Convection-enhanced delivery improves MRI visualization of basal ganglia for stereotactic surgery

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OBJECTIVE Stereotactic deep brain stimulation surgery is most commonly performed while patients are awake. This allows for intraoperative clinical assessment and electrophysiological target verification, thereby promoting favorable outcomes with few side effects. Intraoperative CT and MRI have challenged this concept of clinical treatment validation. Image-guided surgery is capable of delivering electrodes precisely to a planned, stereotactic target; however, these methods can be limited by low anatomical resolution even with sophisticated MRI modalities. The authors are developing a novel method using convection-enhanced delivery to safely manipulate the extracellular space surrounding common anatomical targets for surgery. By altering the extracellular content of deep subcortical structures and their associated white matter tracts, the MRI visualization of the basal ganglia can be improved to better define the anatomy. This technique could greatly improve the accuracy and success of stereotactic surgery, potentially eliminating the reliance on awake surgery.

METHODS Observations were made in the clinical setting where vasogenic and cytotoxic edema improved the MRI visualization of the basal ganglia. These findings were replicated in the experimental setting using an FDA-approved intracerebral catheter that was stereotactically inserted into the thalamus or basal ganglia of 7 swine. Five swine were infused with normal saline, and 2 were infused with autologous CSF. Flow rates varied between 0.5 μl/min to 6 μl/min to achieve convective distributions. Concurrent MRI was performed at 15-minute intervals to monitor the volume of infusion and observe the imaging changes of the deep subcortical structures. The animals were then clinically observed, and necropsy was performed within 48 hours, 1 week, or 1 month for histological analysis.

RESULTS In all animals, the white matter tracts became hyperintense on T2-weighted imaging as compared with basal ganglia nuclei, enabling better definition of the deep brain anatomy. The volume of distribution and infusion (Vd/Vi ratio) ranged from 2.5 to 4.5. There were no observed clinical effects from the infusions. Histological analysis demonstrated mild neuronal effects from saline infusions but no effects from CSF infusions.

CONCLUSIONS This work provides the initial foundation for a novel approach to improve the visualization of deep brain anatomy during MRI-guided, stereotactic procedures. Convective infusions of CSF alter the extracellular fluid content of the brain for improved MRI without evidence of clinical or toxic effects.

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KEY WORDS convection-enhanced delivery; basal ganglia; MRI; stereotactic neurosurgery; image-guided; functional neurosurgery

STEREOTACTIC surgery is commonly used to treat chronic neurological disorders such as Parkinson’s disease, tremor, epilepsy, and psychiatric diseases. Lesioning, stimulation, and local delivery of drugs all rely on the ability to treat specific brain regions that are often small, deep, and indistinct on conventional MRI. Validation of their placement typically requires clinical testing or electrophysiological mapping with microelectrode recordings (MERs), or both of these. Image-guided techniques have been developed to position a stimulating or lesioning electrode with a mean vector error as low as 1.59 mm with intraoperative CT-guided techniques and 0.14–0.86 mm with intraoperative MRI. Current methods for targeting these structures also often include referencing a stereotactic atlas, with potential errors due to patient-specific variations from the atlas. Richter et al. reviewed 35 subthalamic nuclei (STN) in 18 patients and compared their location based on T2-weight-
ed MRI. They then compared the T2-weighted MRI locations to locations as depicted in the Talairach and Tournoux, and Schaltenbrand and Wahren atlases and found the anterior border of the STN to vary from 4.1 mm to 3.7 mm from the midcommissural point, posterior border 4.2 mm to 10 mm, medial border 7.9 mm to 12.1 mm, and lateral border 12.3 mm to 15.4 mm. There have been advances in the use of MRI including coregistering multiple sequences, 7-T imaging, 9.4-T imaging, 18 fast gray matter acquisition T1 inversion recovery, 29 and others. To date, a practical and widely adoptable solution to easily identify these deep subcortical nuclei remains elusive and results in widespread reliance on awake neurosurgery.

We first observed a patient with vasogenic edema around an STN deep brain stimulation (DBS) electrode that dramatically improved the MRI visualization of the deep brain anatomy. This observation was then confirmed by MRI in other patients with edema from a variety of pathologies extending into the basal ganglia. Because vasogenic edema represents an increase in the extracellular water content, we sought to replicate this experimentally in an animal model with convection-enhanced delivery (CED). The preclinical study presented here demonstrates a technique for convecting an infusate to improve the visualization of deep brain structures with conventional MRI. We envision that this technique potentially can be used in combination with MRI-guided surgery to improve stereotactic targeting and obviate the need for awake surgery with MER or stimulation mapping.

Methods

Case Observation

A 59-year-old retired psychologist presented for consideration of DBS surgery. He had been diagnosed 5 years earlier with Parkinson’s disease when he presented with a stooped posture and diminished facial expressions. He developed severe motor fluctuations, short duration responses, and peak dose dyskinesia on a medication regimen consisting of levodopa 25/100 every 2 hours, 5 daily doses of 200 mg of entacapone, and 1.5 mg of pramipexole 3 times a day. The unmedicated (off) motor examination was notable for mild hypophonia with hypomimia, moderately increased tone (especially in the patient’s neck), and significant bradykinesia in the absence of tremor. He was able to independently stand with effort to a stooped posture, and his gait was slowed with delayed initiation and a diminished arm swing. A formal neuropsychological assessment deemed that he was a good candidate for surgery, because he experienced no mood issues and a preservation of cognition.

He underwent successful surgery consisting of bilateral STN DBS with microelectrode mapping and a staged pulse generator implantation. Unfortunately, he developed a *Pseudomonas* infection involving the pulse generator, which required explantation of the pulse generator and the distal portion of the lead extensions. Despite ciprofloxacin therapy, he presented again 2 months later with evidence of infection at the cranial incision. Cerebral MRI with Gd revealed no intracranial abscess; however, there was a hyperintense signal on T2-weighted images around the right DBS electrode tract to the subthalamus (Fig. 1). The remainder of the DBS system was explanted, and the infection was cleared after several weeks of intravenous aztreonam therapy. A second bilateral subthalamic DBS system was eventually reimplanted 1 year after the first.

The presumed vasogenic edema around the infected electrode highlighted the boundaries of the right STN and adjacent deep brain anatomy in contrast to the unaffected, contralateral, left side (Fig. 1). This observation led to the premise of this study, where we believe that the extracellular space could be manipulated experimentally to improve MRI visualization.

Additional Clinical Observations

After we recognized improved MRI visualization of the anatomy surrounding an infected DBS electrode, we noted similar incidences of edema in the deep brain regions from a variety of pathologies (Fig. 2). These shared a common pathophysiology where vasogenic edema extended into surrounding tissues as evidenced by T2-weighted MRI. These cases served as further clinical evidence that an alteration in extracellular fluid content changed the characteristics of T2-weighted MRI. The enhanced definition of deep brain anatomy, and particularly the boundaries between nuclei and white matter tracts, was observed in patients with sarcoma metastasis, thalamic glioblastoma, sarcoidosis of the basal ganglia, large B-cell lymphoma, clear cell meningioma, gliomatosis cerebri, stereotactic thalamotomy for tremor, central glioblastoma, and stereotactic pallidotomy for cerebral palsy athetosis and dystonia.

Swine Model of CED-Enhanced MRI Visualization

Following approval from the University of Virginia Institutional Animal Care and Use Committee, *Sus scrofa domestica* (Yorkshire) female pigs weighing approximately 25 pounds were acquired and acclimated in the vivarium facility for 3 days. Swine nuclei are smaller than human nuclei.
those in humans and more difficult to visualize, but they are still within reasonable limits. For example, a swine STN is approximately 3 mm in maximal dimension.\textsuperscript{11} In humans, the STN measures approximately 6 mm in maximal dimension.\textsuperscript{26} Most intraoperative MRI machines use 1.5-T magnets; therefore, to compensate for the increased difficulty of visualization of the smaller swine nuclei, the CED swine experiments were performed on a 3.0-T MRI machine. The coil used for the swine was a standard head coil used for humans, and the swine were chosen to be the appropriate size to fit within the head coil with no detrimental effects.

Before surgery, the infusion apparatus was prepared. A PHD Ultra syringe pump (Harvard Apparatus) was used with a 500-microliter, airtight glass syringe. The syringe was connected to a series of four 60-inch extension sets (Medex Micro Bore, Smiths Medical), each of which had 0.4-ml priming volume. The extension sets were then connected to an EViTAR microcatheter (NexGen Medical Systems, Inc.). In experiments in which normal saline was infused, the system was primed with normal saline via a 3-way valve at an extension set connection point. Care was taken to ensure there were no air bubbles. When CSF was infused, the priming was performed in the same manner after CSF had been obtained from the lumbosacral region of the anesthetized animal.

On the day of surgery, anesthesia was induced with an intramuscular injection of tiletamine and xylazine and then maintained with inhaled isoflurane. External MRI fiducials were applied, and T2 images (TR 6000 msec, TE 93 msec, 2-mm slice width, no gap, resolution 320 × 320) were acquired in all 3 orthogonal planes on a 3-T MRI system (Siemens Trio with Numaris 4 B17 software). The midthalamic targets were identified on these presurgical MR images and then compared with a published stereotactic atlas.\textsuperscript{11,30} The coordinates for cannula placement were calculated and ranged in relation to the bregma as follows: 0–3 mm anterior, 6–8 mm lateral, and 33–36 mm deep.

The animal was then positioned in a custom, MRI-compatible, stereotactic head frame such that the bregma and lambda points were in the same plane. The scalp was then shaved and prepared with betadine. A 4-cm linear incision was made centered at the bregma so that a small bur hole could be made with a high-speed drill. After the dura was opened, the outer cannula of the infusion catheter, with a stylet, was then connected to the stereotactic manipulator and advanced to the target minus 1 cm in vector length (the infusion cannula is 1 cm longer than the outer cannula). The outer cannula was then affixed to the skull with dental acrylic. Then the animal was positioned in the MRI machine. After removal of the stylet, the inner infusion microcatheter was then advanced through the outer cannula as a final step to ensure there was no movement that could compromise the catheter/brain seal and lead to backflow. The PHD Ultra syringe pump was kept in the MRI control room, and the tubing was passed through the wall. The swine was then advanced into the bore of the magnet. Sagittal, axial, and coronal T2-weighted images were then obtained to verify the placement of the CED catheter. In 2 instances, the CED catheter was misplaced; therefore, the animal was returned to the large animal operating room, and the outer cannula was repositioned without incident.

Once the animal was in the MRI machine, the CED infusion was started. Infusion rates varied from 1 μl/min to 6 μl/min, but imaging was constant at 15-minute intervals for a total of 90–120 minutes, depending on the rate of infusion. The measurement of volume of distribution (Vd) was performed using the average diameter of the infusion front, as measured from T2 changes, and calculating volume of infusion (Vi) based on a sphere.

Following completion of CED infusion and MRI, the infusion catheter was then removed and the scalp was sutured closed. Animals recovered under direct observation for evidence of neurological, gait, or balance dysfunction. Necropsy was performed at either 48 hours, 1 week, or 1 month. The brains were then fixed in formalin and examined for gross abnormalities before undergoing histological analysis with immunohistochemistry by a certified neuropathologist. A total of 7 animals were infused: 5 with normal saline and 2 with CSF. A summary is shown in Table 1.

**Results**

**Volume of Distribution**

Once the model for CED was established, 7 animals underwent convection with varying rates of normal sa-
line (n = 5) or autologous CSF (n = 2). The Vd/Vi, measured from T2 weighted MRI sequences, varied from 2.5 to 4.5 regardless of the infusate. The rate for CED is generally accepted as greater than 0.05 μl per minute. These experimental rates varied between 1 and 6 μl per minute without noticeable differences in the Vd/Vi. Total volume of infusion was bounded by either MRI time for low flow rates (limited to 90 minutes), or by observing no further increase in the volume of distribution when a pial boundary was encountered, and this ranged from 90 to 360 μl.

**MR Imaging**

All MRI assessments were made on T2-weighted sequences. The CED infusion of normal saline or CSF became noticeable with increased T2 hyperintensity at roughly 45 μl. By 90 μl, a clearer definition of nuclear structures began to develop. MRI changes in the infusion ceased once infusate reached the pial boundaries. CED infusions into the thalamus delineated the dorsal medial, ventral anterior, reticular, and central median nuclei, which were not apparent before the infusion (Fig. 3). Similar results were obtained with all animals; qualitatively the enhanced appearance of the nuclear structures was present to the same degree in all animals. The ventral anterior nucleus provided the most distinctive improvement in appearance, with the dorsal medial nucleus being the second most distinctive. None of these nuclear structures were visible prior to the infusion in any animal. Animal 7 had a postinfusion scan performed 30 minutes after the completion of the infusion, and the infusion effects persisted. Long-term imaging was not performed.

**Histological Analysis**

Histological analysis was examined at either acute (within 2 days), subacute (7 days), or chronic (28 days) time points for evidence of early or latent neuronal toxicity due to the infusions. All specimens were analyzed with H & E stains. Animals infused with normal saline demonstrated mild neuronal effects with pyknotic neurons and axonal retractions, possibly attributed to the toxicity of the infusate (Fig. 4). Those infused with autologous CSF had no evidence of neuronal change at any time point.

**Discussion**

We observed that vasogenic edema associated with an infected DBS electrode enhanced the T2-weighted MRI characteristics for improved delineation of the deep brain anatomy (Fig. 1). This phenomenon was then similarly recognized with other CNS diseases that caused cerebral edema in the basal ganglia (Fig. 2). These consistent observations led us to design a laboratory experiment in a large-brain animal model to simulate vasogenic edema by manipulating the extracellular water content in a controlled fashion with CED (Fig. 3). In swine, mild neuronal effects were noted in the thalamus by histological analysis when normal saline was convected (Fig. 4) but not with infusions of autologous CSF.

Convection-enhanced infusion, or convection, is distinguished from diffusion because the infusate is driven by a pressure wave through the extracellular space. More optimal convection with minimal backflow along the catheter occurs with a smaller catheter diameter, infusates of smaller molecular weight (MW), stepped catheter designs, and continuous slow infusion rates.1,2,6,7,16,20,21,23 These experiments involved convection of normal saline or autologous CSF, achieving Vd/Vi ratios of 2.5–4.5. Infusions into white matter tracts distribute to larger distances than in nuclear structures. Our Vd/Vi ratios of between 2.5 and 4.5 are consistent with those of other studies using low-molecular-weight infusates with Vd/Vi ratios of 3.8 and 6 in gray and white matter, respectively.3,16 The distribution of infusates is bounded by the pia, thus decreasing the Vd/Vi ratio.4

It has been demonstrated in previous models that infusates preferentially distribute along white matter tracts compared with denser gray matter. When infusing in the spinal cord, the infusate will appear as cylinders as it infuses along the direction of axons.17 Furthermore, Lieberman et al. infused the striatum of rodents and rhesus monkeys, and they showed that high-molecular-weight compounds like phaseolus vulgaris-leukoagglutinin (MW 126kD) had a gray matter Vd/Vi ratio of 1.3, whereas low-molecular-weight molecules like biotinylated dextran (MW 10kD) were higher at 3.8. Interestingly, they compared the biotinylated dextran Vd/Vi ratio to their previous experience using transferrin (MW 80kD) in white matter infusions (Vd/Vi = 6) and found Vd/Vi for the smaller biotinylated dextran molecule to be 63% of the larger transferrin molecule, highlighting the enhanced infusion in white matter relative to gray matter.3,16 In all of our infusions, the T2 images of the infused side demonstrated significant signal differentiation between gray and white structures relative to the noninfused side. Figure 3A and B are representative samples of 2 animals, infused with saline, in which the ventral anterior nucleus is clearly demarcated from the surrounding white matter tracts and highlights the dorsomedial, centromedian, and reticular nucleus; Fig. 3C shows a CSF-infused animal with similar delineation. Figure 3D is a time-lapse series of a third animal. Our infusions were consistent in demonstrating a reproducible technique that highlights deep nuclear structures. Our hypothesis is that the improved visualization derives from 2 major contributions. First, the convective infusion of saline or CSF increases the water content of the extracellular

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NS = normal saline.
space and leads to an increased T2 signal analogous to that seen in vasogenic edema. Second, the infusate preferentially distributes into white matter, increasing the T2 signal in these structures relative to gray matter.

Safety is paramount in determining whether CED infusions are feasible to enhance MRI during stereotactic procedures. There were no neurological or behavioral effects observed after any of our CED infusions in swine. Histological examination, however, revealed mild neuronal changes from normal saline infusions with axonal retractions and pyknotic neurons. Because the volume infused was much less than 0.5 ml, this likely resulted from an osmotic mismatch, because normal saline is more hypertonic. There were no histological effects when the same volumes of autologous CSF was used as the infusate. These preliminary results indicate that the infusion of CSF does not demonstrate neuronal toxicity and has equivalent effects of improved MRI delineation between white and gray matter.

This work was pursued on the assumption that improved resolution of these deep brain structures will aid stereotactic targeting, ultimately improving patient outcomes. Unfortunately, the actual percentage of DBS electrodes that are suboptimally positioned within a target nucleus is difficult to determine. The assessment of DBS electrode placement relative to a selected target location in x, y, z space is relatively straightforward and requires routine postoperative imaging, but whether this is the correct clinical target cannot be ultimately determined until final clinical outcome. McClelland et al. analyzed electrodes placed using frame-based stereotaxy and MER guidance, and found that 40 of 52 electrodes required repositioning based on MER localization. Unfortunately, one cannot determine whether this is from frame placement error or from MRI target definition error.

MRI-guided surgery was initially developed in the 1990s for a more precise brain biopsy. This may have a more attractive allure to functional neurosurgery for stereotactically implanting DBS electrodes into visualized deep brain targets. Clinically, general anesthesia could

**Fig. 3.** A: Axial view of animal 1 after a 360-μl infusion of saline. B: Axial view of animal 4 after a 450-μl infusion of saline. C: Coronal view of animal 6 after a 450-μl infusion of CSF. D: Axial time-lapsed infusion of animal 3 with time and infusion volume labeled (infusion rate = 5 μl/min). The white matter tract medial to the ventral anterior nucleus, lateral to dorsomedial and anterior to centromedian, is readily apparent after infusion. In panel A, the reticular nucleus is noted lateral to the ventral anterior nucleus. Images A, B, and D are axial MR images.

**Fig. 4.** Photomicrographs of formalin-fixed brain after infusion with normal saline identifying pyknotic neuron (dashed arrow) and axonal retraction figures (solid arrow) in a saline-infused thalamus. Infusion of CSF did not demonstrate any neuronal or neuropil damage (not shown). H & E, original magnification ×200.
be used to decrease patient anxiety and discomfort and the need for unmedicated (off-state) intraoperative assessments. Technically, true image-guided surgery adjusts to brain shifting during the procedure and the inherent registration errors that can be associated with image fusion techniques.\textsuperscript{10,13}

True, real-time image-guided DBS placement has only recently been realized with compatible skull-mounted frames and high-field MRI. Radial vector error during DBS for disease progression has been measured at 1.2 ± 0.65 mm and 0.8 ± 0.4 mm.\textsuperscript{24,28} Clinical outcomes note improved off-motor Unified Parkinson’s Disease Rating Scale (UPDRS) scores by 60% and 49%, respectively, which compares similarly to a recent meta-analysis of 34 studies estimating 52% in disease progression with STN DBS.\textsuperscript{15} Even with highly precise MRI-guided placement, the need for occasional electrode repositioning exists.\textsuperscript{28} CT has been used as a modality to guide asleep DBS surgeries, although it is primarily used for image registration and confirmation of the placement as opposed to true image-guided localization during the procedure. Burchiel et al. reported similar accuracies, but clinical outcomes are not yet available.\textsuperscript{4}

We are interested in finding out if the combined use of MRI-guided electrode placement with improved target selection based on the use of CED would lead to even greater improvements in UPDRS scores on average, and just as importantly, more uniform results among patients. The infusion procedure adds time and a new step to the insertion of DBS electrodes, establishing that the improvements gained are central to evaluating the risk-benefit ratio of such a procedure.

The potential applicability of this technique to humans has many issues. First and foremost, the risk-benefit ratio must be favorable to ultimately consider infusion-enhanced, MRI-guided surgery as a valid surgical option. We perceive the addition of a small-volume infusion to be tagged with low morbidity. The increased risk of microcatheter insertion should be similar to or less than that of the current electrophysiological mapping process that requires sharp microelectrode penetrations. It is impossible to assess or predict the clinical effects of a CED infusion, anticipated as less than 0.5–1.0 ml, into the human basal ganglia without a clinical trial. The safest infusate to insert of DBS electrodes, establishing that the improvements gained are central to evaluating the risk-benefit ratio of such a procedure.

Finally, this study describes a proof-of-concept technique that mainly relies on the improved visualization of structures like the STN from T2 signal manipulation in the laboratory and clinic. Other structures like the internal segment of the globus pallidum or the ventral intermediate nucleus of the thalamus are better visualized with other MR sequences such as inversion recovery or susceptibility-weighted images, respectively. We envision that infusion-enhanced MRI would be tailored to the desired brain target with target-specific sequences and infuses. Imaging of all modalities will continue to improve with technology, but tailored intracerebral infusions may serve as an adjunct for improved visualization, not as a replacement for current imaging.

Conclusions

This preliminary work demonstrates that CED of autologous CSF enhances the T2-weighted MRI visualization of deep subcortical structures without neuronal injury. This technique could potentially be used to better delineate image-guided targets during stereotactic neurosurgery. We envision improved stereotactic targeting with the incorporation of CED-enhanced MRI and higher field magnets during image-guided surgeries.\textsuperscript{25,28}

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Disclosures

Author Contributions
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Supplemental Information
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