Clinical outcomes of globus pallidus deep brain stimulation for Parkinson disease: a comparison of intraoperative MRI- and MER-guided lead placement

*Yarema B. Bezchlibnyk, MD, PhD,^{1,2} Vibhash D. Sharma, MD,^{3,4} Kushal B. Naik, MBBS, MPH,⁵ Faical Isbaine, PhD,² John T. Gale, PhD,² Jennifer Cheng, MD,^{2,6} Shirley D. Triche, NP,⁴ Svetlana Miocinovic, MD, PhD,⁴ Cathrin M. Buetefisch, MD, PhD,⁴ Jon T. Willie, MD, PhD,^{2,4} Nicholas M. Boulis, MD,² Stewart A. Factor, DO,⁴ Thomas Wichmann, MD,⁴ Mahlon R. DeLong, MD,⁴ and Robert E. Gross, MD, PhD^{2,4}

¹Department of Neurosurgery and Brain Repair, Morsani School of Medicine, University of South Florida, Tampa, Florida;

²Department of Neurosurgery, Emory University School of Medicine, Atlanta, Georgia; ³Department of Neurology, University of Kansas Medical Center, Kansas City, Kansas; ⁴Department of Neurology, Emory University School of Medicine; ⁵Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, Georgia, and ⁶Department of Neurosurgery, University of Kansas Medical Center, Kansas City, Kansas

OBJECTIVE Deep brain stimulation (DBS) lead placement is increasingly performed with the patient under general anesthesia by surgeons using intraoperative MRI (iMRI) guidance without microelectrode recording (MER) or macrostimulation. The authors assessed the accuracy of lead placement, safety, and motor outcomes in patients with Parkinson disease (PD) undergoing DBS lead placement into the globus pallidus internus (GPI) using iMRI or MER guidance.

METHODS The authors identified all patients with PD who underwent either MER- or iMRI-guided GPI-DBS lead placement at Emory University between July 2007 and August 2016. Lead placement accuracy and adverse events were determined for all patients. Clinical outcomes were assessed using the Unified Parkinson's Disease Rating Scale (UPDRS) part III motor scores for patients completing 12 months of follow-up. The authors also assessed the levodopa-equivalent daily dose (LEDD) and stimulation parameters.

RESULTS Seventy-seven patients were identified (MER, n = 28; iMRI, n = 49), in whom 131 leads were placed. The stereotactic accuracy of the surgical procedure with respect to the planned lead location was 1.94 ± 0.21 mm (mean $\pm$ SEM) (95% CI 1.54–2.34) with frame-based MER and 0.84 ± 0.007 mm (95% CI 0.69–0.98) with iMRI. The rate of serious complications was similar, at 6.9% for MER-guided DBS lead placement and 9.4% for iMRI-guided DBS lead placement (RR 0.71 [95% CI 0.13–3.9%]; p = 0.695). Fifty-seven patients were included in clinical outcome analyses (MER, n = 16; iMRI, n = 41). Both groups had similar characteristics at baseline, although patients undergoing MER-guided DBS had a lower response on their baseline levodopa challenge ($44.8\% \pm 5.4\%$ [95% CI 33.2%–56.4%] vs $61.6\% \pm 2.1\%$ [95% CI 57.4%–65.8%]; t = 3.558, p = 0.001). Greater improvement was seen following iMRI-guided lead placement ($43.2\% \pm 3.5\%$ [95% CI 36.2%–50.3%]) versus MER-guided lead placement ($25.5\% \pm 6.7\%$ [95% CI 11.1%–39.8%]; F = 5.835, p = 0.019). When UPDRS III motor scores were assessed only in the contralateral hemibody (per-lead analyses), the improvements remained significantly different ($37.1\% \pm 7.2\%$ [95% CI 22.2%–51.9%] and $50.0\% \pm 3.5\%$ [95% CI 43.1%–56.9%] for MER- and iMRI-guided DBS lead placement, respectively). Both groups exhibited similar reductions in LEDDs (21.2% and 20.9%, respectively; F = 0.221, p = 0.640). The locations of all active contacts and the 2D radial distance from these to consensus coordinates for GPI-DBS lead placement (x, ± 20 ; y, +2; and z, –4) did not differ statistically by type of surgery.

CONCLUSIONS iMRI-guided GPI-DBS lead placement in PD patients was associated with significant improvement in clinical outcomes, comparable to those observed following MER-guided DBS lead placement. Furthermore, iMRI-guided

ABBREVIATIONS DBS = deep brain stimulation; GPI = globus pallidus internus; ICL = intercommissural line; iCT = intraoperative CT; iMRI = intraoperative MRI; LEDD = levodopa-equivalent daily dose; MCP = midcommissural point; MER = microelectrode recording; PD = Parkinson disease; STN = subthalamic nucleus; UPDRS = Unified Parkinson's Disease Rating Scale.

SUBMITTED July 24, 2019. **ACCEPTED** December 30, 2019.

INCLUDE WHEN CITING Published online March 6, 2020; DOI: 10.3171/2019.12.JNS192010.

* Y.B.B. and V.D.S. contributed equally to this work.

DBS implantation produced a similar safety profile to that of the MER-guided procedure. As such, iMRI guidance is an alternative to MER guidance for patients undergoing GPI-DBS implantation for PD.

<https://thejns.org/doi/abs/10.3171/2019.12.JNS192010>

KEYWORDS Parkinson disease; deep brain stimulation; intraoperative MRI; ClearPoint; microelectrode recording; functional neurosurgery

DEEP brain stimulation (DBS) of the globus pallidus internus (GPi) (GPi-DBS) effectively controls the motor symptoms of patients with Parkinson disease (PD).^{19,36} Historically, most centers used intraoperative microelectrode recording (MER) and/or macrostimulation in awake patients to define the anatomical target.¹⁰ This can be challenging for patients with severe off-medication symptoms, behavioral issues, or anxiety, and multiple penetrations may be required to identify the optimal location for DBS lead implantation.^{37,38}

Direct targeting of anatomical structures with intraoperative radiological imaging is an alternative to MER-guided lead placement^{2,3,13,21,26,34} and may be done with the patient under general anesthesia while the surgeon employs an intraoperative O-arm (Medtronic), intraoperative CT (iCT), or intraoperative MRI (iMRI) to verify DBS lead placement. Such procedures typically entail a single brain penetration, compared to an average of 2.3 tracts with MER-guided DBS placement, each with an associated risk of adverse events.^{34,38} Additionally, techniques relying on intraoperative imaging other than MRI are subject to errors arising from fusion of these studies to preoperative MR images.^{8,13,18} The use of iMRI obviates these issues and enables visualization of anatomical targets and patient-specific anatomy in high resolution and near real time, thereby allowing neurosurgeons to adjust trajectories or targets intraoperatively and to rapidly recognize procedural complications.

Clinical outcomes using image guidance are reported to be comparable to those using traditional MER-guided placement, suggesting that direct targeting is a viable alternative for lead placement.^{2,4,17,22} However, the literature is limited, and, to our knowledge, there are no direct comparisons between iMRI- and MER-guided DBS lead placements. Here, we report our experience with these methods.

Methods

Patients

We retrospectively identified all PD patients who underwent MER- or iMRI-guided GPi-DBS placement at Emory University (Atlanta, GA) from July 2007 to August 2016 and for whom records were available. Records were reviewed to collect demographic information, surgical details, adverse events, clinical scores (Unified Parkinson's Disease Rating Scale [UPDRS] parts I–IV subscores and total UPDRS scores,⁹ with part II and III scores obtained on and off medications), levodopa-equivalent daily dose (LEDD), motor side-effect thresholds assessed at the initial programming visit, and DBS stimulation parameters.

Lead placement accuracy and adverse events were determined for each patient. Patients were then segregated by surgical procedure, and clinical outcomes were assessed for patients with at least 12 months of follow-up

postoperatively. Since some implantations were unilateral, these assessments were made in two ways: on a per-patient basis and a per-lead basis, wherein each lead was considered independently regardless of contralateral implantation. For clinical outcome analyses performed on a per-patient basis, patients with prior pallidotomy/thalamotomy or gene therapy were excluded. We also excluded patients who previously underwent lead placement in either hemisphere, unless the leads were explanted and new baseline clinical measures obtained in the interim. For patients undergoing staged bilateral lead implantation, postoperative UPDRS scores were obtained after placement of the second lead. For per-lead analyses, we included patients who had previously undergone contralateral DBS lead placement, and postoperative assessments were obtained 1 year following the implantation of each lead individually.

The Emory University Institutional Review Board approved the study.

Surgical Procedure

Both the selection of patients for DBS surgery and the determination of DBS target (GPi, subthalamic nucleus [STN], or thalamus) were reviewed by a multidisciplinary team. Surgeries were performed by one of three surgeons (R.E.G., N.M.B., J.T.W.). Prior to April 2012, all lead placements were performed using MER guidance. For this approach, a preoperative MRI was obtained on the day of the surgery after placement of a Cosman-Roberts-Wells stereotactic frame (Integra), and it was loaded onto a StealthStation (Medtronic) for surgical planning using FrameLink software. The GPi was targeted^{15,35} at 20–21 mm lateral to the intercommissural line (ICL), 1 mm posterior to the midcommissural point (MCP), and 4 mm below the ICL. The y-coordinate was adjusted from the standard coordinate 2 mm anterior to the MCP based on our finding a 3-mm anterior displacement of the lead tip at the target due to the torque placed on the arc by the weight of our frame-based microdrive system (Axon Guideline System 3000, FHC, Inc.) both clinically and in phantom studies (R. E. Gross, unpublished observations, 2005–2011). The entry site was chosen to avoid cerebral veins, sulci, and the lateral ventricle. MERs were obtained, followed by stimulation mapping, and the results were entered into proprietary software (OneTrack, developed at Emory University) to confirm and refine the placement of the DBS lead in the posteroventrolateral GPi, as described elsewhere.^{10,27}

Subsequent to April 2012, with the availability of the MRI guidance platform, lead placements in the GPi were almost exclusively performed using iMRI guidance. This change was possible because the pallidocapsular border can be consistently visualized with MRI to guide direct targeting. As described elsewhere,^{22,33} the placement of DBS leads using iMRI guidance was performed after placing the patient under general anesthesia using a 1.5T Sie-

mens Magnetom large-bore scanner in conjunction with the ClearPoint System (MRI Interventions, Inc.). The standard coordinates for GPi (20–21 mm lateral, 2 mm anterior to the MCP, and 4 mm inferior to the ICL) were individualized using several methodologies as outlined previously.²⁸ Notably, the SmartFrame base (MRI Interventions) was affixed to the skull either directly (skull mount) or percutaneously (scalp mount). With the skull-mounted system, the dura mater was opened widely and the pia/arachnoid pierced with the cannula/blunt stylet assembly, whereas with the scalp-mounted frame, the dura and pia/arachnoid were pierced with a sharp stylet. Quadripolar DBS electrodes (model 3389; Medtronic) were inserted in all cases and secured using the StimLoc cap. A volumetric axial T1-weighted noncontrast imaging study was obtained, and images from both the stylet and DBS lead insertion were loaded into the OneTrack software and the ClearPoint workstation for confirmation of lead insertion accuracy.

Neurostimulators (Activa; Medtronic) were implanted after induction of general anesthesia in a separate surgery 1–4 weeks following lead implantation, although occasionally the lead was connected immediately following implantation. Initial programming was performed approximately 4 weeks following lead implantation by the movement disorders team. The clinical response at each contact was assessed at increasing voltage, with a pulse width of 90 μ sec and a frequency of 135 Hz, and the best contact(s) was/were selected. Subsequent changes in stimulation parameters were made to optimize clinical benefits and minimize adverse effects.

Outcome Measures

The accuracy of lead placement and the frequency and type of surgery-related adverse events were assessed for all patients. For the accuracy of lead placement, we established the location of the tip of each DBS lead from postoperative studies including MR images and/or CT scans and compared this location to the intended target by calculating the 2D radial error, corresponding to the linear distance (mm) from the trajectory of the implanted device to the intended target in the plane perpendicular to the trajectory of the lead. We chose this measure since errors in this plane have a greater impact on the outcomes of DBS surgery than (depth) errors along the electrode trajectory, because the latter can be largely compensated for by stimulating at different contacts along the electrode. We also identified the coordinates of all cathodal contacts used for stimulation for each lead to determine the mean location of all active contacts across all leads, as well as by surgical procedure, and calculated the euclidean distance (accounting for error in the x, y, and z planes) from this point to consensus coordinates. Finally, the accuracy of the ClearPoint targeting system per se corresponded to the 2D radial error between the trajectory of the ceramic stylet and the intended target.

Serious complications were defined as life-threatening medical complications or death within 30 days of surgery, hemorrhages associated with neurological deficits requiring rehabilitation or requiring prolongation of hospitalization by > 24 hours, and infections requiring surgical intervention.

For clinical outcomes, UPDRS III scores off medications/on stimulation 12 months after DBS lead implantation were compared to pre-DBS placement off-medication scores. For per-lead analyses, UPDRS III scores were obtained from the extremities contralateral to the side of the implanted lead, excluding axial scores. Other measures assessed included the change in LEDD, motor side-effect thresholds assessed at the initial programming visit, and stimulation parameters.

Statistical Analysis

Data are shown as mean $\pm$ SEM, together with 95% CIs. Graphically, data are presented as the mean $\pm$ 95% CI. One-way repeated-measures ANOVAs were used to compare postoperative outcome scores to preoperative scores, with time point as the within-subjects measure and surgery as the between-subjects measure. Demographic variables between groups were compared using independent-samples Student t-tests for continuous data and chi-square tests for ordinal data. All tests were two-tailed. A p value ≤ 0.05 was considered to indicate a statistically significant result. Post hoc power analyses were performed with $\alpha = 0.05$. All statistical analyses were performed using SPSS for Windows version 16.0 (SPSS Inc.).

Results

Patients

Seventy-seven consecutive patients underwent GPi-DBS over the course of the study period ($n = 131$ leads). The MER group included 29 patients (28 initial surgeries and 1 revision of a lead previously implanted using iMRI; $n = 42$ leads), whereas the iMRI group included 53 patients (49 initial procedures, 1 patient in whom the contralateral side was previously implanted using MER, and 3 revisions of leads previously placed using MER; $n = 89$ leads) (Fig. 1).

For clinical outcome analyses, 20 patients, corresponding to 13 MER- and 12 iMRI-guided DBS procedures when revisions are taken into account, were excluded (see Fig. 1 for details). Therefore, 57 patients were retained for per-patient clinical outcome analyses: 16 were implanted using MER guidance ($n = 7$ unilateral, 9 staged/bilateral), and 41 using iMRI guidance ($n = 14$ unilateral, 27 staged/bilateral). The baseline clinical characteristics are shown in Table 1.

For per-lead analyses, we additionally included 3 patients who had undergone prior contralateral stereotactic procedures and 1 patient who had undergone a contralateral DBS surgery at another institution prior to his 12-month follow-up visit. These analyses included 98 leads, corresponding to 28 MER-guided procedures ($n = 8$ unilateral, 20 staged/bilateral) and 70 iMRI-guided procedures ($n = 14$ unilateral, 56 staged/bilateral).

Lead Placement and Accuracy

The postoperative location was available for 127 leads (MER, $n = 39$; iMRI, $n = 88$). The mean stereotactic coordinates of the tips of the DBS leads differed by surgical procedure, with those implanted under iMRI guidance being located, on average, more laterally, anteriorly, and

FIG. 1. Overview of all patients included in the current study, considered by surgical procedure. Lead placement accuracy and adverse events were assessed in all patients undergoing DBS lead placement over the course of the study period. Clinical outcome analyses were assessed for all patients with at least 12 months of follow-up, as determined from the time of pulse generator implantation. F/U = follow-up; LTF/U = lost to follow-up; MD = movement disorders.

shallower than those placed using MER guidance (Table 2). However, when we examined the mean locations of all active contacts in all patients included in the clinical outcome analyses ($n = 97$), we found no difference in their location by type of surgery (Table 2, Fig. 2).

Based on the immediate postoperative MRI study, leads placed using iMRI guidance were an average of 0.84 ± 0.007 mm (95% CI 0.69–0.98) from the intended target, compared to 1.94 ± 0.21 mm (95% CI 1.54–2.34) for leads placed using MER. In addition, we assessed the targeting accuracy of the ClearPoint system. Data were available for 84 of the 89 iMRI-guided implantations, demonstrating an overall 2D radial error of 0.66 ± 0.04 mm (95% CI 0.59–0.73). We further compared the 2D radial targeting error across versions 1.2 to 1.5.3 of the ClearPoint software to assess whether software upgrades influenced this variable. Since only 2 leads were placed using version 1.3, these were combined with those placed using version 1.2, as both iterations were used in conjunction with the skull-mounted system (Table 3). We found a significant difference in the targeting accuracy of the ClearPoint system across these groups ($F = 5.796$, $p = 0.004$). Newer versions of this software (1.5 to 1.5.3) were associated with a lower error (0.56 ± 0.04 mm [95% CI 0.48–0.64]) compared to older iterations (0.79 ± 0.06 mm [95% CI 0.68–0.89]).

Finally, we compared the locations of the active contacts relative to “consensus coordinates” for GPi-DBS (x,

± 20 ; y, $+2$; and z, -4). Although the coordinates of the target vary from patient to patient,³⁵ this point from the Schaltenbrand and Wahren stereotactic atlas²⁵ was selected for comparison. The average euclidean distance from this point to the mean location of all active contacts was 4.23 ± 0.16 mm (95% CI 3.92–4.54) for all implantations, or 4.38 ± 0.28 mm (95% CI 3.82–4.93) and 4.17 ± 0.19 mm (95% CI 3.80–4.55) for MER- and iMRI-guided DBS placement, respectively (not statistically different).

Adverse Events and Complications

In the MER-guided DBS group, serious complications occurred in 2 (6.9%) of 29 patients and involved 2 (4.8%) of 42 leads (Table 4). Among patients undergoing iMRI-guided DBS surgery, serious complications occurred in 5 (9.4%) of 53 patients and involved 7 (7.9%) of 89 leads. These complication rates were not statistically different (chi-square = 0.749, $p = 0.387$; chi-square = 0.430, $p = 0.512$, by patient and by lead, respectively). The mean risk ratio following MER- versus iMRI-guided DBS placement was 0.71 (95% CI 0.13–3.9) on a per-patient basis; this difference, too, was not significantly significant ($p = 0.695$).

In addition to serious adverse events, 1 patient in the iMRI group developed cellulitis in the vicinity of one of his cranial incisions that was successfully treated with intravenous antibiotics, and 3 (5.7%) of 53 patients were found to have a small, asymptomatic subdural/subarach-

TABLE 1. Clinical characteristics of patients included in the clinical outcome analysis

Characteristic	All Ops	MER	iMRI	Statistics
No. of patients	57	16	41	
Unilat/bilat; % unilat	21/36; 36.8%	7/9; 43.8%	14/27; 34.1%	$\chi^2 = 0.456$, $p = 0.499$
Male/female; % male	32/25; 56.1%	10/6; 62.5%	22/19; 53.7%	$\chi^2 = 0.365$, $p = 0.546$
Age at surgery, yrs	65.4 $\pm$ 1.2	67.8 $\pm$ 1.6	64.5 $\pm$ 1.6	$t = 1.179$, $p = 0.243$
Duration of illness, yrs	10.2 $\pm$ 0.5	10.2 $\pm$ 1.2	10.1 $\pm$ 0.6	$t = 0.034$, $p = 0.973$
LEDD at baseline	1476 $\pm$ 79.0	1317 $\pm$ 164.6	1538 $\pm$ 88.6	$t = 1.256$, $p = 0.214$
LEDD at 1 yr (% change)	1120 $\pm$ 68.7 (21.0% $\pm$ 3.9%)	1013 $\pm$ 163.3 (21.2% $\pm$ 8.4%)	1162 $\pm$ 71.6 (20.9% $\pm$ 4.4%)	$F = 0.221$, $p = 0.640$
Statistics (LEDD)	$F = 18.73$, $p < 0.001$	$t = 2.400$, $p = 0.020$	$t = 4.730$, $p < 0.001$	
UPDRS I at baseline	3.3 $\pm$ 0.3	3.4 $\pm$ 0.4	3.3 $\pm$ 0.3	$t = 0.255$, $p = 0.800$
UPDRS II at baseline (off Rx)	22.3 $\pm$ 0.9	22.6 $\pm$ 1.5	22.2 $\pm$ 1.0	$t = 0.225$, $p = 0.823$
UPDRS II at baseline (on Rx)	11.7 $\pm$ 0.8	13.9 $\pm$ 1.8	11.0 $\pm$ 0.9	$t = 1.561$, $p = 0.125$
UPDRS III at baseline (on Rx)	16.0 $\pm$ 1.1	20.1 $\pm$ 2.4	14.4 $\pm$ 1.2	$t = 2.425$, $p = 0.019$
L-dopa responsiveness at baseline (% change UPDRS III off vs on Rx)	56.9% $\pm$ 2.3%	44.8% $\pm$ 5.4%	61.6% $\pm$ 2.1%	$t = 3.558$, $p = 0.001$
UPDRS IV at baseline	9.0 $\pm$ 3.2	9.4 $\pm$ 0.9	8.9 $\pm$ 0.5	$t = 0.522$, $p = 0.604$
Total UPDRS at baseline (off Rx)	70.8 $\pm$ 1.9	70.9 $\pm$ 3.3	70.8 $\pm$ 2.3	$t = 0.037$, $p = 0.971$
UPDRS III at baseline (off Rx)	36.3 $\pm$ 1.1	35.4 $\pm$ 1.5	36.6 $\pm$ 1.4	$t = 0.473$, $p = 0.638$
UPDRS III at 1 yr (off Rx/on DBS) (% improvement)	22.4 $\pm$ 1.4 (38.2% $\pm$ 3.3%)	26.5 $\pm$ 2.8 (25.5% $\pm$ 6.7%)	20.8 $\pm$ 1.6 (43.2% $\pm$ 3.5%)	$F = 5.835$, $p = 0.019$
Statistics (UPDRS III)	$F = 75.74$, $p < 0.001$	$t = 3.707$, $p < 0.001$	$t = 10.49$, $p < 0.001$	
No. of leads	98	28	70	
Laterality (lt/rt); % lt	53/45; 54.1%	13/15; 46.4%	40/30; 57.1%	$\chi^2 = 0.925$, $p = 0.336$
Contralat UPDRS III at baseline (off Rx)	11.8 $\pm$ 0.4	11.4 $\pm$ 0.6	11.9 $\pm$ 0.5	$t = 0.701$, $p = 0.486$
Contralat UPDRS III at 1 yr (off Rx/ on DBS) (% improvement)	6.0 $\pm$ 0.4 (46.3% $\pm$ 3.3%)	7.1 $\pm$ 0.7 (37.1% $\pm$ 7.2%)	5.6 $\pm$ 0.4 (50.0% $\pm$ 3.5%)	$F = 5.310$, $p = 0.023$
Statistics (contralat UPDRS III)	$F = 140.9$, $p < 0.001$	$t = 5.661$, $p < 0.001$	$t = 13.26$, $p < 0.001$	

L-dopa = levodopa; Rx = medications.

Data presented as mean $\pm$ SEM unless otherwise noted.

noid hemorrhage on postoperative imaging; 2 of these patients were treated with the skull-mounted system and 1 with the scalp-mounted platform. In the MER group, 3 (10.3%) of 29 patients went on to have uncomplicated unilateral iMRI-guided lead revisions. In the iMRI-guided DBS group, revisions were performed in 2 (3.8%) of 53

patients; one patient underwent bilateral revisions targeting the STN, while in another, the lead was repositioned in a subsequent MER-guided procedure. Thus, the overall complication rate for the MER-DBS group was 17.2% ($n = 5/29$), and for leads it was 11.9% ($n = 5/42$), whereas for the iMRI-DBS group the overall complication rate was

TABLE 2. Mean stereotactic coordinates of lead tips and cathodal contacts relative to the MCP

	All Ops	MER	iMRI	Statistics
Tip of DBS leads, no.	127	39	88	
x	21.0 $\pm$ 0.17	20.4 $\pm$ 0.40	21.3 $\pm$ 0.16	$t = 2.284$, $p = 0.027$
y	-0.03 $\pm$ 0.21	-1.06 $\pm$ 0.52	0.43 $\pm$ 0.19	$t = 2.709$, $p = 0.009$
z	-4.04 $\pm$ 0.27	-5.26 $\pm$ 0.74	-3.50 $\pm$ 0.19	$t = 2.297$, $p = 0.027$
Cathodal contacts, no.	97	27	70	
x	21.38 $\pm$ 0.15	20.95 $\pm$ 0.25	21.54 $\pm$ 0.18	$t = 1.821$, $p = 0.072$
y	2.55 $\pm$ 0.19	2.99 $\pm$ 0.32	2.39 $\pm$ 0.23	$t = 1.404$, $p = 0.164$
z	-0.77 $\pm$ 0.17	-0.48 $\pm$ 0.32	-0.89 $\pm$ 0.19	$t = 1.115$, $p = 0.270$

Data presented as mean $\pm$ SEM unless otherwise noted.

A Targeting in iMRI-DBS **B Stereotactic Coordinates of Active Contacts following MER- vs. iMRI-DBS**

FIG. 2. A: A representative image of the basal ganglia as visualized using quantitative susceptibility mapping, showing the targeting strategy. Briefly, we identified a point (marked with a star) on the axial plane of the ICL, 2.5 mm perpendicular to the pallidum-capsular border at the junction of its posterior one-third and anterior two-thirds, as described by Starr et al.³³ The final target was 4–6 mm deep to this point along the trajectory of implantation. **B:** Coordinates of all active contacts relative to the MCP (x, y, z = 0) were obtained from post-lead placement MRI scans for all implantations in patients for whom clinical outcomes and stimulation parameters were available 12 months postoperatively. The x-coordinate in left-sided implantations is presented as a positive number to simplify the comparison. The mean coordinate of all active contacts is presented for both MER- and iMRI-guided DBS procedures (black symbols), as is the consensus coordinate (X) for GPi (x = 20, y = 2, z = -4).

18.9% (n = 10/53), and for leads it was 15.7% (n = 14/89; not statistically significantly different; chi-square = 0.033, p = 0.855; chi-square = 0.337, p = 0.562, by patient and by lead, respectively). The risk ratio following MER- versus iMRI-guided DBS placement was 0.89 (0.27–2.9) on a per-patient basis; again, this was not statistically significant (p = 0.856).

TABLE 3. Accuracy of lead placement by ClearPoint software version and side of implantation

Software Version	No. of Leads (lt/rt)	Lt Leads	Rt Leads	All Leads
1.2–1.3	13 (7/6)	0.81 ± 0.07	0.65 ± 0.11	0.74 ± 0.07
1.4	24 (14/10)	0.72 ± 0.09	0.94 ± 0.14	0.81 ± 0.08
≥1.5	47 (25/22)	0.56 ± 0.06	0.55 ± 0.06	0.56 ± 0.04
All versions	84 (46/38)	0.65 ± 0.04	0.67 ± 0.06	0.66 ± 0.04

Data presented as mean ± SEM unless otherwise noted.

Baseline Clinical Characteristics

As shown in Table 1, the MER- and iMRI-DBS groups had similar baseline clinical characteristics, including off-medication UPDRS scores. However, patients who underwent device implantation using MER guidance had a higher mean baseline on-medication UPDRS III score and, therefore, a lower response on their baseline levodopa challenge ($44.8\% \pm 5.4\%$ [95% CI 33.2%–56.4%] compared to $61.6\% \pm 2.1\%$ [95% CI 57.4%–65.8%]; $t = 3.558$, $p = 0.001$) than patients who underwent device implantation using MRI guidance. Given that many patients were treated with unilateral leads over the course of this study, we also assessed the baseline UPDRS III off-medication scores for the side of the body contralateral to the implanted lead; no difference was observed between the two groups.

Clinical Outcomes

For all 57 patients included in the clinical outcome analyses, UPDRS III off-medication scores improved sig-

TABLE 4. Adverse events and revisions grouped by type of surgery

Sex	Age at Op, Yrs	AEs	Leads Involved
SAE			
MER-guided DBS		2 SAEs in 2 patients	2
M	61	Infection requiring explantation of unilat DBS lead, extension, & IPG	1
F	66	Infection requiring explantation of unilat DBS lead, extension, & IPG	1
iMRI-guided DBS		5 SAEs in 5 patients	7
F	60	Deep vein thrombosis/pulmonary embolism*	2
M	68	Multiple erosions requiring revision of bilat leads, leading to lt lead explantation & pallidotomy	2
F	72	IPG & extension wire infection requiring explantation	1
M	70	Erosion over lead requiring I&D & Z-plasty	1
F	66	IPG & extension wire infection requiring explantation	1
Other AEs			
iMRI-guided DBS		4 AEs in 4 patients	4
F	60	Small rt SDH*	1
M	73	Small rt SDH	1
M	54	Small lt SDH	1
M	71	Cranial cellulitis treated with IV antibiotics	1
Revisions			
MER-guided DBS		3 revisions in 3 patients	3
M	67	Revision of unilat lead with iMRI-DBS	1
M	35	Revision of unilat lead with iMRI-DBS	1
M	71	Revision of unilat lead with iMRI-DBS	1
iMRI-guided DBS		2 revisions in 2 patients	3
M	37	Revision of bilat leads with bilat STN-DBS	2
F	48	Revision of unilat lead with MER-DBS	1

AE = adverse event; I&D = irrigation and debridement; IPG = internal pulse generator; IV = intravenous; SAE = severe AE; SDH = subdural hematoma; Z-plasty = plastic surgery (rotational flap).

* Same patient with two adverse events.

nificantly ($F = 75.74$, $p < 0.001$) by $38.2\% \pm 3.3\%$ (95% CI 31.7%–44.8%; Table 1, Fig. 3A). The improvement was greater 1 year following iMRI-guided ($43.2\% \pm 3.5\%$ [95% CI 36.2%–50.3%]) as compared to MER-guided ($25.5\% \pm 6.7\%$ [95% CI 11.1%–39.8%]) DBS surgery ($F = 5.835$, $p = 0.019$; Table 1, Fig. 3B). Post hoc power analyses using these group means/variance suggested that our study is expected to be valid 64.6% of the time.

When we assessed patients who underwent bilateral or staged procedures exclusively (MER, $n = 9$; iMRI, $n = 27$), we again found a significant difference in postoperative UPDRS III scores between patients based on type of surgery ($F = 4.395$, $p = 0.044$), with greater improvements following iMRI-guided DBS ($48.3\% \pm 3.6\%$ [95% CI 40.8%–55.8%] vs $28.5\% \pm 11.2\%$ [95% CI 2.7%–54.2%]).

There was also a significant improvement of $46.3\% \pm 3.3\%$ (95% CI 39.8%–52.8%) in UPDRS III scores in the hemibody contralateral to implanted leads across all surgical procedures ($F = 140.9$, $p < 0.001$; Table 1, Fig. 4A). Patients who underwent iMRI-guided DBS exhibited a significantly greater improvement in UPDRS III scores

contralateral to the implanted lead 1 year postoperatively ($50.0\% \pm 3.5\%$ [95% CI 43.1%–56.9%]) when compared to patients who underwent MER-guided DBS ($37.1\% \pm 7.2\%$ [95% CI 22.2%–51.9%]; $F = 5.310$, $p = 0.023$; Table 1, Fig. 4B).

LEDD

The average preoperative LEDD in all 57 patients included for clinical outcome analysis did not differ between the MER and iMRI groups (Table 1). At 1 year postoperatively, the mean LEDD was reduced by $21.0\% \pm 3.9\%$ (95% CI 12.7%–28.2%; $F = 20.629$, $p < 0.001$). The LEDD reduction was significant in both groups ($t = 2.400$, $p = 0.020$ and $t = 4.730$, $p < 0.001$ for MER and iMRI groups, respectively), and it did not differ between them. We additionally assessed the change in LEDD in only those patients who underwent bilateral or staged implantations. The mean baseline LEDD across these patients did not differ by surgical procedure ($t = 0.062$, $p = 0.951$). One year postoperatively, the LEDD was reduced by $22.0\% \pm 4.7\%$

FIG. 3. UPDRS III scores at baseline and 1 year postoperatively in all patients (A) and grouped by surgical procedure (B). Bars represent the means $\pm$ 95% CIs in all cases. * $p \leq 0.05$; *** $p \leq 0.001$.

FIG. 4. UPDRS III scores were established for the contralateral hemibody at baseline and 1 year postoperatively to allow assessment of changes in scores across each DBS lead. These scores are presented for all available leads (A) and for all leads grouped by surgical procedure (B). Bars represent the means $\pm$ 95% CIs in all cases. * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$.

(95% CI 12.4%–31.5%; $F = 11.280$, $p = 0.002$). There was no difference in LEDD reduction following MER- versus iMRI-guided DBS placement ($F = 0.915$, $p = 0.346$).

Stimulation Parameters

Stimulation parameters 1 year following DBS surgery were available for 98 leads. The mean settings for leads implanted via MER guidance ($n = 28$) were 3.5 ± 0.12 V (95% CI 3.2–3.7), 84.6 ± 4.6 μ sec (95% CI 75.1–94.2), and 135.7 ± 5.6 Hz (95% CI 124.2–147.3), whereas those for leads implanted via iMRI guidance ($n = 70$) were 3.3 ± 0.08 V (95% CI 3.1–3.4), 79.8 ± 1.8 μ sec (95% CI 76.2–83.4), and 134.6 ± 2.5 Hz (95% CI 129.6–139.5). The differences were not statistically significant for any parameter. In addition, we identified the motor side-effect threshold at the active contact at the initial programming session. Interestingly, these thresholds were significantly lower in patients who underwent DBS implantation with iMRI guidance than by MER guidance (3.1 ± 0.1 V [95% CI 2.8–3.4] vs 4.1 ± 0.3 V [95% CI 3.4–4.6], respectively; $t = 3.354$, $p = 0.001$).

Discussion

As in previous studies,^{2,4,22,30,33} iMRI targeting was highly accurate. Based on immediate postoperative MR images, the leads were placed an average of 0.84 ± 0.007 mm from the intended target, which is in line with previously published studies using the same technique.^{16,22,33} These results compare favorably to those obtained with other techniques of DBS lead placement,^{3,6,13,26,34} including the 39 leads placed using frame-based MER in the current study. These leads were located an average of 1.94 ± 0.21 mm (95% CI 1.54–2.34) from the intended target, which is consistent with prior studies, suggesting a 2D error of 0.84 mm¹² to 2.1 mm³² when using this technique. Moreover, we found that lead placement accuracy improved with updates to the ClearPoint targeting software, perhaps because of improvements in the targeting algorithm, better recognition of the gadolinium-filled guide cannula that resulted in less variability in its representation (E. Kelly and A. Keebaugh, MRI Interventions, personal communication), or greater familiarity of the surgeons with the targeting platform.

The UPDRS III scores obtained when patients were off medication 12 months postoperatively improved significantly in most cases in our study, whether treated via MER- or iMRI-guided DBS device implantation. In the iMRI-guided DBS group, the improvement was 43.2% when patients with unilateral and bilateral leads were considered jointly and 48.3% when unilateral implantations were excluded. Similarly, Ostrem et al. found a significant improvement of 40.2% in UPDRS III scores 1 year following DBS surgery, although only 4 (20%) of 20 patients underwent GPi-DBS,²² while Sidiropoulos et al. reported 41% improvement in UPDRS III scores for their 6 patients undergoing iMRI-guided GPi-DBS at 1 year after implantation.²⁹ More recently, Brodsky et al.² reported a 35% improvement in UPDRS III motor scores in 30 patients undergoing asleep GPi- or STN-DBS iCT, while Chen et al. observed an improvement of 37.5% in 59 patients undergoing iCT-guided GPi-DBS.⁴

The average improvement in UPDRS III scores among patients undergoing MER-guided GPi-DBS in this study was 25.5%, or 28.5% in patients with bilaterally implanted leads only. This is lower than the outcomes described elsewhere,¹⁴ although it is broadly similar to the level of improvement observed in recent randomized controlled trials comparing STN-DBS to GPi-DBS (Follett et al.,⁷ 28.2%; Odekerken et al.,²⁰ 26%). However, more patients in the MER group remained treated via unilateral leads over the course of this study; in contrast, all GPi-DBS patients described by Ostrem et al.,²² Sidiropoulos et al.,²⁹ and Chen et al.⁴ had bilaterally placed leads. When the pre- and post-MER UPDRS III scores were obtained solely from the side contralateral to each implanted lead, the 37.1% improvement seen was similar to that reported in the literature (see also Andrade et al.¹). Notably, UPDRS III scores obtained in this way necessarily exclude axial symptoms. Thus, the difference between changes in UPDRS III scores obtained in the contralateral hemibody compared to the overall score suggests that axial symptoms may have been less effectively treated with unilateral than with bilateral MER-guided GPi-DBS.

Our findings suggest that iMRI-guided DBS is likely to have outcomes that are at least comparable to those seen following MER-guided DBS. However, patients undergoing iMRI-guided DBS had significantly greater improvement on their baseline levodopa challenge (44.8% vs 61.6% improvement in UPDRS III scores while on vs off medication). As levodopa responsiveness is associated with outcomes of DBS, this may explain, in part, the differences in outcomes between the two groups.

As understanding of the anatomical variation and somatotopic organization of GPi¹¹ increases, techniques enabling the direct visualization of the target structure and intraoperative confirmation of successful implantation therein may optimize clinical outcomes. Our finding of lower thresholds for motor side effects in patients implanted with an iMRI-guided DBS device suggests the possibility that greater benefit might accrue from leads placed closer to the pallidocapsular border. While this implies that lower intraoperative stimulation mapping motor thresholds might potentially lead to increased clinical effectiveness, this observation needs to be confirmed in future studies.

Similar to our study, Brodsky et al.² recently assessed the efficacy of MER-guided compared to iCT-guided STN- or GPi-DBS lead implantation at 6 months after surgery in 69 PD patients at a single institution. They found that iCT-guided DBS was associated with a similar change in UPDRS III scores compared to MER-guided DBS (improvement of 14.8 points [35%] vs 17.6 points [42%], respectively). They also found that iCT-guided DBS was associated with greater improvements in good quality on-medication time, as well as better postoperative speech outcomes.

Both MER- and iMRI-guided GPi-DBS showed similar decreases in LEDD, at approximately 21%, and comparable stimulation parameters 1 year postoperatively. Additionally, both surgeries were well tolerated, with low rates of serious complications (6.9% vs 9.4% for MER- and iMRI-guided DBS, respectively), similar to those re-

ported by Ostrem et al.,²² in which serious complications occurred at a per-patient rate of 11.5%.

Study Limitations

There are several limitations to this study. Post hoc power calculations indicate that the results of this study are expected to be valid 64.6% of the time, suggesting that it is underpowered to demonstrate superiority of iMRI- versus MER-guided DBS. This is an unblinded retrospective cohort study without randomization to surgical procedure. Thus, factors other than the technique could explain, at least in part, the different outcomes between the surgical groups. For instance, it is possible that some of the differences in outcomes between the MER and iMRI groups could result from changes in patient selection and/or programming that may have occurred over the study period. Across all patients undergoing DBS for PD regardless of the implanted brain region, the proportion of patients undergoing GPi-DBS increased from 18.8% in the first 5 years of the study to 57.4% in the last 5 years, beginning roughly 1 year after iMRI-guided DBS became available at our site. By way of explanation, it was our practice initially to preferentially implant DBS leads within the STN in patients with advanced PD. However, as data from several large studies, together with our own data, demonstrated equivalence in motor outcomes between STN and GPi implantations, and increased risk of gait, mood, and cognitive impairment following STN-DBS,^{5,7,23,24,31} a progressively larger proportion of patients underwent GPi lead implantation. With the advent of iMRI-guided DBS, this shift toward GPi-DBS was promoted by our ongoing review of clinical outcomes following DBS, which suggested that iMRI-guided GPi-DBS was at least comparable to MER-guided GPi-DBS. Other factors in this shift included patient comfort and the perception of the greater ease of performing iMRI-guided DBS in older patients. However, we did not systematically select out a different group for MER guidance versus iMRI guidance but, rather, shifted our practice at a set point in time. Nor did we explicitly change our criteria for implantation, though such a change may have occurred over time due to changes in referral patterns, the makeup of the multidisciplinary team, or the evolving experience of the team members. Finally, our results reflect the patient population, surgical approach, and programming strategies at our tertiary referral center, which may not be generalizable to other sites. To arrive at a more general accounting of the benefits and drawbacks of MER- versus iMRI-guided DBS lead placement into GPi, pooling of findings across multiple centers and larger sample sizes are required.

Conclusions

Both MER- and iMRI-guided DBS lead placement are highly accurate and have meaningful antiparkinsonian effects. Our experience suggests that iMRI-guided DBS lead placement may lead to at least comparable improvement in motor scores to traditional MER-guided DBS lead placement. Both surgical techniques had comparably low complication rates. Future studies should compare clinical outcomes and the cost-effectiveness of these procedures in

a larger and more diverse population, ideally on a prospective basis.

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Disclosures

Dr. Bezchlibnyk is a consultant for PMT Medical, Inc.; he is a co-investigator for clinical trials sponsored by Boston Scientific. Dr. Bueteftisch is a co-investigator on a clinical trial sponsored by Boston Scientific. Dr. Willie is a consultant for Medtronic, MRI Interventions, NeuroPace, AiM Therapeutics, and NICO Medical. Dr. Boulis is a consultant for Neurogene, Theracle, Axovant Sciences, Disarm Therapeutics, PTC, Aruna Bio, BlueRock, and Renew Biopharma; he owns stock in CODA Bio and BrainTrust Bio. Dr. Factor has received personal compensation for activities with Lundbeck, Sunovion, Biogen, Acadia, Acorda, CereSpir, Impel, CNS Ratings LLC, and Bracket, as well as royalties from UpToDate, Demos, Blackwell Futura, and Springer; he reports grant funding for clinical trials or fellowship funding from the following: Medtronic, Boston Scientific, Voyager, Sunovion Therapeutics, Lilly, Impax, Vaccinex, Jazz Pharma, Biohaven, US World Meds, the CHDI Foundation, the Michael J. Fox Foundation, and NIH (U10 NS077366). Dr. Gross is a consultant for and/or has received research support from Medtronic, Abbott/St. Jude Medical, Boston Scientific, MRI Interventions, Zimmer Biomet, Monteris Medical, and NeuroPace. These arrangements have been approved by the Emory University Conflict of Interest committee.

Contributions

Conception and design: Gross, Bezchlibnyk, Sharma, DeLong. Acquisition of data: Gross, Bezchlibnyk, Sharma, Isbaine, Gale, Cheng, Triche, Miocinovic, Bueteftisch, Factor, Wichmann, DeLong. Analysis and interpretation of data: Bezchlibnyk, Sharma, Isbaine, Gale, Miocinovic. Drafting the article: Bezchlibnyk. Critically revising the article: Gross, Sharma, Isbaine, Gale, Cheng, Triche, Miocinovic, Bueteftisch, Willie, Boulis, Factor, Wichmann, DeLong. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Gross. Statistical analysis: Bezchlibnyk, Naik. Administrative/technical/material support: Gross, Isbaine, Gale, Triche. Study supervision: Gross, DeLong.

Supplemental Information

Previous Presentations

A portion of this work was presented in poster form at the American Academy of Neurology, April 2016, in Vancouver, Canada, and at the American Association of Stereotactic and Functional Neurosurgery, November 2018, in Denver, Colorado.

Correspondence

Robert E. Gross: Emory University School of Medicine, Atlanta, GA. rgross@emory.edu.