The accuracy placement of an electrode within a specific brain target is an indispensable part of the success of deep brain stimulation (DBS). The globus pallidus internus (GPI) has emerged as a target structure for DBS surgery for the treatment of Parkinson's disease (PD) and dystonia. Although some studies have reported that 15%–34% of DBS procedures on 28,000 patients need revision due to very limited outcomes or adverse effects, one major reason for these revisions is that current imaging techniques lack sufficient spatial resolution and tissue contrast to delineate the target nuclei with surrounding brain tissues, resulting in inaccurate electrode placement within the target. For example, suboptimal DBS electrode placement may result in the activation or damage of adjacent white matter pathways, e.g., the internal capsule (IC) adjacent to the GPi.

There are two ways to perform DBS targeting: direct and indirect methods. Typically, indirect DBS targeting methods are performed by registering a template to the individual patient’s anatomy. However, the variation of size,
shape, and location of the GPi on each individual subject biases the registration accuracy. Therefore, indirect targeting is still not optimal for accurate GPi DBS electrode placement. Direct DBS targeting requires an explicit visualization of the GPi borders on images. However, GPi laminar borders are not always clearly visible on conventional MRI modalities because of the poor contrast of the thin lamina, which challenges the identification of the GPi from the globus pallidus externus (GPe) and also from the IC. Thus, high-contrast imaging techniques for identification of the GPi border in individual patients are greatly needed for DBS targeting.

Modern ultra–high-field-strength MRI techniques significantly improve the image spatial resolution that can be helpful to directly identify DBS targets. Direct visualization of GPi and GPe was achieved on T2-weighted (T2w) images obtained on 7-T MR systems. However, the improved high resolution at 7 T needs a longer acquisition time compared to 1.5- or 3-T MRI systems.12 In addition, it is infeasible to perform routine DBS planning using 7-T MR because it has not been widely clinically available worldwide. Recently, 3D gradient recalled echo (GRE) sequences have been promising to provide more sensitive tissue contrast than T2w images for depicting the subthalamic nucleus.6,12 GPi appears hypointense on T2*w images, and is known to contain a high iron concentration. However, the magnitude of the signal at one location is contaminated by the nonlocal blooming artifacts generated by the surrounding substances.13 More recently, quantitative susceptibility mapping (QSM) has used deconvolution of GRE phase images and removed the nonlocal susceptibility effects, depicting more accurate structural delineation.13 However, one limitation of QSM processing is that skull removal is performed to eliminate nonbrain tissues, which leads to a nonlocal background phase on QSM images. Thus, anatomical landmarks such as the skull are missing. In this study, we introduce a hybrid image contrast based on QSM and T1-weighted (T1w) images for improving identification of the subject-specific GPi target with high delineation of borders for DBS surgery planning, and this has the potential for accurate evaluation of postsurgical lead positions. Furthermore, the hybrid image contrast with preserved skull also makes it easier to integrate into navigation systems commonly used in DBS surgery.

### Methods

#### Human Subjects

Twenty-nine patients with PD (17 men and 12 women, mean age 57.6 ± 20.1 years) underwent bilateral electrode implantation for GPi DBS surgery. Clinical, neuroradiological, and biochemical investigations were evaluated by specialized movement disorder neurologists. The study was approved by Ruijin Hospital, School of Medicine, Shanghai Jiao Tong University. All patients provided written consent for the procedure and anonymous academic presentation.

#### Data Acquisition

**Magnetic Resonance Imaging**

MR examinations were conducted on a 3-T MR scanner (Ingenia, Philips System). Axial T1w and T2w images with 1-mm isotropic spatial resolution were acquired in all subjects. Afterward, a 3D multiecho GRE sequence was performed. Detailed imaging parameters are summarized in Table 1.

**Computed Tomography Scanning**

A CT scanner (LightSpeed VCT, GE Medical Systems) was used to acquire presurgical and postsurgical 3D images in patients with PD. The spatial resolution was 0.7 × 0.7 × 0.625 mm³.

#### Image Processing

QSM images were reconstructed from GRE phase data. Detailed QSM processing was described in our previous QSM studies.27,28 To enhance the contrast within the GP, we created a hybrid image contrast based on T1w and QSM images. The GPi appears hypointense on T1w images but hyperintense on QSM. Meanwhile, the surrounding white matter (e.g., IC) appears hyperintense on T1w images but hypointense on QSM. Therefore, the two complementary image contrasts are fused to generate a new hybrid image contrast in order to enhance the tissue contrast between GPi and surrounding white matter.29 Figure 1 demonstrates the detailed generation of the hybrid contrast images. Specifically, the skull stripping was first performed on T1w and GRE magnitude images by using the Brain Extraction Tool (BET).21 The GRE magnitude

<table>
<thead>
<tr>
<th>Parameter</th>
<th>3D T1w</th>
<th>2D T2w</th>
<th>3D GRE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imaging plane</td>
<td>Axial</td>
<td>Axial</td>
<td>Axial</td>
</tr>
<tr>
<td>Field of view (mm)</td>
<td>256 × 256</td>
<td>256 × 256</td>
<td>240 × 240</td>
</tr>
<tr>
<td>Matrix</td>
<td>256 × 256</td>
<td>256 × 256</td>
<td>320 × 320</td>
</tr>
<tr>
<td>Resolution (mm)</td>
<td>1-mm isotropic</td>
<td>1-mm isotropic</td>
<td>0.75 × 0.75 × 1.5</td>
</tr>
<tr>
<td>TR (msec)</td>
<td>6.9</td>
<td>3000</td>
<td>33</td>
</tr>
<tr>
<td>TE (msec)</td>
<td>3.4</td>
<td>128</td>
<td>TE/spacing/TEé = 11/2.75/29.7</td>
</tr>
<tr>
<td>Pixel bandwidth (Hz)</td>
<td>241</td>
<td>122</td>
<td>289</td>
</tr>
<tr>
<td>Acceleration factor</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Scan time (mins)</td>
<td>6</td>
<td>9</td>
<td>5</td>
</tr>
</tbody>
</table>
images were then coregistered to T1w images by using FSL FLIRT\(^9\) and the transformation field was propagated to the QSM images. Thus, the QSM and T1w images were placed in the same space. The intensity of T1w images was normalized to be \([0, 255]\). Last, the hybrid images were generated by a linear combination of QSM and T1w images: \(\text{Hybrid} = \mu \ast T1w - \text{QSM}\), where \(\mu\) is a weighting factor and set to 0.0025, as described previously.\(^{29}\)

Data Analysis

For each participant, the QSM and T2w images were both registered to the T1w images. A line perpendicular to the IC was selected on QSM images. This line was then applied to the T1w, T2w, and hybrid images. The line profiles of the normalized MR signal intensity were plotted and compared between the T1w, T2w, QSM, and hybrid images. A baseline within the IC was determined in the profile. The slope of the signal intensity increase from the end of the IC to the starting pixel of the GPi area was calculated to determine the edge detection power.

Contrast-to-noise ratios (CNRs) for the GPi on different image contrasts were measured using the following equation: \(\text{CNR} = \left| S_{\text{GPi}} - S_{\text{WM}} \right| / \sigma\), where \(S_{\text{GPi}}\) and \(S_{\text{WM}}\) represent the mean signal intensities in GPi and surrounding white matter (e.g., IC), respectively. \(\sigma\) represents noise measurement calculated as the standard deviation (SD) of the signal intensities in the thalamus.

Actual electrode location was calculated by registering the presurgical MR images to the postsurgical CT images using Leksell software. The coordinates of lead position were calculated using the Leksell coordinate frame. The distance between direct and actual lead positions was calculated as follows:

\[
\sqrt{(x - x_0)^2 + (y - y_0)^2 + (z - z_0)^2},
\]

where \(x\), \(y\), \(z\) and \(x_0\), \(y_0\), \(z_0\) are the coordinates of direct and actual targets, respectively. The mean errors ± SD between the direct targeting method and actual coordinates \((x, y, z)\) of the most ventral contacts were calculated for both left and right electrodes.

Statistical Analysis

The 1-way ANOVA with least significant difference (post hoc test algorithms) was used to compare the slope of signal intensity increase and CNR between different MR image modalities (SPSS, version 15; SPSS, Inc.).

Results

As illustrated in Fig. 1, the hybrid images provide superior delineation of deep gray matter with respect to white matter on the QSM images, resulting in a higher image contrast between the GPi and IC in comparison to T1w and GRE magnitude images.

Figure 2 shows T1w, T2w, QSM, and hybrid images at one representative location in a patient with PD. On the T1w and T2w images, it is difficult to visualize and identify the GPi borders. QSM images clearly show the basal
FIG. 2. Comparison of GPI contrast using different MR contrasts in a patient with PD. A: T1w, T2w, QSM, and hybrid images. B: Enlarged GPI regions from the red box outlined on the T1w image to visualize the substructure within the GP. Red arrows pointing to the GPI and GPe can be well differentiated and separated by the MIL on QSM and hybrid images. C: Comparison of the line plots depicting normalized MR signal intensities along the profiles in the GP area obtained with T1w, T2w, QSM, and hybrid imaging. The intensities of T1w and hybrid images of the plots are inverted for comparison with QSM images. Put = putamen. Figure is available in color online only.
ganglia nuclei, for example, putamen, caudate nucleus, GPi, and GPe. The paramagnetic GPi and GPe can be well differentiated by the diamagnetic medial intermedullary lamina (MIL) on QSM images. Clear delineation between GPi and the lateral border of the IC was observable due to the susceptibility differences existing between the two structures. Similarly, GPi can also be well differentiated from GPe and IC on the hybrid image. A higher contrast between the MIL and GPi/GPe on the hybrid images was observed, as indicated by the red arrows in Fig. 2B.

Figure 2C shows the profile lines of the normalized signal intensities extracted along the lines containing the IC, GPi, GPe, and putamen. The line profile on QSM images exhibited much higher signal variations than the results of T1w and T2w images, which demonstrated that QSM provides superior tissue contrast between GPi and GPe. A larger signal variation (red curve in Fig. 2C) was observed between GPi and the MIL on hybrid images than on QSM images.

The hybrid images yield the best CNR for GPi depiction and the differences were significant between the hybrid and T1w/T2w images (p < 0.01). The CNRs were 0.4, 1.8, 13.5, and 18 for T1w, T2w, QSM, and hybrid images for GPi-IC (Fig. 3). There were significant differences between QSM-based images and T1w/T2w images in terms of the slope of signal increase (p < 0.001). No statistically significant difference was found between the QSM and hybrid images regarding the slope of signal increase (p = 0.053).

Figure 4 shows the postsurgical CT images fused with the corresponding patient’s MRI modalities—e.g., T1w, T2w, and hybrid images. The bilateral electrodes are shown as red dots. Clear electrode locations within GPi were observable and their locations relative to IC could be measured on the hybrid image, whereas they were invisible on T1w and T2w images, indicating the hybrid image contrast is superior for the measurement of the DBS lead positions. The DBS electrode trajectory within the brain volume can be clearly visualized as shown in Video 1.

**VIDEO 1.** The visualization of DBS electrode trajectory within the 3D brain volume attained using the hybrid QSM images. Copyright Fuhua Yan. Published with permission. Click here to view.

The mean errors ± SD between the direct targeting method and actual coordinates (x, y, z) of the most ventral
contacts are $0.5 \pm 0.5$ mm, $0.4 \pm 0.4$ mm, $0.6 \pm 0.5$ mm, and $0.7 \pm 0.5$ mm, $0.5 \pm 0.4$ mm, $0.6 \pm 0.5$ mm for the right and left electrodes, respectively. The coordinate for each individual patient is listed in Table S1.

**Discussion**

Our results demonstrate that tissue contrast on QSM images is superior to that on T1w and T2w images for delineation of GPi from GPe and IC. QSM depicts high-iron-content GPi with a paramagnetic susceptibility, and high myelinated IC and the MIL with a diamagnetic susceptibility, allowing for confident localization of borders for GPi as the DBS target. QSM-based hybrid images improve the CNR of the GPi compared with QSM alone, suggesting that QSM-based hybrid images are suitable to directly target the patient-specific GPi for DBS surgery.

Various MR image–based approaches have been used to improve the accuracy of direct DBS target localization. However, the significance of MRI modalities at 3 T for direct DBS targeting is controversial. The lack of agreement reflects the limitations of sensitivity of conventional MR images. At 3 T, T1w and T2w images have difficulties in clearly identifying the boundaries of a target with respect to surrounding tissues, suggesting that T1w/T2w imaging and QSM rely on entirely different mechanisms of MRI signal generation. Tissue contrast between structures on T1w/T2w images originates from the differences in signal relaxation rates of the water protons, which are rather small, whereas the magnetic susceptibility differences existing between the paramagnetic iron and diamagnetic myelin are relatively larger. Thus, QSM is suitable for the depiction of iron-rich deep brain nuclei, such as GPi. Meanwhile, myelinated white matter—e.g., IC and the MIL—enable QSM to exhibit a diamagnetic susceptibility. Substantially, QSM provides clear borders between iron-rich GPi and myelinated white matter. The electrode locations can be calculated by merging the postsurgical CT and presurgical hybrid images. This allows us to analyze the relationship between electrode location within the GPi and the patient’s clinical metric with greater accuracy compared to T1w/T2w images.

Several studies have shown that combining structural and functional parcellations with GPi parcellation methods has the potential to improve the accuracy of DBS lead localization. Similarly, QSM also exhibits inhomogeneous iron deposition within GPi as shown in Fig. 2B, with more iron deposits in the posterior than in anterior regions, suggesting that this susceptibility heterogeneity may provide additional subregional information complementary to the structural parcellations. One previous study reported that a linear correlation was found between brain iron concentration measured by QSM and axonal densities measured by diffusion tensor imaging in the subthalamic nucleus in patients with PD. Future studies will investigate the potential association between heterogeneously distributed iron within GPi and the white matter axonal connectivity in patients with movement disorders.

Previous studies have shown that the fast gray matter acquisition T1 inversion recovery (FGATIR) sequence provides significantly better visualization of the GPe and/or GPi than T1w/T2w images. Other inversion recovery–based sequences (e.g., the modified driven equilibrium Fourier transform [MDEFT] sequence) were also used to directly localize the GPi. More recently, 1 study has reported that FGATIR displays relatively lower signal-to-noise ratio than QSM in the GP area, which makes GPi only partially visible. FGATIR and other inversion recovery–based sequences are sensitive to scan parameters such as inversion time, repetition time, field of view, matrix size, and parallel imaging factors. In contrast, QSM is independent of the scan parameters, with high reproducibility.

There are a few limitations in the current study. The CNR and the slope of signal increase are only used as the quantitative image contrast measurements and do not relate to any clinical metric. MRI based on 3D GRE sequences is sensitive to patients’ motion during the scan. Thus, tissue contrast on QSM images may be degraded by motion artifacts, especially when performed in patients with movement disorders. Another limitation is that QSM reconstruction takes approximately 10 minutes; thus, faster QSM techniques are greatly needed for DBS planning.

**Conclusions**

We have demonstrated that the dedicated QSM-based hybrid image improves the identification of GPi borders, which are not always visible on T1w and T2w images at 3 T. The hybrid images with the skull included exhibit a similar contrast to T1w images, making it easier to integrate into the DBS navigation systems. The significantly improved tissue contrast associated with magnetic susceptibility indicates potential for direct GPi-DBS surgery planning and postsurgical assessments of the DBS lead positions.

**Acknowledgments**

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Disclosures

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Author Contributions

Conception and design: Yan, Wei, Wang, Li, Sun. Acquisition of data: Yan, C Zhang, Wang, He, Sun. Analysis and interpretation of data: Wei, C Zhang, Li, Y Zhang, Liu. Drafting the article: Wei. Critically revising the article: Wei, Sun.

Supplemental Information

Videos


Online-Only Content

Supplemental material is available with the online version of the article.

*Table S1.* https://thejns.org/doi/suppl/10.3171/2019.7.JNS191254.

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