Locations of Movement-Related Cells in the Human Subthalamic Nucleus in Parkinson’s Disease

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Abstract: The subthalamic nucleus (STN) is an emerging target for deep brain stimulator (DBS) implantation for the treatment of advanced Parkinson’s disease (PD). Understanding the somatotopic organization of the STN is important for surgical navigation within the nucleus. We analyzed intraoperative data obtained during 54 procedures for the implantation of STN stimulators to assess the locations of movement-related cells. Cells were considered movement-related if they exhibited modulation of the cell discharge during passive movement of the contralateral upper or lower extremity. Microelectrode track reconstructions were plotted on a human brain atlas, using the location of the DBS electrode from postoperative magnetic resonance images as a registration mark in reconstructing microelectrode track locations. Movement-related cells were predominantly located in the dorsal part of the nucleus. The majority of the cells were related to proximal joint manipulation. Arm-related cells were located laterally and at the rostral and caudal poles, whereas leg-related cells were located medially and centrally. The finding of three or more leg-related cells on a given microelectrode track was predictive of a medial localization within the motor area. Our findings are consistent with the small number of published studies on STN somatopy in the human and the nonhuman primate. © 2003 Movement Disorder Society

Key words: Parkinson’s Disease; subthalamic nucleus; basal ganglia physiology; microelectrode recording; surgery for movement disorders

Patients and Methods

Patients

We reviewed the intraoperative electrophysiologic data from deep brain stimulator (DBS) implantations in
the STN for the treatment of PD, carried out in 34 consecutive patients at the UCSF Moffitt-Long and San Francisco Veteran Affairs hospitals between 1998 and 2000. These data represent 54 DBS implant procedures because most patients received bilateral implants. Most bilateral surgeries were carried out as staged procedures. All patients had a definite improvement in motor symptoms with administration of levodopa (l-dopa). The mean score on the motor subscale (Part III) of the Unified Parkinson’s Disease Rating Scale (UPDRS) was 48 while off of all anti-parkinsonian medications, and 22 while on medication. Patients were operated after stopping all anti-parkinsonian medications for 12 hours.

**Surgery and Data Collection**

Surgeries for implantation were guided by magnetic resonance imaging (MRI)-based stereotaxy and single-cell microelectrode recording (MER). Stereotactic localization of the STN was accomplished by measurement from the midcomissural point, modified where necessary by direct visualization of the STN on T-2 weighted MRI images. The mean initial target coordinates were 3.35 mm posterior, 12.3 mm lateral, and 4.9 mm inferior, to the midcomissural point. The mean approach angles were 61 degrees from the AC–PC line in the sagittal projection, and 10 degrees from the vertical in the coronal projection.

Single unit extracellular recordings were collected intraoperatively in multiple parallel microelectrode penetrations (mean number of penetrations was 3.8, range 1–7) separated by 2 to 3 mm, with platinum or gold-plated tungsten microelectrodes. Neuronal activity was amplified, displayed intraoperatively, and stored for offline analysis (Guideline System 3000, Axon Instruments, Foster City, CA). Spontaneous discharge characteristics allowed for classification of cells as STN or substantia nigra pars reticulata (SNr) cells and for delineation of nuclear boundaries along each track. SNr cells had a higher mean discharge frequency (>60 Hz) and a more regular pattern of discharge than STN cells. In addition, a small electrically silent gap of 0.5 to 2.0 mm was typically encountered between the two nuclei. As the microelectrode traversed the STN, cells were systematically assessed for movement-related activity every 0.3 to 0.4 mm along the full length of the nucleus.

Cells were considered movement-related if they exhibited modulation of the cell discharge during passive movement of the contralateral shoulder, elbow, wrist (arm-related cells) or hip, knee, or ankle (leg-related cells). Due to the time constraints imposed by awake human surgery, responses to facial, finger, or eye movements, ipsilateral movements, or active rather than passive movements, were not studied systematically. Modulation consisted of audible alteration in the discharge frequency that was reproducible and synchronous with the passive movement. A small number of cells were identified whose discharge was modulated at a regular frequency of 4 to 6 Hz corresponding to the patient’s tremor, but they were included in the analysis only if they also showed modulation in response to passive movement.

**Postoperative MRI**

All patients underwent postoperative MRI to determine DBS lead location. This was a volumetrically acquired spoiled gradient echo (SPGR) protocol with the following parameters: TR = 36, TE = 8.0, matrix = 256 x 192, flip angle = 35 degrees, bandwidth = 15.6 kHz, NEX = 0.75, scan time = 11 minutes. The MRI was computationally reformatted so that the imaging plane was parallel to the intercommissural line and orthogonal to the midsagittal plane (Framelink software; Medtronic-Sofamor-Danek, Minneapolis, MI). The lateral position of the DBS lead from the midline was measured on the axial plane 4 mm inferior to the intercommissural line (corresponding to dorsal STN in most individuals). This lateral lead coordinate was then used as a registration mark to determine the lateral positions of the microelectrode tracks, as detailed below.

**Data Analysis**

Seventeen cases in thirteen patients were selected for determination of mean discharge rate, based on the presence of at least four recordings representative of single cell activity with adequate signal-to-noise ratios. Single units were discriminated using a waveform matching algorithm (Multi-Spike Detector; Alpha Omega Engineering, Nazareth, Israel). Fifteen procedures in 13 patients were selected for further study of STN somatotopy based on the presence of at least seven movement-related cells distributed among at least three tracks.

The locations of the microelectrode tracks with respect to STN boundaries were reconstructed by alignment of the track reconstructions to parasagittal planes from the Schaltenbrand and Wahren human brain atlas, as well as by visualization of the final location of the DBS electrode on postoperative MRI. Cell locations were assigned as follows: the lateral coordinate was derived from the lateral coordinate of the DBS lead location on postoperative axial MRI at a level 4 mm inferior to the midcommissural line. The anterior–posterior (AP) and vertical coordinates were derived from aligning the surgical tracks to parasagittal images of the Schaltenbrand and Wahren atlas, based on visual judgment of best fit.
and assuming a standard approach angle of 60 degrees from the AC–PC line in sagittal projection. For example, if the DBS lead was ultimately placed 2 mm lateral to the initial microelectrode track and was measured to be at lateral 12 mm by postoperative MRI, then the lateral coordinate of all cells in the initial track was assumed to be 10 mm. This method was recently described by Rodriguez-Oroz and colleagues.\textsuperscript{14} Once the lateral coordinate for each track was fixed using the MRI-determined location of the DBS lead as a registration mark, the AP and vertical positions were plotted on the closest available parasagittal section from the Schaltenbrand and Wahren atlas. In the example case it would be the 10.5-mm section because the atlas does not have a section at exactly 10.0 mm from the midline. The segments of the microelectrode maps representing STN and SNr cells were then aligned to the corresponding nuclei on the atlas sections. Care was taken to preserve the spatial registration between different microelectrode maps and different sections of the human brain atlas by aligning each with a registration mark located at the same antero-posterior and vertical position.

Coordinates for the three-dimensional location of each movement-related cell were determined. The center of the coordinate system was chosen arbitrarily to be the mid-point in both the vertical and AP dimension of the STN at its parasagittal atlas section at 12 mm lateral to the midline. To perform statistical testing of the hypothesis that arm-related and leg-related cells have different distributions within the nucleus, we used a non-parametric method, the Mann-Whitney two-tailed test. To determine whether arm-related or leg-related cells occur preferentially in one subregion of the nucleus, we partitioned the nucleus into the following subsections: 1) into medial and lateral halves with respect to the lateral 12 plane; and 2) into anterior, middle, and posterior thirds divided equally by coronal planes passing through the one-third and two-thirds AP length of the nucleus at the lateral 12-mm parasagittal atlas projection. This partitioning method was selected so as to facilitate comparison of our data with that available from the nonhuman primate.\textsuperscript{8,9,13} Fisher’s two-tailed exact test was then used to check for a difference in the probability of a given cell type (arm or leg) occurring in any given subsection of the nucleus, compared to the probability of the other cell type occurring in that subsection of the nucleus. For statistical testing we used a significance cut-off value of $P = 0.05$.

\section*{RESULTS}

\subsection*{Spontaneous and Movement-Related Activity}

The mean spontaneous discharge rate was 34 ± 14 Hz for STN (n = 102 cells) and 86 ± 16 Hz for SNr (n = 6). Of 303 cells examined for movement-related activity, 149 (49\%) were movement-related. There were 49 leg-related cells, 96 arm-related cells, and four cells responsive to both arm and leg movement. The joint specificities of the motor responses are shown in Table 1. The majority of the movement-related cells (75\%) responded to passive movement of only one joint. Most of the remaining 25\% responded to movement of several joints within a single extremity. Proximal joint responses (shoulder, elbow, hip, or knee) were more common than distal ones (wrist or ankle). For the small number of cells (35 total) for which both spontaneous discharge rate and movement-related activity were examined, discharge rate for movement-related cells was 34.8 Hz and that for movement-unresponsive cells was 31.0, which was not statistically significant ($P = 0.371$, two-tailed $t$-test).

\subsection*{Locations of Movement-Related Cells}

A summary plot of all movement-related cells recorded is shown in Figure 1A and a plot of all tracks through the STN is in Figure 1B. All tracks were at least 9 mm from the midline; therefore, the anteromedial part of the nucleus was unexplored. In the region of the STN explored, movement-related cells were predominantly found in the dorsal aspect of the STN. Along the segment of STN recorded on the individual microelectrode penetrations, 77\% of the movement-related cells were located in the dorsal half of the tracks, with only eight cells (5\%) found in the ventral-most quarter of each track. When microelectrode tracks were fitted to Schaltenbrand

\begin{table}[h]
\centering
\caption{Cells responding to passive movement of different joints in each extremity.}
\begin{tabular}{|l|c|c|c|c|}
\hline
 & Proximal joint only & Middle joint only & Distal joint only & Multi-joint & Total \\
\hline
Arm-related & 30 & 40 & 5 & 21 & 96 \\
Leg-related & 19 & 18 & 0 & 12 & 49 \\
Both arm and leg-related & 0 & 0 & 0 & 4 & 4 \\
Total movement-related & 49 & 58 & 5 & 37 & 149 \\
\hline
\end{tabular}
\flushleft{Number of cells responding to passive movement of different joints in each extremity, out of a total of 303 cells examined. Proximal joint, shoulder or hip; middle joint, elbow or knee; distal joint, wrist or ankle.}
\end{table}

\begin{figure}[h]
\centering
\caption{Summary plot of all movement-related cells recorded.}
\end{figure}

\begin{figure}[h]
\centering
\caption{Plot of all tracks through the STN.}
\end{figure}
and Wahren parasagittal projections, approximately two-thirds of the movement-related cells were located in the dorsal half of the nucleus.

The distribution of the arm-related cells along the medial to lateral axis of the nucleus was significantly different from the distribution of the leg-related cells (Mann-Whitney two-tailed test, \( P < 0.001 \)). In considering the nucleus as a whole, distributions of arm versus leg cells did not differ significantly along the dorsoventral or antero-posterior axes. Comparison of cell distributions in individual nuclear subsectors, however, did show further regional clustering. Because the number of cells responding to both arm and leg movements was small, their spatial distribution could not be analyzed statistically.

The numbers of arm-related versus leg-related cells in the various subdivisions of the nucleus are given in Table 2. Most of the leg-related cells (84%) were located in the medial half of the STN explored, defined as medial to 12.0 mm from the midsagittal plane (Fig. 2). Within this medial region, leg-related cells were further concentrated centrally, away from the rostral and caudal poles (Fig. 3). Twenty-four of 41 (58.5%) leg-related cells were found in the middle third of the nucleus in the AP dimension (Fig. 3 and Table 2). Overall, arm-related cells had a more diffuse distribution because arm-related cells pre-
dominated both in the lateral sector and in the anterior and posterior thirds of the medial sector. The proportion of leg cells was significantly greater than the proportion of arm cells, both in the medial half of the nucleus \((P = 0.005, \text{Fisher’s two-tailed exact test})\) and in the central third (along the AP axis) of the medial sector \((P = 0.01, \text{Fisher’s two-tailed exact test})\).

**Table 2. Numbers of arm-related and leg-related cells in six subdivisions of the nucleus**

<table>
<thead>
<tr>
<th></th>
<th>Anterior third</th>
<th>Middle third</th>
<th>Posterior third</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medial half</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm</td>
<td>28</td>
<td>13</td>
<td>6</td>
<td>47</td>
</tr>
<tr>
<td>Leg</td>
<td>16</td>
<td>24</td>
<td>1</td>
<td>41</td>
</tr>
<tr>
<td><strong>Lateral half</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm</td>
<td>15</td>
<td>26</td>
<td>8</td>
<td>49</td>
</tr>
<tr>
<td>Leg</td>
<td>6</td>
<td>2</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>65</td>
<td>65</td>
<td>15</td>
<td>145</td>
</tr>
</tbody>
</table>

*Based on division of the anterior–posterior axis into thirds, and of the medial–lateral axis in halves.*

**DISCUSSION**

We examined the joint specificities and spatial distribution of movement-related cells in the STN of parkinsonian humans undergoing physiological mapping for implantation of deep brain stimulators. Most previous studies of movement-related activity and somatotopy in the STN have been in the normal or parkinsonian nonhuman primate. Rodriguez-Oroz and associates published recently the first study on somatotopy in the human STN. Their study was based on analysis of microelectrode data obtained during surgery for PD.

Spontaneous neuronal activity in the region of the human STN in the parkinsonian state has been described extensively by others. We report on mean discharge rates for STN and SNr mainly to provide confirmation of correct nuclear localization. The mean discharge rate of 34 ± 14 Hz for STN and 86 ± 16 Hz for SNr observed in our study is similar to those reported in most other studies of Parkinsonian patients.

We tested 303 STN cells for movement-related activity and found that 49% modulate their discharge in response to passive contralateral movement of the limbs. We did not systematically test neurons for responses to ipsilateral movement, orofacial or ocular movement, or active limb movements. With regard to joint specificity of neuronal responses, we found: 1) arm responses are more common than leg responses; 2) proximal joint responses are more common than distal ones; 3) most responses correspond to single joints but about 25% respond to multiple joints of the same limb; and 4) only

**FIG. 2.** Distribution of arm-related cells and leg-related cells along the medial to lateral axis of the nucleus.
a very small number of cells (<5%) respond to movements of multiple limbs. These joint specificities are remarkably consistent with those described recently in the parkinsonian human by Rodriguez-Oroz and associates.14

Qualitatively similar joint specificities have been found in the normal nonhuman primate,8,9 although there is one discrepancy. The proportion of cells with multi-joint responses to passive movement was lower in the normal nonhuman primate, <10%,8,9 as compared to 25% in both the study of Rodriguez-Oroz and coworkers14 as well as in the present study. Thus, a cross-species comparison suggests that the parkinsonian state may be associated with an increase in the proportion of multi-joint specific responses, as has been shown previously for the globus pallidus in the nonhuman primate.25

Within the part of the STN explored (9 or more mm from midline), we found limb movement-related cells to be concentrated in dorsal STN. This segregation of movement-related cells within the dorsolateral STN has been shown previously in both the human14 and nonhuman primate.8,9,21 Thus, we add to the existing evidence for functional segregation of the human STN into skeletomotor and non-skeletomotor territories, and support the model of parallel segregated basal ganglia circuits in humans.26 In the nonhuman primate, the ventral region of STN contains cells responding to eye movements.21 Neither our study nor that of Rodriguez-Oroz and colleagues14 attempted to assess ocular responses in the human. The ventral STN, along with the anteromedial region of the STN that was not explored in this study, may also have limbic or associative functions based on their pattern of cortical connections.10,27

We plotted locations of arm-related versus leg-related cells with respect to a standard human brain atlas to assess for differences in their spatial distributions. Within the motor STN, we found that arm-related cells have a fairly widespread distribution, and are located laterally and at the rostral and caudal poles. Leg-related cells are more focally concentrated, medially and centrally. Prior electrophysiologic studies in the human parkinsonian STN,14 as well as the normal nonhuman primate STN,8 also showed that leg-related responses are more commonly found medially. Thus, there appears to be broad agreement about a medial-to lateral segregation in leg-related versus arm-related activity. Although one primate study did not show any clear somatotopic organization of skeletomotor responses, that study primarily focused on oculomotor responses and the number of skeletomotor cells that were mapped (65 cells) was fairly small.21

With regard to the relatively focal clustering of leg-related activity, compared to arm-related activity, this has also been noted in the normal nonhuman primate. Delong and associates9 showed that arm-related activity predominates over leg-related activity at the rostral and caudal poles. Taken together with the finding of Wichmann and coworkers8 that leg-related activity predominates medially, the overall picture in the nonhuman primate points to a relatively greater focal clustering of leg-related activity medially and centrally, as found for the human in the present study.

Rodriguez-Oroz and colleagues14 did not analyze the segregation of arm versus leg cells along the anterior-posterior axis, but did suggest a segregation along the dorsoventral axis. They found that leg-related cells have greater predominance in the dorsal one-third of the nucleus, whereas arm-related cells are distributed more evenly in the dorsal two-thirds. We did not find a statistical difference in arm-related versus leg-related cell locations in the dorsoventral domain. Thus, many fine points of STN somatotopy remain to be elucidated, in-
cluding the detailed organization of limb responses along dorsoventral and anterior–posterior axes. In addition, the location of orofacial responses in the human remains uncertain.

We studied responses to passive movements only, and we studied them in a diseased state. These factors may have distorted our findings. In the normal nonhuman primate STN, the populations of cells responding to passive versus active movements are clearly overlapping but are probably not identical.8,9 Previous observations in other basal ganglia nuclei, however, suggest that active-selective cells co-localize with cells that respond to passive movement.28,29 Thus, it is unlikely that the distributions of active movement-related cells would be radically different from the passive movement-related cells studied here. It is known that movement disorders can be associated with reorganization of receptive fields in thalamic30 or basal ganglia25,31 nuclei. Therefore, somatotopic principles elucidated in parkinsonian humans may not be generalized to the nonparkinsonian state. There is, however, qualitative agreement in the distributions of arm versus leg-related cells in human PD patients with those of normal nonhuman primates, suggesting that PD might not grossly disrupt the normal somatotopic organization.

STN somatotopy has also been studied in nonhuman primates using anatomic tracing techniques. Projections from primary motor cortex terminate in the dorsolateral sector of the nucleus and display a somatotopic arrangement, with leg-related cells medially and arm-related cells laterally.11,12 This is in agreement with the electrophysiologic studies. In addition to the primary motor cortex projection, Nambu and coworkers12 described the somatotopy of the STN termination of the supplementary motor area (SMA) projection, which is medial to, and inverted with respect to, that of primary motor cortex. Neither our study nor other electrophysiologic8,9,14,21 studies have found evidence for a dual body representation. Because SMA neurons have weaker sensory inputs than those of primary motor cortex; the body representation corresponding to SMA in the STN may be more difficult to detect electrophysiologically, or may require a detailed assessment of active movement.

Our methodology was constrained by the risks and time limitations inherent to human surgery. Because it is not possible to perform sufficient MER tracks in a single human patient to derive a statistically meaningful cell location map, we superimposed data from multiple subjects. This introduces a registration problem in superimposing the maps, based on incomplete localizing data in each patient in addition to the inherent variability in size, shape and spatial coordinates of basal ganglia nuclei in different subjects. A subjective visual alignment of our microelectrode track data onto the Schaltenbrand and Wahren atlas20 parasagittal projections formed the basis for assigning the AP and vertical coordinates to cells with movement-related activity. This procedure assumes a reasonably close match between the atlas representation and our patients’ deep brain structures. The determination of the lateral coordinate of each track was based on the lateral location of the DBS electrode on post-operative MRI.18 This assumes maintenance of the spatial coordinates of deep brain structures in the interval between microelectrode mapping and DBS placement, mechanically precise placement of the DBS lead at the intended coordinate, the ability to accurately identify the DBS lead on postoperative MRI, and minimal spatial distortion in the center region of the MR images. To the degree that these assumptions are violated, errors are introduced into the maps. Some groups use intraoperative ventriculography to provide a real-time measurement of electrode positions,32 which would have overcome some of the limitations in our method of assigning cell locations.

CONCLUSIONS

Our results indicate the presence of a motor area at the dorsolateral part of the human STN, with leg-related cells located medially and centrally and arm-related cells found more diffusely. These results are in broad agreement with prior studies in the human and nonhuman primate, and may be useful during physiological mapping of the nucleus carried out in the setting of surgical lesioning or DBS electrode placement.

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