator (IPG; Itrel 2 or Soletra, Medtronic). Postoperatively, patients underwent programming by a movement disorder nurse, who attempted to optimize beneficial effects on tremor while minimizing adverse side effects. Routine postoperative imaging was not performed in the first 7 patients, thereby making meaningful analysis of DBS sites based on imaging impossible. Tremor assessments were made by the treating movement disorder neurologists, using the Clinical Rating Scale for Tremor. All programming details were documented, and follow-up was maintained yearly.

Because a single patient cannot have both a successful lesion and a DBS implant, we used an artificial method to compare lesion to DBS sites. A senior neurosurgeon (R.R.T.), with considerable experience with thalamotomy and not involved in the care or follow-up of the patients, was given the reconstructed brain maps obtained intraoperatively using microelectrode recording and stimulation (Fig 1). He then selected the ideal thalamotomy lesion site or sites based on these maps. He was unaware of the patients’ clinical outcome or DBS implantation site.

Basic trigonometric equations were used to calculate the location of the DBS electrode and lesion site in reference to the anterior–posterior commissural line (AC–PC line = 0 in the y–z plane, with the PC point assigned the value 0,0). Points on the y axis (anteroposterior dimension) were recorded as a ratio of the standard AC–PC distance of 23 mm, per the Schaltenbrand and Wahren brain atlas. The mediolateral dimension was assigned to the x axis where the midline of the brain was 0 and laterality was standardized only for the side. All data points are shown as being in the right thalamus. No standardization was possible for the dorsoventral (z axis) dimension. To determine whether the DBS electrodes were systematically placed by the surgeons into a location different from where they would place a lesion,
FIGURE 1.
similar calculations were performed to measure the site of the tip of the DBS electrode.

An assumption was made to facilitate the comparison of ideal lesion to chronic DBS electrode site. The centre of the electrical current source was compared to the centre of the thalamotomy site, when more than one lesion was considered optimal. A single lesion site was selected in 7 patients and two sites were selected in 4 patients. For monopolar stimulation, the centre of the electrode pole was the current source, whereas with bipolar DBS the point halfway between the two poles was designated as the DBS site, regardless of anodal or cathodal configuration. In this way, a single point source of current could be compared in three-dimensional stereotactic space to the centre of an optimal lesion site.

All results are reported as mean ± SD. Because each of the three axes are determined independently, a t test was used to compare the lesion and DBS sites in stereotactic space when the data were normally distributed. The Mann–Whitney rank sum test was used for data not normally distributed.

### RESULTS

A total of 11 patients had unilateral thalamic DBS insertion for control of essential tremor. All patients have had some degree of benefit and continue to use their DBS. Details of the DBS stimulation parameters, outcomes, and follow-up are reported in Table 1. The average electrical parameters used by the group are 2.8 (±0.9) V, 0.087 (±0.045) msec pulse width, 165 (±24) Hz frequency. Mean follow-up was 26.1 (±15.6) months. A 69% (±23) reduction in tremor scores was achieved. No early surgical complications were observed. One patient has had his IPG changed twice over the course of 5 years because of high voltage requirements. This finding indicates that his DBS electrode is less than optimally positioned, yet it remains effective for his tremor and has allowed him to return to work full-time; therefore, his data were included in analysis.

Figure 2 demonstrates the clustering of optimal lesions and true DBS stimulation sites for each patient (represented by a letter identifier from Table 1). There is no significant difference between lesion and stimulation sites in the mediolateral dimension (P = 0.817, Mann–Whitney rank sum test). However, significant differences were found in the y (P = 0.005, Mann–Whitney rank sum test) and z (P = 0.034, t test) directions. The mean anteroposterior site for stimulation was 0.31 (± 0.10), in comparison to the mean lesion site of 0.21 (±0.06) anterior to PC, expressed as a ratio of the AC–PC length (n = 11). The mean dorsoventral location (n = 11) was 4.25 (±3.72) mm above the AC–PC line for DBS site and 1.43 (±1.73) mm for mock thalamotomy site. There was no significant difference between the distal tip of the DBS electrodes and the mock lesion site selected by the senior neurosurgeon in any of the three axes (P = 0.817 for x dimension; P = 0.264 for y dimension; P = 0.15 for z dimension), confirming the lack of subjective bias of electrode placement. Therefore, if it had been clinically appropriate, the DBS electrodes could have been programmed to stimulate the same brain region as where a lesion was considered optimal.

### DISCUSSION

Whereas surgeons are taught to place DBS electrodes in the same site as one would place a lesion to treat tremor, the chronically used DBS stimulation sites are actually significantly more anterior and dorsal to this ideal thalamotomy target. The simplest and most likely explanation for this mismatch may be that electrodes...
placed too close to the posterovertrally located ventrocaudal thalamic nucleus produce intolerable paraesthesia. Therefore, electrodes farther away were selected for chronic stimulation.\(^1^9\) It has long been known that lesioning a small key group of tremor cells in the thalamus is sufficient to eliminate tremor.\(^6,2^0\) Similarly, stimulation of a 2- to 3-mm zone of Vim is optimal for tremor suppression.\(^2^1\) It is possible that increasing the amplitude and other parameters of stimulation may enlarge the electrical field overlapping the tremor cell zone, but with the active pole itself being farther away from the tremor zone. We attempted to model the spread of current for DBS using the mean voltage required to suppress tremor (2.8 ± 0.9 V) and using the mean impedance measured (1.54 ± 446 Ω), calculating the current passed (2.4 mA). According to Wu and colleagues,\(^1^5\) a monopolar current of 3 mA would be expected to spread up to 2.5 mm, with bipolar stimulation resulting in a smaller volume of spread. The distance between optimal lesion and stimulation site was 3.6 mm (using the mean y, z-coordinates and assuming an AC–PC length of 23 mm). Whereas the center of the lesion is not within the radius of spread of current using these estimates, the lesion size may be 4.5 mm\(^3\) to 6 mm\(^2\) in diameter or up to 500 mm\(^3\) volume,\(^1^3\) suggesting a radius of 4.9 mm. This suggestion indicates that there may be overlap between the entire lesion volume and the volume of tissue stimulated.

Another possible reason for the mismatch observed in this study involves the somatotopy of the thalamus and the type of tremor. All of the patients had essential tremor, which often involves an action component with proximal muscle involvement.\(^2^2\) Proximal limbs are represented more anteriorly and dorsally,\(^2^3,2^4\) and it has been suggested that stimulation in dorsal Vim is better for control of proximal postural tremors.\(^2^5\)

Other explanations for mismatch may relate to the mechanism of action of stimulation versus that of lesions and which neural elements are preferentially activated (excited or inhibited) by DBS. Because there is no clear understanding of the mechanism of either thalamotomy or DBS, these explanations can only be speculative. Large-diameter myelinated axons have a lower threshold for activation than do neuronal cell bodies.\(^2^6\) Perhaps DBS electrodes must, therefore, be placed in less cellular regions, located more dorsally in thalamus and lesions must involve more cellular regions located ventrally.\(^2^3,2^7\) If the mechanism of action of DBS and thalamotomy were similar, then one would expect that lesions placed more anteriorly and dorsally would provide similar tremor relief to that offered by DBS. Yet lesions located as posterior to the ventrocaudal nucleus and as inferior as possible to the AC–PC line provide the best and longest-lasting tremor control.\(^1^3\) Another possibility is raised by work suggesting that DBS in globus pallidus preferentially activates inhibitory axons.\(^2^8\) In thalamus, both excitation and inhibition have been reported.\(^2^9,3^0\) Thus, DBS may provide not only an anatomically wider but also an electrophysiologically broader coverage of the thalamus than a lesion. It certainly suggests that, despite similarities in final outcome, the two techniques work differently.

A potential weakness of this analysis is inherent in the artificial circumstances regarding selecting a lesion site. When a surgeon makes a lesion in the operating room, the neurological condition of the patient is continuously

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**FIG. 2. Stimulation vs. ideal lesion sites in stereotactic space.**

**A:** Three-dimensional graph of deep brain stimulation sites for each patient, shown as a capital letter, and of theoretical lesion site, shown as the matching lower case letter in a circle. All sites are shown on the right brain and the labels are the same identifiers used in Table 1. **B:** View of the y-z sagittal plane showing a significant difference in lesion versus stimulation sites. AC–PC, anterior commissure–posterior commissure.
examiner. If a side effect develops such as hemiparesis or speech disturbance the lesion is halted. Whereas if tremor persists after a single lesion, then further lesions are made as long as no side effects appear. The forced-choice decision asked of the expert surgeon of where to make an ideal thalamotomy without clinical feedback, may explain part of the differences seen with lesioning versus DBS (where one has several months to program and find the optimal stimulation site). It likely cannot explain all of the differences as the expert would still start the radiofrequency lesion at the initial site selected and would only add to the lesion.

The results of thalamic DBS in this group of patients is not as favourable as others have reported. One obvious reason is that all of our patients suffered from essential tremor, which is known to be less responsive than resting tremor to both thalamotomy and DBS. In addition, our follow-up period was longer and complete, than resting tremor to both thalamotomy and DBS. Our results are comparable to that reported by Benabid and coworkers and others, when one includes only those patients for whom follow-up was obtained. We have shown that the chronically used DBS electrodes are not located at the site where one would make a thalamotomy lesion and instead are more anterior and dorsal. Perhaps we should stop referring to thalamic DBS as Vim stimulation, because the actual site of stimulation may be closer to the anteriorly located ventro-oralis posterior nucleus instead. These results suggest a different mechanism of benefit of thalamotomy and DBS.

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REFERENCES


Is FDG-PET a Useful Tool in Clinical Practice for Diagnosing Corticobasal Ganglionic Degeneration?

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Abstract: Seven consecutive patients were suspected to suffer from corticobasal ganglionic degeneration (CBGD) and were studied with 18F-fluorodeoxyglucose (FDG) PET imaging of the brain. At the time of their FDG-PET scan, 4 of 7 patients fulfilled the clinical criteria of CBGD as proposed by Lang and associates [In Calne DB, 1994; Neurodegeneration of the brain. Philadelphia: Saunders]. For 2 of these 4 patients, however, an alternative clinical diagnosis was also considered. Three of the seven patients underwent an FDG-PET scan when their clinical features were not yet developed sufficiently to confirm a clinical diagnosis of CBGD. Simple visual analysis of the FDG-PET scans was carried out. All 7 patients showed an asymmetrical pattern of glucose metabolism that was demonstrated in previous studies to be characteristic in patients who had a clinical diagnosis of CBGD. The PET results helped to confirm the clinical suspicion of CBGD in 2 patients and to rule out other diagnoses in 2 other patients. For 3 patients with no sufficient symptoms to diagnose CBGD, the pattern of glucose metabolism was characteristically asymmetrical. A probable diagnosis of CBGD was made in these patients. Our results suggest that routine visual inspection of a cerebral FDG-PET scan is a useful tool to confirm suspicion of the clinical diagnosis of probable CBGD, to differentiate from other hypokinetic-rigid syndromes, and to support a diagnosis CBGD in patients who do not (yet) sufficiently fulfill the clinical criteria. © 2003 Movement Disorder Society

Key words: corticobasal ganglionic degeneration; positron emission tomography

Corticobasal degeneration (CBGD) is a slowly progressive movement disorder with adult onset, characterized by cortical and basal ganglionic degeneration. First cases were described in 1968 by Rebeiz and associates.2 The cardinal manifestations of CBGD include an asymmetric, akinetic rigid syndrome, cortical sensory impairment, apraxia, and the alien hand phenomenon. In addition, cognitive disturbances may develop as well as reflex myoclonus and oculomotor signs. It is also known that there is no significant response to levodopa (l-dopa) and dopamine agonists.3 The definite diagnosis is made on pathological examination that will show neuronal achromasia and cortical atrophy more pronounced in the frontal and parietal lobes.1,2,4 There is considerable overlap not only in pathological examination, but also in clinical presentation of CBGD and Pick’s disease or Progressive Supranuclear Palsy (PSP). Although several groups published criteria for the clinical diagnosis of CBGD1,3,8–13 the condition still leaves clinicians with a considerable diagnostic challenge.

We evaluated whether routine cerebral fluorodeoxyglucose (FDG) positron emission tomography (PET) scanning can facilitate the diagnostic process in making the diagnosis CBGD in clinical practice. Different groups have published PET findings in CBGD patients.14–22 Patients with probable CBGD showed asymmetrical cerebral glucose hypometabolism particularly affecting the hemisphere contralateral to the most affected limbs. The brain regions involved primarily were the posterior frontal, inferior parietal, and superior temporal regions as well as the basal ganglia and thalamus. We asked whether asymmetries in simple visual examination of transaxial FDG-PET images were detectable and whether these asymmetries could confirm a diagnosis of CBGD when this is suspected.