Tinnitus percept is associated with magnetoencephalography-derived measures of resting state connectivity between temporal and frontal cortices

Corby L Dale[1], Leighton BN Hinkley[1], Jennifer Henderson-Sabes[2,3], Cole Davis[4], Abhishek Bhutada[1,5], Lingwei Ouyang[1,6], Andrew P Walther[1,7], Wenbo Zhang[4], Meredith E Adams[8], Srikantan S Nagarajan[1,2,9], Steven W Cheung[2,10]

[1] Department of Radiology and Biomedical Imaging, University of California San Francisco
[2] Department of Otolaryngology—Head and Neck Surgery, University of California San Francisco
[3] University of the Pacific, Department of Audiology
[4] Minnesota Epilepsy Group, John Nasseff Neuroscience Center at United Hospital in St. Paul, MN
[5] Graduate School of Medicine, Virginia Tech
[6] Graduate program in Psychology, University of Texas at Austin.
[7] Summer undergraduate intern program, ci2 Center for Intelligent Imaging, University of California San Francisco
[8] Department of Otolaryngology—Head and Neck Surgery, University of Minnesota
[9] UCB-UCSF joint program in Bioengineering and Therapeutic Sciences
[10] Surgical Services, Department of Veterans Affairs, San Francisco.

Subjective tinnitus refers to conscious perception of sound for which no external auditory stimulus is identified. Models of tinnitus postulate increased connectivity between auditory cortex and basal ganglia, limbic areas, or frontal areas. Brain imaging may objectively determine presence and magnitude of percept and assist in understanding underlying physiology.

At one of 2 study sites, 380 adults with (N = 185) and without (N = 195) tinnitus underwent 5 minutes of task-free eyes-closed magnetoencephalography (MEG), structural imaging (MRI), audiometry, and tinnitus assessment (TFI). A subset (N=44) repeated the study. Source imaging localized 1 to 4 minutes of MEG activity within brain anatomy. Voxel-based activity, parsed into 6 frequency bands and spatially-normalized, was mapped to 246 Brainnetome atlas regions. Imaginary coherence (ImCoh) and directional phase transfer entropy (dnPTE) were calculated between each unique pair of regions. Analysis of variance (rmANOVA), repeated across frequency with group, age, and site, provided F-ratios and FDR-corrected p-values for pairwise connectivity, as well as relation to TFI. Binomial linear regression queried contribution of band to group effects. Linear discriminant analysis with 10-fold cross validation assessed potential for classification.

Groups differed at 4 pairs out of 30,012 queried. Using ImCoh, tinnitus exhibited increased slow oscillatory connectivity between regions in left temporal and right frontal cortex (LPHG-RIFC: $F=9.00$, $p<.01$) and (LITC-ROFC: $F=9.04$, $p<.01$), driven by delta (1 - 3 Hz, LPHG-RIFG: $B = 25.8$, $t=4.21$; LITC-ROFC: $B = 15.6$, $t=3.14$, both $p<.01$). For dnPTE, tinnitus showed decreases in intrahemispheric high gamma (63 – 117 Hz) connectivity between portions of cingulate and parietal cortex (Left: $F=12.4$, $B = -1.16$, $t=-4.67$, $p<.01$; Right: $F=12.31$, $B = -1.16$, $t=-3.97$, $p<.01$). Using connectivity of these pairs in identified bands as classifiers produced acceptable levels of diagnostic performance (AUC =.74 [.68 - .78]). TFI scores changed from Session 1 to 2 (paired $t=2.13$, $p=.045$), but with considerable distribution overlap (K-S test, $K=.27$, $p=.33$).

Tinnitus-related differences in connectivity can adequately classify tinnitus and non-tinnitus participants. Commonalities among these 4 regions may further our understanding of the underlying physiology of tinnitus. Paradoxically, group connectivity differences did not relate to subjective scores used to diagnose tinnitus. However, TFI appeared to change from session-to-session, while connectivity largely did not, indicating that neural measures of tinnitus may be more stable than subjective measures.