BOLD fMRI investigation of the rat auditory pathway and tonotopic organization

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Abstract

Rodents share general anatomical, physiological and behavioral features in the central auditory system with humans. In this study, monaural broadband noise and pure tone sounds are presented to normal rats and the resulting hemodynamic responses are measured with blood oxygenation level-dependent (BOLD) fMRI using a standard spin-echo echo planar imaging sequence (without sparse temporal sampling). The cochlear nucleus (CN), superior olivary complex, lateral lemniscus, inferior colliculus (IC), medial geniculate body and primary auditory cortex, all major auditory structures, are activated by broadband stimulation. The CN and IC BOLD signal changes increase monotonically with sound pressure level. Pure tone stimulation with three distinct frequencies (7, 20 and 40 kHz) reveals the tonotopic organization of the IC. The activated regions shift from dorsolateral to ventromedial IC with increasing frequency. These results agree with electrophysiology and immunohistochemistry findings, indicating the feasibility of auditory fMRI in rats. This is the first fMRI study of the rodent ascending auditory pathway.

Introduction

The ascending auditory pathway traverses multiple major nuclei before reaching the auditory cortex (Malmierca and Merchan, 2004). Hair cells in the ear conduct the mechanical movements of fluid into electrical signals that are transmitted to the cochlear nucleus (CN). The superior olivary complex (SOC) receives most of the projections from CN and projects to the contralateral central nucleus of the inferior colliculus (IC) via the lateral lemniscus (LL). As the largest auditory subcortical nucleus, the IC has diverse connections with every auditory structure and is a relay center for all ascending projections to the thalamus (Winer and Schreiner, 2004). The IC integrates information from the CN and SOC before projecting to the thalamus and the cortex. The medial geniculate body (MGB) in the thalamus receives projections from the IC and projects to different parts of the auditory cortex (AC). Much of our knowledge of the auditory pathway has been acquired with conventional invasive techniques, which are sensitive and provide high spatial resolution, but lack the field of view (FOV) needed to assess the entire brain in a feasible time period. Most studies using invasive techniques such as immunohistochemistry (Yang et al., 2005) and electrophysiology (Goldberg and Brown, 1968) focus on particular structures along the pathway. Recently, large FOV manganese-enhanced magnetic resonance imaging (MEMRI) was used to trace the auditory pathway (Watanabe et al., 2008; Yu et al., 2005). However, manganese is toxic and MEMRI requires prolonged sound stimulation, which hinder longitudinal studies (Van der Linden et al., 2009).

A noninvasive functional imaging technique with large FOV would be valuable for understanding the complex functional organization of the auditory system and developing treatments for hearing impairments. Functional magnetic resonance imaging (fMRI) can be used to measure the hemodynamic response in the entire brain with relatively high temporal and spatial resolution. Numerous task-based brain mapping studies have been performed using blood oxygenation level-dependent (BOLD) fMRI (Ogawa et al., 1998). The major

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limitation of applying fMRI in hearing studies is the loud acoustic scanner noise. The rapidly switching readout gradients in fMRI produce intense noise and bring adverse effects such as complicating the BOLD response and decreasing its dynamic range (Bandettini et al., 1998; Moelker and Pattynama, 2003). Various techniques have been suggested to reduce the unfavorable effect of acoustic noise. These include modifying the stimulation paradigm to have sparse temporal sampling (Hall et al., 1999), which significantly lengthens scan time but can potentially strengthen responses (Petkov et al., 2009). Nevertheless, continuous scanning still offers advantages over sparse temporal sampling due to superior temporal resolution and faster acquisition (Petkov et al., 2009). It is often used in combination with passive noise attenuation hardware such as ear muffs or active noise reduction techniques (Goldman et al., 1989). Reliable BOLD responses were previously reported in fMRI studies using continuous scanning (Binder et al., 1994; Tanji et al., 2010).

Primary and secondary auditory cortex activations can be consistently observed in humans by fMRI. Recording subcortical activations is considerably more challenging (Guimaraes et al., 1998; Hessellmann et al., 2001; Yetkin et al., 2004). The challenges include the small size of subcortical structures in humans and imaging artifacts related to cardiac pulsation and susceptibility gradients (Di Salle et al., 2003). Rodent studies are therefore valuable in fMRI investigations of auditory function because the rodent subcortex occupies a significantly larger portion of the brain compared with humans (Glendenning and Masterton, 1998). Rats are a commonly used animal model that shares general anatomical, physiological and behavioral features in the central auditory system with humans and has proven useful in hearing studies (Malmierca and Merchant, 2004). Compared with human auditory fMRI studies, animal fMRI studies (Baumann et al., 2011; Boumans et al., 2007, 2008; Petkov et al., 2009; Tanji et al., 2010; Van Meir et al., 2005; Yu et al., 2009) have just begun. The results from these studies suggest that auditory fMRI on animals can provide insights into hearing mechanisms.

In this study, we investigate (1) the entire rat auditory pathway and (2) the tonotopic organization of the IC using monaural stimulation and BOLD fMRI. The work represents the first fMRI study of the rodent auditory pathway.

Methods

Animal preparation

Animals were prepared for fMRI sessions as described in earlier studies (Chan et al., 2010; Lau et al., 2011a, 2011b). All aspects of this study were approved by the local animal ethics committee. Normal male Sprague–Dawley rats \( (n=8, 230 \text{ to } 280 \text{ g}) \) were anesthetized with 3% isoflurane. Controlled dosages were provided by an isoflurane vaporizer (SurgiVet). Anesthesia was maintained with 1% isoflurane throughout the course of setup and MR scanning. Animals were placed in the prone position with a head restraint and tooth bar to restrict motion. They were kept warm with a circulating water pad throughout the experiment while the rectal temperature was monitored. Respiration rate was monitored with a pressure sensor (SA Instruments) attached to the abdominal area. Heart rate and oxygen saturation were monitored with a pulse oximeter (SA Instruments) attached to one of the hindpaws. All eight animals were used to map the auditory pathway and four of the animals were scanned in a second session to map the IC’s tonotopy.

Auditory stimuli

The acoustic stimuli were produced using a closed-field electrostatic loudspeaker (EC1, Tucker Davis Technology) driven by a power amplifier (ED1, Tucker Davis Technology) and a waveform generator (33120A, Hewlett Packard). Sound waves were delivered to the rat via a 1 m long, 8 mm inner diameter (tapered to 2 mm over the last 5 cm) nylon sound delivery tube. The narrow end of the nylon tube was connected to a 6.5 cm long, 2 mm inner diameter polyurethane tube that entered the left ear canal. The right ear was occluded with cotton wool and vaseline.

The block-design auditory stimulation paradigm consisted of an initial 60 s silence followed by four (auditory pathway study) or six (tonotopy study) blocks of 20 s stimulation (amplitude modulated at 4 Hz) and 40 s silence. Four to six scans were performed on each animal during the auditory pathway study and nine scans during the tonotopy study.

Broadband noise generated by the setup was used to examine the auditory pathway throughout the brain. The sound pressure level (SPL) of broadband noise was adjusted by changing the amplifier gain and output voltage from the waveform generator. All broadband noise experiments were performed with the same SPL unless otherwise specified. Pure tone sounds of 65, 69 and 67 dB at 7, 20 and 40 kHz respectively were used to map the IC tonotopy. Different frequencies were presented in random and interleaved order such that there were two blocks of stimuli at each frequency in every scan.

The peak SPL of the broadband and pure tone stimuli were recorded using an omnidirectional condenser microphone (MSO, Earthworks) and a recorder (FR2, Fostex). The separation between the tube and the microphone was 0.5 mm. The SPL in the scanner room was recorded at about 2.5 m from the center of the magnet with the microphone aligned parallel to the horizontal magnet bore.

MRI acquisition

Experiments were performed on a 7 T scanner with a maximum gradient of 360 mT/m (70/16 PharmaScan, Bruker Biospin GmbH). Multi-slice, proton-density weighted scout images were acquired using a 2D rapid acquisition with refocused echoes (RARE) sequence along the coronal, axial and sagittal planes to accurately position fMRI slices. An anatomical scan was subsequently acquired with eight coronal slices, each with 1 mm thickness and 0.2 mm interslice gap. They were positioned to cover the rat brain from bregma – 11.4 mm to – 2 mm and were scanned with the following parameters: RARE, TR/TE = 4200/28 ms, data matrix = 32 × 32 mm², data matrix = 256 × 256. In the study of the rat auditory pathway, single-shot spin-echo echo planar imaging (EPI) volumes of the same localization were acquired with TR/TE = 2000/28 ms and data matrix = 64 × 64 (zero-filled to 128 × 128). In each broadband stimulation scan, 145 volumes were acquired (first 50 s discarded). Animals were allowed to rest for five to 10 min between successive scans. In one animal, an additional RARE scan with fifty coronal slices was acquired with TR/TE = 5500/36 ms, FOV = 32 × 32 mm², slice thickness = 0.5 mm, interslice gap = 0.05 mm, data matrix = 256 × 256 to cover the entire brain and generate a 3D brain rendering.

fMRI acquisitions in the IC tonotopy study were similar except that only one slice covering the IC (bregma – 8.5 mm) was acquired with a TR of 1 s, resulting in 410 volumes (first 50 s discarded) per scan.

fMRI data analysis

fMRI images were realigned to the mean image of all time points using AIR5.2.5 (Woods et al., 1992) and spatially smoothed with a Gaussian filter with full width half maximum of one voxel. Time profiles were correlated with the stimulation paradigm using Stimulate (Center for Magnetic Resonance Research, University of Minnesota). Voxels with correlation coefficient \( (r) > 0.2 \) and were part of a cluster of at least three such voxels were considered activated.

In the auditory pathway study, activated brain structures were identified by comparing with the rat brain atlas (Paxinos and Watson, 1998). The BOLD signal was defined as the time profile of the BOLD response normalized by the average of the profile from 5 s
the linear regression \( r^2 \) was then computed. To assess the effects of acoustic power, the BOLD signal changes of the four voxels with the highest \( r \) values at each SPL in the CN and IC were measured. The changes were then plotted against SPL and fitted to a line with linear regression. The squared correlation coefficient \( r^2 \) of the linear regression was then computed.

Images from the tonotopy study were analyzed in a similar manner, except no spatial smoothing was applied. The eighteen blocks acquired by stimulating with each frequency were averaged and the resulting time profiles were analyzed. \( r \) thresholds for individual frequencies were selected to show minimum spatial overlap between voxel clusters responding to different stimulation frequencies.

Results

The recorded power spectra of the scanner room and scanner room + EPI noises are displayed in Fig. 1a. The EPI noise spectrum peaks at 4.7 kHz. Fig. 1b shows the power spectra of the broadband stimulus (auditory pathway study) and the three pure tone stimuli (tonotopy study). For all three pure tones, the harmonics are at least 30 dB lower than the base frequency and therefore, are unlikely to interfere with tonotopic mapping.

Fig. 2a shows the slice localization used in the auditory pathway study. Fig. 2b shows the structures along the ascending auditory pathway activated by monaural stimulation with broadband noise. Fig. 2c shows the same activated structures using a correlation coefficient \( r \) threshold of 0.2 and cluster size of three voxels. These structures include the CN, SOC, LL, IC, MGB and AC. All eight of the animals in this study show activation in the CN, seven in the SOC, seven in the LL, eight in the IC, six in the MGB, and six in the AC. From all four animals are plotted in Fig. 6. Many of the voxels are activated by more than a single stimulation frequency. However, in each two frequency pair-wise comparison, there are numerous voxels activated by more than a single stimulation frequency. However, in each two frequency pair-wise comparison, there are numerous voxels activated by only one frequency, indicating the pure tone sounds activate different groups of voxels. BOLD signal changes in voxels lying before to onset of stimulation and averaged across all stimulation blocks, scans and animals. BOLD signals were measured from activated voxels in the ipsilateral CN and in other structures contralateral to the stimulated ear. The BOLD signal change was computed by averaging the BOLD signal from 10 to 20 s after onset of stimulation. To assess the changes in BOLD signal, the BOLD signal changes of the four voxels with the highest \( r \) values at each SPL in the CN and IC were measured. The changes were then plotted against SPL and fitted to a line with linear regression. The squared correlation coefficient \( r^2 \) of the linear regression was then computed.

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on the axis oriented at 45° from the midline in the middle of the IC is shown in Fig. 7. They show that the activations overlap spatially, but the peaks of activation shift towards the ventromedial region of the IC with increasing stimulation frequency, demonstrating tonotopic change along the axis.

Discussion

BOLD fMRI with broadband acoustic stimulation reveals activation throughout the rodent auditory pathway. The activated structures include the cochlear nucleus, superior olivary complex, lateral lemniscus, inferior colliculus, medial geniculate body, and auditory cortex. In the CN and IC, the BOLD signal change increases linearly with stimulus SPL. Three frequencies of pure tone stimuli identify the tonotopic organization in the IC. Low frequencies are encoded in the dorsolateral IC and high frequencies in the ventromedial IC. The regions activated by different frequencies overlap, but the location of the maximum BOLD signal change along the dorsolateral-ventromedial direction shifts with frequency.

Effect of stimulus SPL and scanner noise

fMRI studies are prone to interference from scanner noise (Bandettini et al., 1998) and hence, its application in studies of the auditory system have been limited. Such adverse effects largely depend on the spectral overlap between stimulus and scanner noise. The effects of SPL on tonotopy in monkey auditory cortex were recently studied in the presence of EPI noise (Tanji et al., 2010), suggesting that the need for sparse temporal sampling is situation dependent. It has also recently been reported that the BOLD response to EPI scanner noise is steady over a long scan time of 40 min (Hinds et al., 2010), therefore we can assume the BOLD baseline is steady throughout our scans. A previous report showed that the number of activated

![Fig. 4. BOLD signal change (n=8, mean±SD) vs. broadband noise SPL (dB). Seven scans were performed on each animal in a separate session from the auditory pathway study in Figs. 2 and 3. One block-design scan was performed at each SPL. BOLD signal changes were measured from the four voxels with the highest r values at each SPL in the CN and IC. The results show a monotonically increasing trend with stimulus power. 0 dB refers to an absolute sound pressure level of about 75 dB. The squared correlation coefficient (r²) was computed from linear regression of the BOLD signal changes with SPL.](image)

![Fig. 5. a) Acoustic stimulation in the tonotopy study consisted of three different pure tone sounds (red: 7 kHz; blue: 20 kHz; green: 40 kHz) presented in random and interleaved order. Each frequency was presented in two blocks each scan. Nine scans were performed on each animal (n=4). b) Blocks of the same frequency were averaged to compute the cross correlation (r) maps from a representative animal overlaid on an anatomical image of the IC. A large activation area with the cc threshold (r>0.2) is observed for each frequency. Iso-frequency activated voxels cluster in bands, which shift from dorsolateral to ventromedial IC with increasing frequency. c) Tonotopic mapping of IC with r maps overlaid on an anatomical image. The r scales were chosen such that there was minimum overlap between different colors. The results are in close agreement with the previous findings using invasive techniques (Huang and Fex, 1986).](image)
voxels decreased during acoustic stimulation when the stimulation frequency was close to the peak frequency of the scanner noise (Scarff et al., 2004). The effect of scanner noise can therefore be minimized by careful selection of stimulation frequency. From the results of this study, the activated structures are in good agreement with those known to be in the central auditory pathway (Sigalovsky and Melcher, 2006; Watanabe et al., 2008), providing further evidence that fMRI is able to investigate auditory functional activation in the presence of scanner noise.

To further examine the effect of scanner noise, we show that the BOLD signal change with SPL (Fig. 3c) is monotonic and approximately linear in the IC and CN. Therefore, the activations observed in this study could be considered as the additional activation to the baseline activation caused by scanner noise. The relationship between stimulus power and sensation magnitude in many sensory systems has been reported to be linear within a certain range (Stevens, 1970; Werner and Mountcastle, 1965). It has also been reported that there exists a monotonic trend of neuronal firing rate with SPL in IC for stimuli above the minimum threshold, although some of these neurons will saturate or decline at intensities 20 to 60 dB higher than the minimum threshold of hearing (Ehret and Schreiner, 2004). We have not observed such non-monotonic effect on BOLD signals in IC and CN possibly because our applied stimulus (45 to 81 dB) was not loud enough or the monotonic neurons dominated the hemodynamic response. It should be noted that the monotonic trend and linearity can be altered by training (Polley et al., 2004) and the level of anesthesia (Gaese and Ostwald, 2001; Zurita et al., 1994).

**BOLD fMRI of rat auditory system**

The present work demonstrates BOLD activations in many structures along the known auditory pathway without employing sparse temporal sampling or protocol modifications to minimize EPI noise. Monaural stimulation reliably activates the ipsilateral CN and contralateral SOC, LL, IC, MGB and AC (Malmierca and Merchant, 2004; Winer and Schreiner, 2004). Weaker responses are observed in MGB and AC and stronger, more consistent (from animal to animal) responses in CN, SOC, LL and IC. The lateralized responses to monaural stimulation is expected (Loveless et al., 1994) and demonstrates the feasibility of investigating sound localization in the rodent auditory system with fMRI.

Activations in lower-level structures along the ascending auditory pathway are more robust than those in higher-level structures like MGB and AC. This may be due to differences in vasculature, energy consumption, or neuronal activity (Logothetis and Wandell, 2004; Suta et al., 2008). Responses in higher-level structures such as the primary auditory cortex may also be suppressed by anesthesia (Cheung et al., 2001). In the CN and IC, a second peak after cessation of stimulation is observed. This may be due to an “off” response in the auditory system, which triggers neuronal firings when the stimulus is turned off (Henry, 1985), and has also been observed in a visual fMRI study (Pawela et al., 2008).

This study demonstrates that BOLD fMRI can detect sound evoked activity along the ascending auditory pathway, which spans much of the brain. fMRI can serve as a noninvasive tool for longitudinal investigations of damage and plasticity associated with auditory diseases such as tinnitus (Lanting et al., 2008) and unilateral hearing loss (Bilecen et al., 2000) in humans and animal models.

**Tonotopic mapping of inferior colliculus**

IC tonotopy has been explored using noninvasive fMRI in this study. The voxels activated by each frequency are clustered in bands with low frequency bands in the dorsolateral IC and high frequency bands in the ventromedial. This is consistent with the known tonotopic organization in IC (Clopton and Winfield, 1973; Huang and Fex, 1986; Pierson and Snyder-Keller, 1994). Due to the relatively large size of the rat IC and the fact that the anatomy of IC across different species shares anatomical similarities (Faye-Lund and Osen, 1985; Loftus et al., 2008; Malmierca et al., 1993, 1995), the rat can be a good model for investigating IC tonotopy. Despite the fact that there are numerous inhibitory neurons projecting into the IC in rats (Merchant et al., 2005), the tonotopic activation can be clearly observed in this study.

Our analysis made use of the spatial differences in BOLD responses at different frequencies, providing visualization of iso-frequency bands. Similar analyses using differential paradigms have been used.
to study ocular dominance in primary visual cortex (Menon et al., 1997). Many voxels were activated by more than a single frequency (Figs. 5b and 6). The spatial extents of these activations are subject to the choices of thresholds. The activation centers are still in bandshapes (Fig. 5) and BOLD signal analysis (Fig. 7) indicates shift of these bands. The tonotopic organization is revealed, yet a clear border of activation related to each single frequency cannot be clearly defined. Alternative approaches include defining the region of activation according to the center-of-mass analysis of the statistical parametric maps (Yu et al., 2010) or making use of the initial dip in the BOLD response (Kim et al., 2000).

Two limiting factors of the frequency and spatial resolutions of fMRI tonotopic mapping are IC vasculature and EPI distortion. The iso-frequency bands in Fig. 5b are thicker than one voxel and overlap with each other. Such overlapping may be due to neurons operating at a broader region of their tuning curves at high SPL (Moller, 2006), imprecise neuronal representations (Chapin and Lin, 1984) or vascular blurring of the BOLD response. BOLD characterizes the hemodynamic response instead of directly probing the neuronal activity and therefore, tonotopic maps may be blurred by the influence of large draining vessels and to increase the spatial specificity (Zhao et al., 2004). The exact origin of such broadening of BOLD activation requires further investigations. A recent study that mapped the cortical representation of rat forepaw and hindpaw suggested that BOLD fMRI activations in neighboring regions might be due to neuronal activity instead of vascular blurring (Goloshovsky et al., 2011).

As IC tonotopy can be robustly mapped in vivo, fMRI can be applied to detect developmental (Romand and Ehret, 1990; Shnerson and Willott, 1979) and aging (Frisina and Rajan, 2004; Willott, 1984) changes in frequency tuning or plasticity in animal models of tonotopic disorders such as cochlear damage (Frisina and Rajan, 2004; Nordeen et al., 1983). The reliable hemodynamic responses in structures other than IC suggest that it is possible to study tonotopy in these regions. The tonotopy are related to laminar organizations in all subcortical structures except in the LL (Malmierca et al., 1998). The present study may be extended to investigate the complex tonotopic organizations in the LL (Malmierca et al., 1998; Merchan and Berbel, 1996). However, the limited spatial resolution and significant image distortion from EPI will hinder the accurate tonotopic mapping in small structures that are vulnerable to high magnetic susceptibility effect. fMRI using techniques that produce distortion-free images like bSSFP (Lee et al., 2008; Zhou et al., in press) may provide higher signal-to-contrast ratio and spatial fidelity to map the tonotopy in these structures.

Limitations

Although the spatial pattern of activation in this study agrees well with known auditory structures, without sparse temporal sampling, the acquired BOLD temporal characteristics may be complicated by the non-uniform nature of EPI scanner noise. A better characterization of temporal characteristics may require further studies using sparse temporal sampling fMRI techniques.

Conclusions

The present study demonstrates the BOLD activations upon auditory stimulation in the rat auditory pathway. It also demonstrates the first in vivo tonotopic mapping in the rodent IC using pure tone sounds. These in vivo fMRI findings agree well with the previous electrophysiology and immunohistochemistry findings, indicating the feasibility of auditory fMRI in rodent models.

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