Original Article

**BOLD–fMRI study of auditory cortex in patients with tinnitus**

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**Abstract**

Objective Blood oxygenation level–dependent functional magnetic resonance imaging (BOLD–fMRI) was used to study activation signals in the brain cortex evoked by tone stimulation in patients with tinnitus for its potential utility as an objective indicator of tinnitus. Methods BOLD–fMRI examination was conducted in 7 patients with chronic tinnitus and 15 control subjects. The activation signal in the brain cortex was recorded. Results Significant activation was found in temporal lobe in control subjects, with greater signal volume and intensity on the contralateral than ipsilateral auditory cortex ($P<0.01$). However, there was no discernable patterns in the anatomical location, volume and intensity of cortical activation signals in patients with chronic tinnitus. Conclusions Patients with chronic tinnitus may have abnormal neural activities in the auditory cortex.

**Key words** Tinnitus, Auditory cortex, Blood oxygenation level dependent–functional magnetic resonance imaging

Causes of subjective tinnitus are complex. Meikle [1] indicates that cochlea lesions are not the only factor in tinnitus, and peripheral and central lesions can also lead to tinnitus. At present, the hypothesis is that over activities of auditory nerve fibers and synaptic pathways result in tinnitus. Hemodynamic response is closely relative to brain activity. fMRI is developed basing on MRI, which can link brain activity to specific tasks and may reflect the functional status of the detected tissue. There are only a few reports about using fMRI to study tinnitus, and quantitative analysis is deficient. In this study, BOLD–fMRI is used to detect activated signal intensity of brain areas in chronic tinnitus patients and healthy volunteers, in an attempt to study brain activities in tinnitus. Potential utility of Bold–fMRI as an objective tool in inspecting subjective tinnitus is discussed.

**Materials and methods**

**1.1 Clinical material**

Seven patients with chronic tinnitus (4 men and 3 women) were identified. The average age was 32 years (17–53 years). Tinnitus was on the left in 3 cases, on the right in 2 cases and bilateral in 2 cases. The average tinnitus duration was 2.5 years (0.8–5 years) and the causes were not clear. There were no hearing complaints, history of long-term noise exposure, hypertension, hyperlipidemia, cervical spinal diseases or diabetes. Tinnitus was constant and affected daily life, work, mood and sleep in these patients. The control group included fifteen healthy volunteers (8 men and 7 women), with an average age of 31 years (18–43 years). Examination of the external auditory canal, tympanic membrane and middle ear function was normal in all subjects, with the average hearing threshold over 125 to 4000 Hz range being $\leq 25$ dB HL. All subjects were right–handed.

**1.2 Experimental Design**

Block design was used for BOLD–fMRI study. The stimuli were 1000 Hz tone bursts with a duration of 500 ms at 90 dB nHL, delivered at 1 Hz. The sine wave tone was generated by the Adobe Audition 2.0 software.
The E-prime software was used to compile the stimulation program. The left ear was stimulated by tone bursts through the left channel for a duration of 10 TR (repetition time) (L), the right ear by tone bursts through the right channel for 10 TR (R), and the control was silence for 5 TR (S). The test order was S-SL-SR-SL-SR-SR-SL-SR-SL-SR-SL-SR-SL-SR for a total of 185 TR, or 370 s. The sound output from a computer was led to a SAMRTEC SAV-8800 MR-compatible auditory stimulation device with MR-compatible. After the headphones was put on, motion of the subject’s head was restricted by foam support inside the magnetic coil throughout the testing process. Test procedures were fully explained to the subject. The subject was instructed to close his/her eyes, focus on the stimulus sound, minimize body movement with gentle breathing.

### 1.3 Image Acquisition

A GE Signa Exite 1.5T dual-gradient 32-channel magnetic resonance scanner was used.

#### 1.3.1 Positioning imaging: T1-weighted SE sequence, sagittal, TR = 300 ms, TE = 20 ms, slice thickness = 5 mm, pitch = 2 mm, FOV = 240 × 240 mm, matrix = 320 × 192 planes.

#### 1.3.2 Anatomical imaging: T1-weighted FLAIR sequence, TR = 2000 ms, TE = 7.9 ms, FA = 90°, slice thickness = 5 mm, pitch = 1.5 mm, FOV = 240 × 240 mm, Matrix = 256 × 256 mm.

#### 1.3.3 Whole brain 3D imaging: T1-weighted SPGR sequence, TR = 10.5 ms, TE = 4.5 ms, FA = 15 degrees, slice thickness = 1.3 mm, no interval scans, FOV = 240 × 240 mm, Matrix = 256 × 192 mm.

#### 1.3.4 Functional imaging: T2-weighted EPI sequence, TR = 2000 ms, TE = 40 ms, FA = 90°, slice thickness = 5 mm, pitch = 1.5 mm, FOV = 240 × 240 mm, Matrix = 64 × 64 mm, 20-layer scanning to cover the whole brain.

### 1.4 Data processing

BOLD-fMRI raw data in DICOM format were transmitted to a computer workstation running SPM2 software package for off-line data processing. The processing included preprocessing and statistical analysis. Preprocessing involved data conversion, time alignment, motion correction, spatial normalization and spatial smoothing. Data associated with three-dimensional translation of more than 1 mm, and three-dimensional rotation of more than one degree were considered representing excessive movement and discarded. Spatial normalization yielded voxel sets on the Talairach coordinates. The resultant data from preprocessing were subjected to statistical analysis. Threshold of statistical probability was set at $P < 0.005$. Activation of 10 consecutive voxels (2 mm × 2 mm × 2 mm) or more was considered positive for activation. Finally, the activation map and three-dimensional anatomy were superimposed to produce the function map. Independent sample t test was used to compare activation volume and signal strength between the two auditory cortices. Activation volume and signal strength in tinnitus patients were not analyzed, due to the degree of variability.

### 2 Results

The cortex in the temporal lobe area was activated in the 15 healthy volunteers, the highest activation rate found in the superior temporal gyrus, followed by the middle temporal gyrus and transverse gyrus. When one ear was stimulated, activation volume and signal intensity was greater in the contralateral than in the ipsilateral auditory cortex ($P < 0.01$), showing a prevalent conduction of the contralateral hemisphere.

In the 7 tinnitus patients, activation volume and signal strength were greatly variable and showed no obvious patterns.

When stimulating the left ear in the 3 left-tinnitus patients, the cerebral cortex activation was noted in the left occipital lobe in the first patient (see Figure 1), in the left cerebellar lobe in the second patient (see Figure 2), and in the right parietal central gyrus as well as the left temporal lobe in the last patient (see Figure 3). Stimulation of the right ear in these patients induced no obvious activation in the cerebral cortex of the first patient, activation of the left inferior frontal lobe in the second patient, and nearly equal activation of bilateral auditory cortices in the last patient.

In the 2 right-tinnitus patients, stimulation of the left or right ear resulted in activation of the left occipital lobe in one patient. In the other patient, left ear stimulation induced bilateral similar auditory cortex activation, whereas right ear stimulation resulted in greater activa-
Figure 1: Greater activation volume and signal intensity in the left auditory cortex than right in response to right ear tonal stimulation in a normal subject.

Figure 2: Occipital lobe activation following left ear tonal stimulation in a patient with left side tinnitus.

Figure 3: Left cerebellar lobe activation in a patient with left side tinnitus in response to left ear tonal stimulation.

Figure 4: Bilateral temporal lobe activation following left ear tonal stimulation in a patient with right side tinnitus.
tion volume and signal strength in the left auditory cortex than right, which were also greater than in normal subjects (see Figure 4).

In the 2 patients with bilateral tinnitus, left or right ear stimulation induced bilateral similar auditory cortex activation in the first patient. In the other patient, stimulation of the left ear resulted in extensive cerebral cortex activation (see Figure 5), while right ear stimulation induced no cortex activation.

Only the anatomic location of activation was reported in the 7 tinnitus patients. In normal subjects, the auditory cortex showed stronger (more intense) activation than other cortical areas, and stronger activation in the contralateral than ipsilateral auditory cortex. The location, volume and intensity of activation in response to unilateral stimulation in tinnitus patients also lacked discernable patterns and showed great inter-individual variability.

3 Discussion

Under normal circumstance, afferent impulses are generated by sound stimulation. The peripheral nerve can be inhibited by the efferent fibers of the central nervous system. Therefore, activation and inhibition of the auditory center are balanced by a feedback mechanism, which depends on the integrity of cochlear function \[2\]. Cochlear damage leads to the state of auditory system deafferentation due to decreased peripheral auditory input. To compensate for the decrease, the activity level of the auditory pathways is increased \[3\]. Meanwhile, the central inhibition of the cortex – olive – cochlear bundle is weakened by the interruption or change of the incoming signal, leading to disturbed balance and continuous activation of the auditory system, and hence tinnitus.

With advances in magnetic resonance imaging and brain neuroscience, MRI is no more limited to anatomical localization but has been used to study the nervous system as a new development since the 90s. It integrates knowledges of function, imaging and anatomy and is an effective in vivo tool for locating functional areas in the brain. It is generally believed that the cochlear lesion is the main source of the tinnitus, but strong evidence has indicated that the central nervous system is involved in the generation and maintenance of tinnitus. Whey ed, the tinnitus can continue to exist despite recovery of cochlear lesions. Especially, tinnitus remains present or is aggravated in some patients even after the labyrinth is destroyed or the hearing nerve is cut.

Melcher et al \[4\] used fMRI to study functional activities in the cerebral cortex or subcortical structures in the patients with unilateral tinnitus, finding that the abnormal activation of cerebral cortex. Their study indicated that tinnitus may be closely related to abnormal neural activities. In the current study, the activation volume and signal strength of the cerebral cortex lacked discernable patterns in the seven chronic tinnitus patients, with two showing abnormally enhanced activation, suggesting a relation between tinnitus and abnormal neural activities in the auditory cortex.

Arnold (1996) et al \[5\] used PET to study glucose metabolic activity in certain cerebral regions in 11 patients with chronic tinnitus. Metabolic activities were detected in the left primary auditory cortex (PAC, Brodmann 41,

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**Figure 5** Extensive cerebral cortex activation in response to left ear tonal stimulation in a patient with bilateral tinnitus.
area) in 9 patients, and in the right primary auditory cortex in 1 patient. They speculated that tinnitus was related to metabolic reinforcement of the left primary auditory cortex. Lockwood and Salvi et al. studied the change of the cerebral blood flow in patients who were able to change tinnitus loudness with orofacial voluntary movement, finding a correlation between tinnitus loudness change and the change of cerebral blood flow in the contralateral auditory cortex. They concluded that tinnitus was unrelated to the dominant hemisphere. In our study, activation location, signal strength and volume in the central nervous system failed to show a dominant hemisphere pattern in the 7 patients with chronic tinnitus.

The current study shows that the unilateral tonal stimulation in normal subjects resulted in bilateral auditory cortex activation with greater activation volume and intensity in the contralateral than the ipsilateral auditory cortex, showing a prevalent conduction in the contralateral hemisphere. However, the activation volume and signal strength showed no obvious patterns in the seven chronic tinnitus patients, indicating possible relation between tinnitus and abnormal neural activities in the auditory cortex.

Whether there is a dominant hemisphere in patients with tinnitus remains to be further studied.

References


(Rceived May 12, 2010)