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# Identification of the stria medullaris thalami using diffusion tensor imaging☆,☆☆

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ABSTRACT

*Background:* Deep brain stimulation (DBS) via anatomical targeting of white matter tracts defined by diffusion tensor imaging (DTI) may be a useful tool in the treatment of pathologic neurophysiologic circuits implicated in certain disease states like treatment resistant depression (TRD). We sought to determine if DTI could be used to define the stria medullaris thalami (SM), the major afferent white matter pathway to the lateral habenula (LHb), a thalamic nucleus implicated in the pathophysiology of TRD.

*Methods:* Probabilistic DTI was performed on ten cerebral hemispheres in five patients who underwent preoperative MRI for DBS surgery. Manual identification of the LHb on axial T1 weighted MRI was used for the initial seed region for tractography. Variations in tractography depending on chosen axial slice of the LHb and chosen voxel within the LHb were also assessed.

*Results:* In all hemispheres the SM was reliably visualized. Variations in chosen axial seed slice as well as variations in single seed placement did not lead to significant changes in SM tractography.

*Conclusions:* Probabilistic DTI can be used to visualize the SM which may ultimately provide utility for direct anatomic targeting in DBS surgery.



## 1. Introduction

Advances in neuroimaging, along with a greater understanding of pathophysiology of neurophysiologic circuits, have led to the continued investigation of new targets for deep brain stimulation (DBS). Several targets have been implicated in treatment resistant depression (TRD) including subgenual cingulate cortex (SCC), nucleus accumbens (NAcc), ventral capsule/ventral striatum (VA/VS), lateral habenula (LHb), inferior thalamic peduncle (ITP), and the medial forebrain bundle (MFB) (Bewernick and Schlaepfer, 2013; Malone et al., 2009; Holtzheimer et al., 2012; Lozano et al., 2008; Sartorius and Henn, 2007; Coenen et al., 2011). More recently, the use of diffusion tensor imaging (DTI) based fiber tracking has heightened interest in anatomical targeting of white matter tracts that have been implicated in disease states like TRD (Schoene-Bake et al., 2010; Anthofer et al., 2015). Stimulation of the supero-lateral branch of the medial forebrain bundle (slMFB), a white matter tract that interconnects various centers of the reward pathway including the NAcc, ventral tegmental area (VTA), hypothalamus, and amygdala has shown promising results in the treatment of TRD and has spurred interest in the identification and stimulation of other white matter tracts involved in the pathophysiology of TRD (Coenen et al., 2009, 2011, 2012).

The stria medullaris thalamus (SM) is the major afferent pathway to the LHb, a small nucleus located on the dorsomedial surface of the caudal thalamus, adjacent to the third ventricle (Zhao et al., 2015). The habenular complex consists mainly of the lateral and medial components. The LHb receives input from a variety of limbic sources, in particular the septal region, NAcc, dorsomedial thalamus, and internal globus pallidus (GPi) (Zhao et al., 2015). Over activation of the LHb has been implicated in the downregulation of serotonergic, noradrenergic and dopaminergic activity as well as stimulation of the HPA axis (Sartorius and Henn, 2007; Sartorius et al., 2010). To date, DBS of the LHb has been described in only two patients but with promising results (Schneider et al., 2013). Because of its size and location, direct targeting of the LHb, although feasible, requires meticulous planning to both effectively target the structure and avoid side effects (Schneider et al.,

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2013). For this reason, broader targeting of the SM, a structure not visible on conventional MRI, may be more suitable for DBS surgery; however, to our knowledge, DTI-based fiber tracking of the SM has yet to be described. Here, we describe and assess the reliability of a technique using MRI-based probabilistic tractography to identify the SM which could in turn be used for direct targeting during DBS surgery.

## 2. Materials and methods

### 2.1. Subjects

Subjects were five consecutive patients undergoing pre-operative imaging for DBS surgery to treat Parkinson's disease. The subjects provided informed consent before enrolling in this study, which was approved by the Institutional Review Board of the authors' institution.

### 2.2. Image acquisition

Pre-operative MRI was carried out one to two weeks in advance of the scheduled DBS implantation procedure using a 3 T scanner and a 12-channel head coil (Siemens Magnetom Verio, Siemens Healthcare, Erlangen, Germany). No stereotactic frame was in place at the time of MRI, as our DBS workflow includes fusion of the MR images with CT images acquired the morning of surgery.

The routine pre-DBS MRI protocol includes a localizer, thin-slice $T_2$-weighted turbo spin echo sequences in the axial and coronal planes, a 3D gradient echo sequence for susceptibility-weighted imaging (SWI), and a post-contrast 3D T1-weighted sequence (MPRAGE) used for neuro-navigation. In the current work, the MPRAGE images were used as a reference for motion and distortion correction of diffusion images and were acquired using the following parameters: TR = 1.9 s, TE = 2.89 ms, TI = 900 ms, flip angle = 9°, bandwidth = 170 Hz/pixel, a parallel imaging (GRAPPA) acceleration factor of 2.0, 208 axial slices with thickness 1.2 mm, field of view 227.5 mm × 260 mm, acquisition matrix 224 × 256, yielding 1.02 mm × 1.02 mm in-plane resolution that was upsampled to 0.51 mm × 0.51 mm using the scanner's built-in interpolation option. The scan time was 3 min, 54 s.

For the purposes of this study, we also acquired a diffusion-weighted sequence prior to administration of contrast agent, with the following scan parameters: TR = 12.5 s, TE = 90 ms, flip angle = 90°, bandwidth = 1698 Hz/pixel, a parallel imaging acceleration factor of 3.0 to mitigate susceptibility distortions, 65 contiguous axial slices with thickness 2 mm to provide whole brain coverage (acquired in an interleaved fashion), field of view 256 mm × 256 mm, acquisition matrix 128 × 128, yielding isotropic 2 mm × 2 mm × 2 mm voxel dimensions. Using an EPI read-out, we acquired this data with a diffusion weighting factor (b-value) of 1000 s/mm$^2$ along 69 directions that were uniformly distributed in 3D space according to an electrostatic repulsion scheme (Jones et al., 1999), plus 8 acquisitions with no applied diffusion weighting. The scan time was approximately 16 min.

### 2.3. Data processing

Anonymized DICOM images were transferred to an offline workstation and converted to Neuroimaging Informatics Technology Initiative (NIfTI, .nii) format using the 'dcm2niigui' tool (Rorden et al., 2007). We deskulled the MPRAGE volume using FSL's 'bet' module, then imported all images, including the diffusion-weighted data, into TORTOISE (Pierpaoli et al., 2010), a software package for correction of motion, eddy current artifacts, and susceptibility distortions in the diffusion data using a high resolution structural image as a reference (the deskulled MPRAGE in this case) (Smith, 2002). Diffusion images were also upsampled to 1.5 mm × 1.5 mm × 1.5 mm by TORTOISE. Visual inspection of the corrected images revealed superb alignment of the diffusion-weighted data to the anatomic reference image and satisfactory mitigation of distortions, particularly in the thalamic and epithalamic regions, which were of greatest interest in the current work due to our targeting of the SM. We inspected all images for signs of motion artifacts warranting the discarding of individual images prior to tractography, but found none.

### 2.4. Probabilistic tractography

Although we first explored the use of deterministic tractography to highlight fibers of the SM, this technique proved sensitive to the choice of seed size and location in this particular application (see Supplement A). We therefore turned to probabilistic tractography as a potentially more robust means of guarding against aberrations arising from slight inconsistencies in seed placement. To this end, we first employed FSL's 'bedpostx' module to obtain distributions of diffusion parameters, including the principal diffusion direction, diffusivity, and diffusion anisotropy, for each voxel, using essentially the default settings. We chose to use a tool that allows for multiple fiber orientations because we expected there would often be axons from different fiber populations adjacent to and sometimes occupying the same voxels as the SM, which could greatly confound tractography of a white matter bundle as narrow as our target (Behrens et al., 2007).

Because the LHb most prominently receives input from other brain regions via the SM, we hypothesized that this small nucleus could serve as an opportune seed region for probabilistic tractography. Though its internal structure and contrast with adjacent tissue is limited at 3 T, the habenula can be reliably identified by its morphology on typically three consecutive 1.2-mm axial slices of the T1-weighted MPRAGE, in which it appears as a triangular ridge extending into the third ventricle on the medial surface of the thalamus (Lawson et al., 2013; Savitz et al., 2011; Strotmann et al., 2014). This visibility enabled us to manually draw a two-dimensional seed region within the habenula on its most central axial slice of the original, high-resolution MPRAGE images (Fig. 1). A single operator drew seeds for all subjects (ten total seed regions) in FSL's 'fslview' module (Jenkinson et al., 2012), maintaining a one-voxel spacing from the perceived interface between tissue and cerebrospinal fluid. Each seed included approximately 20 voxels.

We then carried out probabilistic tractography using FSL's 'probtrackx' module, with the results of bedpostx and the habenular seed region (left and right treated as separate cases) serving as inputs and utilizing essentially the default settings (Behrens et al., 2007). We

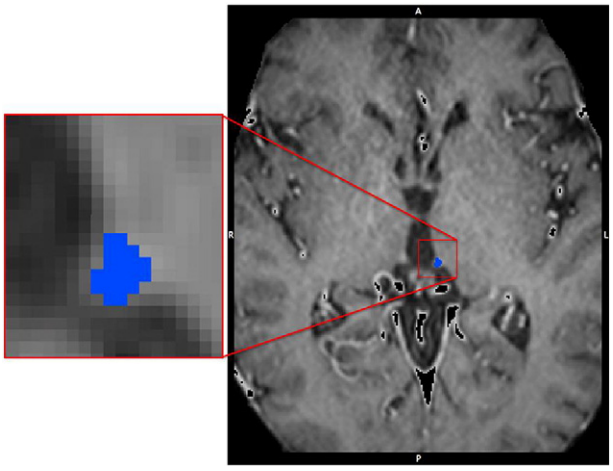


**Fig. 1.** Seeding the habenula. Tractographic identification of the SM requires a seed region from which candidate tracts project. Our seeding strategy initially consists of a two-dimensional region manually drawn within the habenula as identified on this single axial slice of a T1-weighted series.