Three-dimensional SPACE fluid-attenuated inversion recovery at 3 T to improve subthalamic nucleus lead placement for deep brain stimulation in Parkinson's disease: from preclinical to clinical studies

*Suhan Senova, MD, MSc,^{1,4,5} Koichi Hosomi, MD, PhD,^{1,5,6} Jean-Marc Gurruchaga, MD,^{1,4,5} Gaëtane Gouello, MD,^{1,4,5} Naoufel Ouerchefani, MD,^{1,4,5} Yara Beaugendre, MD,¹ Hélène Lepetit, PhD,^{1,4,5} Jean-Pascal Lefaucheur, MD, PhD,^{3,5} Romina Aron Badin, PhD,⁶ Julien Dauguet, PhD,⁶ Caroline Jan, PhD,⁶ Philippe Hantraye, PhD,⁶ Pierre Brugières, MD,^{2,4,5,7} and Stéphane Palfi, MD, PhD^{1,4,5}

¹Service de Neurochirurgie, ²Service de Neuroradiologie, and ³Service des Explorations Fonctionnelles, Assistance Publique des Hôpitaux de Paris, Hôpital H. Mondor, DHU PePsy; ⁴Inserm U955 Team 14; ⁵Faculté de Médecine, Université Paris Est, Créteil; ⁶DSV/I2BM/MIRCen/Laboratory of Neurodegenerative Diseases, CNRS, Commissariat à l'Energie Atomique, Fontenay-aux-Roses; and ⁷DSV/I2BM/Neurospin/UNIACT, Commissariat à l'Energie Atomique, Saclay, France

OBJECTIVE Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is a well-established therapy for motor symptoms in patients with pharmacoresistant Parkinson's disease (PD). However, the procedure, which requires multimodal perioperative exploration such as imaging, electrophysiology, or clinical examination during macrostimulation to secure lead positioning, remains challenging because the STN cannot be reliably visualized using the gold standard, T2-weighted imaging (T2WI) at 1.5 T. Thus, there is a need to improve imaging tools to better visualize the STN, optimize DBS lead implantation, and enlarge DBS diffusion.

METHODS Gradient-echo sequences such as those used in T2WI suffer from higher distortions at higher magnetic fields than spin-echo sequences. First, a spin-echo 3D SPACE (sampling perfection with application-optimized contrasts using different flip angle evolutions) FLAIR sequence at 3 T was designed, validated histologically in 2 nonhuman primates, and applied to 10 patients with PD; their data were clinically compared in a double-blind manner with those of a control group of 10 other patients with PD in whom STN targeting was performed using T2WI.

RESULTS Overlap between the nonhuman primate STNs segmented on 3D-histological and on 3D-SPACE-FLAIR volumes was high for the 3 most anterior quarters (mean $\pm$ SD) Dice scores 0.73 ± 0.11 , 0.74 ± 0.06 , and 0.60 ± 0.09 . STN limits determined by the 3D-SPACE-FLAIR sequence were more consistent with electrophysiological edges than those determined by T2WI (0.9 vs 1.4 mm, respectively). The imaging contrast of the STN on the 3D-SPACE-FLAIR sequence was 4 times higher ($p < 0.05$). Improvement in the Unified Parkinson's Disease Rating Scale Part III score (off medication, on stimulation) 12 months after the operation was higher for patients who underwent 3D-SPACE-FLAIR-guided implantation than for those in whom T2WI was used (62.2% vs 43.6%, respectively; $p < 0.05$). The total electrical energy delivered decreased by 36.3% with the 3D-SPACE-FLAIR sequence ($p < 0.05$).

CONCLUSIONS 3D-SPACE-FLAIR sequences at 3 T improved STN lead placement under stereotactic conditions, improved the clinical outcome of patients with PD, and increased the benefit/risk ratio of STN-DBS surgery.

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KEY WORDS anatomical MRI; Parkinson's disease; deep brain stimulation; subthalamic nucleus; nonhuman primate; translational study; functional neurosurgery

ABBREVIATIONS DBS = deep brain stimulation; eSTN = electrophysiologically identified subthalamic nucleus; H&Y = Hoehn and Yahr; LEDD = levodopa equivalent daily dose; M12 = month 12 after implantation; NHP = nonhuman primate; PD = Parkinson's disease; SPACE = sampling perfection with application-optimized contrasts using different flip angle evolutions; STN = subthalamic nucleus; TEED = total electrical energy delivered; T1WI = T1-weighted imaging; T2WI = T2-weighted imaging; UPDRS = Unified Parkinson's Disease Rating Scale.

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*Drs. Senova and Hosomi contributed equally to this work.

DEEP brain stimulation (DBS) of the subthalamic nucleus (STN) has proven to be an efficient therapy for motor symptoms in patients with pharmacoresistant Parkinson's disease (PD).² However, the procedure remains challenging because the full STN cannot be reliably visualized with 1.5- or 3-T MRI scanners in nonhuman primates (NHPs) or in human patients with PD. DBS requires multimodal perioperative explorations, including imaging, electrophysiological recordings along several trajectories, and/or clinical examination of the awake patient during macrostimulation. The surgical procedure to implant DBS electrodes could be safer and faster and provide better clinical benefit if new MRI sequences were developed.

The STN is a small nucleus that measures 20–30 mm.^{3,25,31} Targeting of the STN is currently done stereotactically, which implies that the STN can be located from outside of the skull. Help from an anatomical atlas may be limited because of intersubject variations of such a small and deep brain structure.^{4,31,40} To minimize electrophysiological trajectories to avoid potential brain-related injuries and adverse effects caused by chronic electrical stimulation of neural structures outside of the STN target or of the associative and limbic subterritories of the STN, it is important to optimize the target coordinate using direct visualization of the STN and segmentation relative to the surrounding structures.²⁰

The imaging gold standard for stereotactic STN targeting is T2-weighted imaging (T2WI) at 1.5 T.¹¹ Even higher-magnetic-field MRI could be adequate for direct visualization of small brain nuclei, enabling higher contrast between gray and white matter. However, MR images at 3 or 7 T may be altered by higher spatial distortions.³ Thus, stereotactic targeting of the STN in patients with PD by direct visualization with ultra-high-field MRI with 3- or 7-T MR units may not be optimal. Furthermore, even at 7 T, the STN of NHPs cannot be delineated without a special contrast medium, such as the ultrasmall superparamagnetic iron oxide.³²

New spin-echo sequences for obtaining volumetric data sets with a great contrast-to-noise ratio in organs other than the brain have been proposed.⁹ Such sequences, termed sampling perfection with application-optimized contrasts using different flip angle evolutions (SPACE,

Siemens), use nonspatially selective refocusing pulses with short-echo spacing to achieve extended echo trains and subsequent volumetric acquisition of a single slab of thin-slice sections. Such turbo spin echo sequences offer the advantages of being less sensitive to susceptibility artifacts and less sensitive to geometrical distortion artifacts than T2WI sequences at 3 T.²⁴ With such a sequence, a higher magnetic field may be used to directly visualize the STN and stereotactically target it accurately and reliably.

The goal of our study was to evaluate preclinically and clinically a 3D-SPACE-FLAIR sequence at 3 T. It was optimized in NHPs and validated after their death using 3D reconstruction of the corresponding brain volume and in vivo through electrophysiological recordings. Then, our translational approach led us to use and validate it in a cohort of patients with PD.

Methods

Preclinical Part

Animals

Experimentation was performed in accordance with the international directive for Animal Welfare Assurance, Office of Laboratory Animal Welfare Number A5826-01, and validated by the local ethical committee 44 (Commissariat à l'Energie Atomique TEA Direction des Sciences du Vivant Ile de France). The veterinarians underwent nationally recognized training for NHP handling and care. Two 5-year-old macaques (*Macaca mulatta*) were included in the study.

MR Image Acquisition in NHPs

The macaques were anesthetized with intramuscular ketamine and xylazine (15 and 1.5 mg/kg, respectively, every 45 minutes). Their heads were fixed in an MRI-compatible stereotactic frame, and MR image acquisition was performed using a clinical 3-T MR scanner (Siemens VERIO) using a human birdcage coil. Three sequences in each monkey were acquired (Table 1).

Surgical Procedures (NHPs)

Each NHP was given general anesthesia and placed in a stereotactic frame. A microelectrode passing through a cannula was lowered from the cortical surface down to the

TABLE 1. MRI parameters

Sequence	No. of Slices	FOV (mm)	Matrix	Slice Thickness (mm)	TR*	TE*	TI*	Band Width (Hz/pixel)	No. of Excitations
NHPs									
T1WI	40 sagittal	154 × 154	192 × 192	0.8	2200	3.18	900	130	1
T2WI	120 coronal	134 × 100	192 × 144	0.7	9500	60		120	1
3D-S-F	144 coronal	192 × 192	256 × 256	0.75	6000	649	2000	698	4
Patients w/ PD									
T1WI	208 sagittal	270 × 270	256 × 256	1	2400	3.69	1000	179	1
T2WI	32 coronal	208 × 256	208 × 256	2	45	40		199	1
3D-S-F	160 sagittal	250 × 250	512 × 512	1	6000	372	2100	781	1

FOV = field of view; 3D-S-F = 3D-SPACE-FLAIR.

* Measurement in milliseconds.

thalamus, zona incerta, STN, substantia nigra, and capsula interna. Targeting of the STN was done by direct visualization of the STN on preoperative 3D-SPACE-FLAIR images, and the appropriate trajectory was confirmed intraoperatively by recording the electrophysiological patterns of cerebral structures penetrated by the microTargeting electrodes (FHC) (impedance 0.8–1.5 M Ω at 1 kHz) (Fig. 1). Multiunit activity was amplified and recorded through a 100- to 3000-Hz band pass by using a Medtronic LeadPoint system. The penetration of the cannula was stopped at the entrance of the STN (Fig. 1).

3D Histological Block (NHPs)

The procedure for obtaining the whole-brain histological volume has been previously described.⁵ It was made from 800 histological slices (each 40 μ m thick). The contour of the STN on each slice of the histological volume was traced manually, and the histological STN volume was built by direct stacking (Fig. 1G). The STN segmentation was made with Anatomist software (CEA-IPBM).

Comparison of Histology and the 3D-SPACE-FLAIR Sequence (NHPs)

We estimated the overlap of the 2 STNs segmented on the histological volume and on the 3D-SPACE-FLAIR volume. The histological volume was registered with the *in vivo* T1-weighted MRI volume using a composition of 3D rigid, affine transformations and 3D cubic B-spline transformation.^{5,15} This transformation was applied to the histological STN volume. Spatial coregistration between the histological STN volume and the 3D-SPACE-FLAIR volume was performed with SPM8 (University College London).

The Dice score quantifies the intersection between 2 regions.⁸ The overlap is considered to be good for regions at which the Dice score is superior or equal to 0.6.¹² Using this score, we evaluated the overlap between the segmentation of the STN derived from histology and the segmentation of the STN made on the 3D-SPACE-FLAIR volume slices (3D-SPACE-FLAIR-STN) (Fig. 1G and H). The STNs were segmented on the 3D-SPACE-FLAIR volume slices by an expert neurosurgeon in DBS surgeries who was blinded to the STN segmentation on the histological volume.

Clinical Part

Patients

Twenty patients with PD (mean 64.1 years old) who underwent bilateral STN-DBS guided with the 3D-SPACE-FLAIR sequence (FLAIR group; *n* = 10) or the gold standard T2WI (control group; *n* = 10) were enrolled prospectively between May 2010 and June 2012 according to technical and ethical standards validated by the Henri Mondor Hospital.

MR Acquisitions in Patients With PD

Up to 2 MRI acquisitions were performed depending on the patient group. The first MRI acquisition was performed with a whole-body 3-T MR scanner (Siemens VERIO) using a 12-channel coil on the day before the opera-

tion for the FLAIR group (Fig. 2 left); the acquisition took 7 minutes. The second acquisition was performed with a whole-body 1.5-T MR scanner (Siemens AVANTO) using a monochannel Tx/Rx coil on the day of the operation for both groups, just after the fixation of a stereotactic frame and before the operation (Fig. 2 right, Table 1); T1- and T2*-weighted images took 4 minutes each to obtain.

Surgical Procedures (Patients With PD)

Each patient underwent surgery performed by the same expert neurosurgeon (S.P.). To implant DBS lead electrodes in the dorsolateral STN, patients with PD were given general anesthesia, and the depth of anesthesia was monitored with a bispectral index sensor. The patients were equipped with a Leksell Type G stereotactic frame (Elekta). MRI was performed. All MR images were imported in a FrameLink workstation (Medtronic), and the 3D-SPACE-FLAIR or T2-weighted image was fused to

FIG. 1. Monkey STN. **A:** Histological STN (dashed oval) and the cannula (arrow). **B:** Electrophysiological targeting. CI = capsula interna; SN = substantia nigra; Th = thalamus; ZI = zona incerta. **C–E:** T1-weighted, T2-weighted, and 3D-SPACE-FLAIR MR images, respectively. **F:** Overlap of the 3D-SPACE-FLAIR and histological STN slices (red circles). **G:** 3D histological (green areas) and 3D-SPACE-FLAIR (red areas) STN. **H:** Corresponding Dice scores. Figure is available in color online only.

FIG. 2. STN visualization in patients with PD on 3D-SPACE-FLAIR imaging (**left**) and T2WI (**right**) with coronal, axial, and sagittal views.

the T1-weighted image. The surgical targets were planned by using the 3D-SPACE-FLAIR sequence (for the FLAIR group) or T2WI (for the control group) according to direct and red nucleus–based targeting.¹ The STN was identified as a hypointense almond-shaped structure located anterolateral to the red nucleus on coronal, axial, and sagittal planes. The target was defined with the x coordinate 3 mm lateral to the lateral border of the red nucleus, the y coordinate the same as that of the anterior border of the red nucleus, and the z coordinate 2 mm inferior to the superior border of the red nucleus. The coordinate of the planned target was located 11–13 mm lateral to the midline, 1–3 mm posterior to the midcommissural point, and 3–5 mm inferior to the midcommissural point.

Electrophysiological recording was performed using 2 simultaneously lowered microTargeting microelectrodes, a central one and a posterior one. Multiunit activity was amplified and recorded through a 100- to 3000-Hz band pass with a Medtronic LeadPoint system. Recorded signals were analyzed with “turns-amplitude analysis” software implemented in LeadPoint.^{29,30} This method quantifies the number of changes in polarity of the signal (turns) and measures the absolute amplitude value between each turn at each millimeter of the track of the microelectrode recorded during the descending phase of the electrode. The numbers of passes of electrodes for the FLAIR and control groups were not different.

Entry into and exit from the STN were visually detected as a frank increase and frank decrease, respectively, in signal amplitude from the background activity and in the number of turns (electrophysiologically identified STN [eSTN]) caused by the density of hyperactive cells within the STN of patients with PD.

Postoperative confirmation of electrode position was made by fusion of preoperative MR images and CT images acquired 5 days after surgery. After surgery, the neurologist who specialized in DBS management optimized the stimulation parameters and medications.

Comparison of 3D-SPACE-FLAIR Imaging and T2WI (Patients With PD)

Spatial coregistration between the 2 sequences was

performed with SPM8. We decided to compare the STN contrast offered by 3D-SPACE-FLAIR imaging and T2WI by delineating the contour of the STN on the 3D-SPACE-FLAIR coronal plane 2 mm posterior to the midcommissural point using Anatomist software. The coronal plane indeed offered the best direct visualization of the STN.

Because the contrast of the STN determined by using MRI (MRI-STN) varied relative to the surrounding structures, we discretized the contour of the MRI-STN by dividing it in elementary segments 6 pixels long (Fig. 3 left). We defined the contrast of the contour of the MRI-STN as the mean of contrasts of all elementary segments. Along and 1 pixel inside (outside) the STN of an elementary segment i , the region is called STN_{int_i} (STN_{ext_i}). The contrast of an elementary segment i is as follows:

$$C_i = \frac{|\text{signal}(STN_{int_i}) - \text{signal}(STN_{ext_i})|}{|\text{signal}(STN_{int_i}) + \text{signal}(STN_{ext_i})|}$$

We measured this contrast in the FLAIR group for the STN segmented on both 3D-SPACE-FLAIR imaging (3D-SPACE-FLAIR-STN) and T2WI (T2WI-STN).

FIG. 3. **Left:** Manual segmentation of the STN on a 3D-SPACE-FLAIR image (coronal view). The **inset** shows a discretization of the internal and external STN contours. **Right:** Contrast of the contours of the STN on 3D-SPACE-FLAIR imaging and T2WI in the coronal view. Figure is available in color online only. *Star* = statistically significant.

FIG. 4. Electrophysiological targeting of STN in patients with PD with multiunit recordings (**A**) and turns-amplitude analysis (**B**). Sagittal (**C**) and coronal oblique (**D**) views of a CT–3D-SPACE-FLAIR fusion image along a trajectory. **E**: The edge of the *white line*, which corresponds to a definitive lead, indicates a tip of the lead (**T**). The dorsal (**D**) and ventral (**V**) limits of the STN can be seen on the CT–3D-SPACE-FLAIR fusion image. **F**: Coronal oblique view of a 3D-SPACE-FLAIR image with the same orientation as that in panel **D**. The *dotted line* indicates the area corresponding to panel **E**. Entrance and exit points of the STN along the trajectory of the electrode: *blue line*, STN identified on 3D-SPACE-FLAIR imaging (**G**) or T2WI (**H**); *red line*, optimal contact; *orange line*, eSTN. Figure is available in color online only.

Comparison of MRI-STN and eSTN

MRI-STN entry and exit points were identified with both 3D-SPACE-FLAIR imaging and T2WI. To identify eSTN entry and exit in the MR image, the postoperative CT image that showed definitive lead electrodes was superimposed on the MR image using the coregistration function of SPM8 (Fig. 4C–F). Coordinates of eSTN entry and exit points along the trajectory were identified on the 3D CT–MRI fusion image (3D-SPACE-FLAIR-STN or T2WI-STN). Optimal contact was the latest active contact(s) used clinically.

Comparison of Clinical Outcomes

We first compared various preimplantation scores, including the Unified Parkinson's Disease Rating Scale Part III (UPDRS III) (on and off medication), the UPDRS IV, the Hoehn and Yahr (H&Y) scale (on and off medication), and the levodopa equivalent daily dose (LEDD),^{16,32,34} with the scores 12 months after implantation (M12). Then, the

clinical efficacy of STN-DBS when using 3D-SPACE-FLAIR imaging for the FLAIR group, or T2WI for the control group, was compared between the FLAIR and control groups as far as UPDRS III (on and off medication), UPDRS IV, H&Y scale (on and off medication), LEDD, and total electrical energy delivered (TEED)¹⁹ were concerned. All evaluations were double-blind relative to the sequence that was used for implantation by an expert neurologist.

Statistical Analysis

Differences in contrast values between the groups were evaluated by a paired t-test. A 2-sample t-test was used to evaluate the differences in position of MRI-STN and eSTN. Differences in UPDRS III, UPDRS IV, H&Y scale (on and off medication), and LEDD scores before implantation and at M12 were evaluated by a paired t-test. Differences in UPDRS III, UPDRS IV, H&Y scale, LEDD, and TEED scores between the groups were evaluated by

a 2-sample t-test. Findings with a p value of < 0.05 were considered statistically significant.

Results

Comparison of Histology and 3D-SPACE-FLAIR Imaging (NHPs)

For each NHP, the histological volume of the whole brain was built. The STNs of 2 monkeys were found to have a classical ovoid shape with a mean ($\pm$ SD) volume of $14.9 \pm 1.5 \text{ mm}^3$ ($n = 4$) (Fig. 1G). The trace of the cannula used for electrophysiological recording was located above the STN, confirming the correct targeting of the STN when using 3D-SPACE-FLAIR imaging in NHPs (Fig. 1A).

On 3D-SPACE-FLAIR coronal slices, the STN was identified on each hemisphere as a deep brain almond-shaped hyposignal bearing sharp visual contrast with surrounding structures (Fig. 1E). STNs could not be seen with T1-weighted imaging (T1WI) or T2WI (Fig. 1C and D).

For overlap quantification between the histologically identified STN and the 3D-SPACE-FLAIR-STN ($n = 4$), mean Dice scores from the most anterior to the most posterior slice were 0.73 ± 0.11 , 0.74 ± 0.06 , 0.60 ± 0.09 , and 0.42 ± 0.10 (Fig. 1G and H).

Comparison of 3D-SPACE-FLAIR Imaging and T2WI (Patients With PD)

The contrast between the STN and its surrounding structures on 3D-SPACE-FLAIR imaging was higher than that on T2WI (0.085 ± 0.023 vs 0.023 ± 0.009 , respectively; $p < 0.001$) (Fig. 3 right).

Comparison of MRI-STN and eSTN

The mean differences between the limits of the 3D-SPACE-FLAIR-STN and eSTN were 0.93 ± 0.61 and $0.84 \pm 0.66 \text{ mm}$, respectively, in the dorsal and ventral limits. The differences between the limits of T2WI-STN and eSTN were 1.51 ± 0.93 and $1.36 \pm 0.88 \text{ mm}$, respectively, in the dorsal and ventral limits (Fig. 4G and H). The discrepancies between the MRI-STN and eSTN in both limits were significantly smaller in the FLAIR group than in the control group ($p < 0.04$). Contact 2 (counting bottom-up from 0 to 3), which corresponded to the dorsal portion of the STN, was mostly selected. The total number of recording trajectories per STN did not differ significantly ($p = 0.12$) between the FLAIR group ($n = 2.4 \pm 0.5$) and the control group ($n = 2.1 \pm 0.22$).

Clinical Outcome

The FLAIR and control groups did not differ statistically in their clinical characteristics before the surgical DBS procedure. UPDRS III (off medication, on stimulation), UPDRS IV, LEDD, and H&Y scale (off medication) scores were significantly lower at M12 than at baseline in both groups (Table 2).

At M12, relative to baseline, the FLAIR group experienced a significant larger decrease in the UPDRS III score (off medication, on stimulation) ($62.2\% \pm 18.2\%$ vs $43.6\% \pm 16.3\%$, respectively; $p = 0.035$) and a significant lower

TABLE 2. Clinical scale scores at baseline and follow-up*

Score	Condition	FLAIR Group	Control Group
Baseline			
UPDRS III	Off medication	37.6 (10.5)	38.4 (8.5)
	On medication	10 (3.4)	13.9 (5.1)
UPDRS IV		9.8 (2.6)	9.2 (2.9)
LEDD		1393 (568.8)	1468.7 (558.9)
H&Y scale	Off medication	3.5 (0.7)	3.6 (0.7)
	On medication	1.3 (0.6)	1.5 (0.7)
Follow-up			
UPDRS III	Off medication, on stimulation	13.5 (6.0)†	20.8 (4.8)†
	On medication, on stimulation	10.3 (2.4)	17 (5.8)
UPDRS IV		3.5 (2.5)†	2.5 (2.5)†
LEDD		674.2 (331.3)†	586.3 (272.2)†
H&Y scale	Off medication, on stimulation	2.6 (1.1)†	2.3 (0.9)†
	On medication, on stimulation	1.5 (1.1)	1.3 (0.7)

* Data are presented as the mean (SD).

† Significant change compared to baseline.

TEED (60.4 ± 25.1 vs $94.8 \pm 29.1 \text{ } \mu\text{W}$, respectively; $p < 0.001$) than the control group.

Discussion

This translational research showed that the 3D-SPACE-FLAIR sequence at 3 T enhanced direct visualization of the STN, and there was a significant increase of contrast relative to surrounding structures in both NHPs and patients with PD over that in the gold standard T2WI.

To our knowledge, this is the first study with 3D histological validation of a 3-T MRI sequence aimed at direct visualization of the STN of NHPs, which constituted a key primary preclinical validation before its use in patients with PD.

A 3-T MRI sequence for direct visualization of the STN was proposed in only 1 other study in NHPs.³ However, that study involved the use of a contrast agent that has not yet been validated for use in patients with PD. In addition, the whole procedure for direct visualization of the STN with 3-T MRI (3D-SPACE-FLAIR imaging) in NHPs took 45 minutes, whereas the 3D-SPACE-FLAIR imaging method we report takes 28 minutes. There is a critical need to improve STN targeting in NHPs when administering viral vector or pharmacological injections into such a small structure.³⁸ Moreover, the 3-T imaging scanner is also a tool that can be used in NHPs and in patients with PD; thus, common procedures may first be developed with and assessed in experimental animals before being translated successfully to use in patients.

This 3D-SPACE-FLAIR sequence was validated in patients with PD as an efficient sequence for direct visualization of the STN. First, this new sequence was compared with a gold-standard T2WI sequence. It increased the contrast between the STN and its surrounding struc-

tures, which is essential for STN segmentation and targeting by neurosurgeons.³¹ Moreover, the 3D-SPACE-FLAIR sequence had a higher spatial resolution than the T2WI sequence. Second, on average, we found 0.9- and 1.4-mm discrepancies for entrance and exit, respectively, in the STN along the trajectory of the stimulation electrode between eSTN and the STN segmented on 3D-SPACE-FLAIR imaging and T2WI, respectively (Fig. 4G and H); 0.9 mm was a satisfying match because stimulation electrodes are made of 4 contacts that are 1.5 mm long. Third, we found a significant improvement in UPDRS III scores using 3D-SPACE-FLAIR imaging over those when using a T2WI sequence to implant the DBS electrodes into the STN. In fact, the UPDRS III scores (off medication, on stimulation) were significantly improved by 62.2% from baseline to M12 in the FLAIR group versus a 43.6% improvement in the control group. Two meta-analyses found average improvements in the UPDRS III score (off medication and on stimulation at M12 vs off medication at baseline) of 54.3% and 52%.^{18,36} Six randomized controlled studies that compared bilateral STN-DBS with other treatments for PD showed UPDRS III improvements that ranged from 25% to 50%.^{7,13,22,23,27,39} Thus, when targeting the STN with a combination of electrophysiological recordings and T2WI only, without clinical tests and with the patients having undergone general anesthesia for their comfort, we achieved clinical results comparable to those in the literature. The same surgical procedure using 3D-SPACE-FLAIR imaging could significantly improve our clinical outcomes to well above the average values found in the literature. Recently, 1 study found a level of improvement of 64%.³⁷ Not only did the authors acknowledge that their inclusion criteria may have been more restrictive than those of previous studies, but they also performed surgery after local anesthesia was administered to the patients, and clinical tests were performed during the surgery. Moreover, they did not reveal their stimulation parameters, whereas we were able to demonstrate a significant reduction of TEED when using 3D-SPACE-FLAIR imaging, which may enable slower battery consumption. A lower TEED also means a smaller volume of diffusion of the electrical field and therefore potentially fewer adverse events. Even if parameters such as voltage, pulse width, and frequency were not different between the FLAIR and T2WI groups, impedance, which is the denominator in the mathematical formula for TEED,¹⁹ was significantly higher in the FLAIR group (1157 ohms) than in the T2WI group (907 ohms) ($p = 0.003$), and as a consequence, the TEED was significantly lower for the FLAIR group. This higher impedance in the FLAIR group may indicate that neural density was higher where the active contact was located when targeting with 3D-SPACE-FLAIR imaging than with T2WI.²⁶ All these data may indicate that active contact was located in a more suitable area of the STN when targeting it with 3D-SPACE-FLAIR imaging than when targeting it with T2WI.

Conventional sequences enable direct visualization of some parts of the STN but with poor contrast with surrounding structures. Moreover, the most anterior part of the STN was hypointense on gold-standard T2WI sequences, whereas the posterior part is not visible in most cases, and it is precisely this posterior part of the STN that

is targeted for the treatment of motor symptoms in patients with PD.¹⁰ Hence, the 3D-SPACE-FLAIR sequence enabled better contrast with surrounding structures than T2WI for the territory of the STN that is targeted for DBS. An improvement in contrast with the 3D-SPACE-FLAIR sequence may reduce the severity of adverse effects caused by the stimulation of nonmotor territories of the STN or neighboring structures.

Higher magnetic fields yield better contrast. T2WI is the gold standard for STN imaging at 1.5 T.¹¹ However, T2WI may be altered by higher spatial distortions at higher magnetic fields.³ The 3D-SPACE-FLAIR sequence at 3 T provided a good delineation of STN in clinical-compatible acquisition-time durations, because it is less sensitive to susceptibility artifacts and less sensitive to geometrical distortion artifacts than T2WI sequences at 3 T, and it constitutes convenient imaging for stereotactic procedures at 3 T.²⁴ Potential geometric distortions at 3 T were evaluated as minimal by comparison with NHP histology. It is hypothesized that contrast of the STN relative to surrounding structures is a result of iron-concentration specificities of the basal ganglia and that the T2 effect has to be exploited. Yet, we demonstrated here that the 3D-SPACE-FLAIR sequence, which involves both T2 and T1 effects, enabled better contrast of the STN than T2WI. Thus, the T1 effect may also account for STN contrast and should be studied further. We decided to use the 3D-SPACE-FLAIR sequence, not the more common 2D-FLAIR sequence, to obtain better spatial resolution and fewer artifacts, because the 2D-FLAIR sequence suffers from artifacts caused by cerebrospinal fluid flow.

The 3D-SPACE-FLAIR sequence has been used during epilepsy surgery³⁵ and acoustic neuroma imaging¹⁷ but has never been described at 3 T for the targeting of a deep brain structure under stereotactic conditions, and it has not been histologically validated.

Other imaging techniques that challenged T2WI by enabling better visualization were developed recently, but none of these techniques have yet been validated by histology.²⁸ In the case of diffusion tensor imaging, it is known that variation in the choice of fraction anisotropy, for instance, may affect considerably the nature of the reconstruction, especially when compared with histological reconstruction of fiber tracts.⁶ Therefore, we preferred to compare 3D-SPACE-FLAIR imaging with the standard T2WI, which has long been used by most teams and was used in most of the clinical series against which we compared our study.

Conclusions

Our study contributes to improvement in the accuracy of STN targeting for PD and reduction of the complexity of this surgery. It may help DBS procedures when the patient has undergone general or local anesthesia. Additional prospective clinical studies are necessary to validate our clinical findings, and the potential reduction in the severity of adverse events related to stimulation remains an open question.

This new imaging method could help the extension of DBS lead implantation when the patient has undergone

general anesthesia, without electrophysiological recordings, and with fewer trajectories for the patient's sake.^{14,21}

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Palfi, Senova, Hosomi, Lepetit, Brugières. Acquisition of data: Palfi, Senova, Hosomi, Gurruchaga, Ouerchefani, Beaugendre, Badin, Jan, Brugières. Analysis and interpretation of data: Palfi, Senova, Hosomi, Gurruchaga, Lefaucheur, Dauguet, Brugières. Drafting the article: Senova, Hosomi. Critically revising the article: Palfi, Gurruchaga, Gouello, Ouerchefani, Beaugendre, Lepetit, Lefaucheur, Badin, Dauguet, Jan, Hantraye, Brugières. Reviewed submitted version of manuscript: Palfi, Senova, Hosomi, Gurruchaga, Lepetit, Brugières. Approved the final version of the manuscript on behalf of all authors: Palfi. Statistical analysis: Senova, Hosomi. Administrative/technical/material support: Palfi, Senova, Hosomi, Lepetit, Badin, Hantraye. Study supervision: Palfi.

Correspondence

Stéphane Palfi, Service de Neurochirurgie, CHU Henri Mondor, 51 Avenue du Marechal de Lattre de Tassigny, Créteil 94110, France. email: stephane.palfi@hmn.aphp.fr.