Interventional MRI–guided deep brain stimulation in pediatric dystonia: first experience with the ClearPoint system

Clinical article

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Object. The placement of deep brain stimulation (DBS) leads in adults is traditionally performed using physiological confirmation of lead location in the awake patient. Most children are unable to tolerate awake surgery, which poses a challenge for intraoperative confirmation of lead location. The authors have developed an interventional MRI (iMRI)–guided procedure to allow for real-time anatomical imaging, with the goal of achieving very accurate lead placement in patients who are under general anesthesia.

Methods. Six pediatric patients with primary dystonia were prospectively enrolled. Patients were candidates for surgery if they had marked disability and medical therapy had been ineffective. Five patients had the DYT1 mutation, and mean age at surgery was 11.0 ± 2.8 years. Patients underwent bilateral globus pallidus internus (GPi, n = 5) or subthalamic nucleus (STN, n = 1) DBS. The leads were implanted using a novel skull-mounted aiming device in conjunction with dedicated software (ClearPoint system), used within a 1.5-T diagnostic MRI unit in a radiology suite, without physiological testing. The Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) was used at baseline, 6 months, and 12 months postoperatively. Further measures included lead placement accuracy, quality of life, adverse events, and stimulation settings.

Results. A single brain penetration was used for placement of all 12 leads. The mean difference (± SD) between the intended target location and the actual lead location, in the axial plane passing through the intended target, was 0.6 ± 0.5 mm, and the mean surgical time (leads only) was 190 ± 26 minutes. The mean percent improvement in the BFMDRS movement scores was 86.1% ± 12.5% at 6 months (n = 6, p = 0.028) and 87.6% ± 19.2% at 12 months (p = 0.028). The mean stimulation settings at 12 months were 3.0 V, 83 µsec, 135 Hz for GPi DBS, and 2.1 V, 60 µsec, 145 Hz for STN DBS). There were no serious adverse events.

Conclusions. Interventional MRI–guided DBS using the ClearPoint system was extremely accurate, provided real-time confirmation of DBS placement, and could be used in any diagnostic MRI suite. Clinical outcomes for pediatric dystonia are comparable with the best reported results using traditional frame-based stereotaxy. Clinical trial registration no.: NCT00792532 (ClinicalTrials.gov).

key Words • dystonia • deep brain stimulation • interventional MRI • functional neurosurgery • pediatrics

Deep brain stimulation (DBS) in children with primary dystonia can be highly effective for long-term symptom suppression.1,4,6,8,18,21 Clinical outcome is critically dependent on exact lead placement in the posterior (motor) area of the internal pallidum,26,28 but surgical methods to achieve excellent lead placement have not been standardized. In adults, the traditional method for DBS lead implantation involves physiological localization while patients are awake.26 Physiological localization methods have included microelectrode recording and/or intraoperative test stimulation to assess for acute stimulation-induced adverse or therapeutic effects.26 Since these methods often require the patient to be calm and cooperative for several hours of testing, they are not appropriate for most children.

To address these issues, we have developed methods for implanting DBS leads using real-time interventional MRI (iMRI) guidance in conjunction with a skull-mounted aiming device. The procedure is performed within the isocenter of a high-field diagnostic magnet in a radiology suite. Our initial work on iMRI-guided DBS implantation, developed in adults with Parkinson’s disease,29,31 used a previously created skull-mounted aiming device (Nexframe, Medtronic Inc.). The Nexframe was not specifically designed for iMRI applications. Based on this experience, we developed a second-generation device (ClearPoint, MRI Interventions, Inc.), which has improved mechanical controls and an integrated software package intended to improve ease of use and accuracy of targeting.11 In the present...
ClearPoint system for DBS in pediatric dystonia

study, we used this iMRI device to demonstrate placement of DBS leads in children and found it to be associated with extremely high accuracy and excellent clinical outcome. This is the first report of DBS lead placement accuracy and clinical outcomes using the ClearPoint system.

Methods

Patient Selection and Clinical Characterization

Patient characteristics are described in Table 1. Six pediatric patients with primary dystonia were prospectively enrolled (clinical trial registration no. NCT00792532 [ClinicalTrials.gov]). The study was approved by the UCSF institutional review board. Parental informed consent for the study was obtained in all cases. Patients were candidates for surgery if they had significant disability and medical therapy had been ineffective. Patients received bilateral globus pallidus internus (GPI, n = 5) or subthalamic nucleus (STN, n = 1) DBS. The patient undergoing STN stimulation was also part of a prospective study of STN DBS in primary dystonia. The Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) was administered at baseline, 6 months, and 12 months postoperatively. Further outcome measures included quality of life, adverse events, and stimulation settings.

Surgical Procedure: Brain Leads

The leads were implanted using a novel skull-mounted aiming device in conjunction with dedicated software (ClearPoint system), used within a 1.5-T diagnostic MRI scanner (Philips Intera, 60-cm bore diameter) in a radiology suite, with the patient under general anesthesia and without physiological testing. The main features of the ClearPoint system have been described in a previously published technical report on device performance in a phantom skull and in cadaver heads. The primary hardware component of the ClearPoint system is the skull-mounted aiming device (“SmartFrame”), pictured in Fig. 1A. It has 4 degrees of freedom, with pitch (angulation in the sagittal plane) and roll (angulation in the coronal plane) controls for coarse angular adjustment, and X (right-left axis) and Y (anterior-posterior axis) controls for fine linear adjustment. The central MRI-visible alignment stem has a hollow lumen with an internal diameter of 2.1 mm for passage of a ceramic styllet within a Silastic peel-away sheath.

After induction of anesthesia in a room adjacent to the MRI unit, the head is positioned in a 4-pin carbon fiber head holder (Malcolm-Rand, Integra Inc.), with flexible surface receiving coils on either side, and moved through the MRI bore so that the top of the head is accessible at the back. For children under 10 years of age, pressure applied to the head holder pins is reduced to avoid excessive bone penetration or fracture. After sterile prep, a drape is used that attaches by elastic cords at each end of the bore to maintain the sterile field during movements of the head between isocenter and the back of the bore (Fig. 1E). The head positioning and draping procedure are identical to those described in our previous report.

A 7.5 × 9–cm MRI-visible marking grid is placed on each side of the scalp to span the coronal suture, and the patient’s head is returned to isocenter. A Gd-enhanced volumetric MRI scan is acquired and imported into ClearPoint software. An approximate target and safe trajectory to that target are selected (Fig. 1B), and the entry point is visualized on the software so as to show the intersection of the trajectory with the marking grid (Fig. 1C).

The patient’s head is moved to the back of the bore, where a sharp marking tool is used to penetrate the marking grid, skull, and scalp at the intended entry location (Fig. 1D), and then the marking grid is removed, a bicornal incision is made, and 1.5-cm bur holes are drilled with an MRI-compatible high-speed drill (Anspach or Stryker). These drill kits also include a craniotome attachment, to allow the surgeon to perform urgent craniotomy in the MRI suite should a significant, surgically accessible hematoma evolve on serial MR images during the procedure. The dura and pia mater are coagulated and opened sharply, and the SmartFrames and Stimloc lead anchoring rings (Medtronic Inc.) are mounted over the bur holes. The mechanical remote controls are attached (Fig. 1E) and the head returned to the isocenter.

Volumetric T1-weighted gradient echo sequences are obtained through the SmartFrames and imported into ClearPoint software for automated recognition of device position and trajectory. High-resolution imaging using T2-weighted fast spin echo and inversion-recovery fast spin echo images are obtained through the basal ganglia to provide optimal definition of target boundaries. The MRI sequences used have been previously described. The target selection method is illustrated in Fig. 2.

Alignment of the SmartFrame cannulas was then performed iteratively, initially using oblique axial scans through the alignment stem (Fig. 3A and B), in conjunction with the prescribed movements of the pitch and roll controls until the predicted radial placement error was less than 1.0 mm. Next, oblique sagittal and coronal scans (Fig. 3A and C) were acquired in conjunction with movement of the X and Y controls until the predicted radial error was less than 0.5 mm. (Measurement of radial error is further described below and in Fig. 4.) An overshoot was planned for each target; this overshoot was standardized for the STN target at 2 mm deep to the targeting plane and customized for the GPI target based on the measured distance between the targeting plane and the dorsal border of optic tract, typically 4–6 mm. A depth stop was placed on the ceramic styllet/peel-away sheath to reflect the intended overshoot, and the styllet/sheath was inserted to target. Oblique sagittal and coronal images were obtained through the trajectory at intermediate steps to confirm appropriate passage without hemorrhage. With both styllets at the target, a high-resolution axial T2-weighted MR image was used to confirm correct positioning (Fig. 3D). The ceramic styllet was removed and replaced with a quadripolar DBS lead (Model 3389–28, Medtronic). After confirming correct lead depth using low-energy axial T2-weighted MRI, the patient’s head was returned to the back of the bore for removal of the peel-away sheath, anchoring of the lead using the clip and cap of the Stimloc system, removal of the SmartFrames, and closure of the scalp. All patients were placed in a Kerlix head wrap for 1 week to protect the incisions.
The implantable pulse generators (IPGs) and lead extenders were placed in a separate inpatient or outpatient procedure 1–2 weeks after lead implantation. The reason for placing the IPGs in a separate procedure was logistical: lead placement occurred in a radiology suite, not an operating room, with a limited set of fully MRI-compatible surgical instruments. Placement of IPGs under the same anesthesia would have required transporting the patient to a waiting, open operating room set up by a separate nursing team.

The free ends of the DBS leads were accessed via parietal incisions 3–5 cm posterior to the frontal bur hole. Four patients had bilateral, single-channel primary cell IPGs (Activa SCs, Medtronic) placed in the pectoral area, connected to the leads using 40-cm lead extenders (Model 37086 Medtronic). One patient requested bilateral Activa SCs placed in the abdomen with 60-cm lead extenders (for cosmetic reasons), and one requested a dual-channel rechargeable IPG (Activa RC) placed in the right chest using 40-cm lead extenders, to avoid having to return regularly for IPG replacement. Patients were again placed in a Kerlix head wrap for 1 week to protect the parietal incisions.

**Surgical Procedure: Pulse Generators and Lead Extenders**

Neurostimulator programming was initiated 1–2 weeks after lead implantation. Each contact was activated separately in unipolar mode. Voltage-limiting adverse effects were noted. In all patients the stimulator was initially programmed using 1 contact in unipolar mode, typically at 60-μsec pulse width using a frequency of 130 Hz. The initial contact chosen was the one for which clinical improvement was most apparent. If no therapeutic effect was noted in the initial programming session, then the contact within the posterior lateral GPi or dorsal STN, based on postoperative MRI, was chosen for chronic stimulation (typically Contact 1). The voltage was slowly increased over the first 2–4 weeks. Patients with GPi stimulators returned for follow-up programming visits every few months if needed, and if dystonia was not controlled at a voltage of 3.5 V, then generally a second contact was used or pulse width was increased. Additional considerations for STN programming have been previously described.20

**Device Programming**

We considered the most clinically relevant measure of lead placement accuracy to be the “radial error,” defined as the difference between the intended and actual lead trajectory, measured in the axial plane used for anatomical targeting (Fig. 4). We also calculated a “trajectory error” defined as the closest distance between the intended and actual lead trajectory (always perpendicular to the trajectories), since some prior papers on the accuracy of DBS placement use this measure preferentially. The trajectory error is slightly smaller than the radial error, with the exact difference depending on the angle of placement with respect to the axial plane used for targeting (Fig. 4). Three-dimensional vector errors between the intended tip and actual tip location are less clinically relevant, as small lead misplacements (> 2 mm) along the
axis of implantation can easily be corrected by selection of a different active contact from the quadripolar lead.

Statistical Analysis

The difference between the BFMDRS movement scores at baseline compared with 12 months (on stimulation) were assessed using the Wilcoxon matched-pairs signed-rank test. Except for mean data pertaining to lead tip location and stimulation settings, and unless otherwise specified, mean values are presented ± SD.

Results

Surgical Experience and Lead Placement Accuracy

A single brain penetration was used for placement of all 12 leads. The mean surgical time (leads only) was 190 ± 26 minutes. The mean radial error (as defined in Fig. 4) was 0.6 ± 0.5 mm. The mean trajectory error (defined in Fig. 4) was 0.54 ± 0.40 mm. For the lead implant with the largest radial error (1.8 mm), we noted upon anchoring the lead that the guidance sheath was slightly deflected by the edge of the dura. The mean lead tip location relative to the midcomissural point for GPi leads (n = 10) was as follows: X = 19.00 mm, Y = 3.13 mm, and Z = -3.52 mm. The mean tip locations for the two STN leads were X = 11.1 mm, Y = -2.25 mm, and Z = -5.60 mm.

DBS Parameters, Clinical Improvement, and Complications

Individual stimulation settings at 12 months are provided in Table 2. The mean settings were 3.0 V, 83 μsec, 135 Hz for GPi DBS) and 2.1 V, 60 μsec, 145 Hz for STN DBS. Individual improvements in the BFMDRS movement scores are shown in Fig. 5 and Table 1. The mean percentage improvement in the BFMDRS movement score was 87.6% ± 19.2% (p = 0.028) at 12 months, and the mean percentage improvement in BFMDRS disability score was 77.2% ± 1.6% (p = 0.033) at 12 months. Quality of life (SF-36v2) scores improved by 52.6% (p = 0.027) overall at 12 months.

Adverse events included the following single events: transient slurred speech, transient dyskinesia, an episode of unexplained nausea and dizziness, right knee pain, left shoulder pain, and an open circuit on one contact of one lead. There were no serious adverse events, no returns to the operating room within the 12-month follow-up period, and no hematomas seen on MRI after lead placement.
Duration of Hospitalization

The mean length of hospital stay following iMRI-guided lead placement was 3.3 ± 2.3 days. This duration of hospitalization did not differ from that (2.7 ± 0.8 days) documented for a cohort of 6 children with primary generalized dystonia of similar age range, in whom implantation was performed by the same surgeon but using traditional frame-based stereotaxy1 prior to the introduction of the iMRI technique. The duration of hospital stay appears to be determined by factors other than surgical technique, such as the temporary increase in dystonic symptoms that may occur postoperatively as a result of the stress of surgery and anesthesia.1

Discussion

We used a novel skull-mounted guidance system, specifically designed for iMRI applications, to perform bilateral DBS implantation in a consecutive series of 6 pediatric patients with primary generalized dystonia. Aiming and advancing of the guidance sheath and DBS leads were performed at the isocenter of a 1.5-T diagnostic magnet in a radiology suite. We achieved a high placement accuracy, exceeding that of earlier hardware systems used for iMRI-guided DBS,25 with clinical outcomes comparable to the best reported results for DBS in primary dystonia when using other surgical methods.

iMRI Approach for Asleep DBS: Comparison With Other Methods

Since the introduction of thalamic DBS for adults with tremor disorders2 and STN or GPi DBS for individuals with advanced Parkinson’s disease,13,23 the predominant technique for implantation has involved physiological testing in awake patients as the final determinant of electrode position. However, this approach is not ideal for some patients who could benefit from DBS, such as children with dystonia or adults with Parkinson’s disease or dystonia who have severe involuntary movements in the off-medication state or significant anxiety about the awake procedure. A number of centers have developed alternative approaches in which DBS implantation is performed under general anesthesia, and brain imaging rather than physiology is used to finalize the lead position. One approach is to use frame-based stereotaxy with the patient under general anesthesia in an operating room to place DBS electrodes, or permanent guide tubes, with immediate transport to an MRI suite for postoperative imaging to confirm location.15,22 If the initial placement is considered inadequate, the patient may have the lead repositioned in the operating room while still under anesthesia. However, the initial placement is then subject to the accuracy limitations of standard stereotactic methods that use preoperative images registered to a frame system4 and involves the logistical complexity of transporting a patient to multiple locations for a single surgery.

Alternatively, intraoperative CT scanning has recently been used for asleep DBS, both for the stereotactic image acquisition and immediate intraoperative check of lead position.3 The intraoperative CT scan is fused to a
preoperative MR image for both target selection and final confirmation of lead placement. The technique is efficient, with short operating room times and no need to transport patients between the surgical suite and radiology suite on the day of surgery. However, the method is limited by the mechanical accuracy of frame-based stereotaxy as well as errors that may be introduced by suboptimal CT-MR fusion. The mean ± SEM “trajectory error” (closest distance between actual and intended trajectories) in a study of 119 electrode placements was 1.24 ± 0.87 mm, with a range of 0–3.4 mm. When targeting errors in the present study are calculated identically (see Fig. 4), our trajectory error is substantially smaller: 0.54 ± 0.40 mm with a range of 0–1.5 mm.

**ClearPoint Compared With Prior iMRI Techniques**

From 2004 to 2010, we performed iMRI-guided DBS placement using the Medtronic Nexframe skull-mounted aiming device, which was primarily designed for neuronavigation-guided DBS implantation rather than...
The Nexframe device has 2 mechanical degrees of freedom. An MRI-visible alignment stem, inserted into the Nexframe, was employed for the iMRI environment. To analyze the accuracy of that system, we primarily used the “radial error,” the 2D difference between the intended and actual lead trajectories in the axial plane used to define the target. This is similar to, but slightly larger than, the trajectory error (Fig. 4). In 53 iMRI-guided lead implants that involved the Nexframe, mean (± SEM) radial error was $1.2 ± 0.65$ mm. Based on our experience with the Nexframe, we designed the ClearPoint system for iMRI DBS with a variety of improvements: an “XY” stage-mounted on the pitch/roll controls that provides for finer mechanical control after approximate initial alignment, an integrated software system, mechanical remote control for easy aiming of the device without reaching into the bore, and an MRI-visible alignment stem with a hollow lumen allowing delivery of devices through the alignment stem without the need to remove the alignment stem and replace it with guidance cannulas.

The present study indicates that the accuracy of the ClearPoint system as used clinically, with a mean radial error of $0.6 ± 0.5$ mm, is improved over that of the prior Nexframe system. This will need to be confirmed in a larger series utilizing the same brain target (STN) as the Nexframe iMRI study. Of note, the mean radial error observed here in clinical use is very similar to that measured in preclinical phantom studies ($0.5 ± 0.3$ mm). The improved accuracy of the ClearPoint system is probably related to the integration of successive imaging steps with progressively finer mechanical control of the aiming system. Following “coarse” angular adjustments with pitch/roll controls, longitudinal MRI through the long axis of the alignment stem is used to make submillimeter linear

![Fig. 4. Schematic of the method for measuring radial error and trajectory error.](image)

**TABLE 2: Active contact locations and stimulator settings at 12 months**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Target</th>
<th>Active Contacts (lt brain)*</th>
<th>DBS Settings (lt brain)</th>
<th>Active Contacts (rt brain)*</th>
<th>DBS Settings (rt brain)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Contacts V μsec Hz X Y Z</td>
<td></td>
<td>Contacts V μsec Hz X Y Z</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>GPi</td>
<td>C+1−</td>
<td>3.7 60 130</td>
<td>−19.7 −2.1 C+1−</td>
<td>3.2 60 130</td>
</tr>
<tr>
<td>2</td>
<td>GPi</td>
<td>C+1−</td>
<td>3.0 90 130</td>
<td>−18.4 −1.84 C+9−</td>
<td>3.2 90 135</td>
</tr>
<tr>
<td>3</td>
<td>STN</td>
<td>C+2−</td>
<td>4.0 60 130</td>
<td>−19.7 3.8 1.41 C+2−</td>
<td>4.0 60 135</td>
</tr>
<tr>
<td>4</td>
<td>GPi</td>
<td>C+1−2−</td>
<td>2.8 160 130</td>
<td>−10.6 −2.5 C+1−2−</td>
<td>1.2 80 130</td>
</tr>
<tr>
<td>5</td>
<td>GPi</td>
<td>C+2−</td>
<td>1.1 90 140</td>
<td>−20.1 4.1 0.12 C+2−</td>
<td>3.5 120 140</td>
</tr>
<tr>
<td>6</td>
<td>GPi</td>
<td>C+1−2−</td>
<td>3.5 120 130</td>
<td>−20.1 5.5 0.07 C+1−2−</td>
<td>3.5 120 130</td>
</tr>
</tbody>
</table>

* Measured with respect to the midcommissural point.
clearing a 1.5-T narrow-bore MRI system, whereas 3.0-T wide-bore systems are increasingly common. The accuracy data reported here would not necessarily generalize to a 3.0-T or wider-bore system, with which image distortion effects may compromise the ability of the software to accurately reconstruct the position of the aiming device.\textsuperscript{29} Users of ClearPoint systems with a magnetic field strength higher than 1.5 T, or a bore diameter greater than 60 cm, should carefully evaluate their own lead placement accuracy data.

Application of the iMRI Method to Younger Children

The purchase lengths of the screws used to mount the SmartFrame aiming device and Stimloc DBS lead anchoring ring are 4 mm and 5 mm, respectively. Since the frontal bone thickness in children under 10 years old is often less than 5 mm,\textsuperscript{12} screws in younger patients may penetrate the full thickness of the skull. Should epidural bleeding occur due to screw penetration, this could be readily detected on subsequent MR images obtained after mounting the device, but no hematomas from screw placement were observed in the present series. For bilateral SmartFrame mounting with bur holes closer than 4.5 cm apart, there is a possibility for the control knobs on the devices to collide, depending on skull morphology and trajectory angles. After marking the scalp entry sites, it is advisable to place both SmartFrames over the intended entry sites to check for physical contact between the devices prior to drilling the bur holes.

In most children, we prefer to place bilateral single-channel pulse generators (Activa SC, Medtronic) rather than a larger, unilateral, dual-channel pulse generator, for the following reasons: 1) the lower profile of the single-channel systems may reduce hardware-related complications;\textsuperscript{24} 2) battery life of two single-channel generators is generally longer than that of one dual-channel generator;\textsuperscript{7} and 3) battery failure, if it affected both sides simultaneously, could result in a rapid recurrence of symptoms that constitute a medical emergency such as “dystonic storm.”

Conclusions

Interventional MRI–guided DBS is technically simple, extremely accurate, provides real-time confirmation of DBS placement, and can be used in any diagnostic MRI facility.

Clinical outcomes are comparable with the best reported results of traditional frame-based stereotaxy. The method is dependent on excellent quality imaging.

Acknowledgments

We thank Salman Qasim, B.S., and Nathan Ziman, B.S., for technical assistance in preparing the manuscript.

Disclosure

This study was funded by a research grant from MRI Interventions, Inc., the manufacturer of ClearPoint. Three of the authors (P.A.S., P.S.L., and A.J.M.) designed the ClearPoint system in collaboration with MRI Interventions, Inc., and continue to receive research funding with salary support for further development and testing of the system. However, the authors hold no intellectual property rights in ClearPoint and have no financial interest in MRI Interventions, Inc.
property in this system, hold no ownership stake or stock options in MRI Interventions, Inc., and do not receive royalty payments from the company. Dr. Ostrem is a consultant for Medtronic, Abbott, and Allergen. She received study-related support from MRI Interventions, and she receives no-study-related support from St. Jude Medical and Ceregene.

Author contributions to the study and manuscript preparation include the following. Conception and design: all authors. Acquisition of data: Starr, Markun, Larson, Volz, Martin. Analysis and interpretation of data: Starr, Markun, Martin. Drafting the article: Starr, Markun, Larson, Volz, Ostrem. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Starr. Statistical analysis: Markun, Martin. Administrative/technical/material support: Markun, Larson, Volz, Martin, Ostrem. Study supervision: Starr, Larson, Volz, Martin, Ostrem.

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