

## Central neural activity in rats with tinnitus evaluated with MEMRI

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**INTRODUCTION:** Tinnitus is the phantom perception of sound in the absence of any external auditory stimulation. Chronic tinnitus is experienced by an estimated 30 million adults in the United States. One in every 200 adults is disabled by their tinnitus with significantly impaired quality of life. Despite decades of research on humans and animals, current understanding of tinnitus pathophysiology remains limited. At present there is no proven therapy for treating tinnitus. The onset of tinnitus is often attributed to damage or dysfunction within the peripheral auditory pathway, since tinnitus most commonly is associated with presbycusis or hearing loss from acoustic trauma. Despite our limited understanding of the disorder, a growing body of evidence implicates inappropriate neural activity in the central nervous system stemming from trauma-induced long-term plastic changes involving loss of inhibition and neural reorganization. The application of imaging techniques in tinnitus research has shown that functional changes at more than one brain level are likely responsible for the development and persistence of tinnitus. fMR imaging of humans with a unique form of tinnitus that can be manipulated with somatic-modulation established that central auditory hyperactivity is associated with the tinnitus sensation. Subsequent work using fMRI successfully imaged tinnitus activity in the inferior colliculus (IC) [1]. Further application of imaging techniques to obtain objective measures of tinnitus and to monitor the response to therapy will contribute significantly to the advance of tinnitus research.

**METHODS:** The present study used the technique of manganese-enhanced MRI (MEMRI) to assess neural activity in the central auditory pathway of Long-Evans rats with psychophysical evidence of tinnitus produced by unilateral acoustic trauma. Manganese ( $Mn^{2+}$ ) acts as an activity-dependent paramagnetic contrast agent by accumulating in active neurons through voltage-gated calcium channels, primarily at synapses. Previous work has demonstrated the sensitivity of MEMRI to sound-evoked neural activity within the cochlear nucleus (CN) and IC of the auditory brainstem of mice [2]. We applied this technique to image the tinnitus-associated activity in these structures, in rats with psychophysical evidence of tinnitus.

**RESULTS AND DISCUSSION:** Long-Evans rats with evidence of tonal tinnitus were imaged using a 14.1 tesla vertical imaging system (Oxford Instruments, Abington, UK) equipped with a Unity console (Varian, Palo Alto, CA). Tinnitus was induced using a single 1-hr unilateral exposure to loud (116 dB, SPL, peak level) octave-band noise centered at 16 kHz, from 1 day to 15 months prior to imaging.  $MnCl_2$  (120 mM / kg body weight) was administered intraperitoneally 24 hrs prior to imaging. Transverse 2-D sections, obtained using a spin echo multi slice pulse sequence (TR = 350ms, TE = 10 ms, FOV: 2.5 x 2.5 cm<sup>2</sup>, matrix size: 256 x 256, slice thickness: 500 $\mu$ m, number of transients: 16), were stored as TIFF images and analyzed using Adobe Photoshop (6.0). Flattened grayscale images were quantified for intensity level using 5 x 5 pixel samples scanned systematically over the structures of interest, with particular attention to the CN and IC. The CN is the first major area processing auditory information in the brain, and its dorsal aspect (DCN) has been implicated by electrophysiological measures to play an important role in tinnitus. The primary rostral target of the DCN is the contralateral IC, which has also been implicated in playing an important role in tinnitus pathophysiology. As expected, it was shown that acute sound exposure 24 hrs prior to imaging produced a significant ( $p < 0.00001$ ) increase in neural activity within the DCN ipsilateral to the exposed ear (Fig. 1). In the same subject, however, activity was increased in the IC contralateral (i.e., direct pathway, Fig. 2) to the ear exposed 15 months prior, and this activity exceeded that of the IC contralateral to the acutely exposed ear ( $p = 0.00004$ ).

**CONCLUSION:** The long-term effects of acoustic trauma are evident as increased neural activity in the IC over a year after the trauma exposure, and this activity exceeds that produced by immediate sound exposure. This evidence, as indicated by MEMRI, may help explain why tinnitus patients complain about the persistent "ringing in their ears" despite ambient sounds levels that might be expected to mask such endogenous auditory activity. Further application of the MEMRI method in tinnitus research may reveal the functional distribution of neuropathology associated with the disorder.

**REFERENCES:** [1] Melcher JR, et al., J. Neurophysiol. 2000 ; 83(2) : 1058-72. [2] X. Yu, et al., Nature Neuroscience 2005 ; 8 (7) : 961-968.

