Minimally Invasive Surgery for Movement Disorders

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KEYWORDS

- Deep brain stimulation • Stereotactic surgery
- Frameless deep brain stimulation • Interventional MRI
- Gene transfer

Surgery for movement disorders has become commonplace over the last decade, and is now considered the standard of care for properly selected candidates with moderately advanced, medically refractory disease. Although many movement disorders have been treated with surgery over the course of the last century including tremor and dystonia, by far the most common indication for surgery today is Parkinson disease (PD). Likewise, there have been several different procedures used, including open craniotomy and stereotactic lesioning, in several different brain targets in the cortical and subcortical regions. In the modern era, deep brain stimulation (DBS) is the procedure of choice. Unlike lesioning procedures, which result in permanent destruction of the brain, DBS provides adjustable and reversible modulation of brain function, thus affording clinicians the opportunity to maximize benefits while minimizing side effects of stimulation. When considering minimally invasive surgical strategies for movement disorders, it is therefore helpful to use DBS for PD as a model; it is the most frequently performed procedure in movement disorders surgery, and many of the principles used in DBS for PD are applicable to other stereotactic procedures.

In comparison with other topics discussed in this book, DBS would already be considered by many to be a minimally invasive procedure. DBS is traditionally performed through a single burr hole with the use of a stereotactic frame; most patients with PD gain the most benefit with bilateral electrode implantation, so patients receive 2 burr holes (approximately 14–15 mm in diameter) through 1 longer or 2 smaller incisions. At present, the most commonly implanted target for DBS implantation in PD is the subthalamic nucleus (STN), although stimulation of the globus pallidus internus (GPi) is equally effective in treating the cardinal symptoms of PD, and parkinsonian tremor in isolation can be treated with stimulation of the thalamus. All of these targets are relatively deep in the subcortex, with the STN being the deepest. As a result, one must choose a trajectory through the brain that causes minimal potential injury and would result in the least amount of morbidity if a hemorrhage were to occur during electrode placement. Virtually all centers place the burr hole at or just anterior to the coronal suture, which provides a trajectory through noneloquent frontal cortex in which a hemorrhage would be well tolerated.

In general, the goals for a minimally invasive approach to DBS would decrease patient discomfort, reduce operative time, and/or minimize penetration of the brain. When contemplating how to approach DBS for PD from a minimally invasive

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perspective, one must accept that the entry point, trajectory, targets, and number of electrodes are relatively inflexible given the knowledge of the brain nuclei involved in PD and the basic principles of safe stereotactic surgery. The variable factors are (1) the delivery device, that is, the device used to place the electrode into the brain, (2) the target localization method, that is, the method used by the surgeon to make sure the electrode is going to the desired target in the brain, and (3) the hardware used to modulate the desired target in the brain. The method by which these variables can be manipulated to provide more minimally invasive methodologies for DBS surgery is examined here. It should be mentioned that these methods could be applied to other stereotactic procedures including lesioning, cannula-based infusions, biopsy, and so forth.

DELIVERY DEVICE

The traditional delivery devices in DBS surgery are a stereotactic frame and a micropositioner that allows precise, mechanical manipulation of both micro- and macroelectrodes during surgery (**Fig. 1**). A variety of frames are available from several major manufacturers including the Leksell (Elekta, Stockholm, Sweden) and CRW (Integra Radionics, Burlington, MA, USA) frames. Most centers that perform DBS use a stereotactic frame with some combination of magnetic resonance imaging (MRI) and computed tomography (CT), and a surgical planning workstation such as the StealthStation (Medtronic, Minneapolis, MN). Although frame-based implantation has a long record of safety and tolerability and remains the most common delivery method for DBS, in the last decade many surgeons have started to adopt so-called frameless techniques, which include use of the commercially available STarFix micro Targeting Platform (FHC, Bowdoinham, ME, USA) and the Nexframe (Medtronic, Minneapolis, MN, USA). The move toward frameless techniques was motivated in part by trying to apply some of the principles of minimally invasive surgery to DBS. In this instance, the variable that was modified was the delivery device, and the goals were to decrease patient discomfort and reduce operative time.

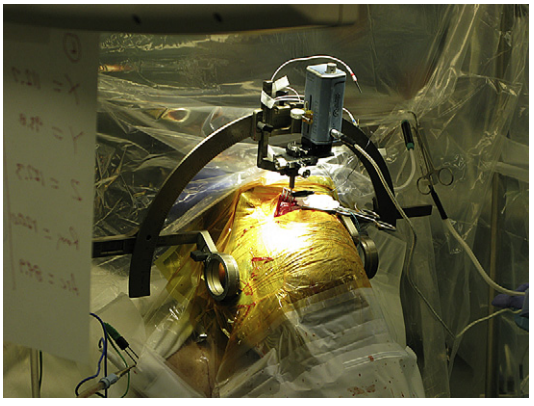

Fig. 1. A typical stereotactic frame and micropositioner system being used intraoperatively for performing multichannel microelectrode recording and DBS electrode placement.

Both the STarFix and Nexframe use bone-implanted fiducial markers, which are significantly more stable and reliable than skin-based fiducials. Such markers allow these platforms to equal the application accuracy of traditional stereotactic frames, which makes frameless DBS a legitimate alternative.[1] Proponents of frameless DBS claim that insertion of the bone-implanted fiducials is more comfortable than application of a stereotactic frame. Moreover, the patients are not rigidly fixed to the operating table as they are when they are in a frame, which allows them to change position slightly during surgery if desired. Perhaps most significant, however, is that the bone-implanted fiducials can be inserted days or even weeks before surgery, meaning that the preoperative imaging, targeting, and planning can all be done before the day of the procedure. This scheduling radically streamlines the patient flow on the day of surgery; the patient can go straight to the operating room instead of having to undergo frame placement, followed by imaging, and then waiting while the surgeon performs targeting and trajectory planning before starting the case. For patients with PD, who are typically kept off parkinsonian medications on the day of surgery to optimize the process of physiologic mapping and avoid dyskinesias, this can be of great advantage. One of the significant sources of patient discomfort during DBS surgery for PD is being in the off-medication state, and anything that reduces the procedure time usually translates to less discomfort for the patient.

Beyond the shared use of bone-implanted fiducials, the STarFix and Nexframe techniques diverge significantly. In the STarFix platform, the bone-implanted fiducials are used not as a basis for optical tracking, but rather as markers to define the geometry of a custom-made, patient-specific, skull-mounted aiming device. Days or even weeks before surgery, the surgeon implants the bone markers in a specified manner around the typical entry point in the frontal region and obtains high-resolution CT and MRI. Target selection, trajectory planning, and burr hole location are all determined within a proprietary software program; when the

surgeon is done, the software generates a blueprint for the STarFix platform. This disposable platform consists of a small ring (which ultimately holds a multilumen insert through which guide tubes and electrodes can be passed), and 3 or 4 legs that angle downward and are designed to anchor to the skull via the previously implanted bone fiducials. Every platform blueprint that the software creates is unique and based on the location of the bone markers as well as the entry point, trajectory, and target as determined by the surgeon. Platforms for unilateral or simultaneous bilateral implants can be created.

Once the surgeon is satisfied, the blueprint is electronically sent to a manufacturing center in which the platform is made using rapid prototyping technologies, then shipped back to the implanting hospital. The platform is sterilized and attached to the bone-implanted markers during surgery, which have been left in the skull during the intervening period between target imaging and surgery. The platform can be attached and removed at will, giving the surgeon free access to the head for opening and burr hole formation. During actual electrode implantation, the platform allows the surgeon to use standard target localization methods including single or multichannel microelectrode recording (MER). Other advantages unique to this frameless system include relatively free access to the burr hole for anchoring the electrode and the freedom from relying on optical tracking devices for registration, which can be a time-consuming and sometimes finicky process. One disadvantage of the STarFix is the relative inflexibility in the trajectory and burr hole site once the platform is manufactured.

The Nexframe is the other commercially available frameless delivery device. Nowadays it is much more widely used than the STarFix, and the way it works is much more familiar to surgeons who use neuronavigation for other cranial and spinal procedures. The Nexframe uses fiducial-based optical tracking technology, with the bone-implanted fiducials in this instance acting truly as markers only; the actual aiming device is mounted directly to the skull around the burr hole with self-tapping screws. Unlike the STarFix platform, which is elevated above the head on tripod-like legs, the Nexframe looks like a broad funnel with its tip attached to the skull (**Fig. 2**). The upper half of the device is dome shaped and can rotate, and a small platform on top of the dome can translate in one direction along a track. These 2 degrees of freedom allow the platform to be aimed at cranial targets that lie within an approximately 50° arc. The location of the burr hole and to some degree the curvature of the skull dictates what brain regions can be targeted with the Nexframe. Although the most common targets such as the STN and thalamus can be easily reached, sometimes care must be taken with more lateral targets such as the globus pallidus. The platform contains an insert with 5 channels through which guide tubes, microelectrodes, and DBS electrodes can pass.

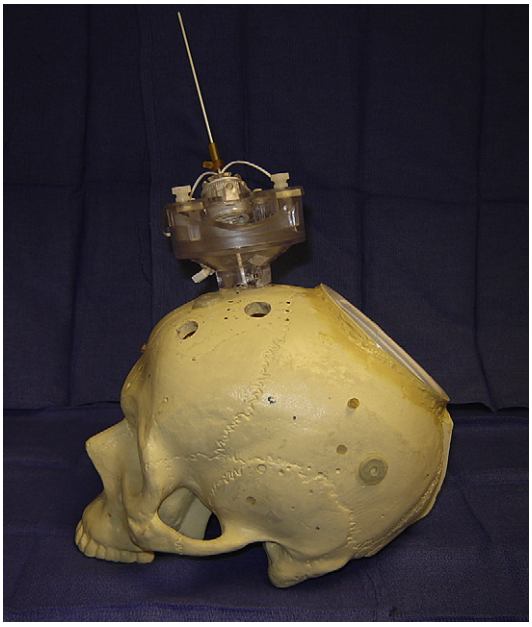

Fig. 2. The Medtronic Nexframe frameless DBS device mounted on a phantom skull.

The bone-implanted fiducials are again placed using local anesthetic in the outpatient setting. Imaging and targeting can be performed beforehand, providing the temporal decoupling of targeting from the day of surgery that is one of the hallmarks of frameless DBS. This again allows patients to get to the operating room faster, thus minimizing their time off medications. In the operating room, registration must be performed using an infrared optical tracking system. Unlike traditional cranial applications in which the patient's head is rigidly fixed with a Mayfield-type device and the reference frame is in turn mounted to the head holder, in frameless DBS the reference frame is mounted to the Nexframe itself. The patient can therefore move his or her head during surgery if desired. The bulkiness of the Nexframe often necessitates mounting one device at a time on each side of the head for bilateral simultaneous implantations so they do not physically interfere with each other, although the author and others have experience with placing 2 Nexframes at once without incident.

TARGET LOCALIZATION

The second variable that can be readily adapted to a more minimally invasive approach is the target localization method. Both frame-based and frameless DBS techniques use a combination of (1) some method of preoperative imaging to define the target in stereotactic space before electrode implantation, and (2) some method of physiologic confirmation that the target has been reached during electrode implantation. Methods of preoperative imaging include MRI, CT, and ventriculography. MRI has the advantage of superior tissue discrimination but is subject to image distortion due to multiple factors, including the inherent inhomogeneities in the magnetic field of all MRI scanners. CT has poor image discrimination but is free from image distortion. Many groups, therefore, use a combination of CT and MRI to perform targeting. Ventriculography was used extensively before the advent of CT and MRI, and although it is still used by some, it is itself invasive and therefore has been largely abandoned.

Methods of physiologic confirmation of target localization during surgery vary significantly based on the target being implanted, the preferences and skill set of the implanting team, the available resources, and even the surgical culture in different parts of the world. In general, the target can be localized by a combination of a micro/recording technique and a macro/stimulation technique in patients undergoing awake surgery. The most common microphysiology technique is MER, which is performed with a small-diameter, fine-tipped electrode capable of performing single-cell (or small number multiunit) neuronal recordings. MER takes advantage of the fact that areas of subcortical white matter are relatively electrically silent, whereas areas of subcortical gray matter (nuclei) are relatively active. Moreover, different nuclei have their own characteristic pattern of spontaneous neuronal activity, which are discernible to the experienced observer. In this manner, one can pass a microelectrode down through the brain to the intended target and usually determine with confidence that the proper region has been reached. Although MER is the most common method, others rely on information obtained by performing stimulation at low amplitude through a microelectrode. Some perform neuronal recordings but via a larger electrode to obtain cellular activity on a larger scale or record local field potentials. Following this micro/recording process (which is often referred to as mapping), many surgeons perform a macro/stimulation technique, often to confirm the final electrode position. Again, the actual process can vary widely, but the most common technique is to place the actual DBS electrode at the desired location and stimulate directly through it. One can observe improvement in some symptoms such as tremor and rigidity if present, and also infer the electrode position by observing adverse effects of stimulating adjacent brain structures at higher levels of stimulation.

These techniques are by definition invasive and can significantly lengthen the time of the procedure (and therefore also increase patient discomfort). In the United States, most teams perform MER with passage of a single microelectrode at a time, with the cumulative information obtained with each pass used to create a physiologic map of the intended target. Once the team feels they have obtained a sufficient amount of anatomic information, MER is stopped. Others in the United States and around the world perform MER by placing up to 5 microelectrodes in the brain and recording simultaneously from the array. The process of MER, therefore, produces somewhere between 1 and 5 brain penetrations for a typical target; this is then followed by insertion of the actual DBS electrode, which itself may be removed and repositioned based on the results of macrostimulation.

An alternative method of target localization that eliminates the need for awake, physiologic mapping with multiple brain penetrations would provide a less invasive approach to DBS surgery. Interventional MRI (iMRI) is a technique that was developed in the early and mid 1990s to allow neurosurgeons to perform cranial procedures within an MRI scanner suite. iMRI has been particularly useful for some brain tumor resections, in which MRI sequences can be obtained intraoperatively to navigate accurately, even in the face of significant brain shift during the procedure. The technique has not been adopted widely, in large part because of the extensive financial and logistical considerations of placing MRI scanners inside operating rooms. In the early 2000s, we started to consider how this method of intraoperative imaging could be applied to DBS electrode implantation. Instead of building an MRI scanner inside an existing operating room, we focused on using diagnostic scanners in the Radiology Department under sterile conditions.

1.5-T iMRI is presently used to place DBS electrodes into the STN and GPi to treat a subset of patients with PD and dystonia.[2,3] The rationale for moving in this direction was the observation that patients with PD with consistently good outcomes had leads centered in the dorsolateral STN, in line with the anterior third of the adjacent red nucleus.[4] This corresponds anatomically with

the motor subterritory of the STN, the region that we seek to identify in the regular operating room through the process of MER and macrostimulation. Because the STN is visible on 1.5-T T2-weighted images, we sought to use real-time MRI to place electrodes into this location instead of using physiologic mapping. As experience with real-time MRI grew, the GPi, which is also easily visualized at 1.5 T, was targeted as well. This approach represents an evolution toward minimally invasive DBS surgery by radically altering the method of target localization. No frame or fiducials are used and no preoperative imaging is needed. As no physiologic mapping is required, the procedure can be done under general anesthesia with only one brain penetration in the overwhelming majority of cases.

iMRI-guided implantation is performed inside a 1.5-T MRI scanner (**Fig. 3**). Traditional high-grade stainless instruments cannot be used in the MR environment, so nonferrous titanium instruments and an MR-compatible pneumatic drill (Anspach, Palm Beach Gardens, FL or Stryker, Kalamazoo, MI) are used during the procedure. Instead of a stereotactic frame, a slightly modified Nexframe is used as the delivery device. This procedure is analogous to the use of the Nexframe in a regular operating room, with the important distinction that no fiducial registration and no optical tracking are required when using iMRI. In this context, the Nexframe is not used as an integrated part of a neuronavigation system, rather it becomes a passive aiming device, with the MRI scanner software acting as the interface between the anatomy and the surgeon. Unilateral or simultaneous bilateral implantations can be performed, provided the entry points are far enough apart that 2 Nexframes can be mounted without interfering with each other.

After the patient is anesthetized, the head is placed in a carbon fiber head holder to prevent inadvertent movement during the procedure. The patient is moved to the isocenter of the MRI bore, and imaging is obtained to determine the entry point and trajectory. Once the entry points are selected, the patient is moved to the distal end of the bore so that the top of the head is easily accessible. The entry points are marked on the scalp and skull using a marking pen and syringe-with methylene blue, and a custom sterile drape is used to establish an accordion-like sterile field that encompasses the distal bore and end of the magnet and allows for patient movement. Opening of the skin, burr hole creation, and mounting of the Nexframes proceeds as it would during a regular frameless case.

The patient is moved to the center of the bore for high-resolution imaging, definitive target selection,

Fig. 3. Photo of a 1.5-T MRI suite during iMRI DBS. A sterile drape creates a sterile field from the distal end of the MRI machine into the bore of the scanner. The top of the patient's head is visible in the bore with bilateral Nexframe devices mounted. Monitors in the MR suite to the left allow the surgeon to see real-time images throughout the procedure.

and implantation. A saline-filled MRI visible alignment stem is placed into the Nexframe; this device has a sphere at its proximal end (actually within the burr hole) that sits at the so-called pivot point or center of rotation of the Nexframe device. The pivot point therefore remains stationary regardless of the Nexframe's orientation. The 3-dimensional coordinates for the center of the pivot point can be determined in MR space by setting up a region of interest (ROI) on its image using the MR console software. When the target is selected and its coordinates in MR space are also determined using an ROI, the target and pivot point coordinates are used to define the "target line," which represents the desired trajectory to the target. The surgeon can reach in to the bore of the magnet and move the Nexframe until the alignment stem is aligned with the target line. A rapid MR acquisition at a rate of 3 to 5 images per second allows the surgeon to visualize the fluid stem during this process in real time. The Nexframe is locked into position, proper alignment is ensured by obtaining additional images, and if no further adjustments are needed a ceramic stylet inside a peel-away sheath is inserted and advanced to the target (**Fig. 4**). Once proper placement is confirmed with high-resolution MRI, the stylet is removed and the DBS lead is placed down the peel-away sheath to the target. High-resolution images are used to confirm final lead position and the peel-away heath is subsequently removed, leaving the DBS lead in the target.

The iMRI technique has several advantages that qualify it as a minimally invasive approach for DBS implantation. It does not require fiducial or frame placement and does not require any preoperative imaging. Moreover, there is no intraoperative physiology necessary, which results in significant time saved over traditional implantation techniques. The patients do not have to be awake or be off medications, which greatly increases patient comfort. The implantation can be done with one penetration of the brain as opposed to multiple penetrations used in physiologically mapped cases, which may eventually be shown to decrease the risk of hemorrhage. Finally, there is a high degree of confidence that the lead is placed in a favorable position prior to the end of the procedure. One disadvantage is that at present, the procedure requires a significant amount of technical expertise from an MR physicist to run the MR scanner. The Nexframe and MR console software are not designed optimally to perform this type of intervention, and possess inherent deficiencies that can create technical challenges during the procedure. A new hardware and software system has been developed specifically for iMRI procedures that addresses many of these shortcomings.[5,6] iMRI also requires institutional commitment to using MRI scanners for interventional procedures and radiology, anesthesia, and operating room personnel who are willing to work in this unique environment.

MODULATION HARDWARE

A final way to make surgery for movement disorders more minimally invasive is to eliminate the

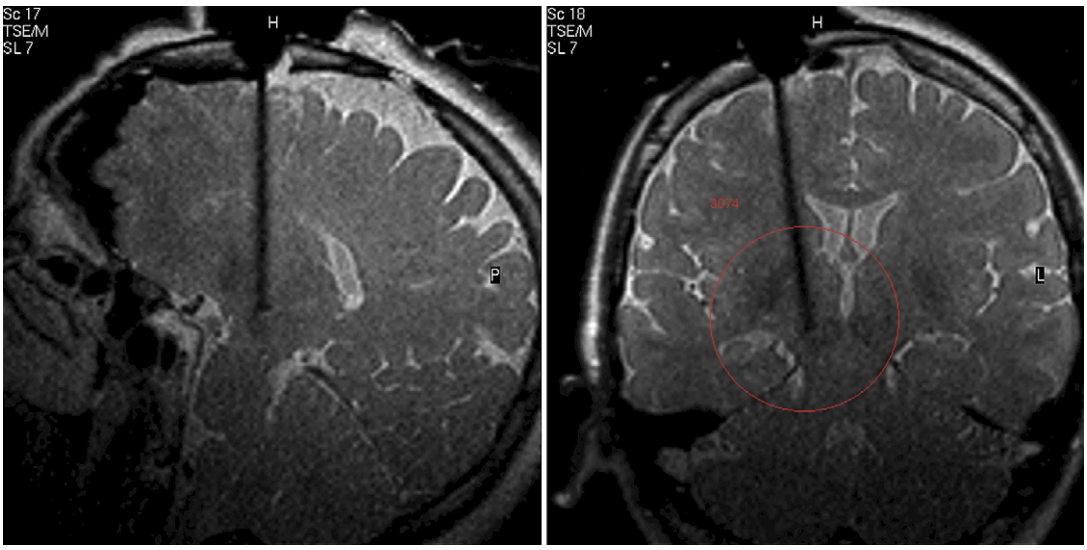

Fig. 4. Intraoperative MR images during an iMRI DBS case. Images obtained at 90° to each other in plane with the target trajectory show a ceramic stylet and peel-away sheath that has been placed in the right STN.

implanted hardware completely and modulate the structures of interest biologically. Although DBS is an effective treatment for movement disorders, it is a hardware-based therapy and is therefore subject to the complexities and potential complications of implanting foreign objects into the body. Lead migration or fracture, skin erosion, and pulse generator failure are all complications that are unique to DBS, and published infection rates in DBS are higher than those seen with other stereotactic procedures that do not involve implanted hardware.[7] In addition, DBS is a time-intensive therapy after surgery, with multiple office visits required to optimize stimulator settings and to balance the effects of stimulation and medication. Finally, DBS is a battery-driven device and requires periodic surgical replacement of the pulse generator that powers the system.

Because PD in particular is caused by degeneration of a well-characterized population of neurons, investigators have long sought a surgical therapy that would "replace" the lost biologic function in this disorder. Although various cell transplantation trials have been disappointing to date, there is presently a strong interest in gene transfer as a potential treatment for PD. Gene transfer uses a viral vector to carry a gene interest into neurons in a particular brain target. The transduced neurons then produce a new protein product; in the gene therapy trials that have been done so far, this product has been either an enzyme that alters local biology or a growth factor that supports and protects local or even distant cells.[8–10] The viral vector for all of these trials has been adeno-associated virus that is selected for a variety of reasons including its lack of pathogenicity, its minimal immune response, and its ability to predictably integrate into the genome of nondividing cells in a stable manner.

From a surgical standpoint, gene transfer for PD so far has been performed using traditional frame-based stereotaxy (**Fig. 5**). The procedures have varied depending on the target of interest. One study involved gene transfer to the STN and used MER for target localization, as the physiologic characteristics of that nucleus are well understood.[9] Other studies targeted the putamen, and as this is not a target well characterized physiologically, the procedures were done strictly on an anatomic basis. The number of cannulas passed to the target regions varied as well, with up to 4 penetrations per putamen being performed in one trial.[10] Delivery of vector was achieved by either intermittent hand injection or pump-driven convection enhanced delivery.

Although these procedures do not meet criteria for minimally invasive surgery based on the number of brain penetrations, a unique delivery device, or target localization method, they deserve mention because they do not involve any implanted hardware at all. These procedures therefore avoid all of the potential complications associated with a hardware-based therapy, and are generally thought to have a lower infection rate than DBS. Gene transfer is also in theory a low-maintenance therapy for patients, because they do not require device programming or battery replacements. Future gene transfer trials that will reduce the number of cannula penetrations required are in the planning stages, and use iMRI for targeting as well as real-time visualization of the infusions; animal studies using these techniques are currently under way.[11]

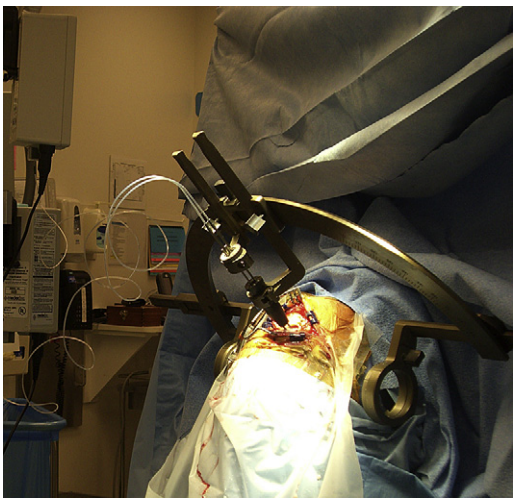

Fig. 5. Intraoperative photo during a gene transfer case for Parkinson disease. A standard stereotactic frame is being used, with infusion occurring through 2 custom-designed cannulas placed in the putamen.

SUMMARY

Although surgery for movement disorders is already a minimally invasive endeavor, the pursuit of less invasive surgery is a noble one regardless of the subspecialty. New frameless stereotactic delivery devices, novel ways of localizing brain targets using real-time imaging, and biologic strategies such as gene transfer are paving the way to shorter, safer, and less traumatic procedures for movement disorders patients.

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