Microelectrode-guided implantation of deep brain stimulators into the globus pallidus internus for dystonia: techniques, electrode locations, and outcomes

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Object. Deep brain stimulation (DBS) of the globus pallidus internus (GPI) is a promising new procedure for the treatment of dystonia. The authors describe their technical approach for placing electrodes into the GPI in awake patients with dystonia, including methodology for electrophysiological mapping of the GPI in the dystonic state, clinical outcomes and complications, and the location of electrodes associated with optimal benefit.

Methods. Twenty-three adult and pediatric patients with various forms of dystonia were included in this study. Baseline neurological status and DBS-related improvement in motor function were measured using the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS). The implantation of DBS leads was performed using magnetic resonance (MR) imaging-based stereotaxy, single-cell microelectrode recording, and intraoperative test stimulation to determine thresholds for stimulation-induced adverse effects. Electrode locations were measured on computationally reformatted postoperative MR images according to a prospective protocol.

Conclusions. Physiologically guided implantation of DBS electrodes in patients with dystonia was technically feasible in the awake state in most patients, and the morbidity rate was low. Spontaneous discharge rates of GPI neurons in dystonia were similar to those of globus pallidus externus neurons, such that the two nuclei must be distinguished by neuro nal discharge patterns rather than rates. Active electrode locations associated with robust improvement (> 70% decrease in BFMDRS score) were located near the intercommissural plane, at a mean distance from the pallidocapsular border of 3.6 mm.

KEY WORDS • deep brain stimulation • dystonia • globus pallidus internus • microelectrode recording

Dystonia is a syndrome of sustained muscle contractions producing writhing movements and abnormal postures. It may be a primary disorder that occurs without other neurological conditions, or it may occur secondary to a central nervous system lesion due to stroke, trauma, cerebral palsy, or degenerative disease. Most forms of dystonia respond poorly to systemic medications and intrathecal baclofen. Botulinum toxin–induced denervation is helpful for focal dystonias, but its efficacy may wane over time, and additionally it is impractical in more generalized cases. Recently, chronic electrical stimulation of the GP has shown benefit for dystonia in a few case series. The rationale for pallidal surgery in patients with dystonia is based solely on empirical evidence of clinical improvement, as there is not yet a clear understanding of the role of pallidal pathophysiology in this movement disorder.

For those seeking to perform pallidal stimulator implantation in patients with dystonia, there are several unresolved technical questions. First, the optimal target point for stimulation within the pallidal complex has not been defined, as there are few published cases in which investigators have adequately documented the locations of the electrically active contacts associated with good clinical outcome. Second, the best means of undertaking MER to confirm the correct target localization is unclear. In awake patients MER is a widely utilized modality applied during surgery for movement disorders. Pallidal recording techniques in humans, however, were developed largely for the treatment of PD. Application of MER techniques to dystonia surgery is more challenging because of the paucity and inconsistency of published data on physiological characteristics of the
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GP in the dystonic state. In the only detailed technical reports on the implantation of a deep brain stimulator for dystonia, the authors have described surgery performed using MR imaging-based stereotaxy as the sole navigational technique in patients in whom general anesthesia has already been induced. Finally, because dystonia is a heterogeneous disorder, it is not yet clear from the limited case series published which patients are good candidates for surgery and how they should be counseled about the expected outcome.

In this study, we report our technical approach, electrode locations, and clinical outcomes after microelectrode-guided implantation of GPI stimulators in a series of 23 patients with dystonia. All but three of the patients underwent MER in the awake state. Anesthetic and electrophysiological considerations unique to surgery for dystonia are described. Using postoperative MR imaging, we documented active electrode locations associated with good clinical outcome. The goal of this study was to provide practical information useful to surgeons performing this new and promising procedure.

Clinical Material and Methods

Inclusion Criteria and Clinical Evaluation

Patients with dystonia were offered surgical treatment if the following criteria were met: 1) unequivocal diagnosis of primary or secondary dystonia established by a movement disorders neurologist; 2) attempted medical management with anticholinergic medication, benzodiazepines, baclofen (oral and/or intrathecal), and, in patients with segmental craniocervical dystonia, botulinum toxin; and 3) significant disability, despite optimal medical management, in which disability was defined as that due to impaired movement, pain, social isolation, or a combination of these factors. All patients provided informed consent according to a protocol approved by the institutional review board. All 23 consecutively treated patients with dystonia who underwent surgery between 1999 and 2004 performed by a single surgeon (P.A.S.) were included in this series.

A quantitative measure of dystonia severity was determined in the month prior to surgery by a movement disorders neurologist (W.J.M. or J.L.O.) who used a standard clinical rating scale, the BFMDRS for motor function. The BFMDRS is a 120-point scale used to rate the severity of dystonia in nine body regions, taking into account both the severity of the dystonic movements and the frequency with which they are provoked. The higher the score, the greater the severity of dystonia. In an individual without dystonia the BFMDRS score would be 0. This scale has been widely used for both pediatric and adult patients but has only been specifically validated for adult patients. Surgery-related outcome was measured at a single postoperative interval, which was 1 year in most patients, but longer (range 1–3 years) in patients whose neurological improvement was still in progress at the 1-year interval.

To provide a comparison group against which to measure pallidal neuronal discharge characteristics, single-unit data obtained in nine PD patients who underwent pallidal DBS are included in this report. In these patients, symptom severity was measured using Part III (the motor subscale) of the Unified Parkinson’s Disease Rating Scale in the off-medication state.

Surgical Procedure

All but two patients underwent bilateral implantation of the electrodes. In the first 16 patients the implants were staged 1 to 3 months apart. As the surgical technique became more routine, all patients needing bilateral electrodes were offered simultaneous implantation.

Anesthetic Technique. Twenty patients underwent MER in the awake state. Because of the inability of most dystonic patients to remain still for frame placement or stereotactic MR imaging, these two steps were performed after deep propofol-induced sedation. Propofol was then stopped at least 30 minutes prior to the start of pallidal recording, and the patients were alert and oriented at the start of microelectrode recording. At this point, rigid fixation of the stereotactic headframe to the operating table prevented excessive head movement due to resting dystonic spasms.

Three of the six pediatric patients were thought unlikely to tolerate awake surgery because of their young age, emotional immaturity, or extremely violent, ballistic dystonic spasms of the neck, trunk, and shoulders. In these three cases, all parts of the procedure, including MER mapping, were performed after induction of general endotracheal anesthesia. In the first case, propofol was used as the anesthetic agent. Because this medication was found by us and others to greatly depress pallidal discharge, we used a mixture of ketamine and remifentanil, which has been found to have comparatively less effect on spontaneous neuronal discharge, in the subsequent two cases.

Stereotactic Targeting. Following placement of the stereotactic headframe, two MR image sets were obtained: 1) a volumetric 3D Gd-enhanced gradient echo MR imaging sequence covering the whole brain in 1.5-mm axial slices, mainly for trajectory planning (TR 20 msec, TE 2.9 msec, matrix 256 × 192, flip angle 3, NEX 1); and 2) an IR-FSE image set covering only the basal ganglia region, in 2-mm axial slices, mainly for direct visualization of the borders of the GPI and surrounding structures (TR 3000 msec, TE 40 msec, TI 200 msec, matrix 256 × 512, NEX 3, bandwidth 120 Hz/pixel, interleaved). Images were obtained using an Intera 1.5-tesla unit (Phillips, Amsterdam, The Netherlands). Both image sets were imported into a stereotactic surgical planning software package (Framelink version 4.1; Medtronic-SNT, Boulder, CO), computationally fused, and reformatted to produce images orthogonal to the AC–PC line and midsagittal plane.

Target selection is illustrated in Fig. 1. The target point for the tip of the stimulator was selected using a combination of direct and indirect targeting. The lateral and vertical coordinates were selected to correspond to the dorsolateral border of the optic tract in a coronal plane 2 mm anterior to the midcomissural point. A “default” trajectory was then set at 60° from the AC–PC line in the sagittal projection and 0° lateral from the vertical line in the coronal projection (for example, a parasagittal approach). This trajectory was visualized on the volumetric MR images by using “navigation” views. Small adjustments in the arc and ring angles were then made to avoid traversing the sulci, cortical veins, and dural venous lakes (easily seen on Gd-enhanced images) and lateral ventricles. Finally, using the axial plane passing through the commissures, the target point was further refined based on visualization of the medial and lateral
borders of the GPI on IR-FSE images. In this plane, the lateral coordinate was adjusted (typically by < 2 mm) so that the lead trajectory passed 1 mm medial to the internal medullary lamina (the white matter boundary between the GPI and GPE). This point on the trajectory is typically 3 to 4 mm anterolateral to the pallidocapsular border, depending on the size of the GPI (Fig. 1B).

**Single-Unit Recording.** Single-unit discharge was recorded with glass-coated platinum/iridium microelectrodes (impedance 0.4–1.0 MΩ at 1000 Hz; Microprobe, Inc., Gaithersburg, MD; or FHC, Inc., Brunswick, ME). Recordings were filtered (300 Hz–5 kHz), amplified, played on an audio monitor, and digitized (20-kHz sampling rate) by using the Guideline System 3000 (FHC, Inc.). Microelectrodes were advanced into the brain by using a motorized microdrive (FHC, Inc.).

Passive movement of the contralateral extremities was performed during all recordings to detect cells responsive to movement. Neuronal activity data were collected for a minimum of 20 seconds. Cells were recorded every 300 to 800 μm along each trajectory. Outside the pallidal base (heralded by the cessation of tonic high-frequency neuronal discharge), the presence/absence of the optic tract was deter-
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mined using light-evoked action potential discharge and microstimulation-induced visual phenomena. Microelectrode recording penetrations were not made greater than 2 mm deep to the pallidal base to avoid the risk of injuring a vessel in the choroidal fissure. The location and discharge characteristics of cells along each microelectrode track were plotted manually on transparency sheets, noting in particular the locations of the optic tract and of the electrically silent white matter laminae. The track reconstructions were then superimposed manually on drawings of parasagittal slices from the Schaltenbrand–Wahren human brain atlas, according to a visual judgment of “best fit” of the tracks to the atlas.

The first MER trajectory was set at 2 mm medial to the anatomical target to increase the likelihood of detecting the optic tract and of recording a relatively long (5–7-mm) trajectory through the GPI. Additional parallel MER penetrations were typically made 2 mm posterior and lateral to the initial penetration. The stimulator lead (model 3387; Medtronic, Inc., Minneapolis, MN) was placed 2 mm lateral to an MER trajectory in which at least a 6-mm segment of GPI was recorded, and 2 mm lateral to a trajectory where the optic tract was identified. In our experience, if the lead is instead placed exactly on such a trajectory (long segment of the GPI with the optic tract at the base) rather than 1 to 2 mm lateral to it, the lead may be too close (<3 mm) to the capsular border, and this could produce unacceptable side effects during chronic stimulation due to activation of the CBT or CST. With respect to the parasagittal planes represented in the Schaltenbrand–Wahren atlas, lead placement corresponded most closely to the 21.5-mm lateral plane, although the actual laterality of the anatomy represented on this atlas plane varied considerably between individuals.

**Intraoperative Test Stimulation.** Test stimulation was performed in bipolar mode using contacts 0, 3, 185 Hz, and a 90-µsec pulse width (model 3625 external tester; Medtronic, Inc.). Voltage was increased at 1 V/second while the patient repeated simple phrases. The voltage threshold for dysarthria or tonic facial or arm contraction was noted. If neither effect occurred, the pulse width was increased up to 200 µsec. With the room lights dimmed and the patient’s eyes closed, the voltage was again increased. The threshold for stimulation-induced visual phenomena (typically reported as “stars” or “flashes”) was noted.

**Lead Anchoring and Implantable Pulse Generator Placement.** Leads were anchored to the skull with a lead anchoring device (Image Guided Neurologics, Melbourne, FL). After scalp closure and headframe removal, general anesthesia was induced to allow placement of the lead extenders and pulse generators (Soleta or Kineta; Medtronic, Inc.). The pulse generators were placed during the same operative session as the leads. The duration of surgery (from initial skin incision until the pulse generators were placed) was 4 to 6 hours for unilateral implantation and 6 to 8 hours for same-session bilateral implantation.

**Measurement of Electrode Location**

Postoperative MR imaging was performed in all patients the day of surgery; we used a standardized prospectively implemented protocol designed to show the DBS lead, the commissures, and the borders of the GPI at high resolution. Two sequences were obtained: the 3D gradient echo imaging sequence, identical to that of the preoperative stereotactic protocol, and a T2-weighted FSE sequence, limited to the basal ganglia, in the axial plane at 2-mm slice thickness (TR 3000 msec, TE 90 msec, matrix 268×512, NEX 6, bandwidth 183 Hz/pixel, interleaved). Because of the thermal effect on the leads due to transmission of radiofrequency electromagnetic radiation, postoperative MR imaging was performed using a transmit–receive head coil with the patient in a 1.5-tesla magnet unit (Phillips or GE) with pulse sequences designed to minimize specific absorption rate, in accordance with the recommendations of the DBS device manufacturer. The MR images were transferred to an image-processing station (Framelink version 4.1; Medtronic SNT) for analysis. All image sets were computationally reformatted so as to be parallel to the AC–PC line and orthogonal to the midsagittal plane.

Lateral, vertical, and AP coordinates of the distal tip of the stimulator and of the entry point were measured on the reformatted postoperative 3D gradient echo MR images with respect to the midcommissural point. The lead was seen as a relatively discrete round signal void, approximately 3 mm in diameter, larger than the actual diameter of the lead. The center of the round signal void was considered to represent the true electrode position. The coordinates of the active electrode(s) with respect to the midcommissural point were calculated trigonometrically from the following information: the choice of contact(s) that were active during the intraoperative testing or postoperative clinical evaluation, the known contact geometry (contacts 1.5 mm long, spaced 3 mm center-to-center), and the location of the coordinates of the tip and entry point. The angulation of the lead array in terms of its vertical relation to the AC–PC line, in both sagittal and coronal projections, was calculated trigonometrically from the coordinates of the tip and entry. The formulas for these calculations have been previously published.

In addition, to account for the substantial variation in the AC–PC coordinates of the posterior GPI, the location of the lead was measured with respect to the internal pallidal anatomy on the T2-weighted FSE images. Measurements were made in two dimensions on the reformatted axial image passing through the commissures (that is, at a vertical coordinate of 0). This plane was chosen because, following programming for optimal benefit, most active electrodes had a vertical coordinate close to 0 (see Results). In the plane of the commissures, both the anteromedial and posterolateral corners of the GPI were visualized. A straight line drawn between the anteromedial and posterolateral corners was considered to represent the pallidocapsular border. The position of the lead with respect to this border and the AP distance of the lead from the posterolateral corner of the GPI (all in the plane of the commissures) were measured.

**Stimulator Programming**

Devices were programmed within the 1st month after surgery. No attempt was made to optimize the parameters to immediate clinical benefit because our early experience has shown that little or no immediate benefits occurred even at stimulation parameters that, months later, proved effective. The typical initial settings were as follows: unipolar mode, electrode 2, frequency 185 Hz, and pulse width 210 µsec.
The voltage was gradually increased over the initial 2 to 6 months to 2.5 to 3.6 V.

**Analysis of Neuronal Activity**

Digitized spike trains were imported into off-line spike-sorting software (Plexon, Inc., Dallas, TX) in which principal component analysis was used to isolate single populations of action potentials. This software generated a record of spike times (msec accuracy) for each action potential waveform detected. The interspike intervals between successive spike times were used to evaluate the so-called stationarity of discharge, to determine the mean discharge rate, and to construct raster displays. Analyses were performed in LabVIEW (National Instruments Corp., Austin, TX) and MATLAB (The MathWorks, Inc., Natick, MA) programming environments.

Neuronal data were analyzed for discharge rate only if the patient had undergone mapping in the awake state, if the action potentials could be discriminated with a high degree of certainty, if the complete record of interspike intervals fulfilled statistical criteria for stationarity of discharge (as tested off-line with the runs-test),14 if the number of recorded action potentials exceeded 600, and if the spontaneous activity of the neuron was recorded for at least 15 seconds.

Nuclear localization was assigned as follows: cells encountered between the internal medullary lamina and the optic tract were considered internal pallidal cells; those recorded between the striatum and the internal medullary lamina were considered external pallidal cells; and those near the presumed GPE–GPI border, on a track where a definite white matter boundary was not identified, were excluded from formal neurophysiological analysis because of their uncertain localization.

**Statistical Analysis**

Hypothesis testing was performed using a statistical package (version 11.0; SPSS, Inc., Chicago, IL). Because the pallidal discharge rates were pooled from multiple cases, rates were not assumed to be normally distributed, and they were compared using the Wilcoxon rank-sum test (independent samples). The distributions of electrode locations associated with different stimulation-induced adverse effects or different clinical outcomes were compared using the Levene test for equality of variances and the t-test for equality of means. To compare pre- and postoperative BFMDRS scores (ordinal data), the Wilcoxon matched-pairs signed-rank test was used. Probability values of less than 0.05 were considered significant. When appropriate, values are presented as the means ± SDs and the means ± SEMs.

**Results**

**Patient Population**

Clinical characteristics are presented in Table 1. The mean (± SD) age at onset of symptoms was 21 ± 17 years, and the mean age at surgery was 32 ± 15 years. The mean baseline BFMDRS score was 51 ± 25.4. Because dystonia is a heterogeneous disorder, different origins of dystonia were represented—for example, idiopathic dystonia (in 14 cases), tardive dystonia (in four cases), and secondary dystonia (in three cases). The cases of idiopathic dystonia were further subdivided into three groups: juvenile onset, positive for the \( \text{DYT1} \) mutation\(^\text{\(2\)} \) (six cases); juvenile onset, negative for the \( \text{DYT1} \) mutation (three cases); and adult-onset cranio-cervical dystonia (five cases). In two additional patients (Cases 22 and 23) the cause of dystonia was classified as unknown because the individuals were adopted at a young age (2 and 5 years), a movement disorder was already present, brain MR images demonstrated normal findings, and medical histories were unknown. In these two cases, secondary dystonia due to cerebral palsy could not be ruled out. In all three patients with definite secondary dystonia MR images revealed abnormal findings. In all other cases unremarkable findings were observed on MR images. No patient had undergone prior intracranial neurosurgery.

In one patient (Case 6) a working baclofen delivery pump was present at the time of DBS surgery. For patients with PD, the mean (± SD) age at symptom onset was 44 ± 6 years and the mean age at surgery was 58 ± 7 years. The mean value, as determined using Part III of the Unified Parkinson’s Disease Rating Scale score, was 43 ± 10. All patients with PD had predominant rigidity and bradykinesia. None suffered significant tremor or off-period dystonia during the electrophysiological recordings.

**Surgical Outcomes and Complications**

Clinical outcomes as assessed by the BFMDRS scores were obtained in 22 of the 23 patients (Table 1). One patient (Case 9) has not yet undergone the follow-up evaluation. The outcomes were measured at a single time point (Table 1), considered the interval at which the patients’ neurological status had reached a plateau of improvement. The mean follow-up duration for all patients was 16 ± 8 months. The mean pre- and postoperative scores, grouped by dystonia subtype, are shown in Fig. 2. Although improvements were seen in all subgroups, the change only reached statistical significance in patients with juvenile-onset \( \text{DYT1} \) mutation–positive dystonia. In this subgroup, in which the mean follow-up duration was 13.3 ± 2.2 months, the BFMDRS score had improved by 65.7 ± 32% (p = 0.028, Wilcoxon paired-sample rank-sum test). The mean reduction in anticholinergic medication dose was 48%, and mean reduction in benzodiazepine dose was 55%. The only patient (Case 4) with \( \text{DYT1} \) mutation–positive dystonia who had less than a 50% improvement in BFMDRS score was an adult with a 20-year history of severe symptoms (unable to sit up in chair) associated with long-standing irreducible hip dislocations and severe scoliosis.

In two patients with juvenile-onset \( \text{DYT1} \) mutation–negative dystonia, BFMDRS scores were substantially improved, by 71 and 61%, but there were too few individuals for this to reach statistical significance. Regarding patients with the other dystonia subtypes, the outcomes were highly variable, ranging from no benefit to 100% improvement (Table 1). In patients in the adult-onset cranio-cervical dystonia group, two of five patients suffered continued progression of dystonia (as reflected by an increase in BFMDRS score at the follow-up examination [Table 1]). Both of these patients suffered from severe cervical degenerative joint disease necessitating one or more spinal fusions prior to or soon after surgical treatment. In three of four patients with tardive dystonia the improvement rate was greater than 50%. Of the three patients with secondary dystonia, in the only patient whose BFMDRS score improved more than...
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</table>

* CCS = cranio cervical spine; CP = cerebral palsy; DYT1+ = positive for the DYT1 mutation; DYT1− = negative for the DYT1 mutation; FU = follow up; PKAN = pantothenate kinase–associated neurodegeneration.
† Outcome data unavailable; patient still undergoing follow up at the time of submission.
‡ This patient had Meige syndrome.
§ The patients in Cases 22 and 23 were adopted at an early age with dystonia already present. These may represent cases of dystonic cerebral palsy (secondary dystonia), but medical history prior to adoption is unknown. The MR images were normal.

The mean programming parameters at the most recent clinical follow-up visit were voltage 3.3 ± 0.5 V, pulse width 225 ± 50 μsec, and frequency 181 ± 6 Hz. One lead was programmed in bipolar mode; 28 leads were programmed in unipolar mode using a single electrode; and 15 leads were programmed in unipolar mode using two adjacent electrodes. The mean time to battery end-of-life was 30 ± 7.5 months.

Surgical complications are listed in Table 2. One man (Case 17), the second oldest in this series, suffered a multifocal left frontal hemorrhage 2 days postsurgery, and MR imaging demonstrated a lesion that appeared to be a venous infarction. He suffered aphasia and contralateral hemipare-

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The GPE pauser cells have a tonic discharge that is interrupted by characteristic 100- to 300-msec pauses in neuronal activity. The GPE bursting cells have irregularly spaced bursts superimposed on a very low background discharge rate. In the dystonic GPI, we noted some cells that exhibited a highly unusual discharge pattern, which we have termed high-frequency bursting cells. In the dystonic GPI, these cells discharged in irregularly spaced bursts of five to 15 action potentials, and the bursts were superimposed on a relatively high background discharge rate, which distinguished them from the GPI burster cell type. In the dystonic state, this high-frequency burster cell type appears distinctive from the GPE burster cell type. In the dystonic state, different types of discharge patterns in the two nuclei were observed, which proved helpful in targeting the transition between them. Representative examples of spontaneous single-unit pallidal discharges in patients with dystonia are shown in Fig. 4. In the GPE, there were two characteristic patterns of discharge, similar to those recorded in patients with PD in whom the mean GPI discharge rate of 96 ± 23 Hz was significantly greater than that of the mean PD GPI of 52 ± 18 Hz (p < 0.001, Wilcoxon rank-sum test). Thus, the transition from the external to internal pallidum was more difficult to recognize intraoperatively in the dystonic state than in the parkinsonian state.

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**Single-Cell Physiology in Dystonia: Significant Features in MER Mapping**

Group statistics for pallidal discharge rates for each nucleus in each disease state were calculated off-line by pooling single-unit data across all individuals who underwent surgery in the awake state. Summary boxplots of discharge rates are shown in Fig. 3. In patients with dystonia, the mean discharge rates in GPI and GPE were nearly identical, 55 ± 22 and 53 ± 23 Hz, respectively. This contrasts with those recorded in patients with PD in whom the mean GPI discharge rate of 96 ± 23 Hz was significantly greater than that of the mean PD GPI of 52 ± 18 Hz (p < 0.001, Wilcoxon rank-sum test). Thus, the transition from the external to internal pallidum was more difficult to recognize intraoperatively in the dystonic state than in the parkinsonian state.

**Microelectrode Mapping**

A total of 155 MER penetrations were made in 44 mapped sides (mean 3.5/side, range 1–8/side). The mean length of GPI recorded on the initial MER penetration was 4.1 mm (range 0–7.3 mm). Of a total of 324 cells in awake patients tested for responses to passive bilateral limb movement, 114 were responsive, 58 of which were arm-related cells and 56 of which were leg-related cells. Movement-related activity was not detected in the five sides mapped in patients in whom general anesthesia was induced. The optic tract was identified by either light-evoked action potential discharge or microstimulation-evoked visual phenomena in 30 of 44 mapped sides. For maps obtained after induction of general anesthesia, the optic tract was identified in four of five mapped sides. In these cases only light-evoked action potential discharge could be used to identify the optic tract.
Pallidal deep brain stimulation for dystonia

...ing the very distinctive bursts seen in Fig. 4D, nevertheless were recognizably different from GPE cells in that they fired more continuously (Fig. 4C), without the characteristic pauses of the predominant cell type of the GPE.

Intraoperative Test Stimulation

Test stimulation was performed in bipolar mode with the most inferior contact a negative charge and the most superior contact a positive charge (frequency 185 Hz, pulse width 90–200 μsec, and 1–10 V). In 41 of 47 lead placements, stimulation elicited a change in speech volume or articulation or tonic muscle contraction within the tested range, attributable to CBT or CST activation. In four of the six leads tested in general anesthesia–induced patients, stimulation-induced tonic muscle contraction was seen. The CBT responses were more frequently elicited by the lowest threshold stimulation-induced effect (35 leads) compared with CST responses (six leads). The median voltage to produce an observable CBT or CST effect at 90-μsec pulse width was 8 V. In 16 of 41 awake patients, test stimulation elicited reproducible subjective visual phenomena (flashes, or “stars,” in the contralateral visual field) attributable to optic tract activation. The median voltage for optic tract activation at a pulse width of 90 μsec was 9.5 V. Visual thresholds could not be tested in patients in whom general anesthesia had been induced. We observed no stimulation-induced improvements in dystonia symptoms with acute intraoperative test stimulation, nor did we observe intraoperative improvement associated with tissue disruption due to lead insertion.

Electrode Locations

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Electrode Locations

Figure 5 provides examples of several postoperative MR images used to measure electrode location. A scatterplot of the location of all contacts in the axial plane of the commissures, with respect to a normalized pallidocapsular border, is shown in Fig. 6. The plot indicates the location of the three leads that required repositioning, as well as those associated with different degrees of improvement in the BFMDRS score. Table 3 provides a summary of coordinates for lead locations. The mean lead tip and active electrode coordinates did not differ between the group with the best clinical outcome (> 70% improvement) and the group with the worst clinical outcome (< 50% improvement) (independent samples t-test). For the measures of lead location with respect to the borders of GPI (pallidocapsular border and posterior end of GPI) in the plane of the commissures, however, the variance of the distribution of lead locations was significantly smaller in the group with the best clinical outcome than that in the group with the worst clinical outcome (p < 0.05 for both measures, Levene test for equality of variances). The angulation of the leads was 32 ± 7° from the vertical line in the sagittal projection and 1 ± 5° from the vertical line in the coronal projection.

Electrode Locations Related to Intraoperative Test Stimulation Thresholds

We sought to determine if voltage or pulse width thresholds for intraoperative stimulation-induced adverse effects could be used to predict electrode location. When analyzed post hoc after determining the electrode’s location, thresholds for CBT/CST activation were predictive of location in the AP dimension. For leads in which the threshold for CBT/CST activation was less than 10 V, at a pulse width of 90 μsec and frequency of 185 Hz, the mean (± SEM) distance anterior to the midcommissural point (measured at the midpoint of the four electrodes) was 4.9 ± 0.3 mm. For leads with a higher threshold (that is, those requiring longer pulse width for activation at 10 V or whose threshold exceeded the maximum tested), the AP coordinate (± SEM) was 6.5 ± 0.2 mm. This difference was statistically significant (p = 0.005, independent samples t-test). The lower threshold leads were also closer to the pallidocapsular border in the plane of the commissures, 3.6 ± 0.2 mm compared with 4.3 ± 0.6 mm (± SEM) for the higher threshold leads, but this difference did not reach statistical significance. The presence or absence of optic activation was not predictive of a midlead location, as the mean (± SEM) vertical coordinate (middle of the active contact array) for leads that elicited visual phenomena was 1.3 ± 0.4 mm inferior to the AC–PC plane, which was not significantly different from the vertical coordinate of leads that did not elicit a visual response, 1.9 ± 0.4 mm inferior to the AC–PC plane.

Discussion

We have described methods, electrode locations, and out-
comes after implantation of deep brain stimulators into the GP in patients with various forms of dystonia. In our technical approach we utilized MR imaging–based stereotaxy, microelectrode recording, and intraoperative test stimulation to check thresholds for stimulation-induced adverse effects, and we used postoperative MR imaging to verify electrode location. Active electrode locations were clustered in an area in the posterolateral internal pallidum close to the plane of the commissures, 3 to 5 mm from the pallido-capsular border. In our surgical approach we emphasize physiological monitoring, whereas in other recent technical reports on pallidal DBS in dystonia the authors described surgery performed exclusively with MR imaging–based targeting in patients in whom general anesthesia has been induced.14,43,44 Physiological mapping, including MER, offers the theoretical advantage of an intraoperative high–spatial resolution method for confirmation of target accuracy. In this series our approach was associated with consistent lead placement and few serious complications.

Anesthetic Considerations for DBS in Dystonia

Historically, stereotactic lesioning surgery in individuals with dystonia has been performed in the awake patient.12 We found awake surgery to be technically feasible in most patients with dystonia, although in many sedation was critical to allow frame placement and stereotactic MR imaging. The main advantages of awake surgery are to facilitate intraoperative physiological monitoring and to allow continuous assessment of the patient’s neurological status. In the few cases in which general anesthesia was required because of the patient’s young age or very severe spontaneous dystonic spasms, MER mapping and test stimulation remained possible. For optimal preservation of neuronal fir-
ing characteristics, propofol and inhalational agents should be avoided.34

Physiological Mapping Differs Between Dystonia and Parkinsonism

Pallidal MER mapping techniques were refined during pallidal surgery for PD, where the distinctive extremely rapid firing rate of the GPI cells at 70 to 100 Hz facilitates the mapping of the borders.29,39,49 In primary dystonia and non-PD secondary dystonia, in contrast, we found that the mean spontaneous neuronal discharge rates in the GPI ranged from 40 to 70 Hz. The mean GPI and GPE discharge rates were not distinct. Nevertheless, we did find that the GPI and the GPE in patients with dystonia could be distinguished by subtle differences in discharge patterns, with bursting superimposed on tonic activity a feature of some neurons in the GPI. The relatively lower mean discharge rate of the GPI in dystonia compared with PD and the consequent similarity between the GPI and GPE discharge rates have been reported in several publications.27,30,34,50 One group of authors found, in contrast, that the GPI discharge rate in dystonia and PD were similar (both ~ 70 Hz), although the GPI and GPE were not specifically compared.19 Reduced GPI firing rates in patients with severe generalized dystonia are consistent with a model proposed by Vitek, et al.,50 in which two populations of striatal cells, those originating in the direct and the indirect intrinsic basal ganglia pathways, are both overactive. This is in contrast to phenomena in PD, which are represented by excessive activity in striatal cells originating in the indirect pathway but reduced activity in striatal cells originating in the direct pathway.50

Role of Intraoperative Test Stimulation for Localization of Leads

Intraoperative test stimulation in the range available using the Medtronic model 3625 external tester should be able

Fig. 5. Postoperative MR images revealing electrode location. A: Axial T2-weighted FSE image 4 mm inferior to the commissures. The round signal void corresponding to the left lead tip is indicated with an arrow. B: Axial T2-weighted FSE image showing electrodes in the plane of the commissures. The signal void corresponding to the left lead is indicated by a vertical arrow; the anteromedial and posterolateral extents of the GPI in this anatomical plane are indicated with horizontal arrows. C: Reformatted coronal-plane 3D-GRE image showing the lead (black arrow) terminating at the superolateral aspect of the optic tract (white arrow). D: Parasagittal reformatted 3D-GPE image demonstrating the lead tip in relation to the choroidal fissure.
to evoke changes in speech volume, articulation, or tonic contraction of the face or contralateral extremities in almost all cases. The threshold for this effect was predictive of the lead location. Leads located near the intended target commonly elicited a motor side effect at 5 to 10 V (with bipolar stimulation spanning the quadripolar array, at a pulse width of 90 μsec and a frequency of 185 Hz). In contrast, visual phenomena due to optic tract activation during test stimulation were elicited in less than one half of the cases. The presence or absence of optic activation did not correlate with lead location. This contrasts with a study of optic tract activation conducted via a lesioning probe prior to radiofrequency pallidotomy; in this the authors found that test stimulation thresholds correlated with the vertical distance from the optic tract. This disparity may relate to differences in probe geometry (the Medtronic model 3387 lead is insulated at its distal tip, unlike most radiofrequency lesioning probes) or to differences in stimulation mode (bipolar compared with unipolar stimulation). Intraoperative stimulation-induced changes in motor signs and symptoms were not observed and are therefore not useful in predicting electrode location.

**Location of the Active Electrode**

The GP is a large target with an irregular shape. When DBS has been performed in cases of PD, lead location has varied widely, from posterolateral locations similar to Leksell’s pallidotomy target to much more anteromedial placements. In the present series, the mean lead tip location was 20 mm lateral, 2.5 mm anterior, and 5.8 mm inferior to the midcommissural point, generally close to the dorsolateral border of the optic tract. Active electrodes were clustered near the axial plane of the commissures, in the lateral part of the motor territory of the GP, 3 to 5 mm from the pallidocapsular border. Because the active electrodes were within 1 to 2 mm of the border with the GPE, we do not exclude the possibility that an effect on the GPE may mediate part of the clinical improvement seen in patients with dystonia who have undergone pallidal DBS. Our active electrode location for DBS in cases of dystonia is similar to our active electrode location for GPI DBS in patients with PD.

The authors of several other publications have also quantitatively documented electrode locations for GPI DBS in patients with dystonia by using postoperative MR imaging. Bereznai, et al., studied six patients with idiopathic dystonia (five cervical and one generalized) treated with bilateral GPI DBS, and they reported a mean improvement rate of the BFMDRS score of 72.5% at 12 months; the mean tip coordinates for the 12 leads were 20.5 mm lateral to the midline, 2.8 mm anterior to the midcommissural border.
studied 22 patients with idiopathic generalized dystonia treated with bilateral GPI DBS, and they reported a mean improvement rate of the BFMDRS scores of 51% at 12 months; the mean tip locations were 20.1 mm lateral to the midline, 14.8 mm anterior to the posterior commissure, and 4.4 mm inferior to the midcommissural point. The tip coordinates in these two series are remarkably similar to those depicted in Fig. 6.

The only patient with the DYT1 mutation–positive gene in our series with less than 50% benefit suffered from long-standing severe orthopedic deformities.

The relative rarity and heterogeneity of dystonia tends to preclude large clinical trials and precise quantification of outcomes for all subtypes of the condition. In both our series and other reports, dystonia subtypes other than juvenile-onset generalized dystonia have been associated with high variability in the degree of benefit due to GPI DBS. Many factors could produce such variability, including dystonia subtype, duration of symptoms, orthopedic comorbidity, and anatomical location of active electrodes providing stimulation. In our series, the variance of the distribution of electrode locations was significantly lower for leads associated with the optimal clinical benefit compared with those resulting in the least clinical benefit, indicating that greater variability in electrode locations may have contributed to a worsened clinical outcome in some patients. Regarding secondary dystonia, adult-onset cervical dystonia, tardive dystonia, and generalized dystonia in which there is no DYT1 mutation, a greater number of patients must be studied to define the indications, outcomes, and proper programming parameters for pallidal DBS. It is also not known if targeting other brain structures, such as the subthalamic nucleus, could offer greater benefit in some types of dystonia.

Vidalhret, et al., studied 22 patients with idiopathic generalized dystonia treated with bilateral GPI DBS, and they reported a mean improvement rate of the BFMDRS scores of 51% at 12 months; the mean tip locations were 20.1 mm lateral to the midline, 14.8 mm anterior to the posterior commissure, and 4.4 mm inferior to the midcommissural point. The tip coordinates in these two series are remarkably similar to those depicted in Fig. 6.

RESULTS OF GPI DBS FOR DYSTONIA

Results of GPI DBS for dystonia have been reported in approximately 150 cases. In only one published study, of 22 patients with idiopathic generalized dystonia (both DYT1 mutation–positive and –negative subtypes) have blinded evaluators assessed clinical outcomes in a randomized study. The investigators reported a statistically significant 51% improvement in the BFMDRS movement score during the 1st year of follow up.

Because our patient group represented various dystonia subtypes, we analyzed clinical outcome separately for each subtype, resulting in a small number of patients in each group. One subtype of dystonia, juvenile-onset generalized dystonia positive for the DYT1 mutation, was sufficiently large (six patients) to show a statistically significant improvement in overall BFMDRS score. Our finding of a 66% improvement in the BFMDRS score in this group at a mean follow-up interval of 13 months is consistent with that noted in several other reports, describing a total of 25 DYT1 mutation–positive patients, whose mean BFMDRS scores improved by 56 to 83% at follow-up intervals ranging from 1 to 4 years. The only patient with the DYT1 mutation–positive gene in our series with less than 50% benefit suffered from long-standing severe orthopedic deformities. This finding suggests that patients with the DYT1 mutation–positive gene should be offered surgery before the onset of fixed orthopedic deformity.

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TABLE 3

Summary of electrode locations stratified by extent of BFMDRS score–based improvement

<table>
<thead>
<tr>
<th>Leads</th>
<th>No. of Leads</th>
<th>Active Contacts</th>
<th>Lead Tip</th>
<th>Distance (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>X   Y   Z</td>
<td>X       Y   Z</td>
<td>From Lead to PCB†</td>
</tr>
<tr>
<td>all leads</td>
<td>45</td>
<td>20.0 ± 1.9 5.8 ± 1.6 −0.5 ± 2.0</td>
<td>19.9 ± 2.0 2.5 ± 1.7 −5.8 ± 2.0</td>
<td>3.9 ± 1.9</td>
</tr>
<tr>
<td>&gt;70% improvement</td>
<td>16</td>
<td>19.8 ± 1.2 5.6 ± 1.6 −0.6 ± 2.5</td>
<td>19.9 ± 1.4 2.4 ± 1.9 −6.1 ± 2.6</td>
<td>3.6 ± 1.2</td>
</tr>
<tr>
<td>in BFMDRS score‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50% improvement</td>
<td>22</td>
<td>20.1 ± 2.1 6.0 ± 1.8 −0.1 ± 1.4</td>
<td>20.0 ± 2.3 2.6 ± 1.7 −5.4 ± 1.7</td>
<td>4.0 ± 2.4</td>
</tr>
<tr>
<td>in BFMDRS score‡</td>
<td></td>
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</tbody>
</table>

* PCB = pallidocapsular border; Pst = posterior.
† Indicates lead associated with BFMDRS score improvement.

Conclusions

Microelectrode-guided placement of pallidal deep brain stimulators in patients with dystonia is a relatively safe procedure resulting in consistent electrode location in the posterior GPI. Spontaneous discharge characteristics of internal pallidal neurons in cases of dystonia differ considerably from those in cases of PD. Nevertheless, the borders of the internal pallidum in dystonia may still be distinguished by using microelectrode recording techniques. Intraoperative test stimulation thresholds for activation of CBT or CST pathways were useful in predicting electrode location, but this was not the case for optic tract activation. Active electrodes associated with good outcome were located near the intercommissural plane at a mean of 3.6 mm from the pallidocapsular border.

Disclosure

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