Predicting Effectiveness of Cortical Stimulation Therapy for Tinnitus using DTI

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INTRODUCTION: Tinnitus affects over 40 millions of Americans with about 12 millions that seek medical attention for its treatment, of which 2 millions are debilitated enough to have problems functioning in day-to-day life (American Tinnitus Association). Most treatments of tinnitus are unsuccessful as a result of poor understanding of the diverse pathophysiology of the disease. Epidural cortical electrical stimulation (EpCS) is a method that has shown promise to alleviate the symptoms for patients suffering from severe tinnitus [1, 2]. However, outcomes of EpCS vary greatly across patients and depend on finding biomarkers that predict its effectiveness and on optimizing the target site for electrode implantation. Recent studies using resting state MEG have shown altered connectivity between auditory and limbic networks in tinnitus patients [3, 4], with abnormally strong oscillations in the delta and theta band spectrum in these networks [5]. Diffusion Tensor Imaging (DTI) has been used previously to characterize neuroanatomical changes in tinnitus patients [6, 7]. Here, we are using DTI tractography as a means to study changes in cortical connections and diffusion metrics to characterize the potential target site with respect to the stimulation effectiveness of EpCS.

METHODS:

Subjects. The study was approved by the Institutional Review Board of the Medical College of Wisconsin. Eight adults (32-67 years old) that were selected for implantation within a clinical trial were included in this study. The inclusion criteria were severe tinnitus that was continuously present for more than one year and failed to respond to other treatments having a tinnitus percept that ranked greater than 35% on the Tinnitus Handicap Questionnaire and was predominantly monaurally with symptomatic tonal presentation below 8kHz. Patients with Meniere's disease, acoustic tumors, medical history of seizure disorders or epilepsy or any neurological condition that would reduce the safety of study participation and MRI scanning were excluded from the study. One subject who could not tolerate the post-op MRI scan was not included in the results.

EpCS and Behavioral Data collection. The EpCS system was implanted at the location found by auditory FMRI for the frequency of maximum tinnitus percept as estimated during audiology evaluation. Electrode positions were confirmed on a post-op CT image. Half of the subjects were sent home with the device activated, based on a blinded randomized treatment plan alternating between a two-week stimulation period and a two-week sham period, followed by continuous stimulation with ongoing optimization of stimulation parameters, details are published elsewhere [2]. Reduction of the tinnitus percept by EpCS therapy was quantified by a Maximum Stimulation Effectiveness Rating (MSER).

MRI and DTI acquisition. After completion of the clinical trial and explantation of the stimulator the tinnitus percept returned to pre-treatment levels and the subjects underwent post-treatment MRI scanning including DTI for the current study. Imaging was done at the Center of Imaging Research of the Medical College of Wisconsin on a Short-Bore GE 3T MRI scanner equipped with an 8-channel phased-array receive coil. Anatomical 3D Spoiled Gradient (SPGR) images were collected followed by a high-order shim protocol and the DTI acquisition. The parameters for the 3D SPGR were TI/TE/TR=450/4/10ms, flip-angle 12º, 180 slices with 1mm thickness, 22cm FOV, 256x256 matrix. The parameters for the DTI were TE/TR=84ms/14s, 24cm FOV, 2mm slice thickness, 128x128 matrix, twice-refocused spin echo, b=1000s/mm^2, 19 directions, 3 repeated scans.

Data Analysis. DTI was analyzed in AFNI [8] correcting for motion and tensor alignment before combining the 3 repeated acquisitions into one dataset with 57 directions for tensor estimation. Fiber tractography was performed in DTI-Query [9] using the Streamline Tracking algorithm (Figure 1A). Results of tractography were used to calculate total number of voxels, streamlines per voxel, average fractional anisotropy (FA), and average mean diffusivity (MD) values associated with the fiber bundles. We used electrode locations from the post-op CT image to calculate average FA and MD values within a 15mm shell beneath the electrode contacts (Figure 1B). Regression analysis was used to determine the correlation between average FA, MD, streamlines per voxel and total number of voxels with the MSER.

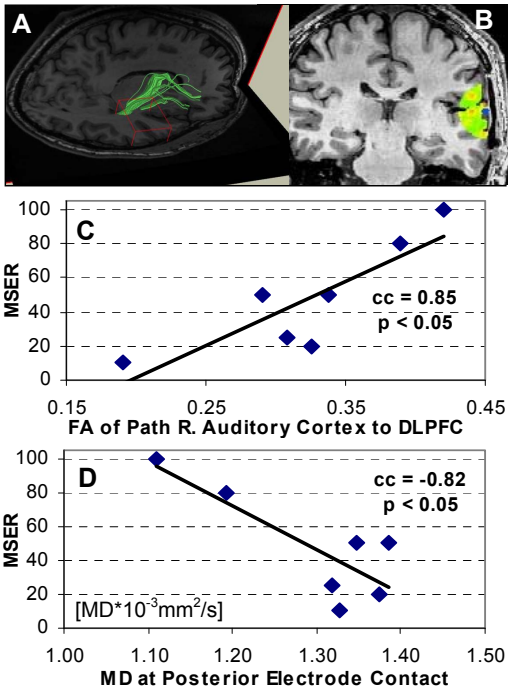

Figure 1. Fiber Tracking for right AC-DLPFC path (A) and relationship of MSER and FA for that fiber path (C). MD within a 15mm shell around posterior electrode (B), and relationship of MSER and MD for that electrode (D).

RESULTS: Figure 1C shows the significant correlation (c=0.85, p<0.05) between MSER and the average FA value for the pathway connecting the right dorsolateral prefrontal cortex (DLPFC) and the right auditory cortex (AC) for all subjects. Figure 1D demonstrates the significant negative correlation (c=-0.82, p<0.05) between MSER and the average MD in proximity (15mm shell around electrode contact) to the posterior electrode for all subjects.

DISCUSSION: The DLPFC has been found in studies of normal subjects and depression patients to modulate attention and emotional control [10, 11]. Transcranial direct current stimulation of the DLPFC has also been shown to reduce pain perception [12] or reduce tinnitus for some patients [13]. In our study, a higher MSER score correlated with a higher FA in the DLPFC-AC pathway suggesting a stronger connection between these areas in better EpCS responders and making DTI a likely predictor for treatment effectiveness. The lower MD at the posterior electrode contact for higher MSER scores is likely to be caused by higher axonal density in proximity to the electrode, influencing the current spread and indicating the importance of electrode placement which we will further study using Finite Element Modeling

REFERENCES: **[1]** De Ridder D, et al. J Neurosurg, 100(3): p.560-4, 2004. **[2]** Friedland DR, et al. Otol Neurotol, 28(8): p.1005-12, 2007. **[3]** Rauschecker JP, et al. Neuron, 66(6): p.819-26, 2010. **[4]** Schlee et al. BMC Biol, 7: p.80, 2009. **[5]** Llinas et al. Trends Neurosci, 28(6): p.325-33, 2005. **[6]** Crippa et al. Open Neuroimag J, 4: p.16-25, 2010. **[7]** Husain et al. Brain Res, 2010. **[8]** Cox RW. Comput Biomed Res, 29(3): p.162-73, 1996. **[9]** Sherbondy et al. IEEE Trans Vis Comput, 11(4): p.419-30, 2005. **[10]** Wang et al. J Cogn Neurosci, 22(3): p.543-53, 2010. **[11]** Bermpohl et al. Neurosci Lett, 463(2): p.108-13,2009. **[12]** Fregni et al. Arthritis Rheum, 54(12): p.3988-98, 2006. **[13]** Vanneste et al. Exp Brain Res, 202(4): p.779-85, 2010.