Defining Critical White Matter Pathways Mediating Successful Subcallosal Cingulate Deep Brain Stimulation for Treatment-Resistant Depression

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Background: Subcallosal cingulate white matter (SCC) deep brain stimulation (DBS) is an evolving investigational treatment for depression. Mechanisms of action are hypothesized to involve modulation of activity within a structurally defined network of brain regions involved in mood regulation. Diffusion tensor imaging was used to model white matter connections within this network to identify those critical for successful antidepressant response.

Methods: Preoperative high-resolution magnetic resonance imaging data, including diffusion tensor imaging, were acquired in 16 patients with treatment-resistant depression, who then received SCC DBS. Computerized tomography was used postoperatively to locate DBS contacts. The activation volume around the contacts used for chronic stimulation was modeled for each patient retrospectively. Probabilistic tractography was used to delineate the white matter tracts traveling through each activation volume. Patient-specific tract maps were calculated using whole-brain analysis. Clinical evaluations of therapeutic outcome from SCC DBS were defined at 6 months and 2 years.

Results: Whole-brain activation volume tractography demonstrated that all DBS responders at 6 months ($n = 6$) and 2 years ($n = 12$) shared bilateral pathways from their activation volumes to 1) medial frontal cortex via forceps minor and uncinate fasciculus; 2) rostral and dorsal cingulate cortex via the cingulum bundle; and 3) subcortical nuclei. Nonresponders did not consistently show these connections. Specific anatomical coordinates of the active contacts did not discriminate responders from nonresponders.

Conclusions: Patient-specific activation volume tractography modeling may identify critical tracts that mediate SCC DBS antidepressant response. This suggests a novel method for patient-specific target and stimulation parameter selection.

Key Words: Antidepressant response, bipolar disorder, deep brain stimulation, diffusion tensor imaging, major depressive disorder, subcallosal cingulate, subgenual cingulate, tractography, treatment-resistant depression

Deep brain stimulation (DBS) is an emerging experimental therapy for treatment-resistant depression (TRD). In the past decade, a number of different stimulation sites have been investigated, including the subcallosal cingulate (SCC) white matter, the ventral capsule/ventral striatum, the nucleus accumbens, the lateral habenula, the inferior thalamic peduncle, and the medial forebrain bundle (1–6). Six-month response rates across studies range from 41% to 66% with sustained and increased response over time. Of the various targets for treating TRD, SCC white matter has been the most studied with published data available for 77 patients implanted at eight separate centers. Within some cohorts, outcome data for patients receiving more than 6 years of chronic SCC DBS suggest significant and lasting antidepressant efficacy (7–14).

The initial rationale for targeting the SCC white matter was based on converging imaging data demonstrating changes in SCC white matter activity with antidepressant response to a variety of standard treatments (15–19). Selection of this target was further supported by an extensive literature demonstrating monosynaptic connections between the subcallosal cingulate and specific frontal, limbic, subcortical, and brainstem sites involved in mood regulation, depression, and the antidepressant response (20–26). Placement of the DBS electrodes was guided by local anatomical landmarks with approximate coordinates derived from positron emission tomography imaging studies localizing the subcallosal cingulate region (Brodmann area [BA] 25) and adjacent white matter and use of standard neurosurgical atlases (21,27).

Although SCC DBS is associated with notable antidepressant effects in patients with TRD, the magnitude of the response varies. Initial efforts to define differences in outcome focused on the anatomical location of the active contacts used for chronic stimulation, but these studies did not differentiate responders and nonresponders (28). There was no difference in anatomical distribution of the active contacts between responders and nonresponders in a second cohort of patients using comparable localization methods (8). Additional positron emission tomography studies suggested that activity changes in brain regions remote

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from the site of stimulation, such as the dorsal cingulate and frontal cortex, were potentially as important to the antidepressant response as activity changes in the vicinity of the SCC DBS target (1). Axonal elements directly modulated by DBS (afferents and efferents projecting to and from the SCC, as well as fibers of passage) may be especially important to the effects of the stimulation (29–32). Characterizing these white matter pathways is therefore seen as a logical next step for optimizing the clinical procedure as well as better delineating mechanisms of action of stimulation.

Fiber tractography techniques have been used in healthy subjects to map the connections of the SCC, identifying midline frontal, cingulate, mesial temporal, striatal, thalamic, hypothalamic, and brainstem pathways (33–35). The same pattern of connections had been previously characterized in nonhuman primates (22,25,36). Detailed computational models of the DBS activation volume have additionally been developed and successfully applied to the study of DBS in Parkinson's disease with newest methods incorporating the location of white matter fibers (37–40). This study used individual activation volumes and probabilistic tractography in patients enrolled in a clinical trial of SCC DBS for TRD to define the combination and location of specific white matter tracts mediating clinical response.

Methods and Materials

Participants and Clinical Protocol

Seventeen chronically depressed, treatment-resistant patients gave written consent to participate in a research protocol at Emory University testing safety and efficacy of SCC DBS in treatment-resistant depression (9) (ClinicalTrials.gov NCT00367003). The protocol was approved by Emory University Institutional Review Board and the US Food and Drug Administration under an Investigational Device Exemption (G060028 held by H.S.M.) and was monitored by the Emory University Department of Psychiatry and Behavioral Sciences Data and Safety Monitoring Board.

Patients underwent implantation of bilateral electrodes in the SCC area as previously described by Holtzheimer *et al.* (9). After a 4-week, single-blind, sham stimulation phase, a 24-week open-label active stimulation phase was conducted. As described in the initial report, after this period, during which psychopharmacologic treatment remained unchanged, patients entered a naturalistic long-term follow-up phase. Response was defined here as in the original report of the clinical trial: 50% decrease in the 17-item Hamilton Depression Rating Scale (41). After 6 months of chronic stimulation, there were 7 responders and 10 nonresponders (41%). There were no significant differences in demographics or clinical characteristics between responders and nonresponders [data available in (9)]. At 2 years of DBS, there were 13 responders and 2 nonresponders. Two subjects were explanted before they reached the 2-year time point. Unfortunately, one of the responders (at 6 months and 2 years) was excluded from analysis due to inadequate quality of the presurgical diffusion tensor imaging (DTI) data. Therefore, the imaging analyses were performed in 6 responders and 10 nonresponders at 6 months and 12 responders and 2 nonresponders at 2 years.

Magnetic Resonance and Computed Tomography Imaging

Multi-sequence structural and diffusion magnetic resonance imaging (MRI) were acquired in a single session 1 week before surgery. T1-weighted and DTI data were acquired on a 3T Tim Trio MRI scanner with a 12-channel head array coil (Siemens Medical Solutions, Malvern, Pennsylvania) that permits maximum gradient amplitudes of 40 mT/m. Single-shot spin-echo echo-planar imaging sequence was used for DTI with generalized autocalibrating parallel acquisition with twofold acceleration ($R = 2$) (42). Diffusion tensor imaging parameters were field of view = 256 × 256; b value = 1000 seconds/mm^2; voxel resolution = 2 × 2 × 2 mm; number of slices = 64; matrix = 128 × 128; 2 averages; 64 noncollinear directions with one nondiffusion weighted image (b = 0); repetition time/echo time = 11300/90 msec. High-resolution T1 weighted images were collected using a three-dimensional magnetization prepared rapid acquisition gradient-echo sequence with the following parameters: repetition time/inversion time/echo time = 2600/900/3.02 msec; a flip angle of 8°, voxel resolution = 1 × 1 × 1 mm; number of slices = 176; matrix = 224 × 256.

Postsurgical high-resolution computed tomography (CT) data were acquired on a LightSpeed16 (GE Medical System, Milwaukee, Wisconsin) with resolution of .46 × .46 × .65 mm^3. These data were used to identify the location of DBS contacts.

DBS Activation Volumes

The DBS contact locations were first identified in native T1 space based on electrode and contact location in a high-resolution CT image that was transferred to native T1 space using the Functional Magnetic Resonance Imaging of the Brain (FMRIB) Linear Image Registration Tool (FLIRT; Oxford University, Oxford, United Kingdom). The patient-specific DBS activation volumes were then created by electrical DBS field model based on identified contact location in native T1 space (see below). For the group-shared fiber tract map, individual activation volume in native T1 space was then transferred to Montreal Neurological Institute (MNI) space to perform probabilistic tractography.

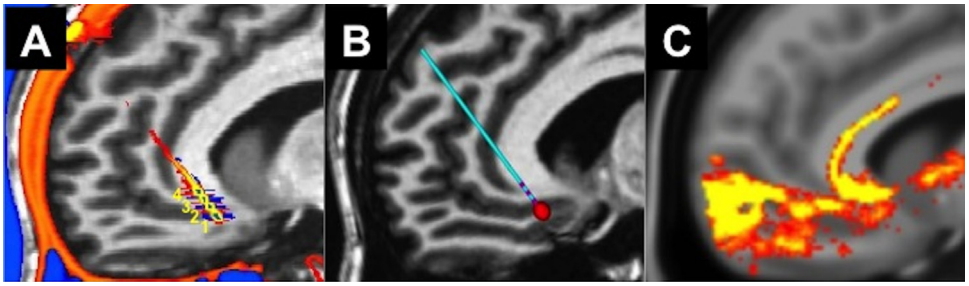

Figure 1. Identification of contact location. **(A)** Postsurgical computed tomography image superimposed on the presurgical T1 image for one subject. Contacts are numbered inferior to superior, 1 to 4. **(B)** Activation volume using contact 1 and typical parameters for a sample subject (6 mA, 130 Hz, 90 microseconds). **(C)** Probabilistic tractography connections from the calculated activation volume for one subject.