Pretherapeutic functional connectivity of tractography-based targeting of the ventral intermediate nucleus for predicting tremor response in patients with Parkinson’s disease after thalamotomy with MRI-guided focused ultrasound

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OBJECTIVE Tractography-based direct targeting of the ventral intermediate nucleus (T-VIM) is a novel method that provides patient-specific VIM coordinates. This study aimed to explore the accuracy and predictive value of using T-VIM in combination with tractography and resting-state functional connectivity techniques to perform magnetic resonance imaging–guided focused ultrasound (MRgFUS) thalamotomy as a treatment of Parkinson’s disease (PD).

METHODS PD patients underwent MRgFUS thalamotomy and were recruited for functional MRI scanning. A subscore of the Clinical Rating Scale for Tremor was used to evaluate tremor improvement. T-VIM and surgical VIM (S-VIM) were defined on preoperative diffusion tensor MRI and 24-hour postoperative T1-weighted imaging, respectively. The overlapping volume and center distance between S-VIM and T-VIM were measured to determine their correlations with 12-month postoperative tremor improvement. Moreover, pretherapeutic functional connectivity of T-VIM or S-VIM, based on region-of-interest connectivity and whole-brain seed-to-voxel connectivity, was measured with the resting-state functional connectivity technique to investigate their correlations with tremor improvement.

RESULTS All patients had excellent tremor improvement (mean [range] tremor improvement 74.82% [50.00%–94.44%]). The authors found that both overlapping volume and center distance between T-VIM and S-VIM were significantly correlated with tremor improvement (r = 0.788 and p = 0.012 for overlapping volume; r = −0.696 and p = 0.037 for center distance). Pretherapeutic functional connectivity of T-VIM with the ipsilateral sensorimotor cortex (r = 0.876 and p = 0.002), subthalamic nucleus (r = 0.700 and p = 0.036), and visual area (r = 0.911 and p = 0.001) was significantly and positively correlated with tremor improvement.

CONCLUSIONS T-VIM may improve the clinical application of MRgFUS thalamotomy as a treatment of PD. Pretherapeutic functional connectivity of T-VIM with the ipsilateral sensorimotor cortex, subthalamic nucleus, and visual area may predict PD tremor responses after MRgFUS thalamotomy.

Keywords Parkinson’s disease; magnetic resonance imaging–guided focused ultrasound; MRgFUS; functional connectivity; tractography; functional neurosurgery
expected to be a therapeutic boon for tremor-dominant PD patients because it is a noninvasive, nonprosthetic, nonradiative, and non–general anesthesia technique with lower infection and hemorrhage risks and fewer hardware-related complications.

However, the VIM is indiscernible on routine MRI as an approximately 4 × 4 × 6-mm thalamic nucleus. Currently, VIM targeting for MRgFUS predominantly relies on the landmark-based targeting technique, but such an indirect targeting method fails to take into account interindividual anatomical variability. The tractography-based direct targeting of the VIM (T-VIM) technique is the most promising method that directly provides an anatomically precise target. This method has been used with MRgFUS thalamotomy as a treatment of essential tremor and showed good clinical efficacy and potential usefulness for decreasing the risks of motor and sensory adverse events. However, there is a lack of reports on the clinical utility of T-VIM for MRgFUS as a treatment of PD tremor. Therefore, we aimed to produce supportive data on the use of the T-VIM technique for MRgFUS thalamotomy to treat PD patients. In addition, previous studies have reported the effects of MRgFUS thalamotomy on remote brain regions involving the CTC circuit and shown that some of these regions were correlated with tremor responses. These findings indicate that tremor control induced with MRgFUS thalamotomy may rely on the modulation of remote brain regions that are functionally connected to VIM. As such, we speculated that the pretherapeutic functional connectivity (FC) of T-VIM to remote brain regions may predict tremor responses induced with MRgFUS surgery.

To confirm our speculation, we performed an exploratory investigation of the accuracy of T-VIM and the correlation between pretherapeutic FC of T-VIM and tremor responses after MRgFUS thalamotomy in patients with PD. The overlapping volume and euclidean distance between T-VIM and surgical VIM (S-VIM) were noted to determine their correlations with 12-month postoperative tremor improvement. The relationships between the pretherapeutic FC strength of T-VIM or S-VIM and tremor improvement were investigated with both region-of-interest (ROI) connectivity analysis and whole-brain seed-to-voxel connectivity analysis.

### Methods

#### Participants

Approved by the ethics committees of Chinese PLA General Hospital, Beijing, China, this study was a part of a pilot clinical trial about the feasibility and safety of MRgFUS thalamotomy for the treatment of PD (ClinicalTrials.gov no. NCT04570046). From April 2019 to September 2019, 87 patients with PD signed up for the trial. Based on ethical considerations, only 10 patients with medication-refractory tremor-dominant PD who met the criteria for surgery were included in the pilot study and underwent unilateral MRgFUS thalamotomy. Written informed consent was obtained from each patient. The criteria for surgery were consistent with those of a previous study.

Specifically, the inclusion criteria included diagnosis of tremor-dominant idiopathic PD, intolerance to the adverse effects of medication or poor response to medication, and severe and disabling tremor. The exclusion criteria included severe systemic disease, other central neurodegenerative disease, cognitive impairment, unstable psychiatric disease, structural brain abnormality, history of intracranial hemorrhage or stroke, history of bleeding or coagulation abnormalities, inability to tolerate a prolonged stationary position in the supine position, history of brain surgery for PD (e.g., DBS, stereotactic ablation), contraindication to MRI scanning, and overall skull density ratio ≤ 0.35 calculated with screening CT. One patient was lost to follow-up 12 months after treatment. Finally, 9 patients who successfully completed 12 months of postsurgical follow-up were included in the current study.

We collected baseline clinical characteristics, preoperative MRI data sets, and 24-hour postoperative S-VIM information for all included patients. Tremor scores of the hand contralateral to thalamotomy were obtained at baseline and approximately 12 months after surgery by using a derived subscale of the Clinical Rating Scale for Tremor. Percent change in hand tremor scores from preoperation to postoperation ([baseline score – follow-up score]/baseline score × 100) was used to measure tremor improvement.

#### MRgFUS Procedure

The MRgFUS procedure was performed in a 3-T MRI suite (Discovery 750, GE Healthcare) using the ExAblate Neuro focused ultrasound system (InSightec) with a hemispheric helmet and a 1024-element phased-array transducer. The surgical techniques were consistent with those of a previous report. Briefly, the patient was placed in a stereotactic head frame, where a degassed and cooled silicone water bath was positioned. Then, triplanar T2-weighted images were acquired and used to target the VIM. The VIM contralateral to the most severely affected extremity was targeted. In patients with ventriculomegaly, thalamotomy was performed at the posterior quarter of the anterior commissure–posterior commissure (AC-PC), 14 mm lateral to the midline and 11.5 mm lateral to the third ventricle lateral wall. Subablative sonication was used to adjust the target, and then therapeutic sonication was administered to the target.

#### MRI Acquisition

MRI was performed with a 3.0-T MRI system. Patients were instructed to lie in the supine position, relax, stay still, and keep their eyes closed, and think about nothing during MRI acquisition. They wore earplugs to reduce noise. To minimize head motion, tight but comfortable foam padding was placed around the head.

Preoperatively, all patients underwent diffusion-weighted imaging (TR/TE 7522/80.8 msec; 224 × 224-mm field of view [FOV]; 112 × 112 matrix; b value 1000 sec/mm²; 64 encoding directions; 4 B0; 2-mm isotropic resolution) and resting-state functional MRI (TR/TE 2000/30 msec; 90° flip angle; 240 × 240-mm FOV; 64 × 64 matrix; 3.5-mm-thick slices; 0.5-mm slice gap; 36 interleaved slices; and 180 volumes). Twenty-four hours
after the operation, sagittal 3D T1-weighted images were obtained (TR/TE 6.656/2.928 msec; inversion time 800 msec; 7° flip angle; 256 × 256–mm FOV; 256 × 256 matrix; 1-mm-thick slices; 192 contiguous slices).

**MRI Data Preprocessing**

For preoperative diffusion-weighted imaging, image distortions from eddy currents were corrected using the eddy function of the FMRIB Software Library (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/). Afterward, the Diffusion Toolkit with TrackVis was used to estimate the diffusion tensors and perform deterministic tractography. Preoperative resting-state functional MRI data were preprocessed using the REST toolbox (version 1.2) of MATLAB (version 2013b, MathWorks Inc.), as described in a previous study. 

Resting-state functional MRI data of patients who underwent right thalamotomy (n = 3) were flipped along the interhemispheric axis before preprocessing, so that the left hemisphere was the operation side for all patients.

**T-VIM Construction and Analysis**

The 2-tract (pyramidal and somatosensory) approach was used to define T-VIM on preoperative diffusion-weighted imaging. To track the pyramidal tract (PT), ROIs were placed in the cerebral peduncle and ipsilateral precentral gyrus, with a tracking angle of 45° and a fractional anisotropy stop value of 0.2 (Fig. 1A). To track the medial lemniscus (ML), ROIs were placed at the dorsal column of the brainstem and ipsilateral postcentral gyrus, with a tracking angle of 60° and a fractional anisotropy stop value of 0.2 (Fig. 1B). These ROIs were manually delineated on preoperative diffusion-weighted imaging. The preoperative diffusion-weighted images were coregistered with the 24-hour postoperative T1-weighted images aligned to the AC-PC line. The deformation vector fields were then used to coregister the binarized deterministic fiber-tracking maps of the PT and ML with the 24-hour postoperative T1-weighted images. Intersecting perpendicular lines were drawn at the anterior border of the ML and medial border of the PT at the AC-PC plane on axial 24-hour postoperative T1-weighted images. To generate T-VIM, a cubic thalamic ROI with a side length of 4 mm was placed with its center 3 mm equidistant from the borders of the PT and ML (Fig. 1C).

S-VIM—the final lesion that encompassed the inner two zones—was manually delineated on axial 24-hour postoperative T1-weighted images using ITK-SNAP (www.itksnap.org). The overlapping volume between T-VIM and S-VIM was calculated, as was the euclidean distance between their centers. The relationships of tremor improvement with overlapping volume and euclidean distance between T-VIM and S-VIM were investigated using Pearson’s correlation analysis.

**FC Analysis**

The 24-hour postoperative T1-weighted images were coregistered with the T1-weighted Montreal Neurological Institute (MNI) template. The obtained transformations were used to normalize T-VIM and S-VIM into MNI space. Right-sided S-VIM and T-VIM (n = 3) were flipped along the interhemispheric axis, so all S-VIM and T-VIM were left-lateralized. The T-VIM and S-VIM of all patients were summed to obtain the peak coordinates of T-VIM and S-VIM, respectively. The seed T-VIM was defined using the peak coordinate of T-VIM, with a radius of 3 mm according to its size of 4 mm × 4 mm × 6 mm. A similar procedure was performed for the seed S-VIM. The FC of seed T-VIM or S-VIM was calculated based on both the a priori–defined ROIs and whole-brain seed-to-voxel connectivity approaches.

Specifically for a priori–defined ROI connectivity, we focused on the brain regions of the CTC circuit. Seven ROIs were included: the left (ipsilateral to the thalamotomy) sensorimotor cortex (SMC), motor striatum, internal globus pallidus (GPi), external globus pallidus (GPe), subthalamic nucleus (STN), substantia nigra, and right (contralateral to the thalamotomy) motor cerebellum. These ROIs were extracted from the motor network atlas as defined by Horn et al., who obtained each ROI by summing the voxels of the same parcel defined by multiple available atlases. We used Pearson’s coefficient of correlation analysis to measure FC between T-VIM or S-VIM and each ROI among the mean time series, which then underwent Fisher’s r-to-z transformation. The z value represents FC strength between T-VIM or S-VIM and each ROI. A series of Pearson’s correlation analyses was performed to determine the associations among the FC strength of T-VIM or S-VIM, the predefined ROIs, and tremor improvement.

For whole-brain seed-to-voxel connectivity, pretherapeutic FC maps of T-VIM or S-VIM were produced by calculating Pearson’s correlation coefficients between the T-VIM or S-VIM time course and the time courses of all other voxels in the whole brain. Then, individual pretherapeutic FC maps were converted to a normal distribution using Fisher’s transformation. The value of each voxel in the pretherapeutic FC map represents the preoperative FC strength between that voxel and the seed T-VIM or S-VIM. Statistical parametric mapping and multiple regression analysis were performed with SPM 12 (https://www.fil.ion.ucl.ac.uk/spm/) to determine specific brain clusters correlated with tremor improvement in the FC maps of T-VIM and S-VIM. Cluster-wise correction for multiple comparisons was performed using the family-wise error (FWE) method, resulting in significant clusters at voxel-level (p < 0.001) and cluster-level (FWE-corrected p < 0.05) thresholds.

**Results**

**Demographic and Clinical Characteristics**

One patient was lost to follow-up 12 months after treatment, and therefore 9 tremor-dominant PD patients who underwent unilateral MRgFUS thalamotomy were included. The mean ± SD disease duration was 8.22 ± 7.19 years. The demographic and clinical characteristics, as well as the therapeutic parameters, are summarized in Table 1. All patients demonstrated substantial tremor improvement after surgery (mean [range] improvement 74.82% [50.00%–94.44%]). Tremor improvement was not significantly correlated with age (r = 0.406 and p = 0.278), disease duration (r = 0.170 and p = 0.687), levodopa-equiv-

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FIG. 1. T-VIM construction. A: PT (blue) and ROIs for tracking PT. B: ML (green) and ROIs for tracking ML. C: PT (blue) and ML (green) are coregistered and overlaid onto T1-weighted images. A 4-mm cubic T-VIM (inset, orange) was drawn with its center equidistant (3 mm) from the 2 intersecting perpendicular lines at the medial border of the PT (blue) and the anterior border of the ML (green) at the AC-PC level. Figure is available in color online only.
alent usage (r = 0.269 and p = 0.484), or baseline tremor score of the treated hand (r = 0.442 and p = 0.234).

**Regional Convergence of T-VIM and S-VIM Correlated With Tremor Improvement**

As shown in Fig. 2A, the overlapping volume and center distance between S-VIM and T-VIM were measured. The mean ± SD overlapping volume between T-VIM and S-VIM was 20 ± 14 mm³, and the mean center distance between T-VIM and S-VIM was 2.7 ± 1.1 mm. S-VIM volume was not significantly correlated with overlapping volume (r = 0.441 and p = 0.234) or euclidean distance (r = −0.091 and p = 0.815) (Fig. 2B). S-VIM volume was not significantly correlated with tremor improvement (Fig. 2C).

In the correlation analysis of tremor improvement 12 months after operation, we found that the overlapping volume and euclidean distance between T-VIM and S-VIM were significantly correlated with tremor improvement (r = 0.788 and p = 0.012 for overlapping volume; r = −0.696 and p = 0.037 for euclidean distance), with greater overlap and closer distance related to greater improvement (Fig. 2D).

**T-VIM, Rather Than S-VIM, Was Functionally Related to Tremor Improvement**

The correlation between pretherapeutic FC of T-VIM or S-VIM and tremor improvement induced by MRgFUS thalamotomy was analyzed to explore the potential use of FC to predict postprocedural tremor response. In the a priori–defined ROI analysis, pretherapeutic FC between T-VIM or S-VIM and the key brain areas of the CTC pathway were calculated. Correlation analyses showed that posttreatment tremor improvement was significantly correlated with pretherapeutic FC between T-VIM and the ipsilateral SMC (r = 0.876 and p = 0.002) and ipsilateral STN (r = 0.700 and p = 0.036), with stronger FC related to greater improvement (Fig. 3A and B, Table 2). These FCs were not correlated with age, duration of disease, levodopa-equivalent usage, or baseline tremor score of the treated hand. Tremor improvement was not significantly correlated with FC between T-VIM and the ipsilateral motor striatum, GPi, GPe, substantia nigra, and contralateral motor cerebellum. Similarly, tremor improvement was not significantly correlated with FC between S-VIM and ROIs, except SMC.

In multiple regression analysis of whole-brain seed-to-voxel connectivity determined with T-VIM, a brain cluster in the ipsilateral visual area was significantly correlated with tremor improvement (cluster size 59 voxels, voxel-level p < 0.001, cluster-level FWE-corrected p < 0.05). The post hoc analysis specified that tremor improvement was significantly correlated with FC between T-VIM and the ipsilateral visual area (r = 0.911 and p < 0.001) (Fig. 3C), whereas FC between T-VIM and the ipsilateral visual area was not significantly correlated with age, duration of disease, levodopa-equivalent usage, or baseline tremor score of the treated hand. In the seed-to-voxel connectivity analysis of S-VIM, no brain cluster was significantly correlated with tremor improvement.

**TABLE 1. Demographic, clinical, and therapeutic characteristics of the included patients**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex</th>
<th>Age (yrs)</th>
<th>Disease Duration (yrs)</th>
<th>Baseline LEDD (mg)</th>
<th>SDR</th>
<th>No. of Sonications</th>
<th>Mean Delivered Power (W)</th>
<th>Mean Delivered Energy (J)</th>
<th>Peak Temperature (°C)</th>
<th>% Improvement in Tremor of Treated Hand</th>
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<tr>
<td>1</td>
<td>M</td>
<td>63</td>
<td>5</td>
<td>825</td>
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<td>8994</td>
<td>59</td>
<td>94.44</td>
<td>80.00</td>
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<td>2</td>
<td>M</td>
<td>69</td>
<td>7</td>
<td>513</td>
<td>0.40</td>
<td>9</td>
<td>14221</td>
<td>59</td>
<td>94.24</td>
<td>80.00</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>60</td>
<td>8</td>
<td>850</td>
<td>0.48</td>
<td>7</td>
<td>501</td>
<td>57</td>
<td>88.24</td>
<td>80.00</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>68</td>
<td>27</td>
<td>569</td>
<td>0.66</td>
<td>15</td>
<td>472</td>
<td>58</td>
<td>85.56</td>
<td>80.00</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>63</td>
<td>9</td>
<td>566</td>
<td>0.43</td>
<td>12</td>
<td>6418</td>
<td>55</td>
<td>81.25</td>
<td>80.00</td>
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<td>6</td>
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<td>3</td>
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<td>743</td>
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<tr>
<td>7</td>
<td>M</td>
<td>64</td>
<td>6</td>
<td>750</td>
<td>0.56</td>
<td>12</td>
<td>450</td>
<td>59</td>
<td>80.00</td>
<td>80.00</td>
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<tr>
<td>8</td>
<td>M</td>
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<td>609</td>
<td>56</td>
<td>74.82 ± 15.33</td>
<td>80.00</td>
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<tr>
<td>Mean ± SD</td>
<td></td>
<td>64.67 ± 6.12</td>
<td>8.22 ± 7.19</td>
<td>610.22 ± 182.20</td>
<td>0.53 ± 0.43</td>
<td>10.89 ± 2.85</td>
<td>546.89 ± 134.31</td>
<td>7542.78 ± 328.35</td>
<td>57.89 ± 15.33</td>
<td></td>
</tr>
</tbody>
</table>

LEDD = levodopa-equivalent daily dose; SDR = skull density ratio.
correlated with tremor improvement. To explore the relationship between the visual area and the CTC circuit, we analyzed the correlations of the FC between T-VIM and ipsilateral SMC and the FCs of T-VIM with the a priori-defined ROIs. The FC between T-VIM and the ipsilateral SMC was significantly correlated with the FC between T-VIM and the ipsilateral visual area ($r = 0.886$ and $p = 0.001$) (Fig. 3D).

**Discussion**

This study has two major findings. One, larger overlap between T-VIM and S-VIM and closer distance between T-VIM and S-VIM were associated with greater tremor improvement. This indicates that the T-VIM method may improve clinical outcomes and optimize the clinical application of MRgFUS thalamotomy as a treatment of PD. Two, tremor improvement was correlated with pretherapeutic FC between T-VIM and the ipsilateral SMC, ipsilateral STN, and ipsilateral visual area. This finding suggests that the pretherapeutic FC of T-VIM may be a valuable tool for triaging MRgFUS thalamotomy candidates and predicting tremor responses.

Precise and accurate localization of VIM is particularly important for the MRgFUS procedure, especially given its irreversible ablative nature. However, current neuroimaging techniques fail to visualize VIM. VIM localization for MRgFUS largely depends on the use of coordinate-based measurements. After determination of the initial coordinates with anatomical landmarks such as the AC-PC line, subablative thermal energy is used to refine the target according to the patient’s responses. In this study, MRgFUS thalamotomy of VIM was performed in this way. However, there are some limitations of this indirect targeting method. One major limitation is failure to account for anatomical variability among individuals. Another limitation is that subablative adjustments are time consuming and limited by the subject decisions and experience of the physician. To overcome these limitations, T-VIM was proposed as a method to identify VIM. The feasibility and accuracy of using TVIM to assist during DBS treatment of tremors have been widely demonstrated. The T-VIM method not only allows for direct targeting of VIM but also helps to account for interindividual anatomical variability. In addition, by providing an accurate target and visualization of the adjacent PT and ML, the T-VIM method may facilitate target adjustment and thereby reduce the intraoperative procedure time.

Recently, the T-VIM method was introduced to the MRgFUS procedure. Using the same T-VIM method used in this study, Ranjan et al. retrospectively compared the T-VIM coordinates with the indirect treatment coordinates.
FIG. 3. FC was correlated with tremor effects due to MRgFUS. A: ROI connectivity analysis showed that tremor improvement was significantly correlated with pretherapeutic FC between T-VIM and ipsilateral SMC and ipsilateral STN. B: ROI connectivity analysis showed that tremor improvement was significantly correlated with pretherapeutic FC between S-VIM and ipsilateral SMC. C: Whole-brain seed-to-voxel connectivity analysis showed that tremor improvement was significantly associated with pretherapeutic FC between T-VIM and the ipsilateral visual area. D: Pretherapeutic FC between T-VIM and the ipsilateral SMC was significantly correlated with pretherapeutic FC between T-VIM and the ipsilateral visual area. Figure is available in color online only.
used to treat 43 essential tremor patients who underwent MRgFUS thalamotomy. They found that the T-VIM coordinates were more anterior and medial and suggested that T-VIM may help decrease the risks of motor and sensory adverse effects of this procedure. Moreover, Krishna et al. prospectively assessed the utility of T-VIM for MRgFUS thalamotomy in 10 patients with essential tremor. They reported that patients obtained sustained tremor improvement 3 months after treatment without motor or sensory deficit and concluded that T-VIM is safe and useful. Besides the 2-tract approach used in this study, 1-tract (dentatorubrothalamic tract) and 3-tract (dentatorubrothalamic tract, PT, and ML) techniques have also been used to define targets for focused ultrasound as a treatment of essential tremor and shown their usefulness. However, these studies were limited to patients with essential tremor. The utility of T-VIM for focused ultrasound treatment of PD has barely been reported. In this study, we observed persistent tremor improvement in all 9 patients. We found that larger overlap and closer distance between T-VIM and S-VIM were associated with greater tremor improvement. This finding indicates that T-VIM may improve the clinical response of PD patients after MRgFUS thalamotomy, thus optimizing the clinical application of this procedure. This indication was further supported by the correlation of pretherapeutic FC of T-VIM with tremor improvement.

In the current study, we innovatively combined T-VIM and resting-state FC to explore the relationship of tremor response with pretherapeutic FC of T-VIM. We found that postoperative tremor improvement was significantly correlated with pretherapeutic FC between T-VIM and the ipsilateral SMC, STN, and visual area, thereby suggesting that pretherapeutic FC of T-VIM could be used to predict the clinical outcomes of patients who undergo MRgFUS thalamotomy as a treatment of PD. The SMC and STN are the classic regions of the CTC tremor network. The SMC is the termination of the CTC motor circuit and receives inputs from VIM. Several studies have shown the involvement of the SMC in tremor generation and conduction. By using 15O-labeled water PET, Fukuda and colleagues found that regional cerebral blood flow in the ipsilateral SMC was significantly reduced after unilateral VIM DBS in PD patients. A diffusion tensor MRI study reported that fractional anisotropy decreased in the ipsilateral sensorimotor subcortical white matter after MRgFUS thalamotomy in patients with essential tremor. These studies indicate that MRgFUS thalamotomy modulates the activity of the SMC, thereby further supporting our findings.

The STN is a well-known excellent target for the treatment of PD. Animal studies have shown that tremor in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine primate model of PD can be reduced or even abolished with lesioning or STN stimulation. Similarly, human studies have demonstrated that lesioning or DBS of the STN may suppress tremor in patients with PD. In addition, studies that recorded the local field potentials of the STN in patients with PD have revealed that these potentials are coherent with tremor electromyography signals. However, the neural mechanisms of lesioning and STN stimulation that alleviate PD symptoms remain unclear. The identification of the relationships between VIM, STN, and PD tremor in this study also indicated that tremor control induced with STN lesioning may be mediated by VIM.

Interestingly, but not surprisingly, pretherapeutic FC between the VIM and ipsilateral visual area was significantly correlated with tremor improvement. The association between visual area and essential tremor was previously reported. Tuleasca et al. reported decreased gray matter density in the visual cortex after VIM radiosurgery in patients with essential tremor and found that baseline gray matter density in the visual area was correlated with tremor control. Moreover, they revealed that the pretherapeutic resting-state FC of the motor thalamus with the visual areas could be used to predict VIM radiosurgery–related tremor improvement in patients with essential tremor. By measuring right-hand grip force with functional MRI while modulating visual feedback, Archer et al. demonstrated that tremor severity in patients with essential tremor was aggravated by increased visual feedback. Reports of the association between PD tremor and visual area are limited. By using the same data set, for the first time we reported the correlation between PD tremor and changes in fractional amplitude of low-frequency fluctuations in the visual area induced with MRgFUS thalamotomy; this finding further supports and strengthens our study. Based on the role of the visual area in sensory guidance of movement via cortico-cortical connections, we speculate that the thalamo-visuo-motor network may

### TABLE 2. Correlations between tremor improvement and resting-state FC of T-VIM or S-VIM with selected ROIs

<table>
<thead>
<tr>
<th>ROI/Connectivity</th>
<th>T-VIM r Value*</th>
<th>T-VIM p Value</th>
<th>S-VIM r Value*</th>
<th>S-VIM p Value</th>
</tr>
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<tr>
<td>Contralat motor cerebellum</td>
<td>0.573</td>
<td>0.107</td>
<td>0.452</td>
<td>0.222</td>
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<tr>
<td>Ipsilat motor striatum</td>
<td>0.662</td>
<td>0.052</td>
<td>0.510</td>
<td>0.161</td>
</tr>
<tr>
<td>Ipsilat SMC</td>
<td>0.876</td>
<td>0.002†</td>
<td>0.752</td>
<td>0.019†</td>
</tr>
<tr>
<td>Ipsilat STN</td>
<td>0.700</td>
<td>0.036†</td>
<td>0.591</td>
<td>0.094</td>
</tr>
<tr>
<td>Ipsilat GPI</td>
<td>0.468</td>
<td>0.204</td>
<td>0.489</td>
<td>0.161</td>
</tr>
<tr>
<td>Ipsilat GPe</td>
<td>0.282</td>
<td>0.462</td>
<td>0.302</td>
<td>0.429</td>
</tr>
<tr>
<td>Ipsilat substantia nigra</td>
<td>0.318</td>
<td>0.404</td>
<td>0.335</td>
<td>0.379</td>
</tr>
</tbody>
</table>

* Positive values indicate a greater correlation between tremor improvement and FC.
† Significant correlation at p < 0.05.
be involved in the generation and arrest of PD tremor. These findings provide new perspectives into our understanding of the pathophysiology of PD tremor.

This study had some limitations. The main limitation was the small number of patients. The sample size was determined based on ethical considerations for the novel and exploratory application of MRgFUS thalamotomy as a treatment of PD. The results of this pilot study need to be verified in large cohorts. In addition, the small number of patients precluded analysis of the correlations between adverse events and other important factors and T-VIM. Thus, future studies with larger numbers of patients are needed to provide further insights into possible correlations. The second limitation was that T-VIM was retrospectively used. Prospective and preferably randomized controlled trials that allow direct comparison between T-VIM and conventional approaches are needed to validate the effectiveness of T-VIM to predict tremor response.

Conclusions

For the first time, we have reported the correlation between tremor improvement and pretherapeutic FC between T-VIM and the ipsilateral SMC, STN, and visual area. These findings reveal that preoperative FC of T-VIM may be useful for triaging candidates and predicting tremor responses to MRgFUS thalamotomy. Moreover, the relationships of the clinical responses with convergence between T-VIM and S-VIM suggest that use of T-VIM to directly localize the VIM may improve the clinical application of MRgFUS thalamotomy as a treatment of PD.

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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: Xiong, Pan. Acquisition of data: Xiong, Zong, Bian, Zhang. Analysis and interpretation of data: Xiong, Lin, Duan. Drafting the article: Xiong. Critically revising the article: Lou, Xiong, Lin. Reviewed submitted version of manuscript: Lou. Approved the final version of the manuscript on behalf of all authors: Lou. Administrative/technical/material support: Lou. Study supervision: Lou.

**Supplemental Information**

**Previous Presentations**

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