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 present their technical approach for placement of electrodes into the GPi in awake patients with dystonia, including the methodology used 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 who had various forms of dystonia were included in this study. Baseline neurological status and improvement in motor function resulting from DBS were measured using the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS). Implantation of the DBS lead 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 is technically feasible in the awake state in most cases, with low morbidity rates. Spontaneous discharge rates of GPi neurons in dystonia are similar to those of globus pallidus externus neurons, such that the two nuclei must be distinguished by neuronal discharge patterns rather than by rates. Active electrode locations associated with robust improvement (> 50% decrease in BFMDRS score) were located near the intercommissural plane, at a mean distance of 3.7 mm from the pallidocapsular border. Patients with juvenile-onset primary dystonia and those with the tardive form benefited greatly from this procedure, whereas benefits for most secondary dystonias and the adult-onset craniocervical form of this disorder were more modest.

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

Dystonia is a syndrome of sustained muscle contractions that produces writhing movements and abnormal postures. It may be a primary disorder that occurs in the absence of other neurological conditions, or it may occur secondary to a lesion that appears in the central nervous system because of stroke, trauma, cerebral palsy, or degenerative disease. Most forms of dystonia respond poorly to systemic medications and intrathecal baclofen.^{13,39} Chemodenervation with botulinum toxin is helpful for focal dystonias, but the efficacy of this treatment may

wane over time and it is impractical for more generalized cases. Recently, chronic electrical stimulation of the GP has shown benefit for dystonia in a few case series.^{3,7,8,12,18,19,36,41}

The rationale for pallidal surgery in dystonia is based solely on empirical evidence of clinical improvement, because there is no clear understanding yet of the role of pallidal pathophysiology in this movement disorder.

For those seeking to perform implantation of a pallidal stimulator for dystonia, there are several unresolved technical questions. First, the optimal target point for stimulation within the pallidal complex has not been defined; there are few published cases in which locations of the electrically active contacts that are associated with good clinical outcome have been well documented.³ Second, the best way to apply microelectrode recording for confirmation of correct target localization is unclear. Microelectrode recording in awake patients is a widely used technique for surgery in movement disorders. Pallidal re-

Abbreviations used in this paper: AC-PC = anterior commissure-posterior commissure; AP = anteroposterior; BFMDRS = Burke-Fahn-Marsden Dystonia Rating Scale; FSE = fast-spin echo; GP = globus pallidus; GPe = GP externus; GPi = GP internus; GRE = gradient recalled echo; IPG = internal pulse generator; IR = inversion-recovery; MR = magnetic resonance; PD = Parkinson disease; PKAN = pantothenate kinase-associated neurodegeneration; SD = standard deviation; 3D = three-dimensional.

cording techniques in humans, however, were developed largely in patients with PD.^{22,37} Application of microelectrode recording techniques to dystonia surgery is more challenging because of the paucity and inconsistency of published data on physiological characteristics of the GP in the dystonic state.^{15,25,38} The only detailed technical reports on implantation of DBS electrodes for dystonia describe surgery performed using MR imaging–based stereotaxy as the sole navigational technique in patients in whom general anesthesia has been induced.^{9,34,35} Finally, given that dystonia is a heterogeneous disorder, the answer to the question of which patients are good surgical candidates and how they should be counseled about the expected outcome is not yet clear from the limited case series published.

In this article we report our technical approach, the electrode locations, and clinical outcomes for microelectrode-guided implantation of GPi stimulators in a series of 23 patients with dystonia. All but three of the patients underwent microelectrode recording in the awake state. Anesthetic and electrophysiological considerations unique to surgery for dystonia are described. Using postoperative MR imaging, we document active electrode locations associated with good clinical outcome. Our goal in this report was to provide practical information that will be useful to those performing this new and promising procedure.

CLINICAL MATERIAL AND METHODS

Inclusion Criteria and Clinical Evaluation

Patients with dystonia were offered surgical treatment if they met the following criteria: 1) unequivocal diagnosis of primary or secondary dystonia, made by a movement disorders neurologist; 2) attempted medical management with anticholinergic medication, benzodiazepines, baclofen (oral and/or intrathecal), and botulinum toxin; and 3) significant disability despite optimal medical management. Disability was due to impaired movement, pain, social isolation, or a combination of these. All participants gave informed consent according to a protocol approved by the Institutional Review Board. All 23 consecutive patients with dystonia who underwent surgery performed by the same surgeon (P.A.S.) between 1999 and 2004 were included in this series.

A quantitative measure of dystonia severity was obtained in the month before surgery, and at regular intervals postoperatively, by a movement disorders neurologist (W.J.M. or J.L.O.) who used a standard clinical rating scale, the BFMDRS.⁴ To provide a comparison group for the analysis of pallidal neuronal discharge characteristics, single-unit data from nine patients with PD who underwent pallidal DBS implantation are included in this report. For these patients, the mean age at onset of symptoms was 44 ± 6 years, and the mean age at surgery was 58 ± 7 years (mean $\pm$ SD). The mean severity of symptoms, as measured using Part III of the Unified PD Rating Scale, was 43 ± 10 .

Surgical Procedure

All but two patients underwent bilateral implantation. For the first 14 patients the implants were staged 1 to 3 months apart. Subsequently, as the surgical technique

became more routine, all patients who needed bilateral implantation were offered simultaneous procedures.

Anesthetic Technique. Twenty patients underwent the surgical procedure after induction of monitored local anesthesia. Because of the inability of most patients with dystonia to remain still for headframe placement or stereotactic MR imaging, these two steps were performed with the patient deeply sedated with propofol. Propofol was then discontinued at least 30 minutes before the start of pallidal recording, and the patients were alert and oriented by the time microelectrode recording began. At this point, rigid fixation of the stereotactic headframe to the operating table prevented excessive head movement associated with resting dystonic spasms.

Three of the six pediatric patients were considered unlikely to be capable of tolerating awake surgery because of their very young age, emotional immaturity, or the extremely violent, ballistic, dystonic spasms of the neck, trunk, and shoulders. For these three children, all parts of the procedure, including microelectrode recording, were performed after induction of general endotracheal anesthesia. In the first case, propofol was used as the anesthetic agent. Because this was found by us and others²⁵ to depress pallidal discharge greatly, the agent used for general endotracheal anesthesia was changed for the next two cases to a mixture of ketamine and remifentanyl, a combination found to have a comparatively smaller effect on spontaneous neuronal discharge.

Stereotactic Targeting. After placement of the stereotactic headframe, two sets of MR images were obtained: 1) a volumetric Gd-enhanced 3D GRE image covering the whole brain in 1.5-mm axial slices, which was obtained mainly for trajectory planning (parameters: TR 20 msec, TE 2.9 msec, matrix 256×192 , flip angle 30, NEX 1); and 2) an IR FSE image set covering only the basal ganglia region in 2-mm axial slices, which was obtained mainly for direct visualization of the borders of the GPi and surrounding structures (parameters: TR 3000 msec, TE 40 msec, TI 200 msec, matrix 256×512 , NEX 3, bandwidth 120 Hz/pixel, interleaved). Images were obtained on a 1.5-tesla imager (Phillips Integra; Phillips Medical Systems, 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 that were orthogonal to the AC–PC line and midsagittal planes.

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 dorso-lateral border of the optic tract in a coronal plane 2 mm anterior to the midcommissural point. A default trajectory was then set at 60° from the AC–PC line in the sagittal projection and 0° lateral from the vertical in the coronal projection (a parasagittal approach). This trajectory was visualized on the volumetric MR image by using navigation views. Small adjustments in the arc and ring angles were then made to avoid traversing sulci, cortical veins, and dural venous lakes (easily seen on Gd-enhanced images) and lateral ventricles. Finally, the target point was further refined based on visualization of the medial and

Fig. 1. Preoperative MR images demonstrating stereotactic targeting of the GPI for dystonia. A: Axial IR FSE image demonstrating the intended location of the electrode tip (arrow) dorsal to the lateral border of optic tract. B: Axial IR FSE image demonstrating the intended location of the lead (arrow) as it crosses the intercommissural line. C and D: Computationally reformatted Gd-enhanced 3D GRE images demonstrating the intended trajectory of the lead in oblique coronal (C) and oblique sagittal (D) views.

lateral borders of the GPI on IR FSE images. After viewing the axial plane passing through the commissures, the lateral coordinate was adjusted (typically by < 2 mm) in this plane 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 (Fig. 1B).

Single-Unit Recording. Single-unit discharge was recorded using glass-coated platinum/iridium microelectrodes at an impedance of 0.4 to 1 Mohm 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 was collected for a minimum of 15 seconds. Cells were recorded every 300 to 800 μ m along each trajectory. After exiting the pallidal base (heralded by the cessation of tonic high-frequency neuronal discharge), we tested for the presence of the optic

tract by using light-evoked action potential discharge and microstimulation-induced visual phenomena.^{22,37} Microelectrode recording penetrations more than 2 mm deep to the pallidal base were not made because of the potential risk of injury to a vessel in the choroidal fissure. The location and discharge characteristics of cells along each microelectrode track were plotted on scaled drawings, noting in particular the locations of the optic tract and of the electrically silent white matter laminae. The tracks were superimposed on drawings of parasagittal slices copied from the Schaltenbrand and Wahren human brain atlas,²⁶ according to a visual judgment of best fit of the tracks to the atlas.

The first microelectrode recording trajectory was set at 2 mm medial to the anatomical target to increase the likelihood of detecting optic tract and of recording a relatively long (5- to 7-mm) trajectory through the GPI. Additional parallel microelectrode recording penetrations were typically made 2 to 3 mm posterior and lateral to the initial penetration. The DBS lead (model 3387; Medtronic, Inc., Minneapolis, MN) was placed 1 to 2 mm lateral to a microelectrode recording trajectory in which at least a 6-mm segment of GPI was recorded, and 1 to 2 mm lateral to a trajectory in which the optic tract was identified. In our experience, if the lead is instead placed exactly on such a trajectory (long segment of GPI with the optic tract at the base) rather than 1 to 2 mm lateral to it, the result may be a placement that is too close (< 3 mm) to the capsular border. This could produce unacceptable side effects during long-term stimulation because of activation of the corticobulbar or corticospinal tracts. With respect to the parasagittal planes represented in the Schaltenbrand and Wahren atlas,²⁶ lead placement corresponded most closely to the 21.5-mm lateral plate, although the actual laterality of the anatomy represented on this atlas plane varied considerably between individuals.²⁹

Intraoperative Test Stimulation. Test stimulation was performed in bipolar mode by using contacts 0- and 3+ at 185 Hz and a 90- μ sec pulse width (model 3625 external tester; Medtronic, Inc.). Voltage was increased at 1 V/second while the patient repeated simple verbal 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 msec. With the room lights dimmed and the patient's eyes closed, voltage was again increased. The threshold for stimulation-induced visual phenomena (typically reported as "stars" or "flashes") was noted.

Lead Anchoring and IPG 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 for placement of the lead extenders and IPGs (Soletra or Kinetra; Medtronic, Inc.). The IPGs were placed in the same operative session as the leads.

Measurement of Electrode Location

Postoperative MR imaging was performed in all patients on the day of surgery by using a standardized, prospectively implemented protocol designed to show the DBS lead, the commissures, and the borders of GPI at high resolution. Two sequences were obtained: the 3D

GRE sequence, which was identical to that obtained in the preoperative stereotactic protocol, and a T_2 -weighted FSE sequence, limited to the basal ganglia, in the axial plane at a 2-mm slice thickness (parameters: TR 3000 msec, TE 90 msec, matrix 268×512 , NEX 6, bandwidth 183 Hz/pixel, interleaved). The MR images were transferred to an image processing station (Framelink version 4.1) 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 GRE MR image with respect to the midcommissural point. The lead was seen as a relatively discrete round signal void approximately 3 mm in diameter, which was 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 clinical evaluation, the known contact geometry (contacts 1.5-mm long, spaced 3 mm center-to-center), and location of the coordinates of the tip and entry point. The angulation of the lead array with respect to the vertical 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 published.²⁸

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 internal pallidal anatomy on the T_2 -weighted FSE images. Measurements were made in two dimensions on the reformatted axial plane passing through the commissures (at a vertical coordinate of 0). This plane was chosen because, after programming for optimal benefit, most active electrodes had a vertical coordinate close to zero (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 perpendicular position of the lead with respect to this border and the AP distance of the lead from the posterolateral corner of the GPi were measured.

Stimulator Programming

Devices were programmed within the 1st month after surgery. No attempt was made to calibrate parameters to immediate clinical benefit, because our early experience showed that little or no immediate benefit was observed, even at stimulation parameters that, months later, proved effective. Typical initial settings were as follows: unipolar mode, Electrode 2, frequency 185 Hz, and pulse width 210 μ sec. Voltage was gradually increased over the initial 2 to 6 months to between 2.5 and 3.6 V.

Analysis of Neuronal Activity

Digitized spike trains were imported into offline spike sorting software (Plexon, Inc., Dallas, TX) for discrimination of single populations of action potentials by principal components analysis. This software generated a record of

spike times with millisecond accuracy for each action potential waveform detected. The interspike intervals between successive spike times were used to evaluate stationarity of discharge, to determine the mean discharge rate, and to construct raster displays. Analyses were performed in Labview and Matlab programming environments. Neuronal data were analyzed for the discharge rate only if the patient had undergone mapping in the awake state, if 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 offline with the runs-test),³² 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 to be GPi cells. Cells recorded between the striatum and the internal medullary lamina were considered to be GPe cells. Cells 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

The mean pallidal discharge rates in different nuclei and the mean electrode locations associated with different stimulation-induced adverse effects were compared using the t distribution.

RESULTS

Patient Characteristics

The clinical characteristics of the patients are presented in Table 1. Dystonia is a heterogeneous disorder, and therefore different disease origins were represented as follows: idiopathic (14 cases), tardive (four cases), and secondary dystonia (three cases). The idiopathic dystonias were further subdivided into three groups: juvenile-onset, positive for the *DYT1* mutation²⁴ (six cases); juvenile-onset, negative for the *DYT1* mutation (three cases); and adult-onset craniocervical dystonia (five cases). The origin of the disorder was classified as unknown in two additional cases (22 and 23) because the patients were adopted at a young age (2 and 5 years) with a movement disorder already present, results of their brain MR images were normal, and their medical history before adoption was unknown. In these two cases, secondary dystonia from cerebral palsy cannot be ruled out. All three patients with definite secondary dystonia had abnormal findings on brain MR images; all other patients had unremarkable MR imaging findings. No patient had undergone prior intracranial neurosurgery. One patient (Case 6) had a working baclofen pump at the time of DBS surgery.

Surgical Outcomes and Complications

Clinical outcomes assessed using the BFMDRS, with at least a 6-month follow-up duration, are available for the first 17 patients. Outcomes are grouped by type of dystonia in Table 2, which shows the percentage of improvement in BFMDRS scores at the last available clinical

TABLE 1
Characteristics of 23 patients who underwent DBS for dystonia*

Case No.	Dystonia Type	Op Type	Age at Op (yrs)	Duration of Sx (yrs)	Baseline BFMDRS Score	Affected Regions	Preop Medications†
1	juvenile-onset DYT1+	bilat staged	12	1	34.0	legs, trunk	none
2	juvenile-onset DYT1+	bilat staged	17	9	52.0	arms, neck, trunk	trihexyphenidyl 80, clonazepam 1
3	juvenile-onset DYT1+	bilat sim	17	10	90.0	generalized	baclofen 30, trihexyphenidyl 42, lorazepam 18, Dantrium 37.5, tizanidine 24, haloperidol 3
4	juvenile-onset DYT1+	bilat staged	27	22	74.0	generalized	trihexyphenidyl 30, diazepam 100, baclofen (oral) 80, carbamazepine 700
5	juvenile-onset DYT1+	bilat sim	15	6	58.0	generalized	none
6	juvenile-onset DYT1+	bilat sim	17	5	49.5	neck, trunk	trihexyphenidyl 30, intrathecal baclofen 0.6
7	juvenile-onset DYT1–	bilat sim	42	27	19.0	neck, face, shoulders	baclofen 20, clonazepam 2
8	juvenile-onset DYT1–	unilat	28	19	35.5	lt hemibody	clonazepam 2, trihexyphenidyl 6, gabapentin 900
9	juvenile-onset DYT1–	bilat sim	28	22	94.0	generalized	trihexyphenidyl 35, clonazepam 25, baclofen 80
10	adult-onset craniocervical	bilat staged	50	13	20.0	neck	none
11	adult-onset craniocervical	bilat staged	29	2	36.0	neck	baclofen 30, amitriptyline 25, clonazepam 0.5, benzotropine 7.5
12	adult-onset craniocervical	bilat staged	58	3	28.0	arms, neck, face	lorazepam 8, temazepam 30
13	adult-onset craniocervical	bilat staged	42	13	41.0	arms, neck	baclofen 60, gabapentin 900, propranolol 240
14	adult-onset craniocervical (Meige syndrome)	bilat sim	63	5	30.0	neck, face	none
15	tardive	bilat staged	36	7	11.0	legs	divalproex sodium 1000, risperidone 8, trazodone 50, benzotropine 16
16	tardive	bilat staged	47	4	38.0	arms, neck, face	lorazepam 3
17	tardive	bilat staged	59	20	57.0	ams, face	clonazepam 3, temazepam 30
18	tardive	bilat sim	36	10	80.0	generalized	gabapentin 1800, benzotropine 6, tizanidine 18, lorazepam 8, diphenhydramine 150
19	secondary, posttraumatic	bilat staged	29	3	54.0	arms, neck, trunk	trihexyphenidyl 16, pergolide 8, levodopa 800, clonazepam 16
20	secondary, CP	unilat	17	16	82.0	generalized	Artane 60, bethanechol 7.5
21	secondary, PKAN	bilat staged	43	13	30.0	arms	levodopa 300, amantadine 200, gabapentin 900
22	UK, early onset‡	bilat staged	18	>13	85.0	generalized	trihexyphenidyl 4, diazepam 10, pramipexole 0.375
23	UK, early onset‡	bilat staged	28	>26	81.0	generalized	diazepam 10

* CP = cerebral palsy; DYT1+ = *DYT1*-positive; DYT1– = *DYT1*-negative; sim = simultaneous; sx = symptoms; UK = unknown.

† Total daily dose in milligrams.

‡ 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 their medical history prior to adoption is unknown. Results of MR imaging were normal.

examination, compared with the baseline preoperative examination. Within each subtype of dystonia the degree of improvement varied widely, although at least some patients in each group achieved a 40% or greater improvement. In two patients with juvenile-onset *DYT1*-positive dystonia, one had 97% and the other had 100% improvement, achieving normal or near normal results on neuro-

logical examinations despite severe disability preoperatively. A third patient with *DYT1*-positive dystonia had a 51% improvement at the last follow-up visit (at 26 months) but continues to improve. Thus, outcomes data up to 2 years postsurgery may not reflect the ultimate degree of benefit from these procedures. The only patient with *DYT1*-positive dystonia in whom little improvement

has been seen is one who has suffered severe symptoms for 20 years (unable to sit up in a chair), and who has had long-standing irreducible hip dislocations due to his severe leg dystonia. Juvenile-onset *DTY1*-negative dystonia may also have an excellent outcome; we observed a 71% improvement in one patient.

Patients with severe juvenile-onset dystonia frequently had a triphasic response to DBS surgery. First, there was an early improvement beginning a few days after surgery and lasting a few weeks, probably due to a pallidotomy-like effect of temporary tissue disruption. Second, with activation of stimulation, there was a period of several weeks in which dystonic spasms were worsened. The third and final phase was improvement in symptoms; this phase began within weeks to months of stimulator programming and continued to evolve for up to several years. We have not seen loss of benefit in any case, except in instances of battery failure.

In the adult-onset craniocervical dystonia group, two patients continued to worsen (negative percentage improvement in Table 2) despite pallidal surgery. Both of these patients suffered from severe cervical spinal degenerative joint disease that necessitated one or more spinal fusions prior to or soon after surgical treatment. The two patients without severe cervical degenerative joint disease experienced modest improvement (34 and 40%). In one patient (Case 13) with myoclonus/dystonia, thalamic stimulators were placed after his GPi stimulators were implanted for control of postural hand myoclonus that was not relieved by DBS of the GPi. The tardive dystonia group also had two patients with excellent benefit, one with 80% and the other with 100% improvement in the BFMDRS score. Among patients with secondary dystonia, the only one with dramatic improvement has dystonia secondary to PKAN, formerly called Hallervorden-Spatz disease (Case 21).

The programming parameters at the most recent clinical follow-up visit were 3.3 ± 0.5 V, pulse width 225 ± 50 μ sec, and frequency 181 ± 6 Hz (mean $\pm$ SD). One lead was programmed in bipolar mode, 28 leads were programmed in unipolar mode by using a single electrode, and 15 leads were programmed in unipolar mode by using two adjacent electrodes. The mean time to battery failure was 30 ± 7.5 months.

Surgical complications are listed in Table 3. One patient

TABLE 2
Change in BFMDRS scores after DBS
according to dystonia category*

Type of Dystonia	No. of Cases	Mean FU Time in Mos (range)	Mean % Imp at Last FU (range)
juvenile-onset DYT1+	4	29 (13–44)	53 (14–100)
juvenile-onset DYT1–	1	7	74
adult-onset craniocervical	4	29 (12–51)	6 (–34 to 40)
tardive	3	30 (17–46)	62 (6–100)
secondary	3	26 (12–33)	42 (8–80)
UK, early onset	2	11 (10–11)	18 (16–20)

* Outcomes available for the first 17 patients in the series. Abbreviations: Fu = follow up; imp = improvement.

† Improvement in BFMDRS scores at last follow up.

TABLE 3
Surgical complications in 23 patients
who underwent DBS for dystonia*

Complication	No. of Occurrences	Incidence	
		Per Patient	Per Lead
hemorrhage			
symptomatic	1	4.3	2.1
asymptomatic, >0.2 ml	1	4.3	2.1
repositioning of lead	3	8.7	6.8
after suboptimal placement			
return to OR for hardware	1	4.3	2.1
exploration			
hardware fractures or	0	0	0
migrations			
infection	0	0	0

* OR = operating room.

(Case 17), the second oldest one in this series, suffered a multifocal left frontal hemorrhage 2 days postsurgery, with the appearance on MR imaging of a venous infarct. This resulted in aphasia and contralateral hemiparesis. He recovered fully by 3 months postoperatively, but his dystonia did not benefit from DBS treatment. Other complications involved three leads implanted early in the series that had to be surgically repositioned because of suboptimal initial placement. Two of the leads were too close to the corticobulbar tract, resulting in inability to activate the device fully without facial contraction. A third lead was relatively lateral, within the GPe rather than the GPi. Although this lead was associated with significant benefit in contralateral proximal leg dystonia, there was persistent foot inversion, as well as stimulation-induced dyskinesia in the therapeutic voltage range. Foot dystonia improved slightly and stimulation-induced dyskinesia disappeared with placement of the lead 2 mm closer to the midline. There were no hardware fractures, migrations, or infections in this series.

Microelectrode Mapping

A total of 155 microelectrode recording penetrations were made in 44 mapped sides (mean 3.5/side, range one–eight). The mean length of the GPi recorded on the initial microelectrode recording penetration was 4.1 mm (range 0–7.3 mm). Of a total of 324 cells in awake patients tested for responses to passive movement of the limbs, 114 were found to be responsive (58 of these were arm-related, and 56 were leg-related cells). Movement-related activity was not detected in the five sides mapped with patients in a state of general anesthesia. The optic tract was identified by either light-evoked action potential discharge or microstimulation-evoked visual phenomena in 30 of 44 mapped sides. For mapping performed 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.

Single-Cell Physiology in Dystonia: Features Important for Microelectrode Recording

The mean pallidal discharge rates for each nucleus in

each disease state were calculated by pooling single-unit data across all patients who underwent surgery in the awake state. A summary plot is shown in Fig. 2. In dystonia, the mean discharge rates in the GPi and GPe were nearly identical (55 ± 22 and 53 ± 23 Hz, respectively). This is in contrast to patients with PD, for whom the mean GPi discharge rate was 96 ± 23 Hz, much higher than that of the parkinsonian GPe, which was 52 ± 18 Hz ($p < 0.001$, two-sample t-test). Thus, the transition from the GPe to the GPi was more difficult to recognize in the dystonic than in the parkinsonian state.

In dystonia, however, we observed different types of discharge patterns in the two nuclei, which proved helpful in localizing the transition between them. Representative examples of spontaneous single-unit pallidal discharge in dystonia are shown in Fig. 3. There were two characteristic patterns of discharge in the GPe, similar to those recorded in PD and in healthy nonhuman primates (Fig. 3A and B): the ubiquitous “pauser” cells and the more rare “burster” cells.¹⁰ The pauser cells in the GPe have a tonic discharge that is interrupted by characteristic 100 to 300-msec pauses in neuronal activity. The bursting cells in the GPe have irregularly spaced bursts superimposed on a very low background discharge rate. We found that approximately 15% of cells in the dystonic GPi showed a highly unusual discharge pattern, which we call “high-frequency bursting cells” (Fig. 3D). These cells discharged in irregularly spaced bursts of five to 15 action potentials. The bursts were superimposed on a relatively high background discharge rate, which distinguished them from the

GPe burster cell type. In the dystonic state, this high-frequency burster cell type appears to be distinctive for GPi and was thus useful for confirming target localization. The majority of dystonic GPi cells, although lacking the very distinctive bursts seen in Fig. 3D, nevertheless were recognizably different from GPe cells in that they fired continuously (Fig. 3C) without the characteristic pauses of the predominant cell type in the GPe.

Intraoperative Test Stimulation

Test stimulation was performed in bipolar mode with the most inferior contact negative and the most superior contact positive, at a frequency of 185 Hz, a pulse width of 90 to 200 μ sec, and a voltage of 1 to 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, which were attributable to corticobulbar or corticospinal tract activation. Stimulation-induced tonic muscle contraction was seen in four of the six leads tested with patients in a state of general anesthesia. Corticobulbar tract responses were more frequently the lowest-threshold stimulation-induced effect (35 leads) compared with corticospinal responses (six leads). The median voltage for observation of a corticobulbar tract or corticospinal effect at a 90- μ sec 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) that were attributable to optic tract activation. The median voltage for optic tract activation at a pulse width of 90 μ sec was 9.5 V. Visual thresholds could not be tested in patients who were in a state of general anesthesia. We did not observe stimulation-induced improvements in dystonia symptoms after acute intraoperative test stimulation, nor did we observe intraoperative improvement associated with tissue disruption caused by lead insertion.

Electrode Locations. Figure 4 shows an example of a postoperative MR image demonstrating lead locations with respect to the borders of the GPi in the intercommisural plane. A scatterplot of the location of all contacts in this plane, with respect to a normalized pallidocapsular border, is shown in Fig. 5. The plot indicates the location of the three leads that required repositioning, as well as those leads associated with a greater than 50% improvement in the BFMDRS score. Table 4 provides summary statistics for lead locations. The means and variances for lead and active electrode locations do not differ between the group with best clinical outcome ($> 50\%$ improvement) and all implanted leads. The angulation of the leads was $32 \pm 7^\circ$ from the vertical in the sagittal projection, and $1 \pm 5^\circ$ from the vertical in the coronal projection (mean $\pm$ SD).

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 determination of electrode location, thresholds for corticobulbar/corticospinal tract activation were predictive of location in the AP dimension. For leads whose threshold for corticobulbar/corticospinal tract activation was less than 10 V, at a pulse width of 90 μ sec and frequency of 185 Hz,

Fig. 2. Graph of pallidal discharge rates in dystonia compared with PD. The center box is the mean and the bars represent the SD. The numbers (N) below each bar are the number of neuronal units analyzed. Data obtained in 19 patients with dystonia and nine with PD were pooled. Microelectrode recording was performed at least 30 minutes after all sedative agents were discontinued.

Fig. 3. Tracings and rasters showing examples of neuronal discharges recorded in the GPe and GPi in dystonia. Microelectrode signals are shown on the left (each trace is 1 second long); the corresponding raster diagrams for each unit are on the right. In the rasters, each line represents 500 msec, and a 15-second segment of the recording is shown. Each vertical tickmark represents a single action potential discharge. A: Recording of GPe burster cell. B: Recording of GPe pauser cell. C: Recording of GPi cell. D: Recording of GPi "high-frequency burster" cell.

the mean distance anterior to the midcommissural point (measured at the midpoint of the four electrodes) was 4.9 ± 0.3 mm (mean $\pm$ standard error). For leads with a higher threshold (for example, those requiring a longer pulse width for activation at 10 V, or whose threshold exceeded the maximum tested), the AP coordinate 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 for the higher threshold leads), but this difference did not reach statistical significance. The presence or absence of optic activation was not predictive of mid-lead location, because the mean vertical coordinate for leads that elicited visual phenomena was -1.3 ± 0.4 mm from the AC-PC plane, which was not significantly different from the vertical coordinate of leads that did not elicit a visual response, that is, -1.9 ± 0.4 mm (mean $\pm$ standard error).

DISCUSSION

In this article we present methods, electrode locations, and outcomes for implantation of deep brain stimulators into the GP for various forms of dystonia. Our technical approach included MR imaging-based stereotaxy, microelectrode recording, intraoperative test stimulation to check thresholds for stimulation-induced adverse effects, and postoperative MR imaging scanning to verify electrode location. Active electrode locations were clustered in an area in the posterolateral GPi that was close to the plane of the commissures, 3 to 5 mm from the pallidocapsular border. Our surgical approach emphasizes physiological monitoring, whereas other recent technical reports on pallidal deep brain stimulator placement in dystonia describe surgery performed exclusively with MR imaging-based targeting in patients who are in a state of general anesthesia.^{9,34,35} Physiological mapping including microelectrode recording offers the theoretical advantage

Fig. 4. Postoperative T₂-weighted FSE MR images, reformatted in the parasagittal plane passing through the lead (A), and in the axial plane at the level of the commissures (B). A gray square is superimposed on the artifact generated by the electrode. The anteromedial and posterolateral extent of the GPi in the plane of the commissures are indicated with arrows. In this case the electrode is slightly more anteromedial than average (see Fig. 5).

of a real-time, 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 Electrode Implantation in Dystonia

Historically, stereotactic lesioning surgery for dystonia has been performed in the awake state.⁶ We also found awake surgery to be technically feasible in most patients with dystonia, although for many sedation was critical for frame placement and stereotactic MR imaging. The main advantages of awake surgery lie in its facilitation of intraoperative physiological monitoring and the fact that it allows continuous assessment with neurological examination of the patient during surgery. In the few patients in whom general anesthesia was required because of their young age or very severe spontaneous dystonic spasms, microelectrode recording and test stimulation were still possible. For best preservation of neuronal firing characteristics, propofol and inhalational agents should be avoided.²⁵

Differences in Physiological Mapping Between Dystonia and PD

Pallidal microelectrode recording techniques were refined during pallidal surgery for PD; the distinctive extremely rapid firing rate of GPi cells at 70 to 100 Hz facilitates the mapping of its borders.^{22,30,37} In primary dystonia and nonparkinsonian secondary dystonia, in contrast, we found that the mean spontaneous neuronal discharge rates in the GPi are 40 to 70 Hz. The mean discharge rates of the GPi and GPe were not distinct.

Nevertheless, we did find that GPi and GPe in dystonia could be distinguished by subtle differences in discharge patterns, with bursting superimposed on tonic activity being 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 rate, has been noted in several other publications.^{20,25,38} One group found, in contrast, that the GPi discharge rate in dystonia and PD was similar (both ~70 Hz), although the GPi and GPe were not specifically compared in that study.¹⁵

Role of Intraoperative Test Stimulation for Localization of Leads

Intraoperative test stimulation in the range available by using the Medtronic model 3625 external tester should be able to evoke changes in speech volume or articulation, or tonic contraction of the face or contralateral extremities in almost all cases. The threshold for this effect was predictive of 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 msec and a frequency of 185 Hz). In contrast, visual phenomena caused by optic tract activation during test stimulation were elicited in less than half of the cases. The presence or absence of optic activation did not correlate with lead location. This contrasts with a study of optic activation through a lesioning probe prior to radiofrequency pallidotomy, in which test stimulation thresholds did correlate with vertical distance from the optic tract.³⁷ This disparity may relate to differences in probe geometry (the model 3387 lead is insulated at its distal tip, unlike most radiofrequency lesioning probes), or

Fig. 5. Scatterplots showing electrode locations at the level of the intercommissural plane, plotted with respect to a normalized pallidocapsular border. The left hemisphere is represented by the left plot. *Black squares* represent leads that required surgical repositioning due to low thresholds for stimulation-induced adverse effects and/or poor efficacy; *white circles* represent leads associated with at least a 50% improvement in BFMDRS score with at least 6 months of follow up; *black circles* represent lead with less than a 50% improvement in BFMDRS score or leads whose efficacy is not yet known; *asterisks* show the mean lead location; and *broken lines* represent the lateral border of the GPi (these are drawn based on the Schaltenbrand and Wahren human brain atlas).

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. In studies in which DBS has been performed for PD, the lead location has varied widely, from posterolateral locations similar to Leksell's pallidotomy target to much more anteromedial placements.^{2,11,27,40} In our series, the mean lead tip location was 19.9 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 GPi, 3 to 5 mm from the pallidocapsular border. Because the active electrodes were within 1 to 2 mm of the border with the GPe, it is possible that an effect on GPe may mediate part of the clinical improvement seen after pallidal DBS in dystonia. Our active electrode location for DBS to treat dystonia is very similar to our active electrode locations for DBS of the GPi to treat PD.²⁷

Bereznai, et al.,³ have also quantitatively documented electrode locations for DBS of the GPi in patients with dystonia. They studied six patients with idiopathic dystonia who were treated with bilateral DBS of the GPi, all of whom attained a marked improvement in their BFMDRS scores. The mean tip locations for the 12 leads, as measured on postoperative MR images, were 20.5 mm lateral

to the midline, 2.8 mm anterior to the midcommissural point, and 5.3 mm inferior to the midcommissural point. These tip coordinates are remarkably similar to those in our study. Furthermore, when the active electrode locations were plotted on axial maps drawn from the Schaltenbrand and Wahren human brain atlas,²⁶ the electrodes were distributed in an area similar to that reported here. This indicates the beginning of a consensus with respect to desirable electrode locations for DBS of the GPi to treat dystonia.

Variable Clinical Outcomes of DBS of the GPi for Dystonia

Results of DBS of the GPi for dystonia have been reported in approximately 135 cases.^{1,3,5,7,8,12,18,19,21,31,33,36,41} Neither our patients nor most of those in earlier reports have been assessed by blinded evaluators in a randomized study design. The relative rarity and heterogeneity of dystonia tends to preclude large clinical trials and precise quantification of outcomes for all subtypes. Both in our series and in other reports, there is variability in the degree of benefit from DBS of the GPi. Many factors could produce such variability, including the dystonia subtype, duration of symptoms, orthopedic comorbidity, and anatomical location of active electrodes providing stimulation. In our series, the mean and variance of the electrode locations did not differ for leads associated with the most clinical benefit compared with other leads, indicating that factors other than electrode locations determined the high variability in outcome in our patients.

Juvenile-Onset Dystonia. Our results and those of oth-

TABLE 4
Electrode locations (mean $\pm$ SD) and efficacy of DBS for dystonia*

Electrodes	AC-PC Coordinates (mm)						Distance of Lead (mm) [†]	
	Active Contacts			Lead Tip			From Pallidocapsular Border	AP From Pst Tip of GPi
	X	Y	Z	X	Y	Z		
all leads	19.9 $\pm$ 1.9	5.8 $\pm$ 1.6	-0.6 $\pm$ 2.1	19.9 $\pm$ 2.0	2.5 $\pm$ 1.6	-5.8 $\pm$ 2.0	3.8 $\pm$ 1.5	8.0 $\pm$ 1.8
leads assoc w/ >50% imp in BFMDRS score	19.3 $\pm$ 1.7	6.1 $\pm$ 1.3	-0.5 $\pm$ 2.5	19.4 $\pm$ 1.9	3.1 $\pm$ 1.5	-5.9 $\pm$ 2.7	3.7 $\pm$ 1.3	8.2 $\pm$ 1.6

* Assoc = associated; pst = posterior.

[†] Measured in the axial plane at the level of the commissures.

ers, however, indicate some general patterns with regard to outcome. We agree with Coubes and colleagues^{7,8} that juvenile-onset idiopathic dystonia is an excellent indication for surgery. Within this group, however, our anecdotal experience indicates that onset at an extremely young age (< 5 years old) or the presence of long-standing severe orthopedic deformities are associated with more limited benefit. Patients with juvenile-onset dystonia should be offered surgery before a fixed orthopedic deformity can evolve.

Secondary Dystonia. Approximately 40 cases of patients treated with DBS of the GPi for secondary dystonias have been reported.^{7,12,18,21,31,33,36,41} Consistent with these reports, we found that patients with secondary dystonia may benefit from this procedure, although the benefits are usually modest. A notable exception to this is secondary dystonia associated with PKAN. The favorable result in our patient is consistent with four other reported cases of DBS of the GPi to treat this condition,^{7,33} and one case report of pallidal lesioning for PKAN.¹⁶ Regarding dystonias associated with stroke, trauma, or birth injury, more patients need to be studied for longer periods to determine if the procedure offers worthwhile benefits. We presently offer surgery to these patients on a case-by-case basis but warn them to have limited expectations.

Tardive Dystonia. Outcome from DBS of the GPi in tardive dystonia has been reported in two cases.^{12,41} Outcomes in three additional cases are provided here. We agree with prior reports in which it was concluded that tardive dystonia is likely to respond favorably to DBS. In our one patient with tardive dystonia, who experienced minimal improvement, damage to the dominant supplementary motor area caused by venous infarction may have been a factor that limited efficacy.

Adult-Onset Craniocervical Dystonia. Finally, the role of DBS of the GPi in botulinum toxin-resistant adult onset craniocervical dystonia remains to be defined. Our results in treating this condition are somewhat less favorable than those reported by others.^{3,12,19,41} The fact that two of our four patients had severe spinal degenerative disease may have limited the benefit of DBS.¹⁷ Another treatment option for cervical dystonia is peripheral denervation surgery, which has shown significant benefit in several recent studies in which standard rating scales of dystonia severity were used.^{14,23} A side-by-side comparison of the results of DBS of the GPi with peripheral cervical denervation procedures has not been done. At this time, DBS of the

GPi in adult onset craniocervical dystonia should be considered a treatment option that is best performed before the onset of severe cervical spondylosis.

CONCLUSIONS

Microelectrode-guided placement of pallidal deep brain stimulators for dystonia is a relatively safe procedure yielding consistent electrode location. The spontaneous discharge characteristics of GPi neurons in dystonia differ considerably from those in PD. Nevertheless, the borders of the GPi in dystonia may still be distinguished using microelectrode recording techniques. Intraoperative test stimulation thresholds for activation of corticobulbar or corticospinal tract 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 3.7 mm from the pallidocapsular border. Pallidal DBS is a highly effective procedure for many cases of juvenile-onset idiopathic dystonia and for tardive dystonia. It may prove to have a useful role in secondary dystonia and in adult-onset craniocervical dystonia, but the degree of benefit in those conditions remains to be defined.

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