

Lateralized Tinnitus Studied With Functional Magnetic Resonance Imaging: Abnormal Inferior Colliculus Activation

J. R. MELCHER,¹⁻³ I. S. SIGALOVSKY,^{1,3} J. J. GUINAN, JR.,¹⁻³ AND R. A. LEVINE¹⁻⁴

¹Eaton-Peabody Laboratory, Massachusetts Eye and Ear Infirmary, Boston 02114; ²Department of Otolaryngology, Harvard Medical School, Boston 02114; ³Speech and Hearing Sciences Program, Harvard-MIT Division of Health Sciences and Technology, Massachusetts Institute of Technology, Cambridge 02139; and ⁴Neurology Service, Massachusetts General Hospital, Boston, Massachusetts 02114

Melcher, J. R., I. S. Sigalovsky, J. J. Guinan, Jr., and R. A. Levine. Lateralized tinnitus studied with functional magnetic resonance imaging: abnormal inferior colliculus activation. *J. Neurophysiol.* 83: 1058–1072, 2000. Tinnitus, the perception of sound in the absence of external stimuli, is a common and often disturbing symptom that is not understood physiologically. This paper presents an approach for using functional magnetic resonance imaging (fMRI) to investigate the physiology of tinnitus and demonstrates that the approach is effective in revealing tinnitus-related abnormalities in brain function. Our approach as applied here included 1) using a masking noise stimulus to change tinnitus loudness and examining the inferior colliculus (IC) for corresponding changes in activity, 2) separately considering subpopulations with particular tinnitus characteristics, in this case tinnitus lateralized to one ear, 3) controlling for intersubject differences in hearing loss by considering only subjects with normal or near-normal audiograms, and 4) tailoring the experimental design to the characteristics of the tinnitus subpopulation under study. For lateralized tinnitus subjects, we hypothesized that sound-evoked activation would be abnormally asymmetric because of the asymmetry of the tinnitus percept. This was tested using two reference groups for comparison: nontinnitus subjects and nonlateralized tinnitus subjects. Binaural noise produced abnormally asymmetric IC activation in every lateralized tinnitus subject ($n = 4$). In reference subjects ($n = 9$), activation (i.e., percent change in image signal) in the right versus left IC did not differ significantly. Compared with reference subjects, lateralized tinnitus subjects showed abnormally low percent signal change in the IC contralateral, but not ipsilateral, to the tinnitus percept. Consequently, activation asymmetry (i.e., the ratio of percent signal change in the IC ipsilateral versus contralateral to the tinnitus percept) was significantly greater in lateralized tinnitus subjects as compared with reference subjects. Monaural noise also produced abnormally asymmetric IC activation in lateralized tinnitus subjects. Two possible models are presented to explain why IC activation was abnormally low contralateral to the tinnitus percept in lateralized tinnitus subjects. Both assume that the percept is associated with abnormally high (“tinnitus-related”) neural activity in the contralateral IC. Additionally, they assume that either 1) additional activity evoked by sound was limited by saturation or 2) sound stimulation reduced the level of tinnitus-related activity as it reduced the loudness of (i.e., masked) the tinnitus percept. In summary, this work demonstrates that fMRI can provide objective measures of lateralized tinnitus and tinnitus-related activation can be interpreted at a neural level.

INTRODUCTION

Tinnitus, the perception of sound in the absence of external stimuli, is experienced chronically by many individuals and, by

some estimates, prevents 1 of every 200 adults from leading a normal life (Coles 1984a; Leske 1981). Tinnitus can occur in conjunction with any of a wide variety of ear diseases and disorders including impacted cerumen, acoustic neuroma, Ménière’s disease, acoustic overstimulation, and otosclerosis (Fowler 1948; Reed 1960). It also can be associated with somatic disorders involving the upper cervical region or head (e.g., whiplash and temporomandibular joint syndrome) (Chole and Parker 1992; Claussen and Constantinescu 1995; Rubinstein et al. 1990). In some cases, tinnitus can be traced to an internally generated sound (e.g., spontaneous otoacoustic emissions), but in the overwhelming majority of serious complainants, there is no obvious sound source to account for the tinnitus percept (Fowler 1944; Penner 1990; Sismanis and Smoker 1994). Although many therapies have been proposed and tried, there is no systematic and proven approach for treating tinnitus (Tyler 1997).

At present, there is no clear view of the neural abnormalities underlying tinnitus, although investigations have been aimed at studying tinnitus-related brain activity in both humans and experimental animals. The animal work has involved performing manipulations that can cause tinnitus in humans (e.g., acoustically overstimulating, administering ototoxic drugs or high doses of salicylate) and assessing the physiological consequences by measuring spontaneous single- or multiunit activity (Chen and Jastreboff 1995; Eggermont and Kenmochi 1998; Evans and Borerwe 1982; Evans et al. 1981; Jastreboff and Sasaki 1986; Kaltenbach and McCaslin 1996; Kaltenbach et al. 1998; Kiang et al. 1970; Manabe et al. 1997; Ochi and Eggermont 1996; Stypulkowski 1990; Zhang and Kaltenbach 1998), the spectra of gross potentials (Cazals et al. 1998; Martin et al. 1993, 1996; Schreiner and Snyder 1987), glucose metabolism (Kauer et al. 1982; Sasaki et al. 1980; Wallhäusser-Franke et al. 1996), or *c-fos* expression (Jastreboff and Jastreboff 1996; Wallhäusser-Franke 1997). A fundamental limitation in this work has been the uncertainty as to whether or not the animals under study have tinnitus. The uncertainty is less in salicylate-treated animals because salicylate uniformly causes tinnitus in normal-hearing humans when serum salicylate reaches sufficiently high levels (Mongan et al. 1973) and therefore might be expected to result in tinnitus in animals when delivered at high doses. A limitation to the salicylate model, however, is that the mechanisms resulting in tinnitus may be quite different from those underlying tinnitus of other causes, so the salicylate results may not be generalizable to

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other forms of tinnitus. The uncertainty as to whether or not an animal has tinnitus is a critical issue for animal models using other manipulations such as acoustic overstimulation or ototoxic drug treatment because such manipulations in humans do not uniformly result in tinnitus even among audiometrically comparable cases (Attias et al. 1993). Although behavioral methods have been described for assessing whether animals have tinnitus (Jastreboff and Sasaki 1994; Jastreboff et al. 1988), there are few physiological data in animals evaluated with this behavioral protocol (Kaltenbach and Heffner 1999).

In human subjects with tinnitus, various noninvasive techniques have been used to probe for tinnitus-related brain abnormalities. For example, there have been numerous reports of evoked potentials recorded in tinnitus patients, but only a fraction have attempted to isolate evoked potential abnormalities related to tinnitus from those related to hearing loss, which often is associated with tinnitus and by itself can result in highly abnormal evoked potential waveforms (Coats and Martin 1977; Coles 1984b; Meikle et al. 1992; Pettigrew et al. 1984; Rosenhamer 1981). Even among studies that have controlled for hearing loss, there have been no consistently reported tinnitus-related abnormalities (Attias et al. 1993, 1996b; Barnea et al. 1990; Maurizi et al. 1985; McKee and Stephans 1992; Rosenhall and Axelsson 1995). One study of evoked magnetic fields reported an apparently robust abnormality, specifically an abnormal amplitude ratio between two response components (M100 and M200) in tinnitus versus nontinnitus subjects (Hoke et al. 1989, 1991; Pantev et al. 1989). Unfortunately, attempts to replicate this result have not been successful, and whether the lack of replication is attributable to the methodological differences between the original and subsequent studies (i.e., stimulus timing, task performed by subjects) remains unresolved (Colding-Jørgensen et al. 1992; Jacobson et al. 1991, 1992; see also Shiomi et al. 1997). Recently, an evoked magnetic field study taking a different approach reported significant differences in cortical frequency organization between audiometrically normal individuals with tonal tinnitus and nontinnitus control subjects (Mühnickel et al. 1998). There also have been reports that some individuals with tinnitus show an abnormal peak in the spectrum of spontaneous gross potentials recorded from the round window or auditory nerve during surgery (Martin et al. 1996) or abnormalities in transient evoked otoacoustic emissions or distortion product emissions (Attias et al. 1996a; Chéry-Croze et al. 1993; Janssen et al. 1998). However, to date electric potential, magnetic field, and otoacoustic emission measurements have not emerged as proven methods for probing the pathophysiology of tinnitus.

Techniques for spatially mapping brain function also have been applied to individuals with tinnitus. For example, one positron emission tomographic (PET) study described abnormally asymmetric activity in the auditory cortices of tinnitus subjects (Arnold et al. 1996). Other PET studies reported changes in brain activity when tinnitus loudness was modulated somatically (Lockwood et al. 1998), when tinnitus was elicited by deviations in eye position (Giraud et al. 1999; Lockwood et al. 1999) and, in response to acoustic tinnitus maskers or injection of lidocaine (a tinnitus suppressor) (Mirz et al. 1999). Functional magnetic resonance imaging (fMRI), another technique for spatially mapping brain function, only has been applied to tinnitus in a few case studies (Cacace 1997;

Cacace et al. 1995, 1999; Levine et al. 1997). Although the PET and fMRI studies have yielded some promising results (see DISCUSSION), these techniques have by no means been applied systematically or exhaustively to the problem of tinnitus.

In the present study, we investigated tinnitus using fMRI with two main goals, identifying objective measures of tinnitus and elucidating the underlying physiology. Here, we 1) describe our approach for applying fMRI to the study of tinnitus, 2) demonstrate through a particular example that this approach can be effective in revealing tinnitus-related abnormalities in brain function, and 3) interpret the findings from this example in terms of underlying neural activity. We chose to use fMRI because it is noninvasive, showing endogenous changes in local blood oxygenation that are correlated with changes in brain activity (Bandettini et al. 1992; Kwong et al. 1992; Ogawa et al. 1992); it can be applied repeatedly to subjects without dose limitations; it can be used to spatially map brain activation from cortex down to the lowest levels of the auditory pathway (i.e., cochlear nucleus) (Guimaraes et al. 1998; Melcher et al. 1997).

Our approach for applying fMRI to the study of tinnitus has four main elements:

One element is to modulate brain activity in ways likely to reveal tinnitus-related abnormalities that are detectable with fMRI. The reason for modulating brain activity is that fMRI detects differences in brain activity (i.e., "activation") between conditions (e.g., sound on vs. off conditions) rather than absolute levels of activity (Bandettini et al. 1992; Kwong et al. 1992; Ogawa et al. 1992). At least two lines of thinking suggest ways for modulating brain activity that might reasonably be expected to reveal tinnitus-related abnormalities. One is based on considerations of what the neural activity underlying tinnitus might be and how that activity might interact with external stimuli such as sound (see DISCUSSION). Another line of thinking is based on considerations of the tinnitus percept and how the percept is altered by external stimuli. For example, in most individuals, the tinnitus percept can be masked by an acoustic stimulus (Feldmann 1971; Fowler 1944; Penner et al. 1981), and in some it can be altered by nonacoustic stimuli (e.g., deviation of eye position or pressure applied to different points on the head and neck) (Cacace et al. 1994; Giraud et al. 1999; Levine 1999; Lockwood et al. 1998; Pinchoff et al. 1998; Rubinstein et al. 1990; Wall et al. 1987). Presumably, changes in percept correspond to tinnitus-related changes in brain activity, so a logical experimental paradigm would involve modulating the tinnitus percept and looking for corresponding changes in brain activity using fMRI. For the present study, we chose an fMRI paradigm in which sound (continuous, broadband noise) was repeatedly turned on and off, resulting in changes in the loudness of the tinnitus percept.

A second element of our approach is to divide tinnitus subjects into subpopulations with shared characteristics and separately consider each subpopulation. This strategy follows from the fact that tinnitus characteristics differ considerably among individuals. For example, the tinnitus percept can be described as tonal or noise-like; it can be fluctuating or constant; it can be localized to one or both ears, or perceived in the head (Douek and Reid 1969; Fowler 1944; Meikle and Griest 1987; Meikle and Taylor-Walsh 1984). These differences presumably correspond to differences in underlying physiology, so we reasoned that more uniform results could be obtained

within a given subpopulation with shared characteristics than across subpopulations. We further reasoned that this greater uniformity would make it easier to identify tinnitus-related abnormalities, hence our strategy of focusing on subpopulations. An additional motivation for adopting this strategy is that it should naturally reveal physiological differences between subpopulations and thus provide insights into the correspondence between tinnitus characteristics and underlying pathophysiology. In this paper, we focused specifically on individuals with tinnitus lateralized to one ear.

A third element of our approach is controlling for intersubject differences in hearing loss. This control is important because hearing loss can result in abnormal activity in the auditory pathway (e.g., in response to sound) either by causing abnormal patterns of excitation in the auditory periphery or by inducing central reorganization (Kiang et al. 1970; Pettigrew et al. 1984; Robertson and Irvine 1989; Willott et al. 1993). Ensuring that abnormalities in brain activity associated with hearing loss do not obscure those associated with tinnitus involves taking two precautions. First, tinnitus subpopulations should be as uniform as possible in terms of audiometry as well as in terms of tinnitus characteristics. Second, because tinnitus subjects must be compared with control subjects to identify tinnitus-related abnormalities, tinnitus and control subjects should be audiometrically comparable (e.g., see Attias et al. 1993, 1996b). For the present study, all subjects had normal or near-normal audiograms.

A final element of our approach is tailoring the experimental design to the characteristics of the particular tinnitus subpopulation under study. Because our lateralized tinnitus subjects had an asymmetric tinnitus percept, we hypothesized that fMRI activation in these subjects might exhibit abnormal asymmetries. To test this, we compared sound-evoked activation in lateralized tinnitus subjects with that in two reference groups, 1) individuals without tinnitus and 2) individuals with nonlateralized (i.e., symmetric) tinnitus in whom abnormal asymmetries would not be expected.

For these initial studies, we focused on one particular auditory structure, the inferior colliculus (IC) because the IC is a major site of convergence for ascending and descending tracts in the auditory pathway (van Noort 1969) and the IC is a compact region ($\sim 6 \times 6 \times 4$ mm) (Kiang et al. 1984) that can be imaged readily in its entirety in a single imaging plane. By imaging a single plane, rather than multiple planes, the background acoustic noise produced during fMRI is reduced, thus reducing any effects of this noise on either the tinnitus percept or sound-evoked activation (Bandettini et al. 1998; Robson et al. 1998; Talavage et al. 1999).¹ In our experiments, sound stimulation produced abnormally asymmetric IC activation in lateralized tinnitus subjects, indicating that our approach can reveal tinnitus-related physiological abnormalities.

METHODS

Thirteen subjects were recruited from the Tinnitus Clinic at the Massachusetts Eye and Ear Infirmary or through personal contacts. The present study was approved by institutional committees on the

use of human subjects at the Massachusetts Eye and Ear Infirmary, Massachusetts General Hospital, and Massachusetts Institute of Technology. Written, informed consent was obtained from each subject.

Three types of subjects were studied: "lateralized tinnitus" subjects had tinnitus largely (*subject 4*) or completely (*1, 2, and 15*) in the right ear; "nonlateralized tinnitus" subjects had tinnitus in both ears equally (*subjects 6 and 7*) or "in the head" slightly right-of-center (*subject 5*); and "nontinnitus" subjects either 1) did not have tinnitus except for the transient episodes experienced by virtually everyone (*subjects 8, 10, and 12*) or 2) had tinnitus that was masked completely by the acoustic noise in the imaging environment (*subjects 9, 11, and 14*).

In all of the tinnitus subjects, the laterality of the tinnitus percept was stable in that 1) it was constant since tinnitus onset or since tinnitus first was noticed (*subjects 1, 2, 15, and 5-7*) and/or was constant for ≥ 1 yr before the imaging session (*subjects 1, 4, 15, and 5-7*) and 2) it remained constant for ≥ 1 yr after imaging (the minimum period of time over which all subjects were followed). One individual was excluded from the present report because the laterality of the tinnitus percept was not stable according to these criteria.

Age, sex, handedness, and audiometric results for each subject are given in Table 1. Nine of 13 subjects had normal hearing (i.e., thresholds were ≤ 25 dB HL for all 6 standard audiometric frequencies). The remaining four subjects had some hearing loss, but their audiograms were symmetric (i.e., the threshold difference between left and right ears was ≤ 10 dB at each audiometric frequency). Three of these four subjects had a mild (≤ 40 dB), high-frequency loss (at 8 kHz, *subjects 5 and 12*; ≥ 4 kHz, *subject 7*), and one had a mild, low-frequency loss (≤ 0.5 kHz, *subject 8*). Subjects had no auditory complaints other than tinnitus.

Twelve subjects had no known neurological disorders or complaints. The remaining subject (2) had had a left cerebellar astrocytoma removed 6 mo before participating in this study.

Tinnitus quality, pitch, and loudness are given in Table 2. Tinnitus quality was reported in a written questionnaire in which subjects were asked to describe their tinnitus in one or two words. Pitch and loudness were measured as follows: for pitch assessments, the subject turned a dial to adjust the frequency of a tone presented at a comfortable level. The tone was delivered to either ear and did not mask the tinnitus percept. Subjects adjusted the tone frequency to best match the pitch of the tone to the dominant pitch of the tinnitus. The "pitch-match frequency" for each subject was the average result of three trials (octave confusions were discounted). For loudness assessments, subjects adjusted the level of a tone at the pitch-match frequency to best match tone and tinnitus loudness. Tinnitus loudness is reported as the tone level yielding a match (expressed relative to detection threshold at the pitch-match frequency).

TABLE 1. *Subject characteristics*

	Subject	Age	Sex	Handedness	Audiogram
Lateralized tinnitus subjects	1	56	F	R	Normal
	2	16	M	R	Normal
	4	51	F	R	Normal
	15	27	F	L	Normal
Nonlateralized tinnitus subjects	5	56	M	R	Mild loss
	6	54	M	R	Normal
	7	48	M	L	Mild loss
Nontinnitus subjects	8	60	F	R	Mild loss
	9	55	F	R	Normal
	10	27	M	R	Normal
	11	20	M	R	Normal
	12	25	F	R	Mild loss
	14	36	F	R	Normal

¹There are also approaches for reducing the background acoustic noise during multislice imaging (Edmister et al. 1999; Hall et al. 1999), but these sacrifice temporal resolution and data-taking efficiency (e.g., see Melcher et al. 1999).

TABLE 2. *Tinnitus characteristics*

	Subject	Quality	Pitch Match, kHz	Loudness Match, dB SL	Annoyance Rating	Loudness During Imaging,* No. of Lights			
						Maximum with noise off	Minimum with noise on		
						Binaural	Right	Left	
Lateralized tinnitus subjects	1	Ringing	6.5	5	95	7.0	0.0	0.0	1.5
	2	Ringing	2.2	7	95	5.0	2.0	1.0	4.0
	4	Ringing, hissing	0.7	13	50	3.0	0.5	0.0	1.5
	15	Ringing, buzzing	7.0	5	60	7.5	0.0	0.0	3.0
Nonlateralized tinnitus subjects	5	Ringing, tonal	8.8	5	10	8.0	7.5	7.0	8.0
	6	Ringing	12.5	10	0	5.0	0.5	1.5	0.5
	7	Hissing	6.5	27	30	7.0	0.0	—	—

* Maximum with Noise Off is an average across all noise OFF periods during functional imaging. Minimum with Noise On is an average across binaural, right monaural, or left monaural noise ON periods. Values are rounded to the nearest half light.

The annoyance associated with the tinnitus percept, in addition to the percept itself, differentiated lateralized tinnitus subjects from subjects in the other two groups. As part of a written questionnaire, each subject with tinnitus was asked to rate annoyance using a number between 0 (no annoyance) and 100 (severely annoying). Annoyance ratings (Table 2) for our lateralized tinnitus subjects ranged from 50 to 95, as compared with 0–30 for nonlateralized tinnitus subjects and 0–10 for the three “nontinnitus” subjects who had tinnitus that was masked in the imaging environment (9, 11, and 14, not included in Table 2).

Acoustic stimulation

The stimulus used during functional imaging was continuous noise delivered either binaurally or monaurally. The noise level was 55 dB sensation level (SL) except in four experiments performed before a standard protocol was established. These used levels of 35, 40, or 60 dB SL. Sensation threshold was determined in the scanner room² immediately before the imaging session. Threshold was defined as the minimum level at which the noise stimulus could be consistently detected (determined to within 5 dB). The spectrum of the noise stimulus at the subject’s ears was low-pass (6 kHz cutoff), reflecting the frequency response of the acoustic system.

Stimuli were delivered through a headphone assembly that also attenuated scanner-generated sounds (Ravicz and Melcher 1998). Specifically, digitally generated noise was converted to an analogue signal, amplified, and fed to a pair of acoustic transducers housed in a shielded box adjacent to the scanner. The output of the transducers reached the subject’s ears via air-filled tubes that connected to couplers incorporated into sound attenuating earmuffs. The couplers linked the tubes to the air cavities under the earmuffs.

Imaging

Subjects lay supine in a 1.5 Tesla scanner (General Electric) retrofitted for high-speed imaging (echo-planar imaging, Advanced NMR Systems) (e.g., Cohen 1999). To minimize head movements, soft materials were packed snugly between the subject’s head and the head coil (General Electric) used for imaging. For each subject, 1) contiguous sagittal images of the whole head were acquired and used to select the functional imaging plane. The plane intersected four audi-

tory structures, the two inferior colliculi (Fig. 1), and the posterior extreme of both Heschl’s gyri. The present study deals only with the colliculi; data for Heschl’s gyri will be presented in a subsequent publication. 2) Echo-planar based shimming was performed (Reese et al. 1995). 3) T1-weighted, high-resolution anatomic images were acquired of the brain slice to be functionally imaged [repetition time (TR) = 10 s; inversion time (TI) = 1,200 ms; echo time (TE) = 75 ms; in-plane resolution = 1.5 × 1.5 mm; thickness = 7 mm]. And 4) subjects were functionally imaged using a cardiac gating method that increases the detectability of activation in the inferior colliculus (Guimaraes et al. 1998). Image acquisitions (asymmetric spin echo, TE = 70 ms, τ offset = -25 ms, thickness = 6 or 7 mm) were synchronized to every other heartbeat in the subject’s electrocardiogram, resulting in an interimage interval (TR) of ~2 s. Postacquisition, image signal strength was corrected to account for variations in TR caused by fluctuations in heart rate.

Functional imaging was performed in “runs” (3–9 per imaging session). For each run, images were acquired while continuous noise was turned on for 30 s and off for 30 s for a total of four repetitions. The noise was binaural, left monaural, or right monaural. Binaural noise was used in all 14 imaging sessions; left and right monaural noise was used in 10 of 14 sessions.

One additional imaging session was conducted using a 3 Tesla scanner (General Electric, retrofitted for echo-planar imaging by Advanced NMR Systems) instead of a 1.5 T scanner. The purpose of this session was to pilot our protocol at a higher field strength and test the replicability of our findings in one lateralized tinnitus subject (1) who 7 mo earlier had been tested at 1.5 T. The methods for this retesting

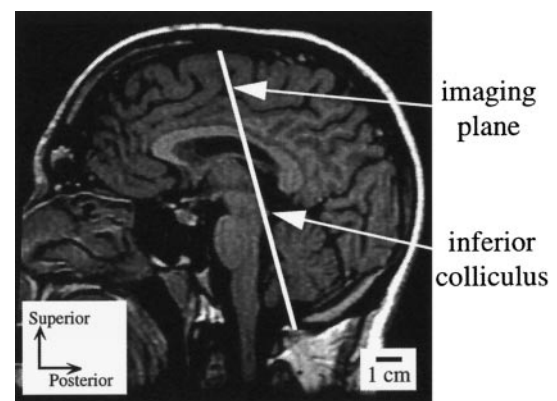


FIG. 1. Functional imaging plane superimposed on a sagittal anatomic image. Imaging plane (thick white line) intersected the inferior colliculi.

² In the scanner room, there is on-going low-frequency background sound produced primarily by a pump for liquid helium (used to supercool the scanner’s permanent magnet). This sound reaches levels of ~80 dB SPL in the frequency range of 50–300 Hz (Ravicz et al. 1997).

session were the same as those described above except for the anatomic (TR = 10 s; TI = 1,100 ms; TE = 57 ms) and functional (gradient echo, TE = 40 ms, flip angle = 90°) imaging parameters. Both binaural and monaural noise were used in this session.

Task

Tinnitus and nontinnitus subjects performed comparable tasks during functional imaging. Tinnitus subjects were asked to rate continuously the loudness of the tinnitus percept on a subjective scale ranging from 0 (no tinnitus) to 10 (maximum tinnitus loudness ever experienced). The ratings were reported by controlling the illumination of 10 lights visible to both the subject and experimenters. By turning a knob held in the right hand, subjects continuously adjusted the number of illuminated lights to correspond to the current tinnitus loudness rating. Nontinnitus subjects were instructed to turn all of the lights off when they heard the noise stimulus, and all of the lights on when they did not (i.e., illuminate the lights as if they had tinnitus that was fully masked by the noise).

Tinnitus loudness usually decreased when the noise stimuli were turned on during functional imaging, and increased when the noise was turned off. Thus tinnitus loudness typically reached a maximum during noise OFF periods and a minimum during noise ON periods. Maximum and minimum tinnitus loudness are given for each subject in Table 2 (expressed as the maximum and minimum number of illuminated lights). Although the most common trend was for tinnitus loudness to decrease each time noise was turned on, there were some exceptions to this rule. For example, in *subject 5*, left monaural noise had no effect on tinnitus loudness (Table 2). In two cases, tinnitus loudness decreased during only some of the ON periods (*subject 5*, binaural noise; *subject 2*, left monaural noise). In most subjects (6 of 7), maximum tinnitus loudness during each OFF period matched (to within 1 light; *subjects 1* and 5–7) or exceeded (2 and 15) the loudness at the start of the functional imaging run. However, in the remaining subject (4), tinnitus loudness only partially recovered each time the noise was turned off because there was residual inhibition of the tinnitus percept (e.g., Feldmann 1983) that lasted longer than the 30-s duration of the OFF periods.

Analysis

To generate activation maps, functional images were processed as follows. First, a standard algorithm (statistical parametric mapping) was applied to the images to correct for any in-plane subject motion (Friston et al. 1995). To ensure spatial alignment of activation maps and corresponding anatomic images, all of the functional images for a given session were corrected to a reference image acquired immediately before or after acquiring an anatomic image of the functional imaging plane. Functional images then were normalized to a constant offset signal strength and corrected for any linear or quadratic drifts in image signal strength over the course of each run. For each imaging session, data from runs using the same stimulus (e.g., binaural noise) were combined by concatenating the image sequences for each run. Activation maps were derived from these concatenated datasets using a Student's unpaired *t*-test to compare image signal strength during stimulus ON versus OFF periods. So activation maps could be superimposed on anatomic images, the activation maps (in-plane resolution 3.1 × 3.1 mm) were interpolated to have the same resolution (1.5 × 1.5 mm) as the anatomic images.

Activation in the IC was quantified in terms of percent change in image signal strength calculated on a voxel-by-voxel³ basis from the concatenated datasets, Percent Signal Change = $(S_{\text{on}} - S_{\text{off}}) / (\text{average of } S_{\text{on}} \text{ and } S_{\text{off}}) \times 100$, where S_{on} and S_{off} are the mean signal strengths during stimulus ON and OFF periods, respectively. First,

regions of interest (ROIs) corresponding to the area of each IC were defined from high-resolution anatomic images of the functional imaging plane. These "high-resolution" ROIs (1.5 × 1.5 mm) then were down-sampled, yielding ROIs with the same resolution as the functional images (3.1 × 3.1 mm). At this lower resolution, the IC typically corresponds to two to four voxels. The voxel with the greatest percent signal change was identified within each ROI. Percent signal change for this voxel provided a quantitative measure of IC activation; the ratio of percent signal change in one versus the other IC provided a measure of activation asymmetry. Statistical comparisons of percent signal change or asymmetry across conditions were made using Wilcoxon's rank sum test.

RESULTS

Noise stimulation reliably produced activation in the IC in "nontinnitus," "nonlateralized tinnitus," and "lateralized tinnitus" subjects. This activation is described in the following text, first for binaural stimulation, then for monaural stimulation. Unless stated otherwise, these descriptions pertain to the 14 imaging sessions conducted at 1.5 T rather than the session conducted at 3 T. In our presentation of the results, we group nontinnitus and nonlateralized tinnitus subjects together because these two groups did not differ significantly with respect to the results described.

Binaural stimulation

Binaural noise produced comparable levels of activation in the left and right ICs in reference subjects (i.e., nontinnitus subjects and nonlateralized tinnitus subjects). This was apparent qualitatively in activation maps (Fig. 2) and quantitatively from analyses of the percent change in image signal strength (Fig. 3). Mean percent signal change in the left versus right IC was not significantly different in either nontinnitus subjects (left: 1.20 ± 0.15 ; right: 1.16 ± 0.12 ; means \pm SE) or nonlateralized tinnitus subjects (left: 1.04 ± 0.07 ; right: 1.26 ± 0.32 ; $P > 0.05$ Wilcoxon's rank sum test).

In lateralized tinnitus subjects, binaural noise consistently produced abnormally low activation in the IC contralateral to the tinnitus percept (i.e., the left IC; Fig. 4). Unlike reference subjects, percent signal change in lateralized tinnitus subjects was always lower in the left IC than in the right IC (4 of 4 subjects, Fig. 3). In the right IC, percent signal change in lateralized tinnitus subjects (1.22 ± 0.19) versus reference subjects (1.19 ± 0.12) did not differ significantly ($P > 0.05$). In contrast, in the left IC, percent signal change was significantly less in lateralized tinnitus subjects (0.71 ± 0.07 vs. 1.15 ± 0.11 in reference subjects, $P < 0.02$).

The ratio of percent signal change in the right versus left IC proved to reliably differentiate lateralized tinnitus subjects from reference subjects (Fig. 5). On average, this measure of activation asymmetry was significantly greater for lateralized tinnitus subjects (1.70 ± 0.11) than for reference subjects (1.05 ± 0.09 ; $P < 0.01$). In addition, asymmetry in every lateralized tinnitus subject exceeded that for all reference subjects.

One lateralized tinnitus subject (1) was retested in a second imaging session 7 mo after the first and showed comparable abnormalities in the two sessions, indicating that our results can be replicated. Because the two sessions were conducted at different field strengths and with different imaging pulse se-

³ A voxel is the volumetric analog of a pixel. In our functional imaging data, one voxel had dimensions of 3.1 × 3.1 × 7 (or 6) mm.

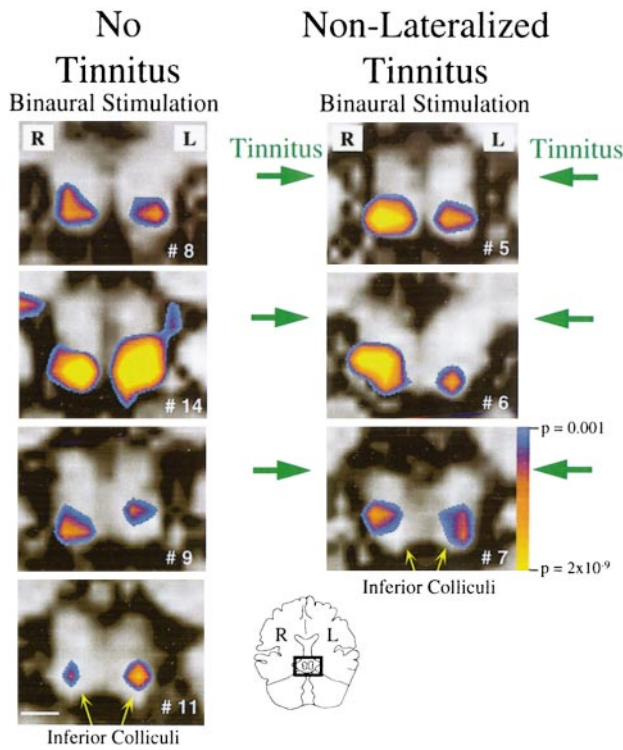


FIG. 2. Inferior colliculus (IC) activation for binaural noise stimulation in nontinnitus subjects (left) and nonlateralized tinnitus subjects (right). Each panel shows a T1-weighted anatomic image (grayscale) and superimposed activation map (color) for a particular subject. Rectangle superimposed on the diagrammatic image (bottom) indicates the area shown in each panel. For the activation maps, regions are colored according to the result of a *t*-test comparison of image signal strength during noise ON vs. OFF periods, with blue and yellow corresponding to the lowest ($P = 0.001$) and highest ($P = 2 \times 10^{-9}$) significance levels, respectively. Activation maps, based on functional images with an in-plane resolution of 3.1×3.1 mm, have been interpolated to the resolution of the anatomic images (1.5×1.5 mm). Each activation map is based on 12 min of data. For nonlateralized tinnitus subjects, the green arrows on both sides of each panel indicate that the tinnitus percept was not lateralized to one ear or the other. Stimulus level was 55 dB SL for all but 2 subjects (subject 7, 35 dB SL; 11, 65 dB). Images are displayed in radiological convention, so the subject's right is displayed on the left. R, right; L, left. Subject number is indicated in right lower corner of each panel. Scale bar in lowest panel corresponds to 5 mm.

quences that can influence absolute activation levels, we compare only relative measures. For the “retest” session, percent signal change in the left IC was less than in the right IC, and the asymmetry index (1.77) fell within the range for lateralized tinnitus subjects in Fig. 5. Thus the retest experiment further supports our finding of abnormal activation asymmetry for binaural stimulation in lateralized tinnitus subjects.

Monaural stimulation

Monaural noise always produced greater activation in the IC contralateral, rather than ipsilateral to the stimulus in reference subjects (Figs. 6 and 7). On average, percent signal change in the IC contralateral to the stimulus was 1.07 ± 0.08 as compared with 0.41 ± 0.05 for the ipsilateral IC ($P < 0.001$).

Lateralized tinnitus subjects also showed greater activation in the contralateral IC for monaural stimulation (Figs. 7 and 8) but differed from reference subjects in two statistically significant respects. First, for left stimulation in the IC contralateral to the tinnitus percept (i.e., the left IC), mean percent signal

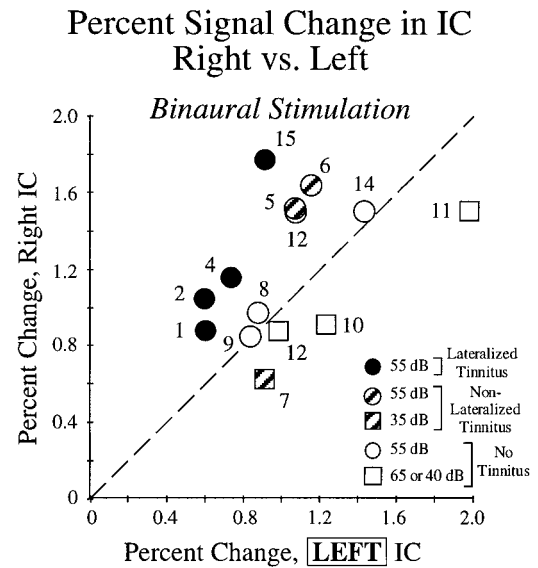


FIG. 3. Percent signal change in the right vs. left inferior colliculus for binaural noise stimulation. Each point corresponds to a particular subject with lateralized tinnitus (darkly filled symbols), nonlateralized tinnitus (diagonally filled), or no tinnitus (unfilled). Stimulus level was 55 dB SL (circles) in all but 4 instances (squares). Value next to each symbol indicates subject number. Highlighted text for the left IC (LEFT) is a reminder that the left IC was contralateral to the tinnitus percept in lateralized tinnitus subjects. Each data point is based on 8 min of functional imaging data (subjects 10 and 12, circle) or 12 min of data (all other points). There are 2 data points for subject 12 because this individual was studied in 2 imaging sessions.

change in lateralized tinnitus subjects (0.14 ± 0.04) was low compared with that for reference subjects (0.32 ± 0.04 ; $P < 0.02$; note distribution of data points along horizontal axis in Fig. 7, top). A consequence of this abnormally low activation was an abnormally high degree of activation asymmetry for left stimulation, where asymmetry was calculated as percent signal change in the right divided by the left IC. This asymmetry

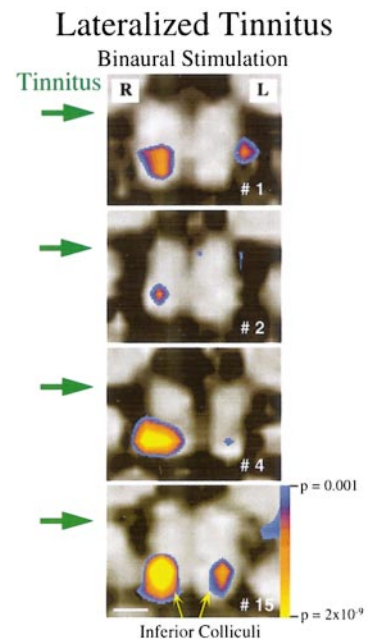


FIG. 4. IC activation for binaural stimulation in lateralized tinnitus subjects. Green arrows next to each panel indicate that the tinnitus percept was lateralized mainly to the right ear. Stimulus level: 55 dB SL. See Fig. 2 legend.

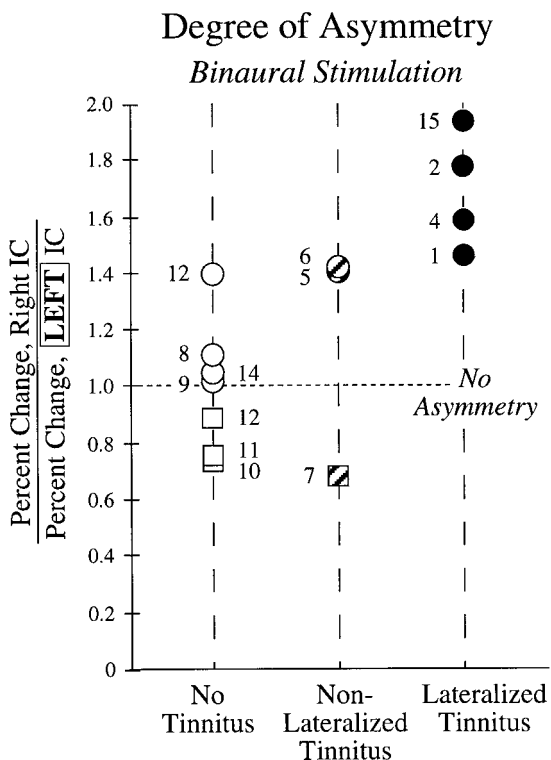


FIG. 5. Degree of activation asymmetry in the inferior colliculi for binaural stimulation. Using the data in Fig. 3, activation asymmetry was calculated as percent signal change in the right IC divided by percent signal change in the left IC. Each data point corresponds to a particular subject and imaging session. See Fig. 3 legend.

index was significantly greater for lateralized tinnitus subjects (10.79 ± 3.35) as compared with reference subjects (3.67 ± 0.48 ; $P < 0.02$; Fig. 9). Thus the abnormalities for left mon-

aural stimulation were comparable with those for binaural stimulation in that IC activation was abnormally low contralateral to the tinnitus percept and was abnormally asymmetric.

The second difference between lateralized tinnitus and reference subjects concerns the relative levels of activation in the IC contralateral to a right versus a left stimulus. In all four lateralized tinnitus subjects, activation in the left IC for right stimulation was less than the activation in the right IC for left stimulation (Fig. 8). In contrast, this situation occurred in only two of six reference subjects. Measurements of percent signal change confirmed these trends. The ratio of percent signal change in the left IC for right stimulation versus the right IC for left stimulation was significantly lower in lateralized tinnitus subjects (0.67 ± 0.04) as compared with reference subjects (0.97 ± 0.08 ; $P < 0.05$). This abnormal ratio may be attributable to abnormally low activation in the left IC for right stimulation, which would represent yet another instance of abnormally low activation in the IC contralateral to the tinnitus percept. However, we cannot definitively distinguish among this interpretation, the interpretation that percent signal change in the right IC for left stimulation was abnormally high, or a combination of the two interpretations (see Fig. 7). Regardless of interpretation, the relative levels of activation in the IC contralateral to a right versus a left stimulus was clearly abnormal in lateralized tinnitus subjects.

The monaural data from the initial and retest imaging sessions for lateralized tinnitus *subject 1* were comparable. For both sessions, the asymmetry index for left stimulation was at the low end of the range for lateralized tinnitus subjects (5.91 and 4.06). When the additional data point from the retest session was combined with the others, the mean asymmetry index for lateralized tinnitus subjects was lower (9.44 ± 2.92 vs. 10.79 ± 3.35) but still significantly greater than that for

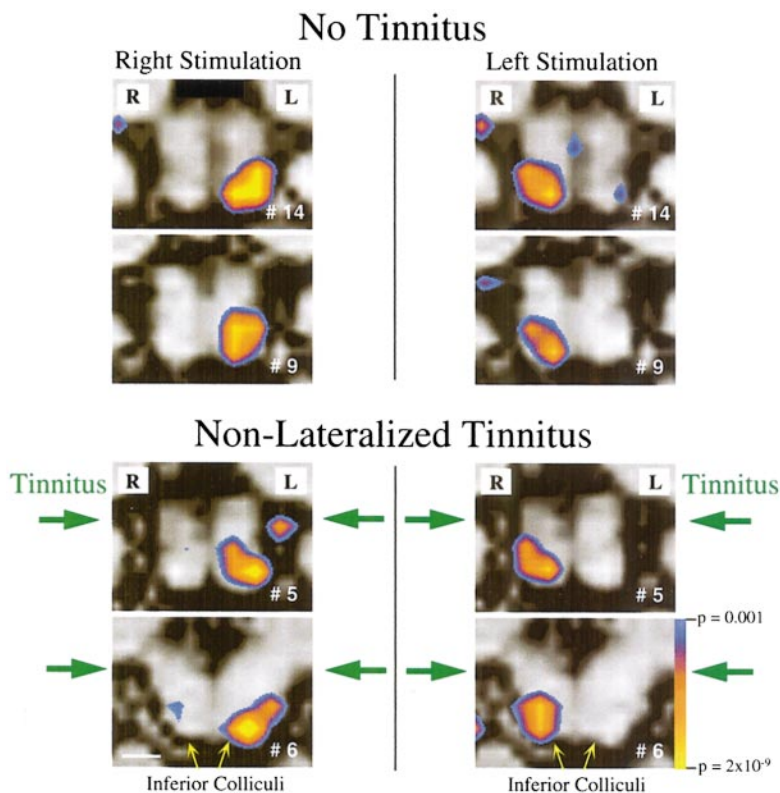


FIG. 6. IC activation for right and left monaural stimulation in 2 nontinnitus subjects (*top*) and 2 nonlateralized tinnitus subjects (*bottom*). Stimulus level was 55 dB SL. Each activation map is based on 12 min of data. See Fig. 2 legend.

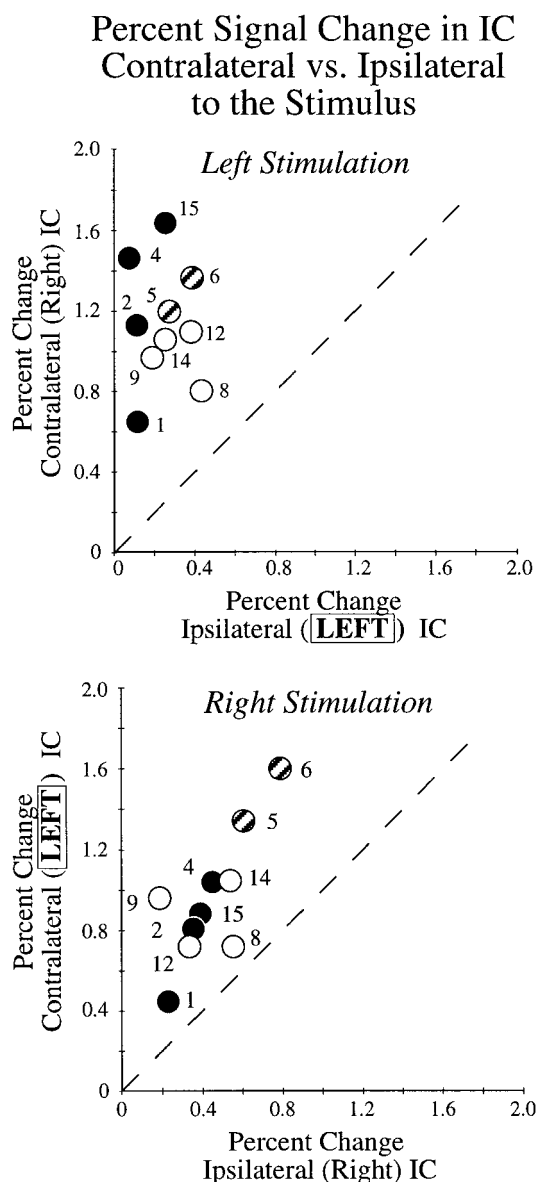


FIG. 7. Percent signal change in the IC for left (*top*) and right (*bottom*) monaural stimulation. Each panel shows percent signal change in the IC contralateral vs. ipsilateral to the stimulus with each data point corresponding to a particular lateralized tinnitus (darkly filled symbols), nonlateralized tinnitus (diagonally filled), or nontinnitus (unfilled) subject. Value next to each symbol indicates subject number. Highlighted text for the left IC (**LEFT**) is a reminder that the left IC was contralateral to the tinnitus percept in lateralized tinnitus subjects. Each data point is based on 8 (*subjects 8 and 12*) or 12 min of functional imaging data. Stimulus level: 55 dB SL.

reference subjects (3.67 ± 0.48 ; $P < 0.02$). In the retest session, the ratio of percent signal change in the IC contralateral to a right versus left stimulus (0.63) was comparable with that from the first session (0.69) and near the average for all lateralized tinnitus subjects in other imaging sessions (0.67 ± 0.04). Thus the retest session for *subject 1* supported our observations concerning the relative levels of activation in the IC contralateral to a right versus left stimulus.

DISCUSSION

We have presented an approach for studying tinnitus using fMRI, applied it, and obtained preliminary results indicating

that the approach is effective. Specifically, we found that lateralized tinnitus subjects were distinguishable from nontinnitus and nonlateralized tinnitus subjects on the basis of fMRI activation in the IC. Both binaural and monaural sound produced abnormal asymmetries in fMRI activation in lateralized tinnitus subjects, an observation consistent with the asymmetry of the tinnitus percept. For both binaural and left monaural stimulation, the abnormal asymmetries were attributable to abnormally low activation in the IC contralateral to the tinnitus percept. For binaural stimulation, the distinction between lateralized tinnitus subjects and reference subjects was particularly clear because *every* lateralized tinnitus subject showed greater asymmetry than the reference subjects. We attribute the observed abnormalities specifically to tinnitus because the participants in this study had no other auditory complaints and little or no hearing loss. Clearly, these results must be viewed as preliminary because the studied sample of subjects was small. Nevertheless our results indicate that fMRI can provide an objective, physiological measure of tinnitus in at least some lateralized tinnitus subjects.

Tinnitus-related activation abnormalities: underlying changes in neural activity

To understand the fMRI abnormalities in lateralized tinnitus subjects at a neural level, we first must consider the relationship between fMRI activation and neural activity. Although the details of this relationship are still being worked out, certain aspects seem clear. For instance, the activation for a given voxel presumably depends on the number of neurons in the voxel that show increases or decreases in activity in response to the fMRI stimulation paradigm. By “activity” we mean excitatory and inhibitory synaptic events, and neural discharges⁴ because these correspond to an increase in neural metabolism leading to a local increase in blood flow, blood oxygenation and, consequently, an increase in image signal strength, i.e., fMRI activation (Bandettini et al. 1992; Fox and Raichle 1986; Fox et al. 1988; Kwong et al. 1992; Ogawa et al. 1992). In response to a sensory stimulus, image signal strength takes at least several seconds to reach peak levels (Kwong et al. 1992; Robson et al. 1998), indicating that fMRI is insensitive to the detailed microsecond timing of neural activity. Given this view, the tinnitus-related abnormalities we detected with fMRI presumably reflect abnormal changes in the overall level of neural activity in the IC not detailed changes in the timing of activity.

Abnormally low sound-evoked activation: possible underlying mechanisms

Because the abnormal asymmetries for binaural and left monaural stimulation in lateralized tinnitus subjects were specifically attributable to abnormally low IC activation, we considered two possible models that might account for this result. Both incorporate the ideas that 1) fMRI activation reflects changes in the level of neural activity, as just discussed and 2) the tinnitus percept corresponds to abnormally high levels of “spontaneous” neural activity (“tinnitus-related” activity). One

⁴ We recognize, however, that these different types of activity may have different metabolic requirements and thus contribute to fMRI activation to different degrees (Nudo and Masterton 1986; Proshansky et al. 1980).

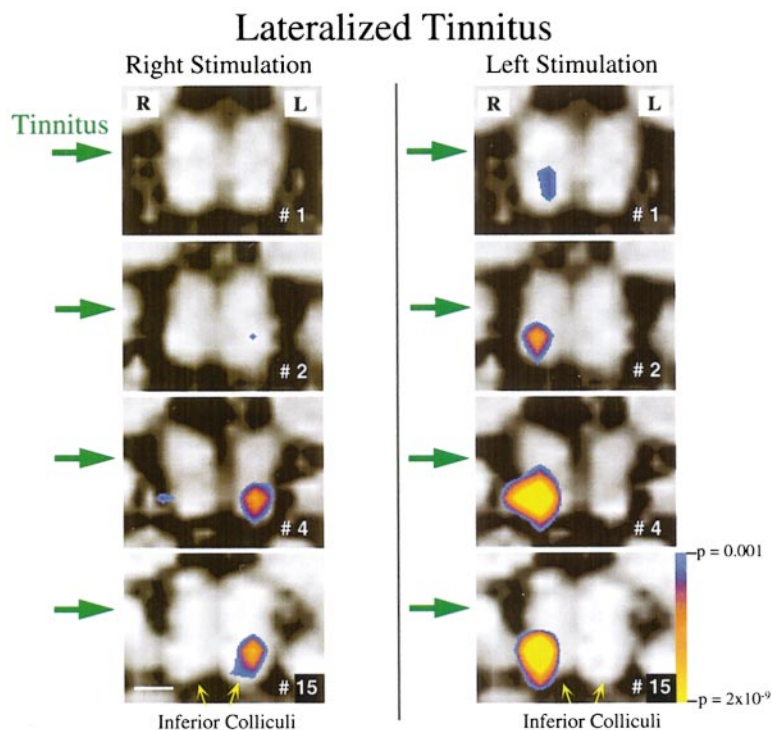


FIG. 8. IC activation for right and left monaural stimulation in 4 lateralized tinnitus subjects. Each activation map is based on 12 min of data. Stimulus level: 55 dB SL. See Fig. 2 legend.

of the models also assumes that any further increase in neural activity in response to sound cannot exceed a maximum (“saturation model”). The other model instead assumes that sound stimulation reduced the level of tinnitus-related activity whenever it reduced the loudness of (i.e., masked) the tinnitus percept (“physiological masking model”).

The two models are illustrated in Fig. 10. For both, we assume that total neural activity in the IC has two components: tinnitus-related activity and sound-related activity, the activity evoked by a sound stimulus. For a nontinnitus subject (Fig. 10, *top*), total neural activity is equal to sound-related activity, and fMRI activation reflects the difference in total activity between sound ON and sound OFF conditions in the fMRI paradigm. For a tinnitus subject and the saturation model (Fig. 10, *middle*), tinnitus-related activity is present during both sound ON and OFF conditions. For sound OFF, total activity equals tinnitus-related activity because there is no sound-related activity. For sound ON, sound-related activity is the same as in the nontinnitus subject (Fig. 10, *top*), and total neural activity would be the sum of tinnitus-related activity and sound-related activity, except that neural activity reaches a maximum (i.e., saturates). As a consequence, fMRI activation is less than normal. For the physiological masking model (Fig. 10, *bottom*), the situation when sound is OFF is the same as for the saturation case. When sound is ON, sound-related activity is the same as in the nontinnitus subject (Fig. 10, *top*) and, tinnitus-related neural activity is presumed to be reduced (i.e., “masked”) because the sound reduces the loudness of the tinnitus percept. In this case, fMRI activation is less than normal because the level of neural activity for sound OFF is abnormally high, while that for sound ON is no greater than in nontinnitus subjects. In fact, if sound-related activity were less than tinnitus-related activity, total activity would be greater during sound OFF, rather than ON, periods resulting in “negative” fMRI activation. In this respect,

the physiological masking and saturation models differ because saturation cannot result in negative activation.

Models incorporating either physiological masking or saturation represent two reasonable explanations for our finding of abnormally low activation in the IC of lateralized tinnitus subjects but certainly not the only ones. For example, it is possible that both mechanisms occurred i.e., during sound ON periods, tinnitus-related activity decreased, while total activity reached a maximum level. It is also possible that abnormally low activation reflects nonneural saturation, for example, metabolic or hemodynamic saturation.

The fact that the models just described agree with our result of abnormally low activation indirectly supports an underlying model assumption, namely that the tinnitus percept is associated with abnormally high spontaneous activity. Support for this idea comes from data in animals manipulated in ways that can cause tinnitus. For example, electrophysiological studies in animals have described salicylate-induced increases in spontaneous activity for auditory nerve fibers (Evans et al. 1981), inferior colliculus neurons (Chen and Jastreboff 1995; Jastreboff and Sasaki 1986), certain single-unit subpopulations in primary auditory cortex (Ochi and Eggermont 1996); and neurons in secondary auditory cortex (Eggermont and Kenmochi 1998). In addition, acoustic overstimulation has been shown to produce abnormally high levels of spontaneous activity in the dorsal cochlear nucleus (Kaltenbach and McCaslin 1996; Kaltenbach et al. 1998; Zhang and Kaltenbach 1998).

Although our fMRI data are consistent with the idea that abnormally high levels of spontaneous neural activity are related to tinnitus, they do not exclude the possibility that there is also abnormally timed neural activity (e.g., abnormal interspike intervals or an abnormally high degree of intercellular correlation) (Eggermont 1990; Møller 1995). An important point, however, is that abnormal timing alone cannot account for our results.

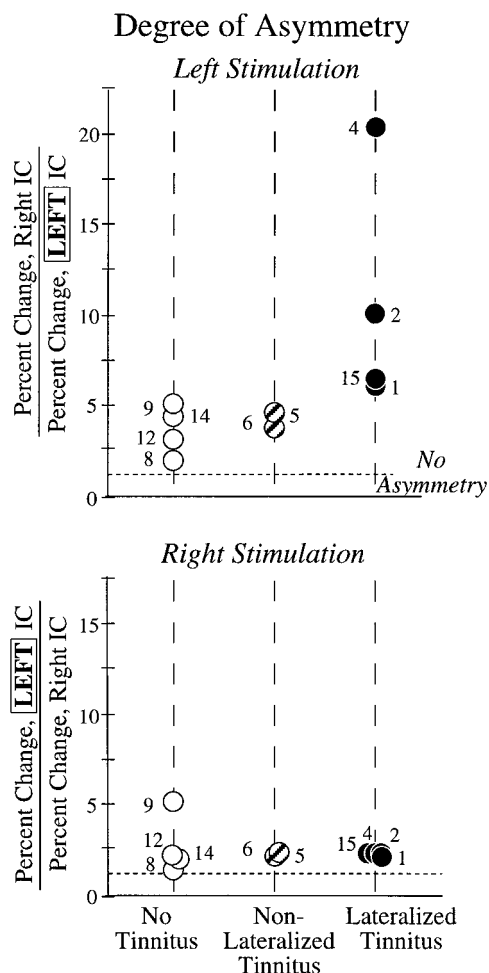


FIG. 9. Degree of activation asymmetry in the inferior colliculi for left (*top*) and right (*bottom*) monaural stimulation. Using the data in Fig. 7, activation asymmetry was calculated as percent signal change in the IC contralateral to the stimulus divided by percent signal change in the ipsilateral IC. Each data point corresponds to a particular subject.

Abnormally low fMRI activation in response to sound also has been reported in schizophrenic patients and may be a consequence of physiological abnormalities similar to those in tinnitus subjects. Specifically, it has been reported that schizophrenic patients exhibit lower levels of sound-evoked activation in auditory association cortex when they are experiencing auditory hallucinations (voices) as compared with when they are hallucination-free (David et al. 1996). The lower activation levels during hallucination were attributed to a reduced dynamic range of response in auditory cortex due to an abnormally high level of baseline activity associated with the hallucinations (i.e., saturation). Alternatively, a physiological masking mechanism might account for the results if the hallucinations were masked by the sound stimulus. Thus abnormally high levels of baseline activity may underlie the complex phantom auditory perceptions experienced with schizophrenia, as well as the simple ones experienced with tinnitus.

Relationship between tinnitus laterality and side of activation abnormalities

Our finding of abnormally asymmetric activation in lateralized tinnitus subjects, or more specifically, abnormally low

activation contralateral to the tinnitus percept, is predicted readily when two ideas are combined. The first idea is that the tinnitus percept corresponds to abnormally elevated neural activity which results in abnormally low sound-evoked activation (e.g., by “saturation” or “physiological masking”). The second idea is that the tinnitus percept is like external sound in terms of the spatial pattern of neural activity associated with it. For lateralized tinnitus, the percept is analogous to the percept for monaural sound. Monaural sound produces greater neural activity in the contralateral, rather than the ipsilateral IC (e.g., Fig. 6) (Melcher et al. 1997). Therefore we hypothesize that any abnormal elevation in “spontaneous” neural activity in subjects with lateralized tinnitus is greater in the IC contralateral to the tinnitus percept. This, coupled with the idea that abnormally elevated “spontaneous” neural activity results in suppressed sound-evoked fMRI activation, predicts abnormally low levels of sound-evoked fMRI activation in lateralized tinnitus subjects, specifically in the IC contralateral to the tinnitus percept.

For the purposes of the present discussion, we have offered the interpretation that the side of abnormally low activation depends on the laterality of the tinnitus percept. However, our data are equally consistent with the alternative view that the left IC is abnormal regardless of the laterality of the tinnitus percept. This is because all of our lateralized tinnitus subjects happened to have tinnitus in the right ear (and abnormal activation in the left IC). Further experiments (e.g., in individuals with tinnitus in the left ear) are required to determine whether or not the side of IC abnormalities is truly correlated with the laterality of the tinnitus percept.

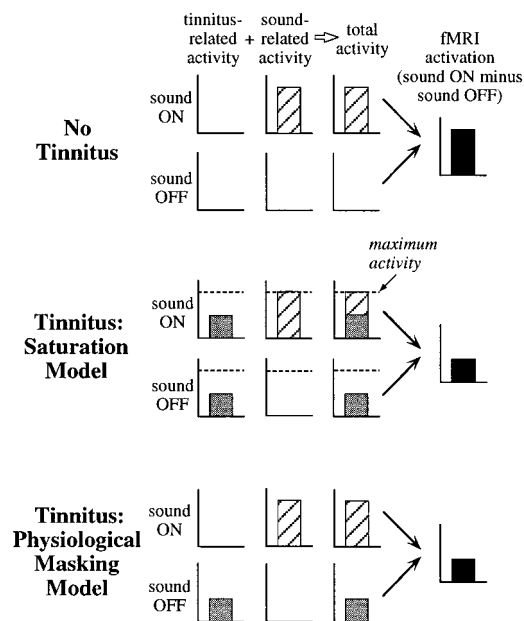


FIG. 10. Hypothetical relationship between neural activity and fMRI activation when there is a sound stimulus and no tinnitus (*top*) or, tinnitus (*middle* and *bottom*). Height of the bars in the 3 columns at the left in each panel indicate the level of tinnitus-related activity, sound-related activity, and total activity. Height of the bar in the right-most column indicates the level of fMRI activation, i.e., the difference in total neural activity between “sound on” and “sound off” conditions. For the case of tinnitus, fMRI activation is abnormally low as a consequence of either saturation (*middle*) or physiological masking (*bottom*). With saturation, total neural activity cannot exceed a maximum level. With physiological masking, tinnitus-related activity is reduced when sound is on because the loudness of the tinnitus percept is reduced.

How might tinnitus-related neural activity in the IC arise?

Several possible scenarios could lead to tinnitus-related neural activity in the IC. For example, the IC may be intrinsically normal, but receive abnormal input activity from lower centers (e.g., dorsal cochlear nucleus, medial superior olivary complex) or higher centers (e.g., medial geniculate body) (Adams 1979; Osen 1972; van Noort 1969). Alternatively, input to the IC may be entirely normal, with abnormal activity arising because of intrinsic abnormalities (e.g., membrane alterations that raise the resting potential of IC neurons).

A combination of extrinsic and intrinsic abnormalities is also possible, for example if abnormal input activity were to induce changes intrinsic to the IC. The plausibility of this scenario is supported by work in adult animals demonstrating that reorganization can occur within the auditory pathway. For example, peripheral high-frequency hearing loss can result in abnormal tonotopic maps in both primary and nonprimary auditory cortices (Rajan et al. 1993; Robertson and Irvine 1989; Schwaber et al. 1993; Willott et al. 1993); acoustic overstimulation can produce abnormally high levels of spontaneous activity recorded from the surface of the dorsal cochlear nucleus (Kaltenbach and McCaslin 1996; Kaltenbach et al. 1998; Zhang and Kaltenbach 1998); months after severing the auditory nerve unilaterally, 2-deoxyglucose labeling in the cochlear nuclei, inferior colliculi, and medial geniculate bodies is left-right symmetric even though acutely such lesions result in asymmetric labeling (Sasaki et al. 1980). All of these abnormalities in tonotopic organization and activity level took time to evolve, indicating that they represented reorganization rather than just the immediate consequences of reduced neural activity in the auditory periphery (Kaltenbach et al. 1998; Robertson and Irvine 1989; Sasaki et al. 1980). "Original" abnormalities eventually triggering "secondary" abnormalities in humans could explain why tinnitus initially caused by a peripheral lesion (e.g., as with Menière's disease) is not necessarily eliminated by 8th nerve section (House and Brackmann 1981; Pulec 1995) and why characteristics of the tinnitus percept (e.g., pitch, location, loudness) can change over time (Meikle et al. 1987).

Why didn't nonlateralized tinnitus subjects show abnormally low activation?

An important point is that nonlateralized tinnitus subjects did not show the IC activation abnormalities that would be predicted by straightforwardly extending our thinking concerning lateralized tinnitus to nonlateralized tinnitus. On the basis of the tinnitus percept, one might expect that spontaneous neural activity levels in the IC would be abnormally high bilaterally in nonlateralized tinnitus subjects, in which case sound-evoked activation might be abnormally low bilaterally (e.g., as a consequence of saturation or physiological masking). This, however, was not the case.

At this point, we cannot say what the underlying differences between the nonlateralized and lateralized tinnitus subjects were. However, we can offer some hypotheses. First, although subjects in both groups may have had abnormally high levels of spontaneous neural activity in the IC (i.e., "tinnitus-related" activity), perhaps the activity levels in the nonlateralized tinnitus subjects were only slightly higher than normal and hence were not detected (i.e., as abnormal fMRI activation). This

hypothesis would be particularly appealing if the tinnitus percept in our nonlateralized subjects (compared with our lateralized subjects) had been less loud (which might correspond to a lower overall level of tinnitus-related activity) or more tonal rather than noise-like (which might correspond to fewer neurons with tinnitus-related activity). However, neither the loudness nor the quality of the tinnitus percept differed systematically between the nonlateralized and lateralized tinnitus subjects (Table 2).

Another possibility is that tinnitus originated in fundamentally different ways in our nonlateralized versus our lateralized tinnitus subjects. For example, the tinnitus percept in our nonlateralized subjects may have been associated with activity in brain structures other than the IC (e.g., cortical areas only), hence the normal IC activation in the nonlateralized subjects as compared with the lateralized subjects. Alternatively, tinnitus-related activity may have resided in different pathways in the lateralized and nonlateralized subjects (e.g., in ascending pathways to the central nucleus of the IC in lateralized subjects, but in extralemniscal pathways through peripheral parts of the IC in nonlateralized subjects) (Møller et al. 1992). It is also possible that tinnitus in the nonlateralized subjects was associated with abnormalities in the timing, rather than the level, of IC activity.

Finally, the annoyance associated with tinnitus was always less in our nonlateralized subjects than in our lateralized subjects (Table 2), so annoyance may be a critical factor related to the normal activation in nonlateralized subjects versus the abnormal activation in lateralized subjects. Our results are consistent with the hypothesis that IC tinnitus-related activity is greater when annoyance is greater. Such a relationship might arise, for instance, through on-going descending neural control of the IC, or feedback to the IC resulting in long-term neural reorganization.

Previous PET and fMRI studies of tinnitus

Although most previous functional imaging studies of tinnitus used PET, they still can be compared straightforwardly with our fMRI results because PET, like fMRI, is sensitive to overall levels of neural activity rather than the detailed timing of activity. Here, we first review each of the previous studies separately. We then consider the results collectively in the context of the present study.

In a study of baseline levels of cortical activity using PET, Arnold et al. (1996) reported that tinnitus subjects showed abnormally asymmetric activity on the transverse temporal gyri (TTG), although it is not clear that this abnormality was specifically tinnitus related. The asymmetry was attributed to abnormally high levels of activity in the left TTG in most instances and in the right TTG in one; the direction of the asymmetry was not related to the laterality of the tinnitus percept. The concern as to whether the abnormal asymmetry for tinnitus subjects was specifically tinnitus related comes from the fact that all but one of the tinnitus subjects had a hearing loss, whereas the nontinnitus subjects that were examined for comparison apparently did not. In addition, the one tinnitus subject with normal hearing did not show abnormally asymmetric activity (but also did not experience tinnitus during the imaging session). One subject with fluctuating tinnitus severity was imaged on three separate occasions and showed

greater activity on the left TTG during sessions with “disabling” tinnitus as compared with a session of “mild” tinnitus. However, whether this difference might be attributable to intersession differences in global brain activity levels is not addressed. Thus although the Arnold et al. data may indicate tinnitus-related elevations in auditory cortical activity, alternative interpretations are also viable.

Another PET study reported tinnitus-related cortical activation in subjects who could modulate tinnitus loudness with oral-facial movements (Lockwood et al. 1998). When these movements were performed, primary and secondary auditory cortical areas, on average, showed greater activity when the tinnitus percept was louder rather than softer. In contrast, similar oral-facial movements performed by nontinnitus subjects did not produce changes in auditory cortical activity. The nontinnitus (normal hearing) and tinnitus (hearing impaired) subjects differed audiometrically, so the possibility that auditory cortical activation in the tinnitus subjects might have been related to hearing loss, rather than tinnitus, cannot be excluded. Nevertheless the fact that there were covariations between tinnitus loudness and brain activity in the tinnitus subjects is compelling and points to a picture of auditory cortical activity increasing and decreasing with increasing and decreasing tinnitus loudness.

The PET findings of Mirz et al. (1999) and Giraud et al. (1999) are also consistent with there being elevated cortical activity associated with tinnitus. Mirz et al. (1999) studied subjects with various forms of tinnitus (unilateral, bilateral) and degrees of hearing loss. Subjects were imaged while experiencing tinnitus and while tinnitus was suppressed with an acoustic masker, with lidocaine, or with both an acoustic masker and lidocaine. PET-detected activity during the unsuppressed tinnitus condition was greater than during conditions of tinnitus suppression in a variety of cortical areas (e.g., middle frontal gyrus, middle temporal gyrus); this is consistent with there being tinnitus-related neural activity in these areas. However, subjects without tinnitus were not studied for comparison, so it remains to be seen whether the reported activity changes were tinnitus-specific. Giraud et al. (1999) studied individuals who, after acoustic neuroma surgery, had a profound unilateral hearing loss and tinnitus that was elicited specifically by horizontal, but not vertical, eye movements. When subjects were imaged during periods of repeated horizontal eye movements (tinnitus condition) and periods of repeated vertical eye movements (no tinnitus), several cortical areas showed greater activity during the tinnitus condition, including posterior auditory association areas. These results are consistent with those of Lockwood et al. (1998) in that auditory cortical activity was greater when the tinnitus percept was louder.

There have been several additional preliminary reports of tinnitus-related brain activity detected using fMRI. Cacace et al. (1995, 1999) piloted the application of fMRI to subjects in whom tinnitus could be modulated by deviations in eye position or cutaneous stimulation. In one subject, activation was detected in posterior auditory cortical areas when tinnitus was elicited by cutaneous stimulation. Also using fMRI, Levine et al. (1997) examined noise-evoked activation in one tinnitus subject. They reported that auditory cortical activation was “negative,” indicating that neural activity decreased when sound was turned on. This negative activation is unlike the positive activation produced by sound in nontinnitus subjects.

Although the functional imaging data in tinnitus subjects are sparse, it is nevertheless worth recognizing that the results are broadly compatible with a single view of auditory cortical activity in tinnitus subjects. In this view, the tinnitus percept would correspond to abnormally high levels of cortical activity (i.e., “tinnitus-related” activity), which would increase and decrease with increases and decreases in tinnitus loudness. The data of Arnold et al. (1996) are compatible with this view because they suggest that baseline levels of cortical activity can be abnormally high in tinnitus subjects. Findings of covariations between the level of auditory cortical activity and tinnitus loudness modulated with oral-facial movements, eye movements or cutaneous stimulation (Cacace et al. 1999; Giraud et al. 1999; Lockwood et al. 1998) are also consistent if the changes in cortical activity are interpreted as changes in the level of tinnitus-related activity. As discussed earlier, negative activation in response to sound, such as that reported by Levine et al. (1997), is explained readily by a model incorporating physiological masking (which assumes covariations between tinnitus-related activity and tinnitus loudness) but not by one based on saturation. Thus a model in which tinnitus-related activity increases and decreases with tinnitus loudness provides a parsimonious explanation for much of the available cortical functional imaging data in tinnitus subjects, in addition to providing a possible explanation for our data in the IC (i.e., Fig. 10, *bottom*).

Implications for animal studies of tinnitus

The present study has direct implications for tinnitus work on animals because it suggests that fMRI can provide an objective indicator of tinnitus. Having such an indicator would solve a major problem for the animal work, namely the uncertainty as to whether the animals under study (e.g., with induced cochlear or auditory nerve damage) have tinnitus. Using fMRI it may be possible to distinguish between tinnitus and nontinnitus animals and perhaps even infer the attributes of each animal’s tinnitus (e.g., tinnitus laterality) based on patterns of activation (e.g., abnormal asymmetries). Once distinguished, tinnitus and nontinnitus animals could be compared using the full spectrum of physiological, anatomic, and pharmacological techniques. Although the millimeter resolution achievable at the field strengths of clinical imagers (e.g., 1.5 Tesla) places considerable size constraints on the animal species and brain structures that can be studied, these constraints can be lessened by using higher field strength imagers specially designed for animal work and capable of providing functional images with submillimeter resolution (Barinaga 1998; Dubowitz et al. 1998; Jezzard et al. 1997; Logothetis et al. 1998; Mandeville et al. 1998; Stefanacci et al. 1998).

Clinical implications

fMRI could ultimately play a major role in the care of tinnitus patients. For example, if tinnitus patients prove to be physiologically differentiable as suggested by the present study, the differences may correlate with prognosis. fMRI evaluations then might provide answers to questions asked by patients such as “Will my tinnitus ever go away or will it worsen?” The ability to distinguish tinnitus patients on physiological grounds also opens new possibilities for evaluating

therapies, both new and old. For example, it is possible that certain treatments only benefit particular physiologically distinguishable subpopulations, and this selective benefit has been missed because there has been no way to differentiate physiologically between tinnitus patients (Levine and Kiang 1995; Tyler 1997). Clinical trials could be geared to identifying such selective benefits by categorizing patients into subpopulations based on fMRI and separately evaluating treatment efficacy for each subpopulation. If effective treatments for particular subpopulations were identified, fMRI ultimately could provide a way to determine the best treatment program for a given patient.

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Address for reprint requests: J. R. Melcher, Eaton-Peabody Laboratory, Massachusetts Eye and Ear Infirmary, 243 Charles St., Boston, MA 02114.

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