Editorial: Imaging Tinnitus

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Recent advances in functional imaging (FI) have opened new possibilities for understanding and ultimately treating tinnitus. Previously, tinnitus has been characterized by its perceptual properties (e.g., pitch, loudness, masking patterns) and its psychological properties (e.g., degree of distress), as well as its relationship to clinical findings such as abnormalities of the audiogram, the cerebellopontine angle, or the soft tissues of the head or neck. In contrast, FI provides an entirely new view of tinnitus by revealing the workings of the brain directly in tinnitus patients. The application of FI to tinnitus is still in its infancy. However, FI is already providing new insights into the neurophysiology of tinnitus, and there are many foreseeable ways for it to eventually impact on patient care.

What is FI? FI techniques reveal spatial patterns of neural activity in the brain. The two most widely-used FI techniques are positron emission tomography (PET) and a particular form of magnetic resonance imaging (MRI) called functional MRI (fMRI). In PET, a radioactive tracer is used to measure physiological indicators of neural activity such as glucose metabolism, neurotransmitter receptor binding, or blood flow. PET can be used (a) to detect the spatial pattern of steady-state brain activity, and (b) to show where activity *changes* in the brain e.g., in response to sound or a change in tinnitus. The second technique, fMRI, can only show changes in brain activity, but does not use a tracer substance. In its most common form, fMRI detects changes in blood oxygenation that occur naturally where brain activity changes.

How has FI been applied to tinnitus? Over the past five years a succession of reports have demonstrated abnormal brain activity in people with tinnitus. While these investigations have focussed mainly on a few particular types of tinnitus, they demonstrate the feasibility of techniques that should be generalizable to tinnitus in its many forms.

FI has been applied to tinnitus in three main ways. One approach has used the fact that tinnitus can sometimes be modulated by oral-facial movements, deviations in eye position, or cutaneous stimulation (Cacace et al., 1995, 1999; Lockwood et al., 1998, 1999; Giraud et al., 1999). When these manipulations were used to alter tinnitus loudness, corresponding changes in cortical activity were detected with PET or fMRI. A second approach has modulated tinnitus using an acoustic masker and localized correlated changes in brain activity (Levine et al., 1997; Mirz et al., 1999; Melcher et al., 2000). The third approach has used PET to examine the level of steady-state activity in the brain of tinnitus patients (Arnold et al., 1996; see also Shulman and Strashun, 1995). The FI data that has accumulated so far are broadly consistent with the idea that the tinnitus percept corresponds to abnormally high levels of neural activity in both cortical and subcortical auditory areas. The reports of Lockwood et al. (1998) and Melcher et al. (2000) raise the possibility that FI may provide insights into the psychological aspects of tinnitus such as the associated distress.

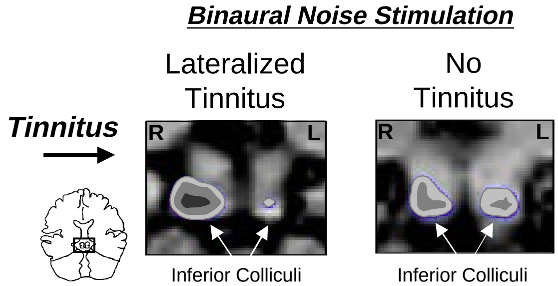

Figure 1: Binaural noise produced abnormal (asymmetric) fMRI activation in the inferior colliculi of patients with lateralized tinnitus. Images are from subjects with (left panel) and without (right panel) tinnitus. The tinnitus percept was lateralized to the right ear (indicated by arrow). In each panel, activation in response to noise is superimposed on an anatomical image of the inferior colliculi. The activation is shown as concentric regions of grayshading; successively darker shades of gray indicate progressively higher levels of activation. The area shown in the two panels is indicated on the diagramatic brain slice at the far left. Right: R, Left: L. (Adapted from Melcher et al., 2000)

Figure 1 shows an example of one brain abnormality that has been seen reproducibly in tinnitus patients. The data are from an fMRI study of individuals with tinnitus lateralized to one ear and normal hearing thresholds. In response to a binaural masking stimulus, the tinnitus subjects showed asymmetric activation at the level of the inferior colliculi (left panel). In contrast, control subjects showed relatively symmetric activation (right panel). The asymmetry in the tinnitus subjects was specifically attributable to abnormally low activation in the inferior colliculus contralateral to the tinnitus percept (i.e., the left inferior colliculus in Figure 1).

A straightforward interpretation of this abnormality is as follows: (a) there was an abnormally high level of neural activity in the inferior colliculus contralateral to the tinnitus percept, and (b) this "tinnitus-related" activity was sufficiently high that any additional activity evoked by sound was limited by saturation. As this hypothesis and others are systematically tested, we expect that the neurophysiological basis of tinnitus will be better understood.

How might FI help tinnitus patients? As FI tells us more about the physiology of tinnitus, what impact can this have on the care of patients?

Predicting treatment outcome. One possibility is that FI will provide new criteria for distinguishing between tinnitus patients – criteria that then correlate with prognosis or responsiveness to treatment. Numerous tinnitus therapies have been proposed and tried such as acoustic therapy (masking, tinnitus retraining therapy), pharmacological therapy (medications and herbs), physical modalities (acupuncture, manipulation, trigger point injections, electrical stimulation), surgery (microvasular decompression, auditory nerve transection), and psychological therapies (cognitive therapy, self-hypnosis, biofeedback). While none of these therapies has proven to be widely effective, reports and anecdotes abound suggesting that at least some may benefit certain fractions of the overall tinnitus population. Unfortunately, perceptual and psychological characteristics of tinnitus have not been successful in predicting whether a patient will respond to a particular treatment. However, by also considering a patient's brain activity patterns, it may finally be possible to predict whether their tinnitus will be relieved by a particular therapy. As a simple example, consider auditory nerve transection, an approach that has provided relief for some individuals, but not for others. It is conceivable that the patients who respond to this surgery are those whose tinnitus arises peripherally (rather than centrally) as might be shown with FI.

Objectively measuring tinnitus in humans. In the past, the effectiveness of tinnitus treatments has been evaluated using indicators such as reports of tinnitus loudness, or the overall feeling of patients. However, these indicators are subjective, so assessing them can be fraught with pitfalls. By providing objective measures of tinnitus, FI can circumvent this problem. In short, it can provide a means for reliably and quantitatively assessing treatments.

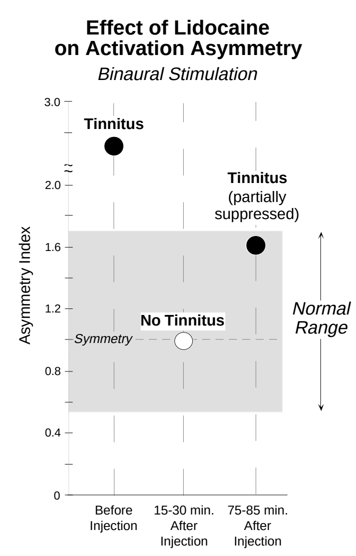

Figure 2: Lidocaine suppressed tinnitus and the fMRI activation abnormality in a patient with tinnitus lateralized to the right ear. Activation asymmetry in the inferior colliculi is plotted vertically for three intervals: before, shortly after, and longer after intravenous lidocaine. Activation asymmetry was quantified as the ratio of right and left inferior colliculus activation. (Adapted from Melcher et al., 1999)

This point is illustrated in Figure 2 which shows results from an fMRI experiment in which we tracked the effects of intravenous lidocaine. The subject was a woman with normal hearing and tinnitus lateralized to her right ear. Prior to lidocaine, binaural noise produced abnormal (i.e. asymmetric) fMRI activation in the inferior colliculi. Shortly after lidocaine, the patient's tinnitus disappeared and her fMRI activation became normal (i.e. symmetric). Later, the patient's tinnitus returned, and the fMRI abnormality (i.e.

activation asymmetry) reappeared. In other words, the pattern of activation was closely coupled to the presence or absence of tinnitus. This particular evaluation was over a short time-period, but one can also imagine longer-term evaluations over the course of clinical trials.

Detecting tinnitus in animals. The fact that FI can provide objective indicators of tinnitus has direct implications for animal models of tinnitus. These models are important because they can be used to investigate tinnitus and explore treatments in ways that are not possible in humans. A long-standing difficulty in animal work has been the uncertainty as to whether the animals under study (e.g., with cochlear or auditory-nerve damage) have tinnitus. While this uncertainty can be resolved using behavioral measures of tinnitus, establishing these measures requires fairly lengthy testing. Using FI, it may be possible to rapidly and objectively determine whether or not a given animal has tinnitus, and even infer some attributes of the tinnitus based on patterns of brain activation (e.g., infer lateralized tinnitus based on abnormal activation asymmetries; Figure 1). As a biological marker for tinnitus, FI abnormalities could be used to rapidly screen candidate treatments in animals as a precursor to clinical trials. In addition, FI abnormalities can point to what are likely to be fruitful sites to target in investigations of the cellular and subcellular mechanisms of tinnitus. Such investigations could take advantage of the full spectrum of physiological, anatomical, and pharmacological techniques, not just the noninvasive ones applicable to human subjects.

Developing new treatments. As FI provides previously unavailable physiological information about tinnitus, new therapies may well emerge. For instance, FI might reveal that certain subgroups of tinnitus sufferers show abnormal activity in specific brain centers (e.g the dorsal cochlear nucleus in patients with lateralized tinnitus due to an otic or somatic insult; Levine R.A., *Am. J. Otolaryngol.* 20: 351-362, 1999). One might then try to influence the abnormal activity by direct electrical stimulation, drugs delivered locally, or even ablative surgery. By playing a role in animal work, FI may assist in improving our understanding of the detailed mechanisms of tinnitus, which in turn may suggest effective drug treatments. One can also imagine ways that work in humans and animals might inform one another in the development of treatments. For instance, if FI in humans were used to identify where intravenous lidocaine acts when it temporarily suppresses tinnitus, those sites could be intensively studied in animals to understand lidocaine's mechanisms of action. The goal would be to identify drugs that act by similar mechanisms, but without the impracticalities of intravenous lidocaine – in other words, a tinnitus treatment.

Conclusion Based upon progress so far, FI has great potential for advancing our understanding of tinnitus and improving our ability to treat the many patients plagued by this disorder.

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