Using Probabilistic Tractography to Assess Optimal Targeting for Subcallosal Cingulate Deep Brain Stimulation: An Informative Case

Ki Sueng Choi[1,2], Paul E. Holtzheimer[3], Alexandre R. Franco[2], Patricio Riva Posse[2], Xiaoping P. Hu[1], and Helen S. Mayberg[2]

[1]Bioengineering(BME), Georgia Institute of Technology / Emory University, Atlanta, GA, United States, [2]Department of Psychiatry, Emory University School of Medicine, Atlanta, GA, United States, [3]Psychiatry and Surgery, Dartmouth Medical School, Lebanon, NH, United States

Introduction: Bilateral deep brain stimulation (DBS) of the subcallosal cingulate cortex (SCC) is being investigated as a therapy for treatment-resistant depression (TRD)[1,2,3,4]. Structural connectivity (SC) analyses may help improve DBS targeting by highlighting which white matter tracts are necessary and/or sufficient for effective stimulation. In this study, we present data on a TRD patient who showed a poor clinical response to 6 months SCC DBS but who subsequently remitted following a second surgery performed to revise and improve the placement of the DBS contact within the predefined SCC WM target. At the second surgery, the electrode was placed slightly more ventral to the initial target. In this abstract we show differences in the white matter projections from the two active contacts (first surgery vs. second surgery) based on probabilistic tractography using diffusion tensor imaging (DTI).
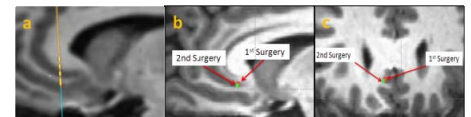

Figure 1. prototypical DBS electrode placement in left hemisphere; b/c: location of active DBS contact for 1st and 2nd surgery in sagittal view, andcoronal views
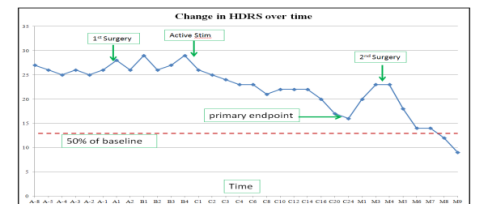
Methods: *A. Subject and image acquisition:* A 34-year old woman, enrolled in a clinical trial of SCC DBS for TRD, participated in accordance with Institutional Review Board policies. The patient underwent bilateral, microelectrode guided, stereotactic neurosurgical implantation of DBS electrodes (Libra XP, St. Jude Medical Neuromodulation, Plano, TX) into the SCC[2]. The surgical revision was performed approximately 9 months after the initial implantation in light of limited improvement following completion of the initial 6 month assessment period and evidence of suboptimal electrode placement on re-review of post-op anatomical studies. MR data were acquired on a 3T Siemens Tim Trio scanner using a Matrix head coil before DBS electrodes were implanted. T_1 images were acquired using an MPRAGE sequence with following parameters: TR/TE=2600/3ms; resolution=1×1*1mm; number of slices=176; matrix=224×256. Diffusion-weighted images were acquired using a diffusion weighted single-shot spin-echo sequence with following parameters: b=1000s/mm^2, voxel resolution=2×2×2 mm, number of slices=64, matrix=128*128, and 64 non-collinear directions with two averages. CT data were acquired on a LightSpeed16 (GE Medical System) with resolution 0.46×0.46×0.65 mm to register the location of the DBS electrodes (Figure 1a). Each electrode has four contacts, of which the bottom contact has a 1.4 mm diameter and 3 mm height, while the other three contacts have the same diameter but with a 1.5 mm height. There is 1.5 mm gab between the contacts. ***B. Preprocessing of CT, T_1 and DTI:*** FSL (http://www.fmrib.ox.ac.uk/fsl) were used for preprocessing. First, T_1 and DTI data were skull stripped to remove non-brain regions. Diffusion data underwent eddy current correction, and local DTI fitting[5,6]. CT and diffusion images were co-registered to T_1 by affine transformation and then normalized to MNI152 template by applying nonlinear transformation information previously calculated by fnirt (FSL) in the nonlinear registration from T_1 to the MNI152 template. The DBS contact locations were first identified on CT space and then transferred to MNI space to later be used as seeds for probabilistic tractography. ***C. Probabilistic tractography for structural connectivity:*** SC was quantified using seed to whole brain probabilistic tractography. For each surgery, the bilateral active contacts were used as the seeds. DBS electrode locations are shown in Figure 1b-c (left only shown); active contact for surgery 1 is shallower than surgery 2. In addition to whole brain tractography, structural connections between left and right contacts to specific *a priori* defined brain target regions in both hemispheres were measured. Twelve cortical and sub-cortical target regions were selected from the Harvard-Oxford structural atlas and modified based on previous functional and structural finding of this DBS target and related PET and fMRI studies: nucleus accumbens, amygdala, cingulate gyrus (anterior division), paracingulate gyrus, anterior orbital frontal, insular, BA9, BA10 (superior and inferior subdivisions), BA11, and middle frontal gyrus. Five thousand streamline threads per voxel were generated from voxels in the left and right electrode, and the number passing through the target regions were counted. The number of threads passing through each voxel divided by the total number of total threads generated was calculated as the probability of connection to that region. Differences in the overall effective SC probability maps between the two surgeries were calculated by contrasting the combined ipsilateral and contralateral tracts for both right and left seeds. Clinical effectiveness of the DBS was assessed using the Hamilton Depression Rating Score (HDRS) measured at several fixed times during the study.

Figure 2. HDRS value change over time. Slope of HDRS (faster clinical response) is seen following 1st relative to 1st surgery. Change $\geq$ 50% percent of baseline represents clinical response.
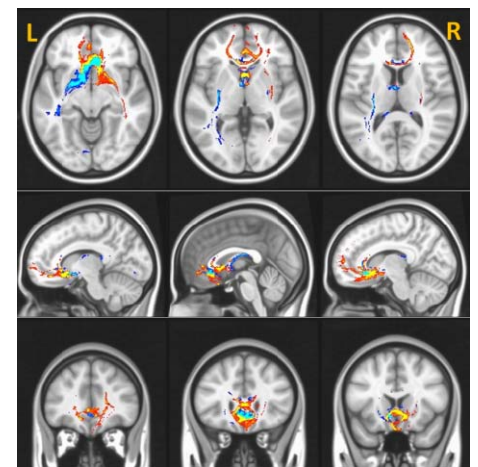

Figure 3. Comparison of Tract Maps of active contacts for Surgery2 minus Surgery1. Red : stronger SC with surgery 2. active contact Blue: stronger SC with surgery 1. Notable differences: SC to medical frontal cortex.

Results & Discussion: Figure 2 presents the change in HDRS over time. Four weeks after the first surgery active stimulation began. Over the next 24 weeks, the HDRS score showed a modest improvement and subsequent worsening; at no point did the patient achieve a clinical response. After the second surgery, the depression rapidly improved and full remission was reached at the second 6 month time point. Figure 3 illustrates SC differences in the probabilistic tract maps between the active contacts used for the first versus the second surgery. The SC contrast maps show that the SC of the surgery 2 active contact was more strongly connected to frontal regions (BA10) in both hemispheres and BA11 in the right hemisphere compared to the active contact used for surgery 1. In contrast, the SC to the nucleus accumbens is stronger for surgery 1. Compared to the left hemisphere active contact from the 1st surgery, the left active contact from the 2nd surgery showed decreased SC to the nucleus accumbens, amygdala, and hippocampus and increased SC to the anterior cingulate, paracingulate, and frontal cortex (BA10 and BA11). Compared to the right hemisphere active contact from the 1st surgery, the right active contact from the 2nd surgery showed increased SC to frontal and middle frontal cortex. These results suggest that precise targeting of specific structural connections between the primary SCC electrode and parts of the medial frontal cortex may be essential for optimal clinical effectiveness of chronic SCC white matter DBS for TRD.

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