Predict the Response of Tinnitus to Cortical Stimulation Using Resting-State Functional MRI

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INTRODUCTION

Epidural cortical stimulation (EpCS) has been demonstrated to be a potential therapeutic intervention for the suppression of severe tinnitus (1). However, individual response rates to EpCS vary substantially. Research on brain mechanisms of tinnitus suggests that tinnitus, in addition to the acoustic component, may have attentional and emotional components (2), and the insula and cingulate are involved in attention and emotion processing (3-5). A recent electroencephalogram (EEG) study found spectral power increased in insular and cingulate areas in tinnitus patients (6). In this study, we hypothesize that the EpCS effectiveness variation can be explained by the intersubject difference in functional connectivity between the insula, the cingulate and EpCS site. The stronger the connectivity, the more tinnitus can be alleviated by EpCS.

MATERIALS AND METHODS

Subjects. The study was approved by the Institutional Review Board of the Medical College of Wisconsin. Eight adults ages 32 to 67 were eligible for implantation based upon inclusion and exclusion criteria (One subject who could not tolerate an MRI scan was excluded in this study). All subjects had tinnitus percept continuously for more than one year, perceived tinnitus predominantly in one ear, perceived tinnitus of tone less than 8,000 Hz and a score greater than 33 on the Tinnitus Reaction Questionnaire (TRQ). Active Me´nie`re's disease, intracranial neoplasm, current substance abuse, or medical conditions preventing safe implantation represented the exclusion criteria.

EpCS and evaluation. Surgical implantation of an investigational epidural electrode was conducted over the posterior superior temporal gyrus (PSTG), contralateral to the side of tinnitus percept, using a functional magnetic resonance imaging (fMRI)-method. The subjects were given a randomized, blinded**,** treatment paradigm consisting of a two-week stimulation period alternating with a two-week sham period. This was followed by continuous stimulation with parameter adjustments to maximize tinnitus suppression. The procedures of preimplantation testing, surgical implantation and postimplant evaluation have been previously published in detail (1). A Maximum Stimulation Effectiveness Rating (MSER) score was used to evaluate the suppression of subjective tinnitus produced by EpCS.

MRI and Resting-state-fMRI (R-fMRI) data were acquired after completion of the treatment trial, specifically when the subjects had been explanted and their tinnitus perception returned to preimplantation level. Imaging was performed using a short-bore General Electric Signa 3T MR scanner with an 8-channel phased-array receiver coil at the Center for Imaging Research at the Medical College of Wisconsin. An automated shimming protocol was used to improve the field homogeneity and reduce image distortion. During the resting-state acquisitions, no specific cognitive tasks were performed. The study participants were instructed to close their eyes and relax. Axial resting-state functional MRI (fMRI) datasets of the whole brain were obtained in 8 minutes with a single-shot gradient echo-planar imaging (EPI) pulse sequence. The fMRI imaging parameters were: TE of 25 ms, TR of 2 s, flip angle of 90º; 32 slices were obtained; slice thickness was 4 mm with a matrix size of 64×64 and field of view of 22×22 cm. High-resolution SPGR 3D axial images were acquired for anatomical reference. The parameters were: TE/TR/TI of 4/10/450 ms, flip angle of 12º, number of slices of 180, slice thickness of 1 mm, matrix size of 256×256. A series of preprocessing steps common to most fMRI analyses was conducted, using the Analysis of Functional NeuroImages (AFNI) software (http://afni.nimh.nih.gov/afni/). The preprocessing includes allowing for T1-equilibration effects; slice-acquisition-dependent time shifts correction; despiking; motion correction; detrending; removal of white matter, CSF and global signal effects; and low-frequency band-pass filtering, as previously described in detail (7). The functional connectivity between the insula, cingulate and implant site (PSTG) was assessed by the Pearson product-moment correlation coefficient of ongoing BOLD fluctuations.

Statistical Analysis. Regression analysis was performed between the functional connectivity values and Maximum Stimulation Effectiveness Rating (MSER).

RESULTS

Figure1A shows significant positive correlation ($r = 0.84$, $P = 0.0168$ uncorrected) between the MSER and functional connectivity between the left insula and the implant site; the brain regions are illustrated in Figure 1B. Figure1C shows significant positive correlation ($r = 0.85$, $P = 0.0142$ uncorrected) between the MSER and functional connectivity between the left cingulate and the implant site; the brain regions are illustrated in Figure 1D.

DISCUSSION

The results support our hypothesis that variations in individual response rates to EpCS can be explained by intersubject differences in functional connectivity between the insula, cingulate and EpCS site. Intersubject differences in functional connectivity between the insula, cingulate and EpCS site could be related to possible tinnitus pathophysiological variations. The attention and/or the emotion component of the tinnitus could be modified by EpCS through neuromodulation. However, because the functional connectivity of the subjects was measured after the subjects were explanted, and it is assumed that their functional connectivity had returned to baseline once their tinnitus perception returned to preimplantation level, our study requires further confirmation by a validation cohort with preimplantation imaging data. Confirmation of these preliminary findings could ultimately lead to the development of efficient and cost-effective approaches in patient selection, and the prediction of EpCS treatment efficacy.

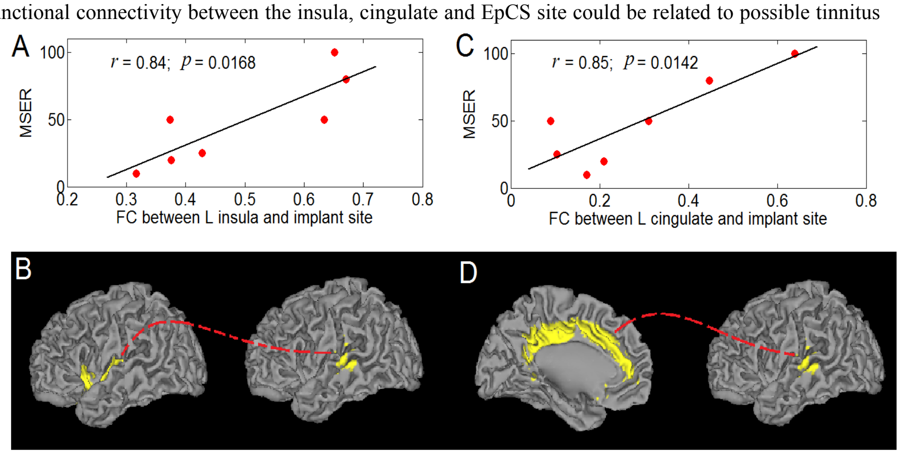

Figure 1. Relationship between the MSER and FC. (A) Correlation between the MSER and FC between the left insula and the implant site. (B) Illustration of left insula and the implant site. (C) Correlation between the MSER and FC between the left cingulate and the implant site. (D)Illustration of the left cingulate and the implant site. MSER=Maximum Stimulation Effectiveness Rating. FC= functional connectivity.

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