Optimizing Subcallosal Cingulate DBS for Treatment Resistant Depression based on structural connectivity

Ki Sueng Choi[1], Patricio Riva Posse[2], Paul E Holtzheimer[3], Cameron C McIntyre[4], Xiaoping P Hu[1], and Helen S Mayberg[2]

[1]*BME, Georgia Institute of Technology / Emory University, Atlanta, GA, United States,* [2]*Psychiatry, Emory University, Atlanta, GA, United States,* [3]*Psychiatry and Surgery, Dartmouth-Hitchcock Medical Center, Lebanon, NH, United States,* [4]*BME, Cleveland Clinic, Cleveland, OH, United States*

Introduction

Bilateral high frequency deep brain stimulation (DBS) of the subcallosal cingulate cortex and adjacent white matter (SCC) results in sustained long-term antidepressant effects for treatment-resistant depression (TRD)[1-7]. Currently, electrode placement is based on local SCC anatomy with clinical efficacy assessed using standardized symptom severity scales. Clinical response may be improved by more precise targeting along specific white matter tracts based on structural connectivity (SC) analysis. Structural connectivity analyses using diffusion tractography may help us address the clinical effectiveness of DBS by revealing the SC differences between responders and non-responders to chronic SCC DBS. In this study, we examine the SC differences between responder and non-responder groups at 6 and 24 months of chronic (six months) SCC DBS.

Methods

A. Subject and clinical/behavioral outcome: Diffusion data were obtained from 15 TRD patients (n=6 resp, n=9 non-resp for six month; n=11 resp, n=2 non-resp for two year (2 patients explanted), with response defined as a ≥50% decrease in depression severity relative to baseline). All patients underwent bilateral, microelectrode guided, stereotactic neurosurgical implantation of DBS electrodes (Libra XP, St. Jude Medical Neuromodulation, Plano, TX) into the SCC[1]. Clinical effectiveness was assessed using the Hamilton Depression Rating Scale (HDRS) at six months and 2 years. Active contact location was adjusted based on HDRS change and clinical assessments. Table 1 shows the active contact location and clinical outcome for six and two year time points. ***B. Image acquisition:*** CT data were acquired on a LightSpeed16 (GE Medical System) to register the location of the DBS electrodes (Figure 1a). 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. 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. ***C. Preprocessing of CT, T_1 and DTI:*** FSL (http://www.fmrib.ox.ac.uk/fsl) was used for preprocessing. First, susceptibility distortion of diffusion data was corrected using a combination of linear and nonlinear transformation of diffusion data to the pre-registered diffusion space T_1 image[8]. Second, T_1 data were skull stripped and segmented into three different tissue types (CSF, GM, and WM) using the Fast (FSL) toolbox. Diffusion data underwent eddy current correction, and local DTI fitting[9,10]. CT and diffusion images were co-registered to T_1 by an affine transformation and then normalized to the MNI152 template using nonlinear transformation information previously calculated by fnirt (FSL) in the nonlinear registration of T_1 to the MNI152 template. ***D. Calculating Volume of Tissue Activated (VTA):*** VTAs were calculated using Cicerone software (http://www.ciceronedbs.org) which was customized to the St. Jude electrode using the following DBS parameters; 6mA, 130Hz, and 90μs pulse width. The DBS VTA locations were first identified and generated in T_1 space based on the registered CT image, and then transferred to MNI space to be used later as seeds for probabilistic tractography (Figure 1b-d). The VTA size and Euclidian distance from brain center were measured and showed no statistical differences. ***E. Probabilistic tractography for structural connectivity:*** Probabilistic tractography was performed from bilateral active VTAs with individual CSF masks used as a stop mask to reduce tracking artifacts. Whole brain tractography was calculated from bilateral VTAs and binarized with a threshold value of 1 to generate the common population map of structural connection in each group (e.g., all subjects have these tracts). For quantitative SC analysis, 25 cortical and sub-cortical target regions were selected from the Harvard-Oxford structural atlas and modified based on previous functional and structural findings of this DBS target and related PET and fMRI studies: bilateral dorsolateral prefrontal cortex (BA9/46), inferior and superior medial frontal cortex (BA10), orbitofrontal cortex (BA11), anterior cingulate and paracingulate gyri, nucleus accumbens, caudate, putamen, thalamus, amygdala, and hippocampus. Five thousand streamline threads per voxel were generated from voxels in the left and right VTA, and the number passing through the target regions were counted. The number of threads passing through each voxel divided by the total number of threads generated was calculated as the probability of connection to that region.

Results & Discussion

Figure 2 illustrates the three groups' common connections based on whole brain tractography. Both responder group maps (a and c) show connections to bilateral medial frontal cortex and limbic regions. In contrast, the non-responder group map (b) shows connections to unilateral frontal cortex but insufficient connections to limbic regions. Interestingly, the two year responder group map (n=12) was nearly identical to the six month responder map (n=6). Notably, five of the 6 month non-responders had their active contacts adjusted during the course of chronic treatment after 6 months resulting in a positive change in clinical outcome. Figure 3 illustrates quantitative SC differences among the three groups. Compared to the six month non-responder group, the six month responder and two responder groups show strong probability of connections to medial frontal, bilateral inferior BA10, nucleus accumbens, putamen, and caudate. These maps demonstrate that a successful clinical outcome is dependent on both bilateral frontal cortex and limbic/subcortical connections, which may be ascertained prior to surgery using probabilistic tractography. Such an approach provides a new strategy for optimizing electrode implantation for SCC DBS.

References: [1] Mayberg HS, et al, Neuron 2005, 45:651– 660. [2]. Lozano AM, et al. Biol Psychiatry 2008, 64(6):461-467. [3]. Lozano Am, et al. J Neurosurg 2012, 116(2):315-322. [4] . Puigdemont D, et al., Int J Neuropsychopharmacol. 2011, 22:1-13. [5] Holtzheimer PE, et al. Arch Gen Psychiatry 2012, 69(2):150-158. [6]. Gutman, DA, et al. Biol Psych, 2009; 65:276–282. [7] Kennedy SH, et al. Am. J. Psychiatry 2011. 168(5),502-510. [8] Choi, K, et al. ISMRM2011 poster#1946. [9] Jenkinson M., et al., *NeuroImage* 2002. 17, 825–841. [10] Behrens TEJ, et al., *Magn. Reson. Med.* 2003. 50, 1077–1088.

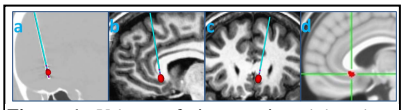

Figure 1. Volume of tissue activated based on individual stimulation parameters (60mA, 130Hz, 90 μs). a) Identifying electrode on CT image, b-c) Anatomical location of VTA in T1 space, d) Registered VTA on MNI space as a seed for tractography.

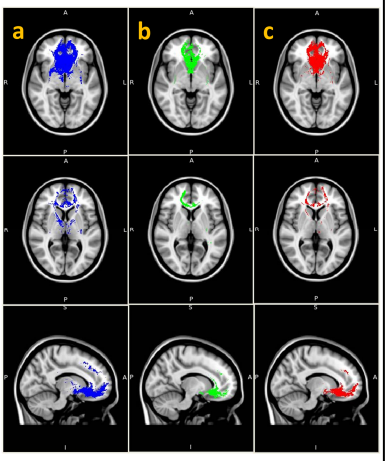

Figure 2. Common population map of whole brain structural connection a) in six month responder (Blue) and b) non-responder (Green), and c) Two year responder (Red).

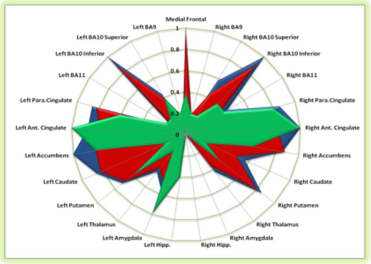

Figure 3. Structural connectivity from bilateral VTAs to 25 brain target regions for six month non-responder (Green), six month responder (Blue), and two year responder (Red). Compared to the six month non-responder group, six month and two year responder show strong connection to medial frontal, bilateral inferior BA10, nucleus accumbens, putamen, and caudate.

ID	Six month Active		Clinical Outcome (Six months)	Two years Active		Clinical Outcome (two years)
	Left	Right		Left	Right	
1	2	1	Non-Responder	3	3	Responder
2	2	2	Responder	3	3	Responder
3	4	4	Non-Responder	3	3	Responder
4	3	3	Non-Responder	Explanted		-
5	2	2	Non-Responder	Explanted		-
6	2	3	Non-Responder	2	3	Non-Responder
7	2	2	Responder	2	2	Responder
8	3	4	Non-Responder	3	4	Responder
9	2	3	Responder	3	2	Responder
10	2	2	Responder	2	2	Responder
11	2	3	Non-Responder	2	3	Responder
12	3	4	Responder	3	4	Responder
13	4	3	Responder	4	3	Responder
14	3	3	Non-Responder	3	3	Responder
15	3	2	Non-Responder	2	3	Non-Responder

Table 1 Active stimulation contact and clinical outcome for six months and two years