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Direct visualization of deep brain stimulation targets in Parkinson disease with the use of 7-tesla magnetic resonance imaging

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Abstract

Object—A challenge associated with deep brain stimulation (DBS) in treating advanced Parkinson disease (PD) is the direct visualization of brain nuclei, which often involves indirect approximations of stereotactic targets. In the present study, the authors compared T2*-weighted images obtained using 7-T MR imaging with those obtained using 1.5- and 3-T MR imaging to ascertain whether 7-T imaging enables better visualization of targets for DBS in PD.

Methods—The authors compared 1.5-, 3-, and 7-T MR images obtained in 11 healthy volunteers and 1 patient with PD.

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Disclosure

Dr. Lozano is a consultant for Medtronic and St. Jude.

Author contributions to this study include the following. Conception and design: ZH Cho, HK Min, AM Lozano, KH Lee. Acquisition of data: HK Min, SH Oh, JY Han, SH Paek. Analysis and interpretation of data: HK Min, CW Park, JG Chi, YB Kim. Drafting the article: ZH Cho, HK Min. Critically revising the article: AM Lozano, KH Lee. Reviewed final version of the manuscript and approved it for submission: ZH Cho, HK Min, SH Oh, JY Han, CW Park, JG Chi, YB Kim, SH Paek, AM Lozano, KH Lee. Statistical analysis: HK Min, S Oh. Study supervision: ZH Cho.

Results—With 7-T imaging, distinct images of the brain were obtained, including the subthalamic nucleus (STN) and internal globus pallidus (GPi). Compared with the 1.5- and 3-T MR images of the STN and GPi, the 7-T MR images showed marked improvements in spatial resolution, tissue contrast, and signal-to-noise ratio.

Conclusions—Data in this study reveal the superiority of 7-T MR imaging for visualizing structures targeted for DBS in the management of PD. This finding suggests that by enabling the direct visualization of neural structures of interest, 7-T MR imaging could be a valuable aid in neurosurgical procedures.

Keywords

deep brain stimulation; Parkinson disease; subthalamic nucleus; internal globus pallidus; 7-tesla magnetic resonance imaging

Deep brain stimulation is an emerging neurosurgical technique for treating many neurological and psychiatric disorders such as PD,^{9,19} tremor,^{12,43} dystonia,^{23,58} chronic pain,^{28,42} obsessive-compulsive disorder,^{4,34,38} and depression.³⁶ In contrast to ablative procedures, DBS is reversible and has additional benefits that include stimulation parameter adjustment and programmability. Long-term and follow-up studies have shown that DBS can lead to significant and sustainable improvements in a patient's clinical status.⁴⁴

However, major challenges in DBS are the precise identification of the therapeutic target and delivery of the stimulating electrode to the target. Although direct targeting of the neural structures of interest has been based on brain images,^{21,51} the current use of a 1.5-T MR imaging system for this purpose has limitations. This system cannot provide sufficient resolution and contrast to accurately delineate the target nuclei, including the STN, GPi, and potential targets that have only recently garnered interest such as the internal capsule,^{4,38} zona incerta,⁴¹ and pedunculopontine nucleus.⁴⁰ As a result, many functional neurosurgical centers rely on indirect or intermediate-direct targeting methods when performing DBS surgery.^{1,2,6,8} But indirect targeting methods do not accommodate individual variability in the size, functional segregation, and location of target structures and the specific subregions they contain. It has recently been realized that it is important to identify the subregions of target areas, as they seem to be related to the efficiency and adverse effects of DBS.^{29,35}

The recently emergent higher-field-strength MR imaging systems, including 3- and 7-T MR units, exhibit substantial improvements in image resolution and sensitivity and can be used to directly identify neurosurgical targets such as the STN and GPi.^{17,47,56} The purpose of the present study was to determine whether brain images obtained with 7-T MR imaging are more efficacious than those obtained with 1.5- and 3-T MR imaging in allowing direct visualization of targets for DBS in PD, including the STN and GPi. We also present the first clinical 7-T MR images of a patient with advanced PD before bilateral STN DBS surgery.

Methods

Participant Characteristics

Eleven healthy volunteers with a mean age of 26 years (range 21–30 years) and one 48-year-old patient with PD were recruited for this study. The patient with PD had been treated with antiparkinsonian drugs for the past 8 years; 1 year prior to our study she began to experience intolerable motor fluctuations and dyskinesia while using the medication. The institutional review boards of Gachon University of Medicine and Science and Seoul National University and the Korea Food and Drug Administration approved the procedures of the present study. All study participants provided written informed consent.

Magnetic Resonance Imaging

Three MR imaging units were used: a 7-T research prototype (Magnetom, Siemens), a 3-T system (Verio, Siemens), and a 1.5-T system (Avanto, Siemens). All images were acquired using a conventional 2D gradient echo technique. Image slices were aligned with the line passing through the anterior and posterior commissures of the brain (AC-PC line). For each participant, a 7-T MR imaging coronal section was used to select a reference plan in which the area of the STN was maximized. The distance between the anterior part of the AC and the reference plan was determined and applied to each 1.5- and 3-T MR image so that the coronal slice closest to the 7-T reference slice was obtained.

The specific imaging pulse sequence parameters used are summarized in Table 1. All parameters were adjusted for maximizing the contrast of DBS targets. For 7-T MR imaging, a 7-T, optimized, 8-channel SENSE radiofrequency coil (200 mm in length and 300 mm in diameter) was used to cover the entire brain.¹⁷ Axial, sagittal, and coronal plane views of the STN were acquired for all participants. The coronal view showed good discrimination of the STN and SN and was selected for analysis (Fig. 1). Uniformity correction was performed using a linear model to eliminate bias field distortion of the 7-T MR images.

Computed Tomography Scanning

A CT scanner (Brilliance 64, Philips Medical Systems) was used to obtain immediately postoperative 3D images from the patient with PD. The resolution was $0.47 \times 0.47 \times 1.00$ mm.

Data Analysis

For each participant, the 7-T coronal reference plan was the basis for realigning the 1.5- and 3-T coronal images by using a rigid-body coregistration. A profile (line) vertically intersecting the STN and SN was selected in the 7-T reference image. This profile was applied to the realigned 1.5- and 3-T coronal sections (Vinci 2.0, Max-Planck-Institute). Plots of the normalized MR signal intensity (signal intensity/maximum intensity, 3-pixel averaged) were used to compare the results of 7-, 3-, and 1.5-T MR imaging. A neurologist and an anatomist manually traced the boundary of each structure of interest. A baseline containing the zona incerta and thalamus was determined in the profile. An average of the normalized signal intensity in the profile passing through the baseline, STN, and SN was used for statistical analysis.

To determine the edge detection power, the slope of signal increase between the STN and baseline was calculated. The pixel intensity at the end of baseline and the starting pixel of the STN area in the profile were used for this calculation.

The SNR was calculated in accordance with a Rician distribution of intensity using

$$(S^2 - \sigma^2)^{1/2} / \sigma,$$

where S and σ represent the measured signal (mean) within the regions of interest and noise (standard deviation) outside the brain, respectively.¹¹ Specifically, SNR values were determined for the gray matter areas (in the thalamus) encompassing at least 500 pixels in the coronal reference plane as visualized with 7-T MR imaging as well as those seen with 1.5- and 3-T MR imaging.

We used 1-way ANOVA with least-significant-difference post hoc tests to compare the tissue contrast, slope of signal increase, and SNR among MR images of different field strengths (SPSS, version 15, SPSS, Inc.; Table 2).

Phantom Study

Image distortion, particularly with high-field-strength imaging, is a potential cause for concern in stereotactic procedures. To evaluate the geometrical distortion of 7-T MR imaging, we used a commercial 3D anthropomorphic phantom (CIRS, Inc.) to compare 7-T MR and CT images. The phantom skull was manufactured from an epoxy-based tissue substitute, and the interstitial and surrounding soft tissues were made from a proprietary water-based polymer. The cranial portion of the skull was filled with a matrix of acrylic grid rods (diameter 3.2 mm) spaced 2 cm apart; these covered an area 8×8 cm in the skull base and distances of 8 cm (laterally) and 6 cm (anteroposterior) in the upper skull. The 7-T MR imaging pulse sequence was identical to that used in the human volunteers. A CT scan (Biograph, Siemens) with a resolution of $0.50 \times 0.50 \times 1.25$ mm was obtained. On the basis of the 7-T MR image, the CT image was coregistered using a 6-parameter (x, y, and z rotation and x, y, and z translation) rigid-body transformation (FSL, FM-RIB Analysis Group).^{48,61} The centroid coordinates of 248 points in the rod's coronal cross-section were obtained semi-automatically (Analyzer 9.0, Mayo Clinic). The difference in the distance between centroid coordinates in 7-T MR imaging and those in CT was then compared.⁵

Geometrical Distortions of 7-T MR Imaging

In MR technological terms, geometrical distortions are dependent on bandwidth or, more specifically, the bandwidth/pixel resolution. A larger bandwidth is associated with smaller effects of chemical shift and/or susceptibility and as a consequence with a decrease in the SNR.⁵ We confirmed that the geometrical distortion of 7-T MR imaging at bandwidths ≥ 40 kHz along with commercially offered preinstalled second-order active shimming, compared with CT, lies within a less-than-submillimeter range. Considering our previous reports that the 30-kHz bandwidth optimizes the contrast and SNR of 7-T MR images, 40 kHz is acceptable with less compensation in the SNR.^{15–17} In the present study, we used a bandwidth of 40 kHz, for which the maximum deviation in the phase and frequency encoding directions was 0.78 and 0.42 mm, respectively (Fig. 2). The mean ($\pm$ SD) absolute value of the centroid deviation was 0.12 ± 0.13 mm in the coronal orientation.

Results

Comparisons of 1.5-, 3-, and 7-T MR Imaging

Figure 3 shows images of selected brain areas, including the STN and GPi. These structures are the most widely chosen target nuclei for DBS in PD and were used to compare the images obtained with the 3 different MR imaging field strengths (1.5, 3, and 7 T). Figure 3A shows both original and magnified ($\times 3$) views obtained with 7-T MR imaging. Figure 3B and C are the corresponding images obtained with 3- and 1.5-T MR imaging, respectively. On the 1.5-T MR image, it was difficult to identify the STN and GPi, indicating the inherent difficulty associated with currently available MR imaging methods for direct localization of target nuclei. Images obtained with higher-field-strength MR imaging techniques clearly showed the STN, SN, putamen, GPi, and GPe. Figure 3D shows an image from the Schaltenbrand-Wahren atlas of human brain anatomy, which is the most widely utilized atlas for stereotactic brain surgery.⁴⁵ The STN and GPi area are clearly seen in the coronal section from the Schaltenbrand-Wahren atlas depicting a level 3 mm posterior to the midcommissural point (F.p3). For each of 1.5-, 3-, and 7-T MR imaging methods, Fig. 3E shows plots of normalized MR signal intensities along the profile containing the baseline, STN, and SN.

In displaying averaged normalized signal intensities, Fig. 4 reveals the significance of 7-T over 3- and 1.5-T MR imaging. With 7-T imaging, there were approximately 1.5- and 2-fold improvements in tissue contrast between the baseline and STN over 3- and 1.5-T imaging, respectively ($p < 0.001$ for both comparisons). Intertissue differences of STN and SN did not differ significantly in group comparisons of 7- and 3-T imaging ($p = 0.119$) but showed significance in paired t-test values ($p < 0.05$) representing the interindividual variance. There was almost no difference in signal intensity between the STN and SN on 1.5-T MR imaging. The edge detection power between the STN and baseline was represented by the steepness of the slope of signal increase; the value obtained for 7-T MR imaging was 2 times that for 3-T MR imaging and 4 times that for 1.5-T MR imaging. Finally, 7-T imaging provided a 24% greater SNR than 3-T imaging ($p < 0.05$) and a 58% greater SNR than 1.5-T imaging ($p < 0.001$).

There were significant differences between 3- and 1.5-T MR imaging in terms of tissue contrast ($p < 0.05$) and the slope of signal increase ($p < 0.001$). The difference in the SNR did not quite reach the level of statistical significance ($p = 0.052$).

Our results demonstrate the feasibility of rapid, whole-brain, ultra-high-resolution, 7-T MR imaging using submillimeter voxels. Artifacts were minimal in 7-T MR images, and there were significant improvements in tissue contrast, edge detection, and SNR over 3- and 1.5-T MR images.

Preoperative 7-T MR Imaging of the STN in a Patient With PD

As an example of its clinical applications, Fig. 5 features a 7-T MR image preoperatively obtained from a patient with PD. Although this image was not used for electrode targeting, it was used for postprogramming and evaluation. Figure 5 also includes coronal images obtained preoperatively by using 7-T MR imaging and immediately postoperative by using CT at levels 2 and 4 mm posterior to the midcommissural point; the bilateral STN, SN, GPi, and GPe can be seen. Figure 5C is a merged 7-T MR image and CT image constructed using the mutual information technique, with bilateral electrodes shown in red. The postoperative CT image was used to locate the electrodes and measure their positions. Figure 5D shows that the right electrode was positioned 3.0 mm posterior and 5.8 mm inferior to the midcommissural point, with a coronal angle of 69.1° and a sagittal angle of 63.2° . The left electrode was placed 5.0 mm posterior and 6.4 mm inferior to the midcommissural point, with a coronal angle of 66.7° and a sagittal angle of 64.4° . After bilateral STN DBS surgery, the merged image was used for post-DBS programming.

Discussion

Although the mechanisms by which DBS works are not completely understood, precise localization of the deep brain structures targeted is critical for the procedure to have clinical efficacy.^{10,29,30,37} It is difficult to localize DBS targets because of their small size and deep position where they are surrounded by several vital structures. Moreover, DBS targets exhibit interindividual (including age-related) topographic variations in size, shape, and location.^{7,25,32,50} The STN appears particularly prone to minor variations, as compared with larger targets such as the GPi and thalamus.^{13,20,53,57} These factors increase the difficulty of accurately localizing a target by using only statistical considerations and stereotactic atlases. Therefore, many functional neurosurgical centers use simultaneous multitrack microelectrode recordings to map electrophysiological function and confirm the placement of DBS electrodes.^{1,6,55} A combination of 1.5-T MR imaging and intraoperative microelectrode recording mapping of the STN borders has proven to be the most reliable technique for optimizing targeting of the STN for DBS.²⁷ However, mapping can lengthen the procedural time and, at least theoretically, is associated with an increased risk of

intraparenchymal hemorrhage related to the number of electrode penetrations into the brain.^{1,26,54,55}

Direct Targeting Approach Using MR Imaging

Various image-guided approaches designed to increase the accuracy of DBS target localization have been described,^{27,51,52} and direct visualization and targeting of the DBS targets with MR imaging has been utilized and improved at certain neurosurgical centers.^{3,27,39,51,52} Recent reports of clinical trials in which 3-T MR imaging was used in DBS surgery for PD have shown reliable results with respect to direct targeting;^{47,56} however, the significance of MR images for direct targeting is controversial.^{18,24,49}

We believe that the lack of agreement regarding the use of MR imaging for direct targeting primarily reflects the limitations of conventional MR imaging methods such as 1.5-T MR imaging, which cannot delineate the borders of a target with sufficient contrast and resolution. An option for overcoming such problems when visualizing targets (the STN in particular) is to use the higher-field-strength MR imaging systems that are emerging and have the advantages of a high resolution and an improved SNR as well as an improved contrast-to-noise ratio. As noted above, the importance of identifying the subregions of target areas has recently been realized, as the efficiency and adverse effects of DBS appear to be related to such subregions, including the dorsolateral part of the STN associated with sensorimotor functioning and the anteromedial part of the associative-limbic component.^{34,35}

The number of installed 7-T MR imaging systems is increasing worldwide (with ~ 30 units in 2009).⁴⁶ In the present study, ultra-high-resolution images obtained using 7-T MR systems were shown to be useful for directly visualizing the STN and GPi. Accordingly, 7-T MR imaging is a technique that is potentially applicable to direct targeting approaches in DBS surgery.

Improvements in 7-T MR Imaging

The image resolution and contrast improvements associated with 7-T MR imaging are primarily attributable to the increased strength of the magnetic field used, which enhances the SNR.^{17,63} The higher-field-strength MR imaging systems, in particular, create longer T1 recovery times and shorter T2 and T2* relaxation times in the hydrogen spins.⁶² Therefore, a shorter echo time (TE) was used in 7-T MR imaging to compensate for a shorter T2* while maintaining a similar repetition time (TR), which may have led to less signal loss from magnetization transfer. Because of the higher B1 available in 7-T MR imaging, the shorter echo time was possible without changes in the receiver bandwidth, which makes the SNR directly comparable among the field strengths.⁶³

In general, gradient echo sequences with T2*-weighted images result in the appearance of hypointense (dark) signals within regions of the basal ganglia (STN, GPi, red nucleus, and SN), which are strongly indicative of a high iron concentration.^{14,17,31} Our results with better tissue contrast seem to be the effect of this susceptibility-induced signal difference through shorter T2* relaxation times in 7-T MR imaging.⁵⁹ In addition, by eliminating partial volume effects, small voxel images differentiate adjacent tissues on the basis of differences in contrast.²² Furthermore, the use of an elongated 7-T MR imaging 8-channel SENSE radiofrequency coil with a tight inner diameter size (300 mm) and covering the entire brain (including the midbrain, cerebellum, and brainstem areas) appeared to be an additionally important factor for facilitating homogeneous image intensity and higher SNR.¹⁷

Overall, compared with 1.5- and 3-T MR imaging systems, the improvements associated with a higher magnetic field include greater spatial resolution with high contrast in a shorter acquisition time.

Possible Applications of 7-T MR Imaging

We envision that other neurosurgical procedures, including gene therapy, cellular transplantation, and radiosurgery, could also benefit from the improved visualization of target structures possible with 7-T MR imaging. The enhanced spatial resolution associated with this technique may also help in the identification of subnuclei within target structures; of particular importance in this regard is the delineation of adjacent eloquent structures that must be avoided. Structures to avoid can include adjacent functional territories within the target nuclei and axonal projections, whose electrode penetration or stimulation may produce functional deficits.^{29,44}

Technical Challenges of 7-T MR Imaging

Although results of the present study are encouraging, direct targeting continues to pose a number of technical challenges. We have confirmed that with commercially offered preinstalled second-order active shimming, the geometrical distortion of 7-T MR imaging is comparable with that of 1.5- and 3-T MR imaging.^{33,60} However, the identification of subject- and motion-dependent distortions as well as the application of other sequences (spin echo, 3D, and so forth) for improving the distortions would be challenging. The 7-T head coil used in the present study was not designed for the stereotactic headframe (Leksell, Compass, Brown-Roberts-Wells, Cosman-Roberts-Wells, and so forth) to fit, and geometrical distortion associated with this frame would need to be addressed in future studies.

Despite the expected MR imaging geometrical distortion, the accuracy of MR images obtained with stereotactic systems will depend on physical space registration accuracy. The practical issues associated with using 7-T MR imaging, including brain shift and the mechanical limitations of current stereotactic methods, will be encountered in the operating room. Accordingly, further research and developments are required to overcome the practical issues associated with the use of 7-T MR images for DBS surgery in patients with advanced PD.

Conclusions

In the present study, we have demonstrated that submillimeter-range, ultra-high-resolution images (0.25×0.25 mm) of the midbrain area can be obtained with 7-T MR imaging. Compared with 1.5- and 3-T MR imaging, the significantly improved tissue contrast associated with 7-T MR imaging allowed for enhanced edge detection. The improved images enabled distinct visualization of structures targeted in the DBS management of PD, including the STN and GPi. Overcoming the technical issues and validating the targeting techniques, in terms of improved visualization and direct targeting of DBS electrodes, will lead to reductions in surgical time and the need to perform extensive electrophysiological mapping while also increasing the precision of targeting in DBS surgery and other therapeutic interventions. Furthermore, improved visualization of brain targets may lead to developments in other applications currently in use with stereotactic and functional neurosurgery.

Abbreviations used in this paper

AC-PC	anterior commissure–posterior commissure
DBS	deep brain stimulation
GPe	external globus pallidus
GPI	internal globus pallidus
PD	Parkinson disease
SENSE	sensitivity encoding
SN	substantia nigra
SNR	signal-to-noise ratio
STN	subthalamic nucleus

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Fig. 1. Axial (A), sagittal (B), and coronal (C) views of the STN and surrounding structures in a study participant. The coordinates for the center of the right STN are 4 mm inferior, 2 mm posterior, and 10 mm lateral to the midcommissural point (AC-PC length = 25.5 mm).

Fig. 2.

Graph showing the distribution of geometrical distortions of 7-T MR imaging in both the frequency and phase-encoding directions, as compared with CT. For the 248 points the mean centroid difference was 0.12 ± 0.13 mm, and the maximum deviation in the phase-encoding direction was 0.78 mm.

Fig. 3.

Coronal images of 2 important target nuclei, the STN and GPi, obtained using 3 different imaging modalities: 1.5-T (A), 3-T (B), and 7-T MR imaging (C). A coronal section (D) from the Schaltenbrand-Wahren brain atlas at the level 3 mm posterior to the midcommissural point (F.p3) is shown as a reference. Graph (E) depicting normalized MR signal intensities along the profiles in the STN area obtained with 1.5-, 3-, and 7-T MR imaging. Image in D reproduced with permission from Schaltenbrand G, Wahren W: *Atlas for Stereotaxy of the Human Brain*, ed 2, Thieme, 1977.

Fig. 4. Graph of averages of normalized signal intensity demonstrating the power of 7-T MR imaging over 3- and 1.5-T MR imaging. All averages associated with 7-T MR imaging showed significantly greater tissue contrast, slope of signal increase, and SNR. MRI = MR imaging.

Fig. 5.

Coronal 7-T MR images obtained from a 48-year-old woman with PD treated with antiparkinsonian drugs for the past 8 years. Preoperative coronal image (**A**) obtained at the level of 2 mm and 4 mm posterior to the midcommissural point showing the STN, SN, GPi, and GPe. Coronal CT scan (**B**) at the same level obtained immediately postoperative. A merged preoperative 7-T MR image and immediately postoperative CT image (**C**) constructed using the mutual information technique, with bilateral electrodes shown in red. Postoperative CT image (**D**) was used to locate the electrodes and measure their positions. The right electrode was 3.0 mm posterior and 5.8 mm inferior to the midcommissural point, with a coronal angle of 69.1° and a sagittal angle of 63.2°. The left electrode was 5.0 mm posterior and 6.4 mm inferior to the midcommissural point, with a coronal angle of 66.7° and a sagittal angle of 64.4°.

TABLE 1

Two-dimensional gradient echo MR imaging pulse sequence parameters *

Parameter	7-T MRI	3-T MRI	1.5-T MRI
TR (msec)	500	625	750
TE (msec)	17.8	30	30
flip angle (°)	30	30	30
FOV (mm)	176 × 176	192 × 192	192 × 192
matrix	704 × 704	384 × 384	384 × 384
resolution (mm)	0.25 × 0.25	0.5 × 0.5	0.5 × 0.5
slice thickness (mm)	2	2	2
NEX	1	1	1
bandwidth (kHz)	40	40	40
scan time (min)	5:54	4:02	4:50

* FOV = field of view; MRI = MR imaging; NEX = number of excitations.

TABLE 2

Post-hoc ANOVA

Dependent Variable	Significance	F	Total Significance
tissue contrast (baseline vs STN)		13.659	0.000
7 T			
3 T	0.003		
1.5 T	0.000		
3 T			
7 T	0.003		
1.5 T	0.066		
1.5 T			
7 T	0.000		
3 T	0.066		
tissue contrast (STN vs SN)		15.985	0.000
7 T			
3 T	0.119		
1.5 T	0.000		
3 T			
7 T	0.119		
1.5 T	0.001		
1.5 T			
7 T	0.000		
3 T	0.001		
signal increase slope (baseline vs STN)		12.989	0.000
7 T			
3 T	0.001		
1.5 T	0.000		
3 T			
7 T	0.001		
1.5 T	0.254		
1.5 T			
7 T	0.000		
3 T	0.254		
SNR		8.948	0.001
7 T			
3 T	0.035		
1.5 T	0.000		
3 T			
7 T	0.035		

Dependent Variable	Significance	F	Total Significance
1.5 T	0.052		
1.5 T			
7 T	0.000		
3 T	0.052		