Brain Topogr (2017) 30:685–697
DOI 10.1007/s10548-017-0547-1

ORIGINAL PAPER

High-Resolution fMRI of Auditory Cortical Map Changes in Unilateral Hearing Loss and Tinnitus

Naghmeh Ghazaleh[1,2] · Wietske van der Zwaag[3,4] · Stephanie Clarke[5] · Dimitri Van De Ville[1,2] · Raphael Maire[6] · Melissa Saenz[1,7]

Received: 30 June 2016 / Accepted: 18 January 2017 / Published online: 6 February 2017

Abstract Animal models of hearing loss and tinnitus observe pathological neural activity in the tonotopic frequency maps of the primary auditory cortex. Here, we applied ultra high-field fMRI at 7 T to test whether human patients with unilateral hearing loss and tinnitus also show altered functional activity in the primary auditory cortex. The high spatial resolution afforded by 7 T imaging allowed tonotopic mapping of primary auditory cortex on an individual subject basis. Eleven patients with unilateral hearing loss and tinnitus were compared to normal-hearing controls. Patients showed an over-representation and hyperactivity in a region of the cortical map corresponding to low frequencies sounds, irrespective of the hearing loss and tinnitus range, which in most cases affected higher frequencies. This finding of hyperactivity in low frequency map regions, irrespective of hearing loss range, is consistent with some previous studies in animal models and corroborates a previous study of human tinnitus. Thus these findings contribute to accumulating evidence that gross cortical tonotopic map reorganization is not a causal factor of tinnitus.

Keywords Tinnitus · fMRI · Primary auditory cortex · Neural plasticity

✉ Naghmeh Ghazaleh
naghmeh.ghazaleh@epfl.ch

1 Institute of Bioengineering, École Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland

2 Department of Radiology and Medical Informatics, University of Geneva, Geneva, Switzerland

3 Spinoza Centre for Neuroimaging, Royal Netherlands Academy for Arts and Sciences, Amsterdam, Netherlands

4 Center for Biomedical Imaging, University of Lausanne, Lausanne, Switzerland

5 Service of Neuropsychology and Neurorehabilitation, Department of Clinical Neurosciences, Lausanne University Hospital, Lausanne, Switzerland

6 Department of Otorhinolaryngology, Head and Neck Surgery, Lausanne University Hospital, Lausanne, Switzerland

7 Neuroimaging Research Lab (LREN), Department of Clinical Neurosciences, Lausanne University Hospital, Lausanne, Switzerland

Introduction

Tinnitus, or 'ringing in the ear', is a common and potentially debilitating hearing disorder for which treatment options are lacking. Tinnitus is estimated to affect at least 10% of adults, and approximately 2% of adults to the degree that it negatively impacts quality of life, potentially contributing to stress, anxiety, and insomnia (Axelsson and Ringdahl 1989). In the vast majority of cases, tinnitus is not generated in the ear itself, but rather stems from pathological activity in auditory centers of the brain (Roberts et al. 2010; Schaette and McAlpine 2011a; Eggermont 2015; Elgoyhen et al. 2015). Peripheral hearing loss triggers downstream central neural activity that generates a "phantom" sound perception, ranging from tonal to broadband, of which the center frequency tends to occur in the hearing loss range (Norena et al. 2002; Schecklmann et al. 2012). Treatment options are currently limited and a better understanding of central auditory changes is needed to guide treatment strategies.

In animal models of tinnitus, induced cochlear damage is associated with behavioral evidence of tinnitus symptoms. These studies consistently report numerous downstream neurophysiological changes in the central auditory system (midbrain, thalamic, and cortical areas) including

increased spontaneous and driven neural activity, increased neural synchrony, and reduced inhibitory synaptic activity. However, it remains inherently difficult to disentangle changes related to tinnitus from other co-occurring effects of peripheral hearing loss, including hyperacusis (decreased sound tolerance) (Sheldrake et al. 2015).

In the primary auditory cortex, animal studies have shown distortions in the normal mapping of sound frequency preference, known as the tonotopic map. Some studies describe an overrepresentation of the hearing loss or hearing-loss edge frequencies (Eggermont and Komiya 2000; Seki and Eggermont 2003; Noreña and Eggermont 2003, 2005), and this finding has been taken to support a hypothesis that map distortion causes tinnitus (*maladaptive reorganization hypothesis)*. Other studies, quite differently, describe a broader pattern of distortions that favors hyperactivity in low frequency areas, notably away from the hearing-loss and presumed tinnitus range (Engineer et al. 2011; Yang et al. 2011).

Based on animal models, it is likely that hearing loss and tinnitus in humans is associated with altered activity in the tonotopic maps of primary auditory cortex, although the exact pattern of changes to expect is unclear. We have tested for such changes by applying high spatial resolution fMRI at ultra-high field (7 T) to measure tonotopic maps of the primary auditory cortex in human patients suffering from unilateral hearing loss and tinnitus. 7 T imaging offers distinct advantages for imaging small functional subunits in the cortex and facilitates fine-scale tonotopic mapping at the individual subject level, as we have previously shown in normal hearing adults. The increased signal-to-noise ratio and available BOLD signal associated with ultra-high magnetic field imaging at 7 T allows the use of smaller voxel sizes. Additionally, the BOLD signal is better restricted to cortical gray matter because the signal strength of blood in draining veins is reduced due to shortened T_2* relaxation time at higher fields, thus improving spatial localization (van der Zwaag et al. 2009, 2015).

In this clinical investigation, we studied patients with unilateral sensorineural hearing loss and tinnitus of at least 6-months duration (n = 11) compared to normal hearing controls (n = 7). The inclusion of patients with only unilateral hearing loss allowed the presentation of sound stimuli via the normal hearing ear, thus side-stepping the problem of unequal peripheral stimulation between hearing-loss and control groups. High-resolution 7 T fMRI imaging (1.5 mm isotropic voxels) was acquired over the auditory cortex to assess the organization of the primary tonotopic maps bilaterally. Notably, we observed map distortion and hyperactivity in a region of primary auditory cortex corresponding to relatively low frequency sounds, peaking at 250–354 Hz, irrespective of the patient's hearing loss and tinnitus frequency range. These results do not support the hypothesis that tinnitus is caused by the overrepresentation of hearing loss (or near) frequencies, but do corroborate recent findings from animal models (Engineer et al. 2011; Yang et al. 2011) and a previous human neuroimaging study of tinnitus (Langers and Kleine 2012).

Materials and Methods

Patients

All subjects gave written, informed consent. Experimental procedures were approved by the Ethics Committee of the Faculty of Biology and Medicine of the University of Lausanne.

Patients (n = 11, age 37.5 ± 12 years, age range 26–49 years, 6 male, 5 female) were recruited from the outpatient clinic of Otolaryngology of the Lausanne University Hospital and underwent a complete ear, nose, and throat (ENT) assessment including standard pure tone audiometry (PTA) and evaluation of tinnitus characteristics. Selected patients had chronic subjective non-pulsatile tinnitus associated with moderate to severe unilateral sensorineural hearing loss (SHL) in one ear only with a decrease in hearing thresholds of at least 40dB on three consecutive frequencies between 1 and 4 kHz, duration >6 months; and normal age-adjusted hearing thresholds in the unaffected ear. Age-matched control subjects (n = 7, 39.2 ± 10 years, age range 29–50 years, 3 male, 4 female) (Newman et al. 1996) had normal bilateral hearing. Exclusion criteria for all subjects included a history of neurological or psychiatric illness and standard MRI contraindications. Hearing loss originated from acoustic neuroma (noncancerous tumor of the auditory nerve), Meniere's disease (disorder of the inner ear typically affecting one side only), or unilateral cochlear damage caused by head trauma, infection, or blood clot. Some patients subjectively reported hyperacusis—a decreased tolerance to sounds—which often co-occurs with tinnitus. Table 1 provides an overview of patient characteristics.

Tinnitus pitch was assessed by matching external tones presented to the unaffected ear from 125 Hz to 12 kHz in half-octave steps. Tinnitus loudness was subsequently assessed by matching the selected tinnitus pitch to sound levels starting at 15 dB above auditory threshold and increasing by 5 dB increments. Tinnitus discomfort was assessed by the French version the Tinnitus Handicap Inventory (Newman et al. 1996). Patients reported THI rankings from 2 to 5 indicating mild to severe tinnitus discomfort (Table 1).

The recruitment of patients with unilateral hearing loss allowed for the unimpaired delivery of sound stimuli via the unaffected ear. As such, both patient and control groups

Table 1 Tinnitus patients' characteristics

ID	Sex	Age	Hearing loss side	Hearing loss degree and frequency range	Tinnitus center frequency	THi grade (1–5)	Tinnitus duration	Hyper-acusis	Hearing loss origin
P1	F	54	L	>40 dB, >1000 Hz	Noise 8000 Hz	3	>1 year	Yes	Cochear
P2	M	35	R	>90 dB, full spectrum	Noise 8000 Hz	3	>2 year	No	Cochlear
P3	M	44	R	>60 dB, full spectrum	Noise 1000 Hz	2	>2 year	No	Acoustic neuroma
P4	M	46	L	>60 dB, full spectrum	Noise 2000 Hz	4	>1 year	Yes	Cochlear
P5	F	46	L	>40 dB, full spectrum	Noise 1000 Hz Tone 6000 Hz	3	>5 year	Yes	Meniere's disease
P6	M	48	R	>50 dB, full spectrum	Noise 6000 Hz	3	>7 year	No	Meniere's disease
P7	F	20	L	>40 dB, <1000 Hz	Noise 1000 Hz	2	>3 year	No	Acoustic neuroma
P8	M	46	R	>50 dB, >2000 Hz	Tone 6000 Hz	5	>6 month	Yes	Cochlear
P9	F	26	L	>50 dB, >2000 Hz	Noise 1000 Hz	4	>5 year	Yes	Acoustic neuroma
P10	M	27	L	>90 dB, full spectrum	Tone 8000 Hz	2	>10 year	No	Cochlear
P11	F	20	R	>90 dB, full spectrum	Noise 1000 Hz	3	>2 year	No	Cochlear

(both stimulated unilaterally) received the equivalent stimulation and any eventual differences in the measured fMRI response could be attributed to altered cortical rather than to altered peripheral processing. Note that a different effect of background scanner noise may remain between groups (See Discussion). Stimulation of either ear activates auditory cortex bilaterally (van der Zwaag et al. 2011) allowing measurement of tonotopic maps in both brain hemispheres (See Discussion).

MRI Data Acquisition

Blood oxygenation level dependent (BOLD) functional imaging was performed with an actively shielded 7 T Siemens MAGNETOM scanner (Siemens Medical Solutions) at the Centre d'Imagerie BioMedicale in Lausanne, Switzerland. fMRI data were acquired with an 8-channel head volume RF-coil (RAPID Biomedical GmbH) (Salomon et al. 2014) large enough to comfortably fit the headphones used for auditory stimulation, and a continuous EPI pulse sequence with sinusoidal read-out (1.5 × 1.5 mm in-plane resolution, slice thickness = 1.5 mm, TR = 2000 ms, TE = 25 ms, flip angle = 47 deg, slice gap = 0.07 mm (5%), matrix size = 148 × 148, field of view 222 × 222, 30 oblique slices covering the superior temporal plane). A T_1-weighted high-resolution 3D anatomical image (resolution = 1 × 1 × 1 mm, TR = 5500 ms, TE = 2.84 ms, slice gap = 1 mm, matrix size = 256 × 240, field of view = 256 × 240) was acquired for each subject using the MP2RAGE pulse sequence optimized for 7 T MRI (Marques et al. 2010). Susceptibility induced distortions are small in the area of the brain covered by our imaging slab (van der Zwaag et al. 2009) and were further limited by the use of a limited matrix size in combination with parallel imaging to keep the read-out duration short. As a result co-registration between the functional images and the MP2RAGE was successful for all subjects, as verified by visual inspection.

fMRI data preprocessing steps were performed with BrainVoyager QX software including linear trend removal, temporal high-pass filtering (2 cycles), and motion correction. Spatial smoothing and slice-timing correction were not applied. Functional time-series data were interpolated into a 1 × 1 × 1 mm volumetric space and registered to each subject's own 3D Talairach normalized anatomical dataset. Cortical surface meshes were generated from each subject's anatomical dataset using automated segmentation tools in BrainVoyager QX.

Sound Stimulation (General Parameters)

Sound stimuli were generated on a laptop computer using Matlab and The Psychophysics Toolbox (www. Psychtoolbox.org) with a sampling rate of 44.1 kHz, and were delivered via MRI-compatible optical headphones (Audio-System, Nordic NeuroLab). Sound level intensities were between 82 and 97 dB SPL, and were adjusted per frequency to approximate equal perceived-loudness of 85 phon according to standard equal-loudness curves (ISO 226). Stimulus intensities were further attenuated approximately 24 dB by the required use of protective earplugs. Earplugs inevitably attenuate sound spectrum unevenly, affecting high frequencies more than low. All subjects reported hearing all tone frequencies at a clear and comfortable level, and were instructed to listen passively with eyes closed. Patients were stimulated in the unaffected ear only (Table 1) and control subjects were equivalently stimulated in one ear only, randomly selected. Overall time in the scanner including set-up, two fMRI tonotopy runs, and

an anatomical scan was approximately 45 min, sufficiently brief for patient comfort.

Tonotopic Mapping Paradigm and Analysis

Tonotopy refers to the spatial layout of auditory neurons in gradients of sound frequency preference. Tonotopy originates on the basilar membrane of the cochlea which due to mechanical properties resonates best to high-frequency sound waves on the basal end and to progressively lower sound frequencies towards the apical end, hence creating a spatial gradient of sound frequency selectivity along its length. Tonotopic organization of auditory neurons is maintained in the auditory nerve, mid-brain, thalamus, and cortex. In human primary auditory cortex, two tonotopic gradients with mirror-symmetry ('high-to-low' followed by 'low-to-high' preferences) are found running across Heschl's gyrus in each brain hemisphere, along an overall posterior-to-anterior axis. Figure 1 illustrates the primary auditory cortex tonotopic gradients with a color spectrum: red shows where neurons respond best to low frequency tones, and blue to high frequency tones.

These two mirror-symmetric gradients appear to correspond to primary auditory cortex fields A1 and R, (Da Costa et al. 2011; Langers and Dijk 2012b; Saenz and Langers 2014). In monkeys, both of these fields are considered part of the core koniocortical cortex along with a third smaller field RT which has not yet been reliably confirmed in humans (Hackett 2011; Baumann et al. 2013). In humans, visualizing the two tonotopic gradients with fMRI allows localization of primary auditory cortex in individual human subjects (Saenz and Langers 2014), although the exact lateral border remains difficult to define (See Discussion). No difference in function is known between fields A1 and R and they are treated together here as primary auditory cortex.

To map tonotopy in the cortex, we employed a "phase-encoded" mapping paradigm, a technique commonly used in the visual system for retinotopic mapping (Engel 2012), as well as in the somatosensory cortex for somatotopic mapping (Sanchez-Panchuelo et al. 2010). Briefly, the mapping stimulus is designed to sweep the parameter space of the map (in this case, low to high sound frequencies), thus generating a wave of response across the cortical surface. Recorded activity peaks earliest at the low frequency map endpoint and progressively later in parts of the map preferring higher frequencies. The phase of the response reveals the preferred frequency of each responsive voxel.

The mapping stimulus (Fig. 1a) cycled through tones of 15 different sound frequencies (88, 125, 177, 250, 354, 500, 707, 1000, 1414, 2000, 2828, 4000, 5657, 8000, and 11,312 Hz, half-octave spacing), as in our previously described methods (Da Costa et al. 2011). During each cycle, pure tone bursts of the first frequency were presented during a 2 s block before stepping to the next frequency until all 15 frequencies were presented, followed by a 4 s silent pause (Fig. 1a). During each 2 s block, pure tone bursts of the given frequency had variable onset times (50 and 250 ms duration randomly interspersed with 50 ms inter-stimulus intervals) to avoid a fixed periodicity. Each 34 s cycle (sounds plus silent pause) was repeated 14 times for a scan run duration of 7 min and 56 s. Each subject participated in two scan runs (one with stimulus sweeps from low-to-high, and one in reverse order) since tonotopic preferences should be independent of stimulus order, and the resulting maps of the two runs were averaged. Linear cross-correlation analysis was used to determine the response phase that best fit the measured fMRI time course of each

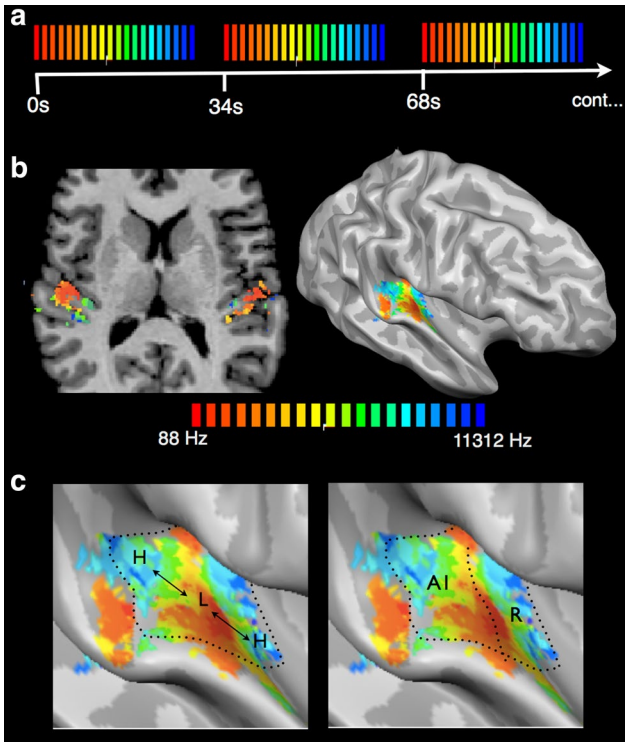

Fig. 1 Tonotopic mapping in auditory cortex with 7 T fMRI. **a** Sound stimuli were pure tone bursts ranging from 88 to 11,312 Hz. As illustrated, tones were presented in *slow cyclical sweeps* from low frequencies to high (or in reverse order). These frequency sweeps are designed to induce a traveling wave of response across the tonotopic maps of primary auditory cortex. The time-to-peak, or phase, of the response in the measured fMRI time series of each voxel reveals its preferred frequency. Color-coded maps (*red* = low, *blue* = high) of preferred frequency are shown (**b**, *left*) in volumetric anatomical space and (**b**, *right*) on a cortical surface mesh of one sample control subject. A close-up of the temporal plane shows the outlined mirror-symmetric frequency gradients from high to low and back to high (**c**, *left*). The same maps are relabeled (**c**, right) to show how the two gradients correspond to anatomical fields A1 and R which together comprise the primary auditory cortex in each brain hemisphere. (Color figure online)

responsive voxel. The assigned frequency preferences are color-coded from red-to-blue to indicate low-to-high.

Data analysis was performed in 3-D volumetric space in each subject individually (Fig. 1b, left). Resulting maps were projected onto cortical surface meshes to facilitate viewing (Figure b, right). On the cortical surface, contiguous areas containing the two primary gradients of auditory cortex (high-to-low followed by low-to-high) were manually selected using drawing tools within BrainVoyager QX, as illustrated with dotted lines (Fig. 1c). Anterior and posterior borders were drawn along the outer edges of the high-frequency zones. Lateral and medial borders were conservatively drawn to include approximately the medial two-thirds of Heschl's gyrus, in accordance with human architectonics (Rivier and Clarke 1997; Hackett 2011) (See "Discussion") and as in our previous studies (Da Costa et al. 2011, 2013). The exact borders did not depend upon the particular correlation threshold used for display since the overall pattern was observable across a large range of display thresholds. Figure 2 displays the selected surface regions for all subjects. Next, the selected regions were projected into each subjects $1 \times 1 \times 1$ mm volumetric space width of 2 mm (−1 mm to +1 mm from the white/gray matter boundary). Our relatively thin gray matter projection was effectuated in order to avoid contamination by voxels from abutting cortical folds.

The data analysis of Fig. 3 included all volumetric fMRI voxels ($1 \times 1 \times 1$ mm interpolated) falling within this 2 mm thick region-of-interest (ROI) in each subject's hemisphere. Relative frequency histograms show the percentage of the total number of voxels in the volumetric ROI assigned to each sound frequency (%voxels). Response amplitudes were measured as the maximal signal change in the average fMRI signal of all voxels assigned to each sound frequency within the volumetric ROI, as in (Da Costa et al. 2015).

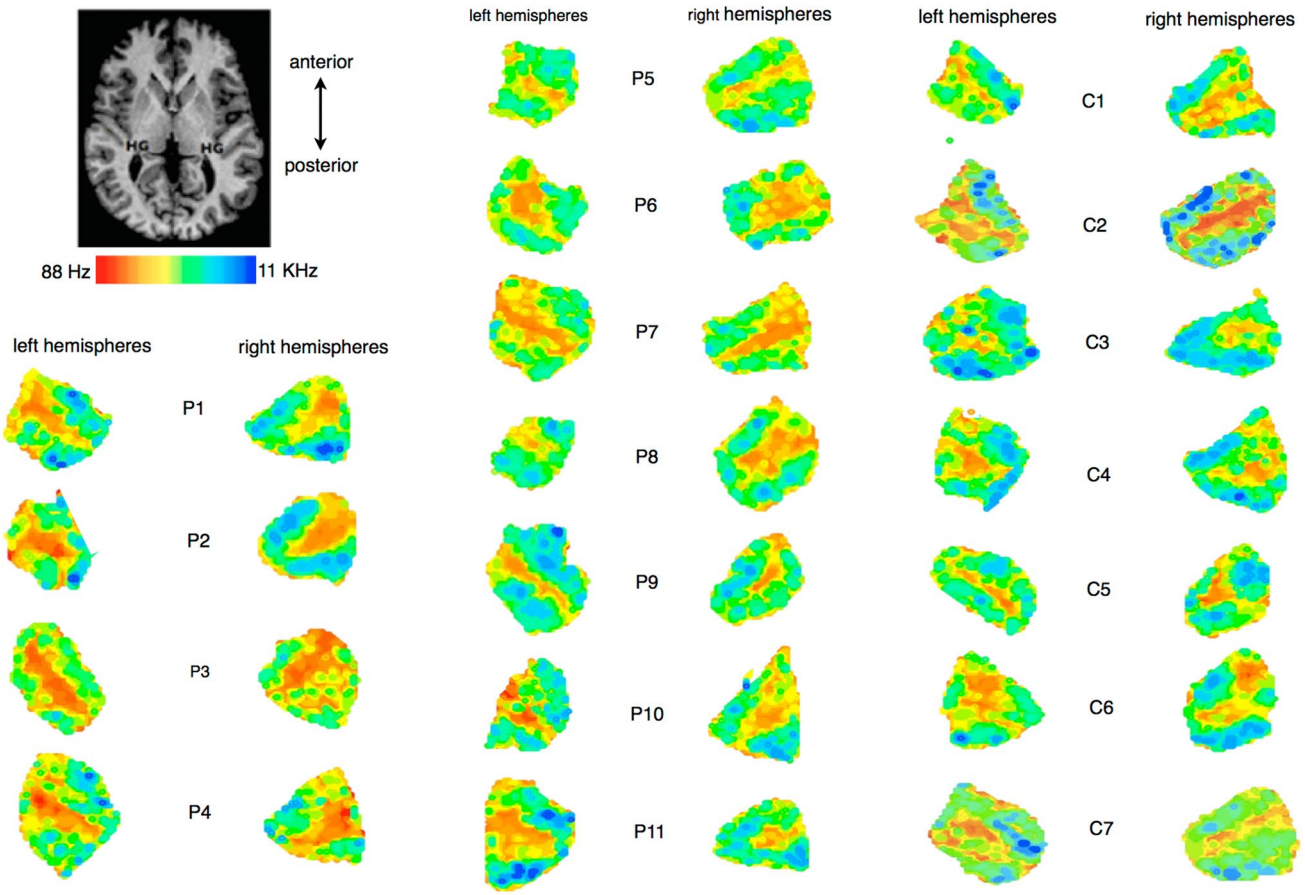

Fig. 2 All individual subject tonotopic maps from the cortical surface meshes are shown for patients with unilateral heaing loss and tinnitus (P1-P11) and normal hearing control subjects (C1–C7) in left and right hemispheres. The *upper-left inset* is provided as a reference of the anatomical orientation of all the plots (HG = Heschl's gyrus). At a macroscopic level, patient maps were normal in terms of location and orientation, running along a posterior-to-anterior axis across Heschl's gyrus

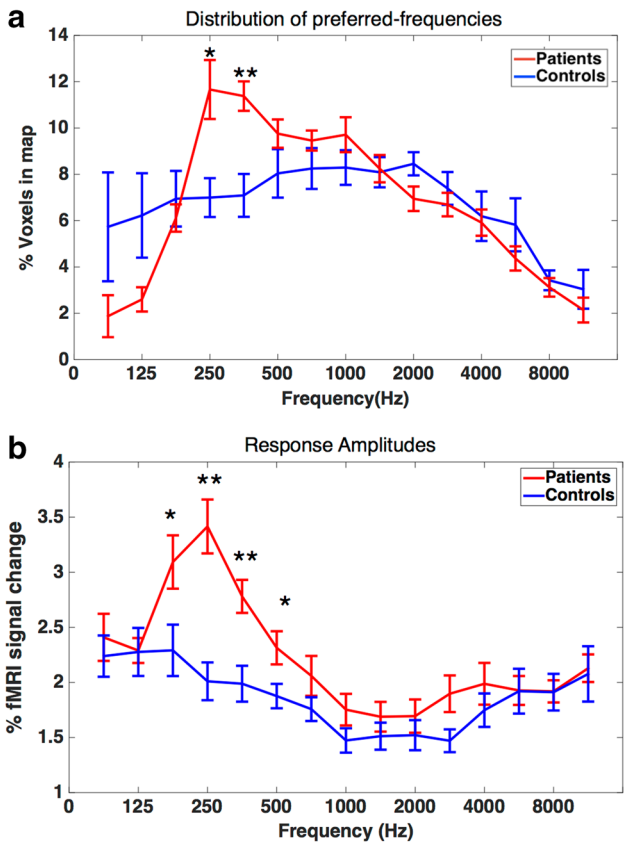

Fig. 3 Quantitative comparison of maps reveals differences between tinnitus patients and healthy control subjects. **a** Distribution of preferred-frequencies. Patients had a higher proportion of voxels preferring low frequencies peaking at 250–354 Hz indicating an enlarged representation of those sound frequencies. **b** Response amplitudes at each frequency. Patients had higher response amplitudes also peaking in the low-frequency range indicating hyperactivity in that part of the map. (*p < 0.05 Mann–Whitney U test uncorrected, **p < 0.05 following FDR correction for multiple comparisons, *error bars* = SEM across subjects and hemispheres)

Results

Tonotopic maps of the primary auditory cortex, consisting of two mirror-symmetric frequency gradients (high-to-low followed by low-to-high) running across Heschl's gyrus, could be identified in both hemispheres of all patients and controls (Fig. 2). At a macroscopic level, the mappings in patients were normal in terms of location and orientation, running along a posterior-to-anterior axis across Heschl's gyrus on the temporal plane in both left and right brain hemispheres, and were consistent with the maps of control subjects and with expectations based on our previous studies in normal hearing subjects (Da Costa et al. 2011; Da Costa et al. 2013; Da Costa et al. 2015).

Quantitative differences between patients and controls were observed. Figure 3a compares the distribution of preferred-frequencies across the maps in both groups. Patients showed a higher proportions of voxels preferring a range of low frequencies peaking at 250–354 Hz (*Mann–Whitney U test uncorrected*: $p < 0.05$ at 250 and 354 Hz; *following FDR correction for multiple comparisons*: $p < 0.05$ at 354 Hz), indicating an enlarged representation of those sound frequencies. Next, Fig. 3b compares response amplitudes at each frequency in both groups. Patients showed higher response amplitudes peaking in the same low-frequency range (*Mann–Whitney U test uncorrected*: $p < 0.05$ at 117, 250, 354 and 500 Hz; *following FDR correction for multiple comparisons*: $p < 0.05$ at 250 Hz and 354 Hz) indicating a hyperactivity in that part of the map. These patterns were observed in both hemispheres, ipsilateral and contralateral to the hearing ear, and both sides are combined in Fig. 3a, b. In Fig. 4, map frequency distributions and response amplitudes are re-plotted separately for both hemispheres, ipsilateral and contralateral to the normal hearing ear (i.e. the side of sound presentation). As can be seen, the low-frequency over-representation and hyperactivity are common to both hemispheres.

The low-frequency area of over-representation and hyperactivity in patients did not correspond with the ranges of hearing loss, which were either across the full spectrum or limited to higher-frequencies (Table 1); nor did they correspond with tinnitus pitch judgments which ranged form 1000–8000 Hz (Table 1). No significant correlation was found between response amplitudes at 250 Hz and tinnitus center frequency ($R = -0.49$, $p > 0.05$), THI score ($R = -0.36$, $p > 0.05$), years of tinnitus duration ($R = -0.03$, $p > 0.05$), or patient age ($R = -0.01$, $p > 0.05$), nor was there an association with hearing loss side, or presence of hyperacusis ($p > 0.05$). The occurrence of Heschl's gyrus duplications (See Discussion) was similar across both groups: 10 partial duplications out of 22 hemispheres in patients: 6 partial and 1 complete duplication out of 14 hemispheres in normal hearing controls.

Discussion

We applied high-resolution fMRI at 7 T to image the tonotopic sound frequency maps of primary auditory cortex in individual patients with unilateral hearing loss and tinnitus, and in normal hearing controls. Evidence of cortical map distortion in patients was two-fold: increased representation and increased response amplitudes of low frequency sites in primary auditory cortex. These changes peaked at 250–354 Hz, considerably lower than the tinnitus frequency ranges of the patients. Given this mismatch, we do not interpret these map distortions as a causal factor of tinnitus, and consider them more likely to be a co-occurring effect of hearing loss. As discussed below, the finding of low-frequency hyperactivity, irrespective of the

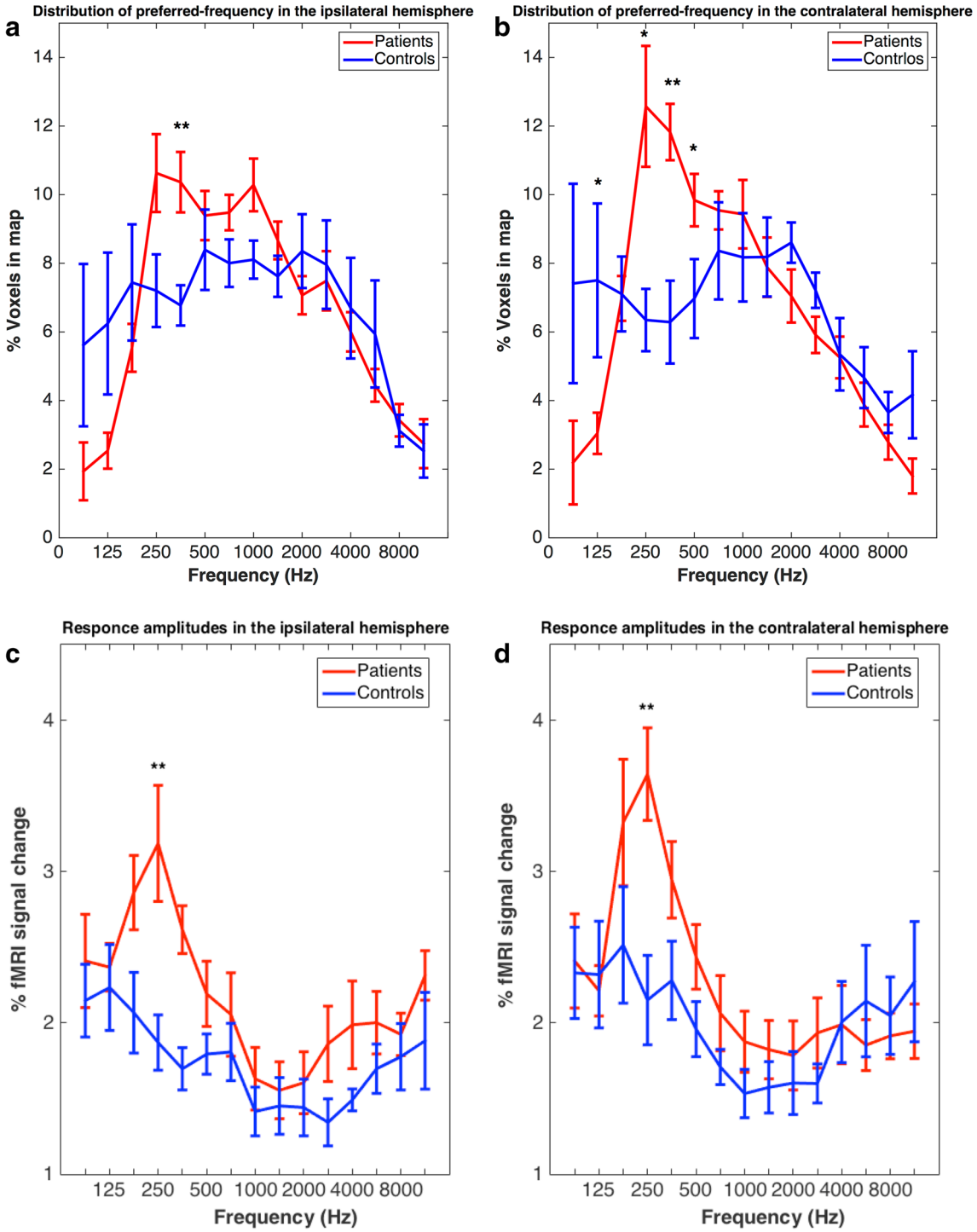

Fig. 4 Distribution of preferred frequencies re-plotted separately for both hemispheres **a** ipsilateral and **b** contralateral to the normal hearing ear (the side of sound presentation). Response amplitudes at each frequency re-plotted separately for both hemispheres, **c** ipsilateral and **d** contralateral to the normal hearing ear. As can be seen, the patterns of low-frequency map over-representation and hyperactivity are common to both hemispheres. (*$p < 0.05$ Mann–Whitney U test uncorrected, **$p < 0.05$ following FDR correction for multiple comparisons, *error bars* = SEM across subjects)

hearing loss or tinnitus range, is consistent with recent studies in animal models (Engineer et al. 2011; Yang et al. 2011) and corroborates a previous human fMRI study in tinnitus patients with normal hearing thresholds (Langers and Kleine 2012a). Our results do not rule out the possibility, and indeed likelihood, of other changes in the

functional properties of neurons within the hearing loss and tinnitus range, which may not have been detected by our methodology.

Neurophysiological Mechanisms

The pathological mechanisms underlying tinnitus have not been resolved, however many clues have emerged from research in humans and in animal models. A key observation is that tinnitus perception typically corresponds to the side and frequency range of maximum hearing loss (Norena et al. 2002; Schecklmann et al. 2012), an association that implicates neurons within the hearing loss range are responsible for tinnitus generation (Roberts et al. 2010). Although some tinnitus patients present with a normal audiogram, these cases may be accompanied by "hidden" hearing loss, occurring at high intensity levels not detected by standard audiometry (Schaette and McAlpine 2011b). Other consequences of hearing loss, namely hyperacusis, are not necessarily limited to the hearing loss range and thus might stem different from mechanisms than tinnitus (Sheldrake et al. 2015).

Animal studies associate cochlear damage (induced by noise exposure or drug induction) with increases in spontaneous activity, driven activity, neural synchrony, and excitatory glutamatergic neurotransmission, with cortical tonotopic map distortions, and with reductions in inhibitory GABAergcic and glycinergic neurotransmission across auditory midbrain (Brozoski et al. 2002; Kaltenbach et al. 2004), collicular (Ma et al. 2006), thalamic, and cortical sites (Seki and Eggermont 2003; Noreña and Eggermont 2003, 2005; Engineer et al. 2011; Yang et al. 2011). Overall, these physiological effects of cochlear damage generally implicate the involvement of homeostatic plasticity mechanisms (Turrigiano and Nelson 2004) and are in some cases correlated with behavioral evidence of tinnitus in the hearing loss range (Brozoski et al. 2002; Kaltenbach et al. 2004; Middleton et al. 2011). Notably, increased neural synchrony appears to localize well with the hearing loss and presumed tinnitus range (Noreña and Eggermont 2003; Eggermont and Roberts 2012). It has been recently demonstrated, however, that the gap-detection behavioral test for tinnitus commonly used in animal studies can confounded by hearing loss and hyperacusis, evoking the difficulty in disentangling the effects specifically related to tinnitus (Salloum et al. 2016).

Regarding cortical tonotopic maps, some studies describe an overrepresentation of sound frequencies within or at the edge of the hearing loss range (Eggermont and Komiya 2000; Seki and Eggermont 2003; Noreña and Eggermont 2003, 2005), leading to the hypothesis that cortical map reorganization is a causal factor of tinnitus (maladaptive plasticity hypothesis). That hypothesis predicts that an overrepresentation of hearing loss or hearing loss-edge frequencies coupled with spontaneous activity would lead to a frequency-specific tinnitus percept. However, other studies describe a broader pattern of neural activity changes, with map distortions occurring in relatively low frequency areas away from hearing loss and presumed tinnitus range (Engineer et al. 2011; Yang et al. 2011). These latter results do not support the idea that map reorganization is the cause of tinnitus.

In Yang et al. hearing-lesioned animals displayed evidence of high-frequency hearing-loss and tinnitus, and these were associated with distinct changes in different zones of the cortical map: (1) decreased inhibitory neurotransmission in the hearing-loss zone, and (2) increased inhibitory and excitatory neurotransmission in the low frequency normal-hearing zone (Yang et al. 2011). In these animals, there was an enlarged cortical representation of low-frequency sound that was, at least partly, a result of enhanced cortical responses to low-frequency tones. While, the receptive fields of high-frequency neurons tended to be discontinuous, rendering the corresponding cortical area less tonotopic. Interestingly, pharmaceutical manipulations that enhanced inhibition, and not those that reduced excitation, appeared to alleviate the tinnitus percept, thus implicating the neurons in the hearing-loss zone as having a causal role in tinnitus. In Engineer et al. 2011, the data also suggested over-representation at lower frequencies, with lower neuronal thresholds and higher amplitudes, in the noise-exposed animals (Engineer et al. 2011).

We compare these results in animal models to our findings in human patients, keeping in mind the important differences in species, etiology, and methodology. Of the multiple cortical pathologies seen in animal models, the low frequency hyper-excitability was relatively prominent in magnitude and thus perhaps the most likely to be detectable by non-invasive BOLD fMRI. We do not provide evidence nor claim that tonotopic map distortions are causal of tinnitus perception. Hyper-excitability could be related to hyperacusis, which commonly occurs with tinnitus and might be due to a generalized increase in auditory gain (Sheldrake et al. 2015). Some patients reported subjective complaints of hyperacusis which, in our study, did not correlate with response amplitudes. Future studies could utilize quantitative measures of loudness discomfort levels to more directly test this possibility (Knudson et al. 2016). Tonotopic distortions and tinnitus perception may be parallel consequences of a common underlying cause, namely neural deafferentation due to hearing loss.

It is important to note the difference in how tonotopic maps are measured in animal compared to human neuroimaging studies. In animal research, tonotopic maps are based on the spatial mapping of characteristic frequencies (CF), which are the best frequency response at threshold sound

levels (Rajan et al. 1993). In human neuroimaging, high intensity sounds are required to evoke measurable BOLD responses and tuning is thus based on the best frequency response at highly suprathreshold sound levels. In the normal brain, these two maps (threshold and suprathreshold tuning) appear to correspond well (Joly et al. 2014). However, in cases of hearing loss, which are likely associated with neural gain changes, differences could arise, thus imposing limitations in the comparison of human and animal mapping data.

Our findings contribute to increasing evidence against the idea that tinnitus is caused by maladaptive reorganization of hearing loss edge frequencies in tonotopic maps. Observational studies indicate that tinnitus tends to occur at the peak rather than the edge of the hearing loss range (Schecklmann et al. 2012), and studies of map reorganization have found either a lack of it (Langers and Kleine 2012, 2014), or that it occurs mostly in non-hearing loss regions (Yang et al. 2011; Engineer et al. 2011). Maladaptive map plasticity has also been much discussed in the context of phantom limb pain, and interestingly, its role there is also currently under question (Makin et al. 2013, 2015). It is unknown to what extent these two phenomena, tinnitus and phantom pain, share common neurophysiological origins.

More generally, auditory map plasticity has been studied in a broad context of behavioral and environmental manipulations (Schreiner and Polley 2014) and there are different mechanisms by which auditory maps could reorganize. Changes in neurophysiological properties of auditory neurons that could contribute to map plasticity include changes in: spectral tuning, response magnitudes, and dependence on sound intensity, tuning to sound location, response timing and neural synchrony. Inhibitory synapses have been indicated as 'critical gatekeepers' of plasticity and have also been implicated in tinnitus pathology (Middleton et al. 2011; Yang et al. 2011).

Human Studies

Human neuroimaging findings emphasize a broad anatomical network of tinnitus related pathology (Elgoyhen et al. 2015). Studies have shown altered responses in the auditory thalamus and cortex (Gu et al. 2010; Leaver et al. 2011; Langers and Kleine 2012; Melcher et al. 2000), and also implicate limbic and other non-auditory brain areas in modulating tinnitus perception and distress (Leaver et al. 2011; Seydell-Greenwald et al. 2012; Emmert et al. 2014; Lanting et al. 2014; Boyen et al. 2014). Alterations in functional connectivity patterns between auditory cortex and other brain regions emphasize increased interaction with attentional and limbic networks and possible impairments in thalamocortical gating (Maudoux et al. 2012; Schmidt et al. 2013; Lanting et al. 2014; Boyen et al. 2014). In contrast, a recent neuroimaging study of patient with a rare, high-intensity, tonal objective tinnitus (stemming from a physical sound generated in the ear) found a lack of changes in brain activity, underscoring the difference from centrally generated tinnitus (Guinchard et al. 2016). In Weisz et al. 2007, tinnitus patients showed a marked increase in auditory cortex gamma-band oscillations, thought to reflect underlying neural synchrony (Weisz et al. 2007). This evidence is compelling in that the oscillatory activity correlated with the laterality of the tinnitus percept and may relate to neural synchrony findings in animals, however see Sedley et al. 2012 for an alternate interpretation (Sedley et al. 2012).

Our results corroborate previous fMRI findings from a cohort of tinnitus patients with normal hearing thresholds (Langers and Kleine 2012a). That study used high-resolution 3 T fMRI to assess the integrity of the primary tonotopic maps and reported an overall lack of macroscopic changes in tinnitus sufferers (thus not supporting the maladaptive plasticity hypothesis). Additionally, using a conventional linear regression model, they reported increased activation in patients in the region of the low-frequency part of the tonotopic map in left lateral Heschl's gyrus. The authors note that this low-frequency response did not agree with the typical high-pitched tinnitus of their patients. It is encouraging that our studies converge upon coherent findings in two, rather different, patient groups. The bilaterality of the effect in our study could be related to the more extensive hearing loss in our patients, and also potentially to methodological differences.

It should be noted that the boundaries of primary auditory cortex are not fully discernable with human neuroimaging. The anterior and posterior borders are revealed by frequency reversals, but the lateral and medial borders cannot be distinguished by tonotopy alone (Da Costa et al. 2011). In monkeys, isofrequency bands of the primary (core) gradients extend continuously into lateral and medial non-primary (belt) auditory fields (Hackett 2011). As in our previous work (Da Costa et al. 2013), medial and lateral borders were manually drawn to include the medial-two-thirds of Heschl's gyrus in accordance with expectations from human architectonics (Rivier and Clarke 1997; Hackett 2011). We thus cannot rule out the inclusion of voxels belonging to non-primary auditory cortex in some subjects, particularly on the lateral end of Heschl's gyrus. The search for complementary measures to parcellate human auditory cortex such as myelin density (Dick et al. 2012; Martino et al. 2015) and tuning width or other spectral properties (Moerel et al. 2012; Thomas et al. 2015) is an active area of research. However, as yet no other solution has emerged as a gold standard.

Tonotopic maps were measured bilaterally based on ipsilateral stimulation, in both patients and controls. Unilateral stimulation induces clear bilateral activation of BOLD responses in the auditory cortex (van der Zwaag et al. 2011), although more strongly in contralateral cortex (Scheffler et al. 1998). In our study the same pattern of response was observed on contralateral and ipsilateral sides, and so both sides were combined in the analysis. The extent to which map accuracy differs given contralateral vs. ipsilateral stimulation is unknown, and this could be assessed by future studies, for example, designed to estimate population receptive fields (Thomas et al. 2015).

We included patients with unilateral hearing loss so that sound stimuli could be presented to unaffected ear, equivalently to control subjects. However, there remains an unequal effect of scanner noise since controls are more exposed to it in both ears. The effect of scanner noise on the mapping aren't known, but the most likely consequence would be sound masking which could lower BOLD response amplitudes in controls relative to patients. The acoustic resonance of the scanning protocol peaks strongly at approximately 1700 Hz (corresponding to the pulse sequence bandwidth) and does not have substantial energy in the 250–500 Hz range. We suspect that this may contribute to the dip in response amplitudes that we see here in both groups in the 1000–2000 Hz range, and in our previous studies with the same 7 T protocol (Da Costa et al. 2011; Da Costa et al. 2015). However, it is not obvious that this could account for the difference in patients and controls that peaks at 250–354 Hz range. Another approach to equating sound stimuli is to study the subgroup of tinnitus sufferers with normal hearing thresholds; however these patients are likely to suffer from 'hidden', high-intensity hearing-loss not assessed by standard audiograms (Schaette and McAlpine 2011b). Adequate sound delivery and, indeed, the broader problem of dissociating the effects of hearing loss and tinnitus are among the main challenges of human tinnitus studies. Utilizing sparse fMRI protocols and including tinnitus patients without hearing loss are among the methods that have been used to address these issues (Langers et al. 2012a).

Previous anatomical MRI studies have associated tinnitus with structural brain changes in the auditory cortex (Schneider et al. 2009; Boyen et al. 2013) and non-auditory areas (Mühlau et al. 2006). Heschl's gyrus is known for high anatomical variability in the normal population (Da Costa et al. 2011; Marie et al. 2013). The variability in the presence of an intermediate sulcus along its length that can divide the gyrus and make partially or complete duplications. Here, the rate of Heschl's gyrus divisons was similar in patients and controls, and within the previously reported range (Leonard et al. 1998; Da Costa et al. 2011; Marie et al. 2013). Thus, gross anatomical changes are not an obvious explanation for the functional changes we observed.

Comparing Findings from Humans and Animal Models

Tinnitus is an inherently subjective phenomenon and it is difficult to assess whether animal models (primarily rodent) have the same perceptual experience as human tinnitus sufferers. Hence there is a clear need to assess tinnitus-related pathology in humans. Our findings indicate a potential parallel in neurophysiological changes across human and animal models of tinnitus. In light of the observed hyperexcitability, treatments which aim to reinstate the balance between neuronal excitation and inhibition in auditory brain centers may help to alleviate tinnitus (Richardson et al. 2012). Experimental sound exposure therapies, and also neurofeedback, based on restoring normal activity levels in auditory cortex have shown potential in human patients (Haller et al. 2009; Okamoto et al. 2010; Tass et al. 2012) and may also induce changes in large-scale networks (Van De Ville et al. 2012; Haller et al. 2013).

Caution needs to be taken however in comparing findings from animal models and humans as there are many differences. Our patients had different etiologies and none of the patients presented hearing loss due to acoustic trauma or to sound exposure as in the majority of animal models. Indeed, investigations of tinnitus many challenges because the disorder is heterogeneous in terms of multiple factors including: etiology, loudness and quality of the percept, degree of hearing loss, level of associated distress, co-occurrence of hyperacusis, and potential interaction with age-related brain changes. Hearing loss is not always accompanied by tinnitus and the discriminating factors are not known (Schecklmann et al. 2012). Approximately 15% of tinnitus cases present without detectable changes in hearing thresholds but these cases may present hearing loss which is not detected by standard audiometry (Weisz et al. 2007; Schaette and McAlpine 2011a). Tinnitus risk factors may interact with age-related factors such as down-regulation of neural inhibition in the cortex (Caspary et al. 2008; Llano et al. 2012). Additionally human studies must consider differences in neuroimaging and data analysis methods.

Clinical Applications at 7T

Ultra-high field fMRI imaging offers a bridge between clinical and basic neuroscience research. Mapping of small functional subunits such as ocular dominance columns in the human visual cortex (Yacoub et al. 2007), tonotopic organization in human auditory cortex (Da Costa et al. 2011; Da Costa et al. 2013) and inferior colliculus (De Martino et al. 2013), or finger somatotopy in somatosensory

cortex (Martuzzi et al. 2012) and cerebellum (van der Zwaag et al. 2013) requires high-spatial resolution which is more easily achieved with ultra high field fMRI (van der Zwaag et al. 2009, 2015; Da Costa et al. 2015). Our study demonstrates the applicability of high-resolution mapping methods to clinical groups with auditory neurological disorders. We further illustrate the applicability of individual subject assessments, as opposed to group brain-averaged based analysis, in order to take full advantage of the spatial resolution achievable at ultra high field and to facilitate the relation of results to neurophysiological studies in animal models.

Conclusions

Here, we successfully employed high spatial resolution ultra-high field fMRI to demonstrate functional changes in primary auditory cortex related to hearing loss and tinnitus. In future studies, high-resolution imaging could be applied to track potential renormalization of auditory cortex during the testing of tinnitus treatments.

Acknowledgements This work was supported by Swiss National Science Foundation Grant 320030_143989 and by the Centre d'Imagerie BioMédicale (CIBM) of the Université de Lausanne, Université de Genève, Hôpitaux Universitaires de Genève, Lausanne University Hospital, École Polytechnique Fédérale de Lausanne, and the Leenaards and Louis-Jeantet Foundations.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

References

Axelsson A, Ringdahl A (1989) Tinnitus—a study of its prevalence and characteristics. Br J Audiol 23:53–62

Baumann S, Petkov CI, Griffiths TD (2013) A unified framework for the organization of the primate auditory cortex. Front Syst Neurosci 7:11.

Boyen K, Langers DRM, de Kleine E, van Dijk P (2013) Gray matter in the brain: differences associated with tinnitus and hearing loss. Hear Res 295:67–78

Boyen K, de Kleine E, van Dijk P, Langers DRM (2014) Tinnitus-related dissociation between cortical and subcortical neural activity in humans with mild to moderate sensorineural hearing loss. Hear Res 312:48–59

Brozoski TJ, Bauer CA, Caspary DM (2002) Elevated fusiform cell activity in the dorsal cochlear nucleus of chinchillas with psychophysical evidence of tinnitus. J Neurosci 22:2383–2390

Caspary DM, Ling L, Turner JG, Hughes LF (2008) Inhibitory neurotransmission, plasticity and aging in the mammalian central auditory system. J Exp Biol 211:1781–1791

Da Costa S, Zwaag W van der, Marques JP et al (2011) Human Primary Auditory Cortex Follows the Shape of Heschl's Gyrus. J Neurosci 31:14067–14075

Da Costa S, Zwaag W van der, Miller LM et al (2013) Tuning In to sound: frequency-selective attentional filter in human primary auditory cortex. J Neurosci 33:1858–1863

Da Costa S, Saenz M, Clarke S, van der Zwaag W (2015) Tonotopic gradients in human primary auditory cortex: concurring evidence from high-resolution 7 T and 3 T fMRI. Brain Topogr 28:66–69

De Martino F, Moerel M, van de Moortele P-F et al (2013) Spatial organization of frequency preference and selectivity in the human inferior colliculus. Nat Commun 4:1386

Dick F, Tierney AT, Lutti A et al (2012) In vivo functional and myeloarchitectonic mapping of human primary auditory areas. J Neurosci Off J. Soc Neurosci 32:16095–16105

Eggermont JJ (2015) Animal models of spontaneous activity in the healthy and impaired auditory system. Front Neural Circuits 9:19.

Eggermont JJ, Komiya H (2000) Moderate noise trauma in juvenile cats results in profound cortical topographic map changes in adulthood. Hear Res 142:89–101

Eggermont JJ, Roberts LE (2012) The neuroscience of tinnitus: understanding abnormal and normal auditory perception. Front Syst Neurosci 6:53.

Eggermont JJ, Roberts LE (2015) Tinnitus: animal models and findings in humans. Cell Tissue Res 361:311–336

Elgoyhen AB, Langguth B, De Ridder D, Vanneste S (2015) Tinnitus: perspectives from human neuroimaging. Nat Rev Neurosci 16:632–642

Emmert K, Ville DVD, Bijlenga P et al (2014) Auditory cortex activation is modulated by somatosensation in a case of tactile tinnitus. Neuroradiology 56:511–514

Engel SA (2012) The development and use of phase-encoded functional MRI designs. NeuroImage 62:1195–1200.

Engineer ND, Riley JR, Seale JD et al (2011) Reversing pathological neural activity using targeted plasticity. Nature 470:101–104

Gu JW, Halpin CF, Nam E-C et al (2010) Tinnitus, diminished sound-level tolerance, and elevated auditory activity in humans with clinically normal hearing sensitivity. J Neurophysiol 104(6):3361–3370. doi:10.1152/jn.00226.2010.

Guinchard AC, Ghazaleh N, Saenz M, Fornari E, Prior JO, Maeder P, Adib A, Maire R (2016) Study of tonotopic brain changes with functional MRI and FDG-PET in a patient with unilateral objective cochlear tinnitus. Hear Res 341:232–239

Hackett TA (2011) Information flow in the auditory cortical network. Hear Res 271:133–146

Haller S, Birbaumer N, Veit R (2009) Real-time fMRI feedback training may improve chronic tinnitus. Eur Radiol 20:696–703

Haller S, Kopel R, Jhooti P, et al (2013) Dynamic reconfiguration of human brain functional networks through neurofeedback. NeuroImage 81:243–252.

Joly O, Baumann S, Balezeau F, Thiele A, Griffiths TD (2014) Merging functional and structural properties of the monkey auditory cortex. Front Neurosci 8:198

Kaltenbach JA, Zacharek MA, Zhang J, Frederick S (2004) Activity in the dorsal cochlear nucleus of hamsters previously tested for tinnitus following intense tone exposure. Neurosci Lett 355:121–125

Knudson IM, Melcher JR (2016) Elevated acoustic startle responses in humans: relationship to reduced loudness discomfort level, but not self-report of hyperacusis. J Assoc Res Otolaryngol 17(3):223–235

Langers DRM (2014) Assessment of tonotopically organised subdivisions in human auditory cortex using volumetric and surface-based cortical alignments. Hum Brain Mapp 35:1544–1561

Langers DRM, van Dijk P (2012b) Mapping the tonotopic organization in human auditory cortex with minimally salient acoustic stimulation. Cereb Cortex 22:2024–2038

Langers DRM, Kleine E de (2012a) Tinnitus does not require macroscopic tonotopic map reorganization. Front Syst Neurosci 6:2.
Lanting CP, de Kleine E, Langers DRM, van Dijk P (2014) Unilateral tinnitus: changes in connectivity and response lateralization measured with fMRI. PLoS ONE 9(10):e110704
Leaver AM, Renier L, Chevillet MA et al (2011) Dysregulation of limbic and auditory networks in tinnitus. Neuron 69:33–43
Leonard CM, Puranik C, Kuldau JM, Lombardino LJ (1998) Normal variation in the frequency and location of human auditory cortex landmarks. Heschl's gyrus: where is it? Cereb Cortex 8:397–406
Llano DA, Turner J, Caspary DM (2012) Diminished cortical inhibition in an aging mouse model of chronic tinnitus. J Neurosci 32:16141–16148.
Ma W-LD, Hidaka H, May BJ (2006) Spontaneous activity in the inferior colliculus of CBA/J mice after manipulations that induce tinnitus. Hear Res 212:9–21
Makin TR, Scholz J, Filippini N et al (2013) Phantom pain is associated with preserved structure and function in the former hand area. Nat Commun 4:1570
Makin TR, Scholz J, Henderson Slater D et al (2015) Reassessing cortical reorganization in the primary sensorimotor cortex following arm amputation. Brain 138:2140–2146
Marie D, Jobard G, Crivello F, et al (2013) Descriptive anatomy of Heschl's gyri in 430 healthy volunteers, including 198 left-handers. Brain Struct Funct 220:729–743.
Marques JP, Kober T, Krueger G, et al (2010) MP2RAGE, a self bias-field corrected sequence for improved segmentation and T1-mapping at high field. NeuroImage 49:1271–1281.
Martino FD, Moerel M, Xu J et al (2015) High-resolution mapping of myeloarchitecture in vivo: localization of auditory areas in the human brain. Cereb Cortex 25:3394–3405
Martuzzi R, van der Zwaag W, Farthouat J et al (2012) Human finger somatotopy in areas 3b, 1, and 2: A 7 T fMRI study using a natural stimulus. Hum Brain Mapp 35(1):213–226
Maudoux A, Lefebvre P, Cabay J-E et al (2012) Auditory resting-state network connectivity in tinnitus: a functional MRI study. PLoS ONE 7:e36222
Melcher JR, Sigalovsky IS, Guinan JJ, Levine RA (2000) Lateralized tinnitus studied with functional magnetic resonance imaging: abnormal inferior colliculus activation. J Neurophysiol 83:1058–1072
Middleton JW, Kiritani T, Pedersen C, et al (2011) Mice with behavioral evidence of tinnitus exhibit dorsal cochlear nucleus hyperactivity because of decreased GABAergic inhibition. Proc Natl Acad Sci 108:7601–7606.
Moerel M, De Martino F, Formisano E (2012) Processing of natural sounds in human auditory cortex: tonotopy, spectral tuning, and relation to voice sensitivity. J Neurosci 32:14205–14216
Mühlau M, Rauschecker JP, Oestreicher E, et al (2006) Structural brain changes in tinnitus. Cereb Cortex 16:1283–1288.
Newman CW, Jacobson GP, Spitzer JB (1996) Development of the tinnitus handicap inventory. Arch Otolaryngol Head Neck Surg 122:143–148
Norena A, Micheyl C, Chéry-Croze S, Collet L (2002) Psychoacoustic characterization of the tinnitus spectrum: implications for the underlying mechanisms of tinnitus. Audiol Neurootol 7:358–369
Noreña AJ, Eggermont JJ (2003) Changes in spontaneous neural activity immediately after an acoustic trauma: implications for neural correlates of tinnitus. Hear Res 183:137–153
Noreña AJ, Eggermont JJ (2005) Enriched acoustic environment after noise trauma reduces hearing loss and prevents cortical map reorganization. J Neurosci 25:699–705
Okamoto H, Stracke H, Stoll W, Pantev C (2010) Listening to tailor-made notched music reduces tinnitus loudness and tinnitus-related auditory cortex activity. Proc Natl Acad Sci 107:1207–1210.
Rajan R, Irvine DR, Wise LZ, Heil P (1993) Effect of unilateral partial cochlear lesions in adult cats on the representation of lesioned and unlesioned cochleas in primary auditory cortex. J Comp Neurol 338(1):17–49
Richardson BD, Brozoski TJ, Ling LL, Caspary DM (2012) Targeting inhibitory neurotransmission in tinnitus. Brain Res 1485:77–87
Rivier F, Clarke S (1997) Cytochrome oxidase, acetylcholinesterase, and NADPH-diaphorase staining in human supratemporal and insular cortex: evidence for multiple auditory areas. NeuroImage 6:288–304.
Roberts LE, Eggermont JJ, Caspary DM et al (2010) Ringing ears: the neuroscience of tinnitus. J Neurosci 30:14972–14979
Saenz M, Langers DRM (2014) Tonotopic mapping of human auditory cortex. Hear Res 307:42–52
Salloum RH, Sandridge S, Patton DJ, Stillitano G, Dawson G, Niforatos J, Santiago L, Kaltenbach JA (2016) Untangling the effects of tinnitus and hypersensitivity to sound (hyperacusis) in the gap detection test. Hear Res 331:92–100
Salomon R, Darulova J, Narsude M, van der Zwaag W (2014) Comparison of an 8-channel and a 32-channel coil for high-resolution FMRI at 7 T. Brain Topogr 27:209–212
Sanchez-Panchuelo RM, Francis S, Bowtell R, Schluppeck D (2010) Mapping human somatosensory cortex in individual subjects with 7 T functional MRI. J Neurophysiol 103:2544–2556
Schaette R, McAlpine D (2011) Tinnitus with a normal audiogram: physiological evidence for hidden hearing loss and computational model. J Neurosci 31:13452–13457
Schecklmann M, Vielsmeier V, Steffens T et al (2012) Relationship between audiometric slope and tinnitus pitch in tinnitus patients: insights into the mechanisms of tinnitus generation. PLoS ONE
Scheffler K, Bilecen D, Schmid N et al (1998) Auditory cortical responses in hearing subjects and unilateral deaf patients as detected by functional magnetic resonance imaging. Cereb Cortex 8:156–163
Schmidt SA, Akrofi K, Carpenter-Thompson JR, Husain FT (2013) Default mode, dorsal attention and auditory resting state networks exhibit differential functional connectivity in tinnitus and hearing loss. PLoS ONE 8:e76488
Schneider P, Andermann M, Wengenroth M, et al (2009) Reduced volume of Heschl's gyrus in tinnitus. NeuroImage 45:927–939.
Schreiner CE, Polley DB (2014) Auditory map plasticity: Diversity in causes and consequences. Curr Opin Neurobiol 24:143–156
Sedley W, Teki S, Kumar S, Barnes GR, Bamiou D-E, Griffiths TD (2012) Signle-subject oscillatory gamma responses in tinnitus. Brain 135(10):3089–3100
Seki S, Eggermont JJ (2003) Changes in spontaneous firing rate and neural synchrony in cat primary auditory cortex after localized tone-induced hearing loss. Hear Res 180:28–38
Seydell-Greenwald A, Leaver AM, Turesky TK et al (2012) Functional MRI evidence for a role of ventral prefrontal cortex in tinnitus. Brain Res 1485:22–39
Sheldrake J, Diehl PU, Schaette R (2015) Audiometric characteristics of hyperacusis patients. Front Neurol 15(6):105
Tass PA, Adamchic I, Freund H-J et al (2012) Counteracting tinnitus by acoustic coordinated reset neuromodulation. Restor Neurol Neurosci 30:137–159
Thomas JM, Huber E, Stecker GC, et al (2015) Population receptive field estimates of human auditory cortex. NeuroImage 105:428–439.
Turrigiano GG, Nelson SB (2004) Homeostatic plasticity in the developing nervous system. Nat Rev Neurosci 5:97–107
Van De Ville D, Jhooti P, Haas T, et al (2012) Recovery of the default mode network after demanding neurofeedback training occurs in spatio-temporally segregated subnetworks. NeuroImage 63:1775–1781.

van der Zwaag W, Francis S, Head K, et al (2009) fMRI at 1.5, 3 and 7 T: characterising BOLD signal changes. NeuroImage 47:1425–1434.

van der Zwaag W, Gentile G, Gruetter R, et al (2011) Where sound position influences sound object representations: A 7-T fMRI study. NeuroImage 54:1803–1811.

van der Zwaag W, Kusters R, Magill A, et al (2013) Digit somatotopy in the human cerebellum: a 7 T fMRI study. NeuroImage 67:354–362.

van der Zwaag W, Schäfer A, Marques JP et al (2015) Recent applications of UHF-MRI in the study of human brain function and structure: a review. NMR Biomed 29(9):1274–1288

Weisz N, Müller S, Schlee W et al (2007) The neural code of auditory phantom perception. J Neurosci 27:1479–1484

Yacoub E, Shmuel A, Logothetis N, Uğurbil K (2007) Robust detection of ocular dominance columns in humans using Hahn Spin Echo BOLD functional MRI at 7 T. NeuroImage 37:1161–1177.

Yang S, Weiner BD, Zhang LS, et al (2011) Homeostatic plasticity drives tinnitus perception in an animal model. Proc Natl Acad Sci 108:14974–14979.