Feasibility and performance of a frameless stereotactic system for targeting subcortical nuclei in nonhuman primates

Felipe Branco de Paiva, MD,¹ Brett A. Campbell,^{1,2} Leonardo A. Frizon, MD,^{3,5} Adriana Martin, MD,⁴ Andres Maldonado-Naranjo, MD,³ André G. Machado, MD, PhD,^{1,3} and Kenneth B. Baker, PhD^{1,2}

Departments of ¹Neurosciences, ³Neurosurgery, and ⁴Anesthesia, Cleveland Clinic, Cleveland, Ohio; ²Department of Biomedical Engineering, Case Western Reserve University, Cleveland, Ohio; and ⁵Postgraduate Program in Medicine: Surgical Sciences, Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, Rio Grande do Sul, Brazil

OBJECTIVE Deep brain stimulation (DBS) is an effective therapy for different neurological diseases, despite the lack of comprehension of its mechanism of action. The use of nonhuman primates (NHPs) has been historically important in advancing this field and presents a unique opportunity to uncover the therapeutic mechanisms of DBS, opening the way for optimization of current applications and the development of new ones. To be informative, research using NHPs should make use of appropriate electrode implantation tools. In the present work, the authors report on the feasibility and accuracy of targeting different deep brain regions in NHPs using a commercially available frameless stereotactic system (microTargeting platform).

METHODS Seven NHPs were implanted with DBS electrodes, either in the subthalamic nucleus or in the cerebellar dentate nucleus. A microTargeting platform was designed for each animal and used to guide implantation of the electrode. Imaging studies were acquired preoperatively for each animal, and were subsequently analyzed by two independent evaluators to estimate the electrode placement error (EPE). The interobserver variability was assessed as well.

RESULTS The radial and vector components of the EPE were estimated separately. The magnitude of the vector of EPE was 1.29 ± 0.41 mm and the mean radial EPE was 0.96 ± 0.63 mm. The interobserver variability was considered negligible.

CONCLUSIONS These results reveal the suitability of this commercial system to enhance the surgical insertion of DBS leads in the primate brain, in comparison to rigid traditional frames. Furthermore, our results open up the possibility of performing frameless stereotaxy in primates without the necessity of relying on expensive methods based on intraoperative imaging.

<https://thejns.org/doi/abs/10.3171/2019.12.JNS192946>

KEYWORDS frameless stereotactic surgery; nonhuman primate; deep brain stimulation; basal ganglia; subcortical nuclei; functional neurosurgery

ACCURATE targeting and surgical placement of deep brain stimulation (DBS) leads is key to maximizing benefit for patients with Parkinson's disease or other approved indications.^{17,22,31} This is also true for chronic, in vivo preclinical research, where efforts to advance DBS indications, refine current approaches, or better understand the pathophysiological and treatment-related changes in neural activity across subcortical circuits depend similarly on precise electrode placement, typically

within targets that are substantially smaller than their analogous targets in the human brain. In the case of mechanistic research, the need for precision typically extends beyond placement of the DBS lead to also include depth probes implanted across key nodal points of the relevant neural circuit for the purpose of characterizing electrophysiological changes.^{9,11,24} Moreover, subcortical targets may go beyond locations within the cerebral hemispheres to include deep cerebellar nuclei,³² which can be more dif-

ABBREVIATIONS DBS = deep brain stimulation; DN = dentate nucleus; EPE = electrode placement error; MC = midcommissural; NHP = nonhuman primate; STN = subthalamic nucleus.

SUBMITTED November 21, 2019. **ACCEPTED** December 30, 2019.

INCLUDE WHEN CITING Published online March 6, 2020; DOI: 10.3171/2019.12.JNS192946.

difficult to target with traditional stereotactic frame-based approaches without penetrating the tentorium.

Depth electrodes have historically been implanted in preclinical models through frame-based stereotactic surgery using target coordinates derived from published atlases,^{1,14} a process not unlike early human stereotaxy. It is well-established, however, that this methodology presents challenges that limit its overall precision,^{26,33} including its inability to correct for inherent variability in neuroanatomy across specimens. Human neurosurgery has made progress in enhancing targeting accuracy through the use of patient-specific anatomical imaging to refine surgical target localization.^{7,12,21} A similar approach has been developed for preclinical animal models, however it continues to require the use of the fixed, stereotactic frames.²³ More recent efforts in human surgery combining patient-specific localization with enhanced targeting flexibility have yielded “frameless” approaches,^{2,3} including FHC’s microTargeting platform (FHC Inc.). The targeting platform is custom-made to the target, and trajectory plans created upon coregistration of preoperative MR images with a CT dataset, acquired following the placement of a series of skull fiducials. Prior research suggests this approach is a safe and effective alternative to traditional stereotactic frame systems and demonstrates comparable accuracy and outcomes.¹⁸ In the present study, we report on the feasibility and accuracy of targeting basal ganglia as well as cerebellar nuclei using the platform for placement of depth electrodes in the nonhuman primate research model.

Methods

Animals

A total of 5 female rhesus monkeys (*Macaca mulatta*) and 2 female cynomolgus monkeys (*Macaca fascicularis*) ranging from 10 to 16 years of age were used in this study. The study was performed in accordance with protocols approved by the institutional animal care and use committee of the Cleveland Clinic.

MRI Sequences

MR images (sagittal MP2RAGE, 0.47-mm isotropic voxels, 120 mm × 120 mm × 90 mm field of view, TE/TR/TI1/TI2 = 3.29/6000/700/2700 msec) were acquired on a 7-T Siemens Magnetom machine (Siemens Medical) with a single-channel transmit/28-channel receive knee coil (Quality Electrodynamics). All animals were imaged in the naïve state, prior to surgical intervention. A second MRI scan was acquired only for animals that had their DBS leads revised, to verify that no structural brain damage had been caused by the previous insertion or subsequent removal of the DBS leads.

Stereotactic Fiducial Implantation and Preoperative CT Scan

Approximately 2 weeks prior to the stereotactic lead placement surgery, each animal underwent a minor surgical procedure during which a minimum of 4 WayPoint fiducial anchors (FHC Inc.) were implanted across the calvarium to serve as reference points for creating and,

subsequently, securing the custom stereotactic platform. Under general anesthesia and local anesthetic, the head was shaved and prepared using standard sterile technique. Fiducials were placed in the frontotemporal and parietal areas in such fashion as to optimize the stability of the platform and remain clear of the planned entry point. Each screw was inserted and secured to the bone via a small (< 1 cm) incision in the scalp. After placement, each scalp incision was closed with a simple suture. Because the skull of the nonhuman primate is significantly thinner than the skull of the human, care was taken to utilize smaller screws and to not drive the screws to the end. Rather, the screws were advanced into the bone just enough to achieve adequate stability.

Following fiducial placement, a noncontrast CT scan using a Dyna-CT (Axiom Artis system, Siemens Medical Solutions) was acquired while the animal remained under general anesthesia. Thereafter, the animal was weaned from anesthesia, extubated, and returned to its home cage. Prophylactic pain medication and antibiotics were administered according to institutional protocol under veterinary oversight.

Platform Design

Preoperative MRI and postfiducial CT scans were coregistered using the WayPoint navigator software (FHC) and each implanted fiducial was identified using the CT dataset. The deep brain target was selected using the MR images with the aid of a primate stereotactic atlas²⁵ followed by selection of an entry point and trajectory that minimized the risk of intersecting cerebral vasculature and sulci (Fig. 1). The manufacturer’s software was again used to render the platform model, which was then uploaded to its file transfer website. After approximately 1 week, the custom-made platform and its phantom were delivered to our facility. The latter is a representation of the selected target point in the brain and of the fiducials selected to support the platform. It is prototyped to match the platform and allows for calibration of the stereotactic system before insertion of the DBS lead into the brain. It is an important resource for accurate targeting, particularly when microelectrode recording is not feasible to further refine surgical targeting.

DBS Lead Implantation

All animals underwent implantation of the DBS lead under general anesthesia. The head was immobilized using a large-animal stereotactic frame (David Kopf Instruments). In cases targeting the cerebellar nuclei, the eye and palate components of the frame were not placed in order to allow flexion of the neck and exposure of the suboccipital region.

Following shaving and surgical preparation, each bone fiducial was reexposed through a small incision in the scalp and the stereotactic platform was rigidly attached to the four fiducials. A manual microdrive (guide tube drive [60–00–1] and XY drive [60–02–0], FHC) was attached to the platform and a metal stylet used to mark the scalp entry point. After the scalp incision, this process was repeated to mark the entry point on the bone, followed by

FIG. 1. Reconstructed visualization of the skull from the preoperative CT scan containing the fiducials with potential microTargeting platform generated using WayPoint navigator software. Targeting the STN (upper) and DN (lower).

creation of a 2–3-mm burr hole that left dura intact. Three screws were inserted into the calvaria around the burr hole to serve as anchor points for the bone cement that secures the implanted lead.

The platform was disconnected from the fiducial anchors and connected to the platform phantom for calibration (Fig. 2), which was performed as follows: 1) a guide cannula was inserted in the microdrive and advanced toward the target representation in the phantom; 2) the guide cannula was positioned with its tip 2–3 mm from the phantom's target; 3) the position of the cannula was marked and a cannula stopper secured to the cannula; and 4) the stylet was removed from the cannula and the DBS lead inserted through the cannula until its tip reached the phantom target point. The position of the DBS lead was marked and a small vascular clip was used to avoid movement of the DBS lead past the marked point. The DBS lead was removed from the cannula and replaced with a stylet. The cannula was then partially retracted to allow for movement of the platform and fixation onto the ani-

FIG. 2. The Microdrive loaded with a cannula and DBS lead anchored to the phantom for calibration prior to insertion.

mal's head. The platform, together with the microdrive and the cannula/stylet, was decoupled from the phantom and moved to the surgical field, where it was rigidly connected to the skull fiducials. The cannula/stylet was lowered to the level of the dura and then advanced through the meninges into the brain. Once at depth, the stylet was removed and the DBS lead was inserted through the cannula and advanced to the premeasured depth. Thereafter, the cannula was slowly retracted until the body of the DBS lead was exposed at the level of the skull, whereupon it was secured in place using an initial coat of bone cement (PALACOS MV+G, Heraeus Co.). Thereafter, the cannula, microdrive, and frame assembly were removed and the extracranial end of the lead was buried under the scalp.

Targeting Error Analysis

To avoid distortion caused by pneumocephalus, the postoperative CT scan was acquired at least 2 weeks after implantation of the DBS lead. The pre- and postoperative CT scans were coregistered using the WayPoint software (Figs. 3 and 4). To calculate the electrode placement error (EPE), the coordinates from the tip of the electrode (x_2 , y_2 , z_2) on the postoperative CT scan were compared to the coordinates of the intended target point (x_1 , y_1 , z_1) on the preoperative CT scan and quantified as vector components in millimeters relative to the midcommissural (MC) point. The magnitude of the vector of error between the tip of

FIG. 3. Postexplant MRI of an animal with a prior implant in the DN shown in grayscale and color based on voxel intensity. Original target marked with a red cross.

the DBS lead and the intended target point was calculated using the distance formula:

$$d = \sqrt{(x_2 - x_1)^2 + (y_2 - y_1)^2 + (z_2 - z_1)^2}$$

in which x_n , y_n , and z_n correspond to the medial-lateral, anterior-posterior, and inferior-superior components, respectively.

The radial distance between the DBS lead and the planned trajectory at a prespecified plane was calculated as well. The prespecified plane selected varied depending on the brain target. For subthalamic nucleus (STN) implantations, the axial plane 2 mm inferior to the MC point was selected. For cerebellar dentate nucleus (DN) implantations, the coronal plane 19 mm posterior to the

MC point was selected. The calculation of the radial distance followed the same method used for determining the magnitude of the vector of error.

The EPE was estimated by two authors of this paper independently and the final EPE was calculated as the average between both observations as follows:

Observer 1:

$$d_{Observer\ 1} = \sqrt{(x_2 - x_1)^2 + (y_2 - y_1)^2 + (z_2 - z_1)^2}$$

Observer 2:

$$d_{Observer\ 2} = \sqrt{(x_2 - x_1)^2 + (y_2 - y_1)^2 + (z_2 - z_1)^2}$$

Final EPE:

$$Average = \frac{(d_{Observer\ 1} + d_{Observer\ 2})}{2}$$

Interobserver Variability

The mean of the difference between raters was evaluated using the two 1-sided t-tests equivalence testing procedure,²⁹ with upper and lower equivalence bounds set to -0.1 and 0.1 mm, respectively. The upper and lower equivalence bounds were selected to represent a negligible amount of error between raters based on the resolution of the image sets acquired.¹⁶ A significant result from the equivalence test indicates that the observed effect falls within the equivalence bounds, and thus the interrater error is considered negligible.

Results

Eleven leads were implanted in a total of 9 surgical procedures (Table 1). Six of the 9 procedures targeted the STN, with the remaining procedures targeting the DN. Two of the STN implantations targeted the nuclei bilaterally and one of the DN implantations targeted the right-side nucleus, with the remaining 6 procedures targeting the left side of the brain. Rhesus monkeys (*Macaca mulatta*) were used for STN implantation, while cynomolgus monkeys (*Macaca fascicularis*) were used for DN implantations.

Data from animal “T” were lost due to perioperative complications unrelated to the surgical technique, and therefore were excluded from the image analysis (procedure X1). Animal “M” was initially implanted with DBS leads bilaterally in the STN, however, due to infection of the externalized electrodes, the hardware had to be explanted and a single new electrode was inserted in the left STN after antibiotic treatment and recovery. Both implantation procedures have been included in the image analysis. Animal “B” was initially implanted with an electrode in the right DN (procedure X2). During the postoperative assessment it was noted that there was failure of adhesion of the bone cement securing the electrode. The electrode in the animal was explanted and a new DBS lead was implanted in the left DN after the animal recovered. Because of failure to secure the electrode in place, the first procedure was excluded from the image analysis. The selection of the surgical procedures included in the final image analysis of the EPE are described in Fig. 5.

FIG. 4. Coregistered MRI, fiducial scan, and postsurgical CT scan showing DBS lead artifact relative to planned location (STN). Planned trajectory marked by yellow lines (**A and B**) with target location marked by a red cross. Panels **C** and **D** show the same coregistration, but without the trajectory (the target location is also marked by a red cross).

The EPE measured by each independent observer and the final EPE are shown in Tables 2 and 3. The medial-lateral, anterior-posterior, and inferior-superior components of the EPE are also detailed in Tables 2 and 3. The mean vector error was 1.29 ± 0.41 mm and the mean radial error was 0.96 ± 0.63 mm.

Interobserver Variability

The mean vector interrater error was 0.012 ± 0.069 mm and the mean radial interrater error was -0.017 ± 0.077 mm. Both vector and radial interrater errors were found to fall within the a priori–defined equivalence region ($p = 0.003$ for vector, $p = 0.009$ for radial), indicating negligible error.

Discussion

Our data corroborate the feasibility and accuracy of adopting the microTargeting platform used in human stereotactic procedures in the NHP research model. DBS is an important therapeutic modality for a growing number of neurological and psychiatric diseases and extensive preclinical investigation will be required to guide human translation, the validity of which depends heavily on achieving precise and accurate placement of depth electrodes.

The rigid stereotactic frame has been widely used in preclinical experiments in conjunction with stereotactic atlases, but the results of this strategy are frequently inaccurate (see Zhu et al., 2016³³) despite recent advances in customizing atlas-based coordinates. In addition, a rigid, frame-based approach may not allow for the selection of

a variety of trajectories tailored to an individual animal's anatomy, which limits the development of preclinical protocols that emulate human procedures.

To improve accuracy in relation to atlas-based targeting, fiducial markers have been traditionally implemented in animal studies in conjunction with subject-specific MRI.^{15,27} Fiducials can be placed in the skull and used to calculate stereotactic coordinates without using the frame. This strategy eliminates the necessity of scanning the animal with the frame in place immediately prior to the surgical procedure, allowing for reduction of anesthesia time and complications related to transportation of the anesthetized animal fixed to the frame. However, fiducials need to be positioned in a specific fashion to place their fixation points close to the target region in the brain during the

TABLE 1. Animal specifications and surgical targets

Procedure	Animal ID	Species	Target	Side
1	M	Rhesus	STN	Bilat
2	I	Rhesus	STN	Lt
3	S	Rhesus	STN	Lt
4	B	Cynomolgus	DN	Lt
5	M	Rhesus	STN	Lt
6	N	Rhesus	STN	Lt
7	Sp	Rhesus	STN	Bilat
X1	T	Cynomolgus	DN	Lt
X2	B	Cynomolgus	DN	Rt

FIG. 5. Procedures included in the final analysis of the EPE.

co-registration process and thus minimize implantation errors.¹³

Alternatives to overcome the difficulties imposed by the inflexibility of conventional rigid frames in animal studies involve the construction of special adaptors and frames.^{6,15,30} Such devices are usually cumbersome and frequently difficult to reproduce, requiring the fabrication of complex parts.^{6,30} In addition, many frameless adaptors used in animal research have been developed for intraoperative MRI guidance,^{28,30} an emerging technique that presents high costs, several restrictions, and is not widely available, especially in a preclinical scenario.²⁰ Furthermore, many of these stereotactic devices have been built for specific neurosurgical procedures^{10,15,24,30} and it is incorrect to infer easy and direct adaptability of these devices to DBS lead implantation.

The microTargeting platform is built using subject-specific imaging and delivered with a short turnaround time. It has already been tested and validated in phantom and clinical studies, but this is the first study to directly address its use in preclinical research using a large animal model. Previous studies of this platform have shown varied results,⁵ which is expected because results must be interpreted taking not only the type of study into account, but also the methodology. One phantom study found an average vector error of 0.42 ± 0.15 mm for the microTarget-

ing platform,² however, reported errors have been larger in clinical studies.^{7,18} Notably, while phantom studies only measure the mechanical accuracy of the hardware, clinical studies involve extra sources of error such as imprecisions of the imaging method, inaccuracy of localization of the electrode, electrode fixation error, and brain shift. The analysis of a large series of 263 patients who underwent implantation of a total of 497 DBS electrodes using the microTargeting platform showed an average error of 1.99 ± 0.9 mm.¹⁸ A subgroup analysis of this series showed that brain shift related to pneumocephalus leads to overestimation of the error. The average vector error magnitude was reduced from 1.99 ± 0.92 mm to 1.24 ± 0.37 mm when pneumocephalus was taken into account,⁸ a result similar to the mean vector error magnitude that we report in this work. Brain shift can also be caused by factors other than pneumocephalus, which suggests that the true vector error magnitude of this platform in a clinical setting might be smaller than 1.24 ± 0.37 mm.

The frameless stereotactic technique described here is feasible, easily adaptable to NHPs, and less costly than acquiring other commercially available alternatives such as intraoperative imaging-guided surgery. The only financial expense in executing this approach was the cost of printing each single-use platform. The phantom study results² indicate that the mechanical accuracy built into the platform

TABLE 2. Vector error

Procedure	Observer Rating ($x_2 - x_1$)		Observer Rating ($y_2 - y_1$)		Observer Rating ($z_2 - z_1$)		Observer Vector Magnitudes		Final Vector EPE Magnitude
	O ₁	O ₂	O ₁	O ₂	O ₁	O ₂	O ₁	O ₂	
1									
Lt	1.09	0.97	0.89	0.77	0.08	0.01	1.41	1.24	1.32
Rt	0.47	0.48	-0.12	-0.13	1.21	1.15	1.30	1.25	1.28
2, Lt	-0.05	-0.03	-0.27	-0.42	-0.69	-0.69	0.74	0.81	0.78
3, Lt	0.23	0.25	0.57	0.57	0.89	0.87	1.08	1.07	1.07
4, Lt	-0.16	-0.18	-0.77	-0.78	0.38	0.37	0.87	0.88	0.88
5, Lt	0.72	0.75	-1.70	-1.69	0.71	0.76	1.98	2.00	1.99
6, Lt	1.30	1.32	1.37	1.33	0.28	0.23	1.91	1.89	1.90
7									
Lt	0.73	0.70	0.64	0.64	0.67	0.67	1.18	1.16	1.17
Rt	-0.20	-0.20	0.34	0.36	1.14	1.19	1.20	1.26	1.23
Mean $\pm$ SD									1.29 $\pm$ 0.41

O₁ = observer 1; O₂ = observer 2.

TABLE 3. Radial error

Procedure	Observer Rating ($x_2 - x_1$)		Observer Rating ($y_2 - y_1$)		Observer Rating ($z_2 - z_1$)		Observer Radial Error		Final Radial EPE
	O ₁	O ₂	O ₁	O ₂	O ₁	O ₂	O ₁	O ₂	
1									
Lt	1.09	0.96	0.8	0.79	0	0	1.35	1.24	1.30
Rt	0.58	0.65	-0.50	-0.61	0	0	0.77	0.89	0.83
2, Lt	0.05	0.04	-0.29	-0.27	0	0	0.29	0.28	0.28
3, Lt	0.21	0.30	0.06	0.05	0	0	0.22	0.31	0.26
4, Lt	0.00	0.32	0	0	0.44	0.41	0.44	0.52	0.48
5, Lt	0.8	0.81	-1.89	-1.91	0	0	2.05	2.07	2.06
6, Lt	1.19	1.17	0.87	0.84	0	0	1.47	1.44	1.45
7									
Lt	0.99	0.97	0.04	-0.02	0	0	0.99	0.97	0.98
Rt*	—	—	—	—	—	—	—	—	—
Mean $\pm$ SD									0.96 $\pm$ 0.63

* The lead was not visible in the axial plane analyzed, and therefore no result was available.

is enough to target a small nucleus such as the primate STN, which is shorter than 3 mm in its longest axis,²⁵ and support our efforts to apply this method in preclinical research. Accordingly, we report a vector error magnitude slightly larger than 1 mm, which is a result comparable to what has been observed in the clinical setting, where the accuracy of this platform leads to outcomes comparable to those associated with traditional human stereotactic systems.¹⁸ Additionally, the methodology used here in the verification of target accuracy parallels that of clinical methods for evaluating lead placement and its connection to therapeutic efficacy.¹⁶ Comparable clinical and preclinical accuracy as demonstrated in this study regarding the placement of DBS leads is essential for the continued improvement and evaluation of DBS therapy.

Limitations of our work involve limited visualization of the macaque STN on MRI and lack of intraoperative neurophysiological evaluation to confirm placement of the DBS lead in the motor region of the STN. However, our data characterize the accuracy of the stereotactic technique in relation to the selected target point in the brain and, in this way, poor characterization of the STN in the image sets does not invalidate our results. Concerning the use of intraoperative neurophysiological evaluation, even though it constitutes a standard practice used to refine placement of the DBS lead in humans,⁴ it requires the subject to be awake¹⁹ and preferentially cooperative during surgery, something hardly achievable with NHPs.

Conclusions

The microTargeting stereotactic system can be successfully and reproducibly adapted for the primate DBS model. The results are comparable to those observed in the clinical setting.

Acknowledgments

We thank the Cleveland Clinic Innovations team: Jackie Kattar, RVT, and Mary Lachowski, RVT; Tobias Kober of Siemens Healthcare for use of the MP2RAGE WIP package; Mark Han-

cock, VT; and Olivia Hogue for statistical assistance. This work was supported by NIH grant no. R01 NS092730, the Cleveland Clinic, and St. Jude Medical.

References

- Alvarez-Royo P, Clower RP, Zola-Morgan S, Squire LR: Stereotaxic lesions of the hippocampus in monkeys: determination of surgical coordinates and analysis of lesions using magnetic resonance imaging. *J Neurosci Methods* **38**:223–232, 1991
- Balachandran R, Mitchell JE, Dawant BM, Fitzpatrick JM: Accuracy evaluation of microTargeting Platforms for deep-brain stimulation using virtual targets. *IEEE Trans Biomed Eng* **56**:37–44, 2009
- Balanescu B, Franklin R, Ciurea J, Mindruta I, Rasina A, Bobulescu RC, et al: A personalized stereotactic fixture for implantation of depth electrodes in stereoelectroencephalography. *Stereotact Funct Neurosurg* **92**:117–125, 2014
- Bejjani BP, Dormont D, Pidoux B, Yelnik J, Damier P, Arnulf I, et al: Bilateral subthalamic stimulation for Parkinson's disease by using three-dimensional stereotactic magnetic resonance imaging and electrophysiological guidance. *J Neurosurg* **92**:615–625, 2000
- Bentley JN, Khalsa SSS, Kobylarek M, Schroeder KE, Chen K, Bergin IL, et al: A simple, inexpensive method for subcortical stereotactic targeting in nonhuman primates. *J Neurosci Methods* **305**:89–97, 2018
- Chen L, Li N, Gao L, Yang C, Fang W, Wang XL, et al: Improved stereotactic procedure enhances the accuracy of deep brain stimulation electrode implantation in non-human primates. *Int J Neurosci* **125**:380–389, 2015
- D'Haese PF, Cetinkaya E, Konrad PE, Kao C, Dawant BM: Computer-aided placement of deep brain stimulators: from planning to intraoperative guidance. *IEEE Trans Med Imaging* **24**:1469–1478, 2005
- D'Haese PF, Pallavaram S, Konrad PE, Neimat J, Fitzpatrick JM, Dawant BM: Clinical accuracy of a customized stereotactic platform for deep brain stimulation after accounting for brain shift. *Stereotact Funct Neurosurg* **88**:81–87, 2010
- Dougherty DD: Deep brain stimulation: clinical applications. *Psychiatr Clin North Am* **41**:385–394, 2018
- Emborg ME, Joers V, Fisher R, Brunner K, Carter V, Ross C, et al: Intraoperative intracerebral MRI-guided navigation for

- accurate targeting in nonhuman primates. **Cell Transplant** **19**:1587–1597, 2010
11. Escobar Sanabria D, Johnson LA, Nebeck SD, Zhang J, Johnson MD, Baker KB, et al: Parkinsonism and vigilance: alteration in neural oscillatory activity and phase-amplitude coupling in the basal ganglia and motor cortex. **J Neurophysiol** **118**:2654–2669, 2017
 12. Finnis KW, Starreveld YP, Parrent AG, Sadikot AF, Peters TM: Three-dimensional database of subcortical electrophysiology for image-guided stereotactic functional neurosurgery. **IEEE Trans Med Imaging** **22**:93–104, 2003
 13. Fitzpatrick JM, West JB, Maurer CR Jr: Predicting error in rigid-body point-based registration. **IEEE Trans Med Imaging** **17**:694–702, 1998
 14. François C, Yelnik J, Percheron G: A stereotaxic atlas of the basal ganglia in macaques. **Brain Res Bull** **41**:151–158, 1996
 15. Frey S, Comeau R, Hynes B, Mackey S, Petrides M: Frameless stereotaxy in the nonhuman primate. **Neuroimage** **23**:1226–1234, 2004
 16. Frizon LA, Nagel SJ, May FJ, Shao J, Maldonado-Naranjo AL, Fernandez HH, et al: Outcomes following deep brain stimulation lead revision or reimplantation for Parkinson's disease. **J Neurosurg** **130**:1841–1846, 2019
 17. Frizon LA, Shao J, Maldonado-Naranjo AL, Lobel DA, Nagel SJ, Fernandez HH, et al: The safety and efficacy of using the O-arm intraoperative imaging system for deep brain stimulation lead implantation. **Neuromodulation** **21**:588–592, 2018
 18. Konrad PE, Neimat JS, Yu H, Kao CC, Remple MS, D'Haese PF, et al: Customized, miniature rapid-prototype stereotactic frames for use in deep brain stimulator surgery: initial clinical methodology and experience from 263 patients from 2002 to 2008. **Stereotact Funct Neurosurg** **89**:34–41, 2011
 19. Krishna V, Hodaie M: Editorial: Operating outside the operating room: how do we measure the implications? **J Neurosurg** **126**:106–107, 2017
 20. Larson PS, Willie JT, Vadivelu S, Azmi-Ghadimi H, Nichols A, Fauerbach LL, et al: MRI-guided stereotactic neurosurgical procedures in a diagnostic MRI suite: Background and safe practice recommendations. **J Healthc Risk Manag** **37**:31–39, 2017
 21. Machado A, Rezai AR, Kopell BH, Gross RE, Sharan AD, Benabid AL: Deep brain stimulation for Parkinson's disease: surgical technique and perioperative management. **Mov Disord** **21** (Suppl 14):S247–S258, 2006
 22. Matias CM, Frizon LA, Nagel SJ, Lobel DA, Machado AG: Deep brain stimulation outcomes in patients implanted under general anesthesia with frame-based stereotaxy and intraoperative MRI. **J Neurosurg** **129**:1572–1578, 2018
 23. Miocinovic S, Noecker AM, Maks CB, Butson CR, McIntyre CC: Cicerone: stereotactic neurophysiological recording and deep brain stimulation electrode placement software system. **Acta Neurochir Suppl** **97** (Pt 2):561–567, 2007
 24. Mugge L, Krafcik B, Pontasch G, Alnemari A, Neimat J, Gaudin D: A review of biomarkers use in Parkinson with deep brain stimulation: a successful past promising a bright future. **World Neurosurg** **123**:197–207, 2019
 25. Paxinos G, Huang XF, Petrides M, Toga AW: **The Rhesus Monkey Brain in Stereotaxic Coordinates**, ed 2. Amsterdam: Academic Press, 2008
 26. Percheron G, Lacourly N: [The lack of precision of thalamic stereotaxy based on Horsley and Clarke cranial coordinates in Macaca (author's transl).] **Exp Brain Res** **18**:355–373, 1973 (French)
 27. Rebert CS, Hurd RE, Matteucci MJ, De LaPaz R, Enzmann DR: A procedure for using proton magnetic resonance imaging to determine stereotaxic coordinates of the monkey's brain. **J Neurosci Methods** **39**:109–113, 1991
 28. Richardson RM, Kells AP, Martin AJ, Larson PS, Starr PA, Piferi PG, et al: Novel platform for MRI-guided convection-enhanced delivery of therapeutics: preclinical validation in nonhuman primate brain. **Stereotact Funct Neurosurg** **89**:141–151, 2011
 29. Schuirmann DJ: A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. **J Pharmacokinet Biopharm** **15**:657–680, 1987
 30. Sudhakar V, Mahmoodi A, Bringas JR, Naidoo J, Kells A, Samaranch L, et al: Development of a novel frameless skull-mounted ball-joint guide array for use in image-guided neurosurgery. **J Neurosurg** **132**:595–604, 2020
 31. Voges J, Volkmann J, Allert N, Lehrke R, Koulousakis A, Freund HJ, et al: Bilateral high-frequency stimulation in the subthalamic nucleus for the treatment of Parkinson disease: correlation of therapeutic effect with anatomical electrode position. **J Neurosurg** **96**:269–279, 2002
 32. Wathen CA, Frizon LA, Maiti TK, Baker KB, Machado AG: Deep brain stimulation of the cerebellum for poststroke motor rehabilitation: from laboratory to clinical trial. **Neurosurg Focus** **45**(2):E13, 2018
 33. Zhu GY, Chen YC, Shi L, Yang AC, Jiang Y, Zhang X, et al: Error analysis and some suggestions on animal stereotactic experiment from inaccuracy of Rhesus macaques atlas. **Chin Med J (Engl)** **129**:1621–1624, 2016

Disclosures

Drs. Machado and Baker have potential financial conflict of interest with this research related to intellectual property and distribution rights in Enspire, ATI, and Cardionomics. Dr. Machado reports being a consultant to Spinal Modulation, Functional Neuromodulation, and Abbott; receiving clinical or research support for the study from Enspire and Abbott; and receiving support for the fellowship program from Medtronic. None of these entities had any role in the research or preparation of the manuscript.

Author Contributions

Conception and design: Baker, Branco de Paiva, Campbell, Machado. Acquisition of data: all authors. Analysis and interpretation of data: Baker, Branco de Paiva, Campbell, Frizon, Maldonado-Naranjo, Machado. Drafting the article: Branco de Paiva, Campbell, Frizon, Maldonado-Naranjo. Critically revising the article: Baker, Campbell, Maldonado-Naranjo, Machado. Reviewed submitted version of manuscript: Baker, Campbell, Machado. Approved the final version of the manuscript on behalf of all authors: Baker. Statistical analysis: Branco de Paiva, Campbell, Frizon. Administrative/technical/material support: Martin. Study supervision: Baker, Machado. Surgical support: Frizon, Maldonado-Naranjo, Machado. Anesthesia support: Martin.

Correspondence

Kenneth B. Baker: Cleveland Clinic, Cleveland, OH. bakerk6@ccf.org.