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Representation of lateralization and tonotopy in primary versus secondary human auditory cortex

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Functional MRI was performed to investigate differences in the basic functional organization of the primary and secondary auditory cortex regarding preferred stimulus lateralization and frequency. A modified sparse acquisition scheme was used to spatially map the characteristics of the auditory cortex at the level of individual voxels. In the regions of Heschl's gyrus and sulcus that correspond with the primary auditory cortex, activation was systematically strongest in response to contralateral stimulation. Contrarily, in the surrounding secondary active regions including the planum polare and the planum temporale, large-scale preferences with respect to stimulus lateralization were absent. Regarding optimal stimulus frequency, low- to high-frequency spatial gradients were discernable along the Heschl's gyrus and sulcus in anterolateral to posteromedial direction, especially in the right hemisphere, consistent with the presence of a tonotopic organization in these primary areas. However, in the surrounding activated secondary areas frequency preferences were erratic. Lateralization preferences did not depend on stimulus frequency, and frequency preferences did not depend on stimulus lateralization. While the primary auditory cortex is topographically organized with respect to physical stimulus properties (i.e., lateralization and frequency), such organizational principles are no longer obvious in secondary and higher areas. This suggests a neural re-encoding of sound signals in the transition from primary to secondary areas, possibly in relation to auditory scene analysis and the processing of auditory objects.

Introduction

The central auditory system is organized into hierarchically organized processing stages that are distributed over several structures in the brainstem, midbrain, thalamus, and cerebral cortex. Numerous studies have been carried out in humans and primates regarding the parcellation and functional organization of the auditory cortex in particular. As a result, a distinction has been made between primary processing areas that form a core region in the superior surface of the temporal lobe, and secondary areas that are located in an adjacent belt region. In addition, associative and multimodal regions in a parabelt area and various other areas are thought to be involved in higher order processing of auditory information (Kaas et al., 1999).

The distinction between primary and secondary auditory processing areas has originally been made on the basis of differences in cytoarchitectonic features, i.e., the cell densities, types, and sizes in the various cortical layers (Brodmann, 1909; Morosan et al., 2001; Rademacher et al., 2001; Shapleske et al., 1999). However, functional differences have been reported as well. For instance, some studies have reported that responses occur slightly earlier in primary auditory cortex than in secondary cortex (Belin et al., 1999; Liegeois-Chauvel et al., 1994). Whereas both primary and secondary regions respond during the perception of sound, only secondary regions are active during sound imagery (Bunzeck et al., 2005). Furthermore, the primary auditory cortex has been found to respond to a broad range of auditory stimuli, while the secondary cortex seems to respond preferably to stimuli with sufficiently complex spectral dynamics (Specht and Reul, 2003; Thivard et al., 2000). Secondary regions have been reported to be sensitive to slower temporal modulations and broader spectral modulations than primary regions, indicating that some form of temporal and spectral integration is taking place (Giraud et al., 2000; Langers et al., 2003). This may indicate a specialization towards the processing of acoustic and phonetic sound features in primary and secondary auditory regions, respectively, which may be corroborated by the role of the planum temporale in the analysis of voice onset times (Jäncke et al., 2002a). Still, we note that the role of secondary auditory regions in spectro-temporal processing is likely broader than for speech alone (Griffiths and Warren, 2002).

Two basic features regarding the functional organization of the auditory cortex that have been well established in animal studies and that have also been confirmed in humans (Konig et al., 2005) are [i] the contralateral dominance of responses to monaural

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stimulation and [ii] the presence of tonotopic gradients on the cortical surface. However, neuroimaging studies in humans that concern these characteristics mostly report summary values for the auditory cortices as a whole. For instance, response lateralization is usually quantified using a laterality index that expresses the lateralization of the extent or magnitude of activation (Bilecen et al., 2000; Jäncke et al., 2002b; Scheffler et al., 1998; Woldorff et al., 1999). Tonotopic progressions have often been demonstrated by mapping effective activation foci in response to a range of stimulus frequencies, e.g., using source locations in electro/magnetoencephalography (Cansino et al., 2003; Fujioka et al., 2003; Langner et al., 1997; Liegeois-Chauvel et al., 2001; Romani et al., 1982) and observations or calculations of the 'center of mass' of activation clusters in positron emission tomography and functional magnetic resonance imaging (fMRI) (Bilecen et al., 1998; Engelien et al., 2002; Lockwood et al., 1999; Schmid et al., 1998; Schönwiesner et al., 2002; Wessinger et al., 1997; Yetkin et al., 2004). Such methods quantify overall response behavior but do not distinguish between functional subdivisions of the auditory cortex. Therefore, they will not reveal differences in the functional characteristics between, e.g., the primary and secondary auditory cortices. To our knowledge, small-scale spatial variations in preferences regarding stimulus lateralization have not yet been mapped, and although some recent studies thoroughly characterized the cortical gradients in optimal stimulus frequency (Formisano et al., 2003; Talavage et al., 2004), tonotopic arrangements in humans are not fully understood either.

The aim of this study was to reinvestigate response lateralization and tonotopic organization by mapping both the optimal stimulus lateralization and frequency at the detailed level of individual voxels. An active listening task and an adapted fMRI paradigm were employed to improve the detection of activation signals. Furthermore, by investigating both response lateralization and tonotopic organization in a single study, the presence of interactions between these two characteristics could be assessed for the first time.

Materials and methods

Subjects

Ten healthy subjects were recruited on the basis of written informed consent, in approved accordance with the requirements of the medical ethical committee at the Maastricht University Hospital. The subjects comprised 3 females (#1–#3) and 7 males (#4–#10); 7 subjects were right-handed (#1–#7), 2 left-handed (#8–#9), and 1 ambidextrous (#10) (Oldfield, 1971). Ages ranged from 23 to 43 years (mean 31 years). All subjects were tested by an audiologist using standard pure tone audiometry (Katz, 2001) and had thresholds better than 20 dB hearing level in the range of 250–8000 Hz.

Auditory task

During the fMRI sessions, subjects performed an active listening task to enhance the recorded responses (Hall et al., 2000). A tone-in-noise detection task with band-limited stimuli was chosen. Noise bursts had a center frequency equal to either 125, 500, 2000 or 8000 Hz, a bandwidth of 1/4 octave, a duration of 1.5 s, and a rise/fall time of 10 ms; pure tones had frequencies identical to the center frequencies of the noise, a duration of 0.5 s, and a rise/fall time of 10 ms. Noise bursts were spaced by 0.5 s and preceded the following functional acquisition by 0.75 s (see Fig. 1). The tone presentations coincided with either the first or the second noise burst in a pseudo-random fashion. The onset of the tone occurred 0.5 s after the onset of the noise stimulus. Subjects were instructed to indicate whether the additional tone coincided with the first or the second noise stimulus by pressing one of two fiber-optic button devices that were held in each hand. The results were used only to monitor that the subjects understood the task and stayed alert during the fMRI session.

The target tones and the background noise were both presented at an intensity of 60 dB sensation level by means of modified electrostatic head phones (Sennheiser HE 60, Sennheiser) that were built into a noise protection headset (Palmer et al., 1998) and connected to a PC setup equipped with a sound card with 16-bit DAC output capability (Sound Blaster Live! Platinum 5.1, Creative). Stimulus waveform data were generated in advance using digital Fourier transformation techniques, and were stored in the form of standard 16-bit uncompressed sound files with a sampling frequency of 44.1 kHz.

MR acquisitions

Subjects were placed in supine position in the bore of a clinical 1.5-T MRI system (Philips Intera, Philips Medical Systems), which

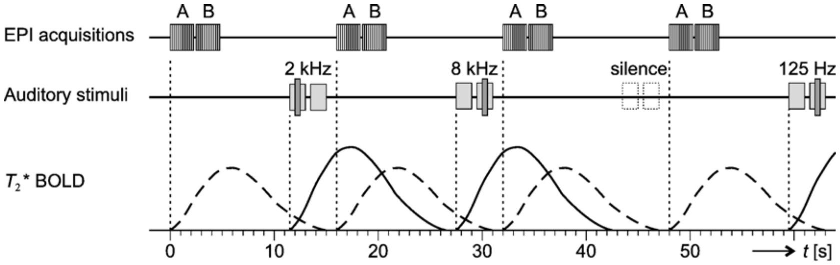

Fig. 1. Schematic representation of the experimental paradigm. Functional echo planar imaging (EPI) acquisitions were performed in pairs (labeled 'A' and 'B') at intervals of 16 s using a sparse acquisition paradigm. Preceding each acquisition pair, two 1.5-s band-passed noise bursts were delivered with a center frequency of 125, 500, 2000 or 8000 Hz. An additional 0.5-s pure tone stimulus was presented 0.5 s after the onset of one of the noise bursts. The tone frequency was equal to the center frequency of the noise. Subjects were instructed to indicate by means of a button press whether the tone coincided with the first or the second noise burst. The stimulus and acquisition timing were chosen such that the expected hemodynamic response to the noise stimuli (solid curves) was approximately maximal at the time of the EPI acquisitions, whereas the hemodynamic response to the acoustic noise of the previous MRI acquisitions (dashed curve) had faded to a negligible level.

was equipped with a standard quadrupolar head receiver coil. A sagittal 3D T_1-weighted fast-field echo scan was acquired for anatomical orientation (repetition time TR 10.2 ms; echo time TE 3.5 ms; flip angle 15°; matrix 256 × 256 × 75; voxel dimensions 1.0 × 1.0 × 2.0 mm). On these high-resolution images a central imaging plane was positioned approximately parallel to the Sylvian fissure of both hemispheres, containing the superior temporal gyri of both temporal lobes. An additional 3D T_1-weighted fast-field echo scan (TR 10.34 ms; TE 3.5 ms; flip angle 15°; matrix 256 × 256 × 12; voxel dimensions 1.0 × 1.0 × 2.0 mm) was acquired parallel to this imaging plane and served as anatomical reference. The functional scans were acquired covering the same brain volume, and consisted of a dynamic series of 2.5-s single-shot T_2*-sensitive echo planar imaging (EPI) sequences with twelve 2.0-mm-thick adjacent slices (TE 50 ms; flip angle 90°; matrix 192 × 192; field of view 192 × 192 mm).

A sparse clustered volume acquisitioning paradigm was employed to reduce the influence of acoustic scanner noise (Hall et al., 1999). This paradigm was modified to include two contiguous acquisitions, henceforth referred to as ‘A’ and ‘B’. These pairs of acquisitions were performed every 16 s such that the scan-to-scan interval alternated between 13.5 s and 2.5 s for acquisitions A and B respectively (see Fig. 1). Auditory stimuli were presented during the 11-s gap of scanner silence between acquisition pairs.

For every subject the fMRI session consisted of six runs of 20 acquisition pairs each, excluding initial start-up scans. Between successive scan pairs, the four different stimulus frequencies and a silent baseline condition were cycled. This allowed each of the stimulus frequencies as well as the silent condition to be presented four times per run. In the first and fourth functional run, all stimuli were presented binaurally; in the second and fifth run, stimuli were presented to the left ear only; and in the third and sixth run, stimuli were presented to the right ear only.

Image analysis

In the data analysis we made use of the MatLab programming environment (The MathWorks Inc.) and routines from the SPM2 software package (Wellcome Department of Cognitive Neurology). The functional image volumes were sorted into two sets, respectively containing the images from acquisitions A and B (see Fig. 1). Both sets were separately corrected for motion effects. Image set B was coregistered with respect to image set A using rigid body transformations on the basis of the mean images of each set, and subsequently the images of all subjects were spatially normalized with respect to each other using affine transformations. To improve signal to noise ratio (SNR) characteristics, spatial smoothing was performed using an isotropic 3-mm Gaussian kernel and images were interpolated to voxel dimensions of 2.0 × 2.0 × 2.0 mm.

General linear models were set up for each voxel to quantify the cortical responses (Friston et al., 1999), both for individual subjects and for the group of all 10 subjects collectively. All models had a similar design and involved regressors for the 13 stimulus conditions (i.e., four stimulus frequencies, each presented binaurally or monaurally left or right, and a single silent baseline condition). To correct for drifts of the scanner signal, the baseline signal was modeled by a first order polynomial for each of the functional runs separately. The models were evaluated using multiple linear regression.

Estimates were derived for the activation in the form of statistical parametric maps (SPMs) by contrasting conditions (or combinations thereof) with the silent baseline condition using T-test statistics (Friston et al., 1995). Because of inherent differences in SNR characteristics between the two image sets, image set A was weighted twice as strong as image set B. By exploring various weightings (results not shown), this weighting had been determined to lead to optimal signal detection in this experiment, and it approximately corresponds with the expected optimal ratio on the basis of single-scan interactions (Langers et al., 2005a).

The responses of all voxels to specific stimulus characteristics were determined by grouping the conditions that shared a particular characteristic, and contrasting these conditions against the silent baseline condition. For instance, the activation to left ear stimulation was determined by contrasting the four conditions corresponding with left ear stimulation (comprising the four different stimulus frequencies) against the baseline (silence). Similarly, the activation to stimuli with a particular frequency was determined by grouping over the three corresponding conditions with different stimulus lateralizations. Activation levels (ALs) for each voxel were defined as the average signal change percentage in a particular contrast relative to the baseline signal intensity. Per subject, a 5.0-cm^3 region of interest (ROI) was defined that comprised the most active brain regions, by selecting 625 voxels in the superior surfaces of the left and right temporal lobes with the most significant activation in the contrast involving all twelve stimulus conditions equally. A mean AL was determined by averaging the voxel ALs over this subject-dependent ROI.

In order to be able to differentiate between sub-regions of the auditory cortex, the ROIs were partitioned into four areas by straight lines that ran along the front and back flanks of Heschl's gyrus and sulcus (see the subdivisions in Figs. 2b, 3b and 4b). From anterior to posterior, the resulting areas correspond with the planum polare (PP), Heschl's gyrus (HG), Heschl's sulcus (HS), and the planum temporale (PT). Alternatively, these areas can be approximately identified with the previously proposed regions T1a, T1b, T2, and T3, respectively (Brechmann et al., 2002).

Topographic mappings

To demonstrate potential topographic mappings in the cortex, the ALs of individual voxels were corrected for overall differences in sensitivity of the whole brain to different stimulus conditions. To this end, the responses to the three different stimulus lateralizations and the four different stimulus frequencies were normalized by dividing the ALs of individual voxels by the mean AL of all voxels in the previously determined ROI. Each active voxel was assigned an index that corresponded with the stimulus lateralization or frequency that led to the largest normalized AL. For the lateralization mapping, this index was in the range 1 to 3 (1 = monaural left; 2 = bilateral; 3 = monaural right) whereas for the frequency mapping the range was 1 to 4 (1 = 125 Hz; 2 = 500 Hz; 3 = 2 kHz; 4 = 8 kHz). The average index of all active voxels that projected perpendicularly onto the same location in a transverse anatomical slice was displayed using a red-to-yellow color code for the entire range of index values.

To test whether the response lateralization depended on the stimulus frequency, lateralization mappings were also constructed on the basis of the available data for each of the stimulus frequencies separately. The presence of systematic differences between the four resulting mappings was tested for using a

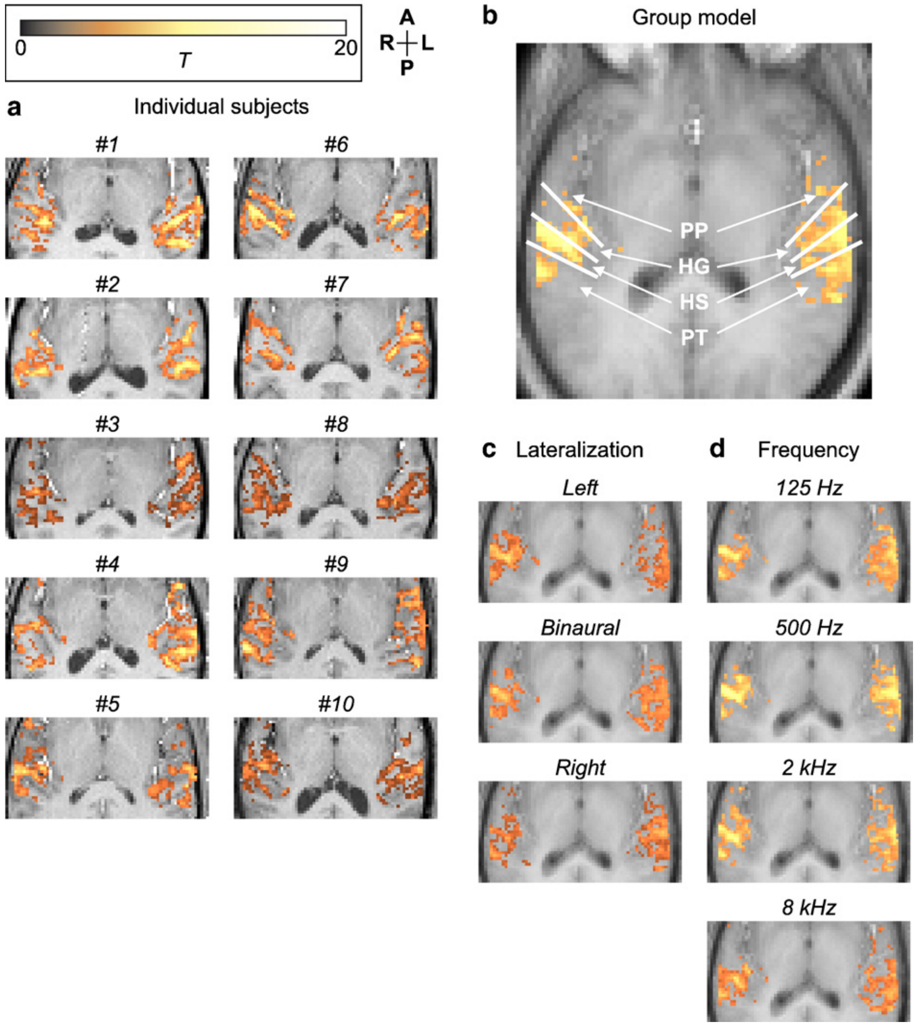

Fig. 2. Activation patterns. Using a subject-dependent threshold, equal volumes of activation in the upper surface of the temporal lobes are projected on an anatomical slice by means of a color code that represents the T-value of the activation. (a) Activation in the ten individual subjects. All stimulated conditions were contrasted with silence. The activation was clustered in the temporal lobes, forming stripe-like patterns in the (antero)lateral to (postero)medial direction approximately parallel to Heschl's gyrus. (b) The data of all subjects combined into a single group model. In the right hemisphere the activation was strongly clustered along Heschl's gyrus (HG) and Heschl's sulcus (HS), whereas in the left hemisphere the activation was more diffuse. Some additional activation was found in the planum polare (PP) and the planum temporale (PT). (c, d) The activation patterns, segregated with regard to stimulus lateralization and frequency, respectively. Patterns were similar in the sense that the activation was located at approximately the same locations. However, inter-hemispheric differences are visible, as activation to monaural stimulation was found most strongly in the contralateral hemisphere. In the right hemisphere activation to low-frequency stimuli was located more laterally than that to high-frequency stimuli.

repeated measures analysis of variance (ANOVA) on the assigned indices in the ROI. Similarly, to test whether the optimal frequency depended systematically on the stimulus lateralization, frequency mappings were constructed for each of the three stimulus lateralizations, and the significance of differences between these mappings was again assessed using a repeated measures ANOVA.

Results

Activation characteristics

The activation in the auditory cortex in response to the various stimuli was determined using T-test statistics. Fig. 2 shows the activation patterns that were found for individual subjects as well as for the group as a whole. To facilitate the comparison of activation patterns and mappings between subjects, differences in the overall level of activation were taken into account by adjusting the statistical thresholds in such a way that equal volumes of activation were detected for each subject. This resulted in thresholds for significance in a range that corresponded with p-values of 8×10^{-5} to 0.016 with a median of 6×10^{-4} for individuals, and a threshold at $p=2\times10^{-9}$ for the group analysis (uncorrected for multiple comparisons).

Activation was found in both temporal lobes for all subjects (Fig. 2a), and was distributed over HG, HS, PT, and in some subjects PP. The activation was clustered in stripe-like patterns, typically in a direction parallel to HG and HS (see e.g. subjects #1, #6 and #7). The stripe-like patterns that were found in the individual subjects were also discernable in the group data (Fig. 2b). Especially in the right hemisphere, a dominant elongated

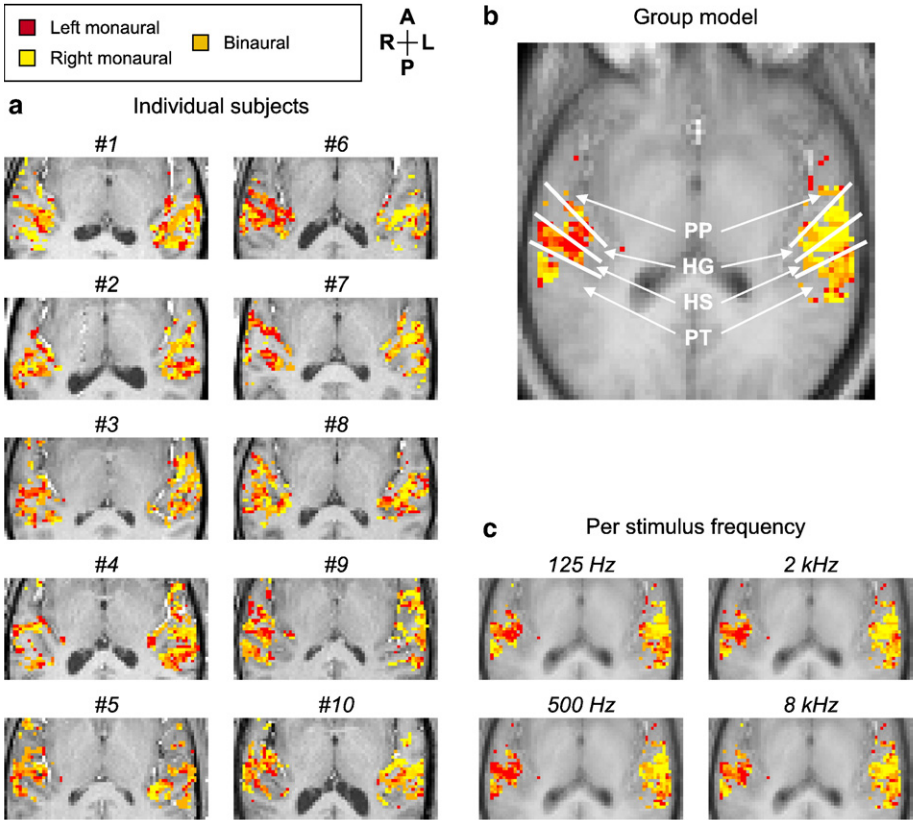

Fig. 3. Topographic cortical mappings of preferred stimulus lateralization. (a) Individual subjects. Considerable variability in response preference was found across individual subjects, although in most subjects there was a general tendency for the auditory cortices to be more responsive to stimulation of the contralateral ear. (b) Group model. Systematic contralateral response behavior was found in the Heschl's gyrus (HG) and Heschl's sulcus (HS). In the planum polare (PP) and planum temporale (PT), response lateralization was more erratic and not systematically contralateral to the ear of stimulation. (c) Preferential lateralization for each of the four stimulus frequencies. The response characteristics are very similar to those in panel b and do not differ significantly.

cluster of activation was found along HS, bordering on the posterolateral side of HG. In the left hemisphere, activation appeared more diffuse and was concentrated towards the lateral side of the brain.

Figs. 2c–d show group activation patterns split up with respect to the stimulus conditions. Equal activation volumes according to the respective contrasts have been shown. Regarding the stimulus lateralization, activation following monaural stimulation was dominantly present in the hemisphere contralateral to the stimulated ear. For binaural stimulation the activation appeared more symmetrical, although it was more concentrated in the right hemisphere and diffuse in the left. Regarding the stimulus frequency, the activation in the elongated cluster in the right hemisphere was located more (antero)laterally for the lower frequencies than for the highest frequency. The general activation patterns seemed similar for all conditions in the sense that activation clusters were found at similar locations.

Lateralization maps

For all conditions, the voxel ALs were divided by the ROI mean in order to correct for differences in the overall brain sensitivity to the various stimuli. Topographic activation maps were constructed by determining the stimulus condition that led to a maximal normalized voxel response. Fig. 3a shows the projected maps with regard to the preferred stimulus lateralization in individual subjects. For most of the subjects, responses were strongest in the hemisphere contralateral to the stimulated ear (see e.g. subjects #6, #7 and #9). Joint results from the group model (Fig. 3b) clearly confirmed the contralateral preference for a majority of the voxels. Especially in the regions of the auditory cortex corresponding with HG and HS as outlined in Fig. 3, a contralateral preference was evident. In these combined areas, 66.6% of the active voxels responded most strongly to contralateral stimulus presentation while only 4.5% responded most strongly to ipsilateral stimuli. In contrast, preferences with regard to stimulus lateralization were more erratic and randomly organized in the anteriorly located PP and the posteriorly located PT. In these areas, 33.9% and 34.3% of the active voxels responded most strongly to contralateral and ipsilateral stimulation, respectively.

Mappings of the preferred stimulus lateralization in the group model for the four stimulus frequencies individually (Fig. 3c) were similar to each other and to those in Fig. 3b. Only minor differences were observable, and these were not significant according to a repeated measures ANOVA on the indices that were assigned to the voxels in the ROI ($p>0.1$).

Frequency maps

A similar analysis was performed with regard to preferences for stimulus frequency. For some individual subjects (Fig. 4a), gradients were found stretching out along the elongated activation

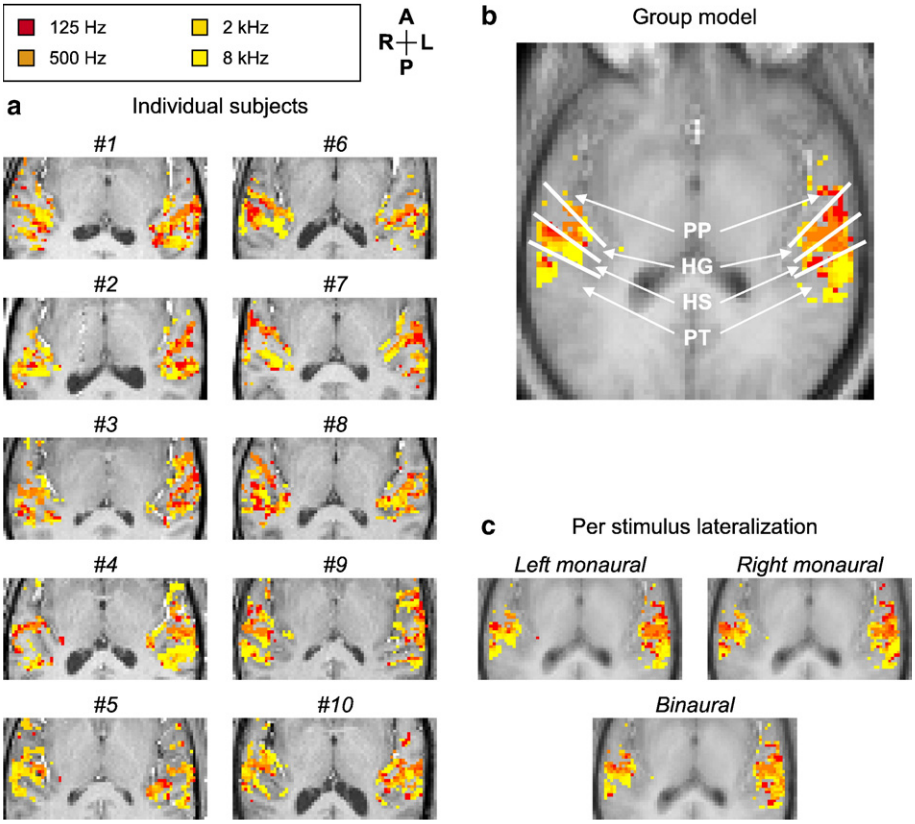

Fig. 4. Topographic cortical mappings of preferred stimulus frequency. (a) Individual subjects. Frequency mappings appeared highly variable across subjects. However, in several subjects topographic gradients were found stretching out along the length of the stripe-like activated regions. (b) Group model. Preferential responses to high-frequency stimuli were found in the medial parts of the activated regions in the Heschl's gyrus (HG) and Heschl's sulcus (HS), while responses shifted towards the lateral side for lower frequencies. A distinct tonotopic gradient is visible especially in the right hemisphere. There are no clear tonotopic gradients in the planum polare (PP) and the planum temporale (PT). (c) Tonotopic mappings for three stimulus lateralization conditions. These maps are similar to that in panel b and do not differ significantly. Apparently, tonotopic organization does not depend on stimulus lateralization.

clusters that border HG, from low to high frequencies in the anterolateral to posteromedial direction (see e.g. subjects #1, #6 and #7). However, there was considerable variability between the subjects. For the group as a whole (Fig. 4b), low-to-high frequency gradients could be observed in an anterolateral-to-posteromedial direction along HG and HS. Although such a gradient was present in both hemispheres, it was less prominent in the left hemisphere than in the right. In addition, some voxels that were situated on the extreme lateral end of the active regions in HG and HS in both hemispheres showed preferential responses to high-frequency stimuli. In the PP and PT local variations in response characteristics were visible, but on a larger scale systematic frequency gradients could not be identified in the individual subjects or in the subjects as a group.

Fig. 4c shows frequency mappings for each of the three different stimulus lateralization conditions. These mappings are highly similar, and differences were insignificant according to the repeated measures ANOVA ($p > 0.5$).

Discussion

In this study, cortical activation was determined in response to monaurally and binaurally presented stimuli of various frequencies. The response characteristics of individual voxels were calculated and compared to the whole brain average to determine their relative preferences regarding stimulus lateralization and frequency. Results were visualized to show the presence of topographic mappings in various subdivisions of the auditory cortices. The significance of differences in lateralization mappings as a function of frequency and in frequency mappings as a function of lateralization was also assessed.

Activation patterns

Our results were all obtained using an active listening paradigm, which involved two noise bursts and a tone. Because both the noise bursts and the tones were presented preceding each MRI acquisition, the activation corresponds to the combined response to these stimuli. Since the tones were spectrally centered in the 1/4-octave noise bursts, all derived activation patterns (i.e., Figs. 2, 3 and 4) represent the brain response to narrowband stimuli.

The activation showed multiple stripe-like regions of activation parallel to the Heschl's gyrus (HG) and Heschl's sulcus (HS) of both hemispheres. Because the activation from all slices was projected on a single image, the clusters cannot be an artificial result of displaying only a cross-section through a 3D activation volume. Therefore, multiple active regions with an elongated shape running in the (antero)lateral to (postero)medial direction were present in both hemispheres. Such regions have been described in other studies as well (Brechmann et al., 2002; Di Salle et al., 2001; Langers et al., 2003; Scheich et al., 1998) and might reflect the location of different functional areas in the cortex. Alternatively, they may be related to the morphology of the local vasculature: the measured response in fMRI has a vascular origin and the courses of the veins on the cortical surface follow the cerebral sulci to some extent.

For the group model, response patterns were more diffuse in the left hemisphere than in the right. This might be caused by functional or anatomical inter-hemispheric asymmetries in individuals. However, because the stripe-like patterns were observed in comparable fashion for both hemispheres in individual subjects, it seems more likely to be the result of larger variations in the left hemisphere regarding the spatial location of functional and anatomical features across subjects (Leonard et al., 1998; Rademacher et al., 2001). Nevertheless, multiple activated subregions could be identified in the group analysis, especially in the right hemisphere, indicating that the stripe-like features are similar and reproducible across subjects.

The spatial response patterns to all types of stimuli were similar in the sense that the location and shape of the activated regions were similar (Figs. 2c–d). However, a preferential hemispheric response to stimulation of the contralateral ear was evident. In addition, in the right hemisphere some evidence for the presence of a tonotopic gradient was observed, as activation to high-frequency stimuli was found more posteromedially than that to low-frequency stimuli. Because differences between activation images are not easy to interpret, additional color-coded mappings were constructed on the basis of which stimulus conditions led to the largest activation levels for individual voxels. To prevent the lateralization and frequency mappings from being dominated by the stimulus with the largest overall response level, the voxel response characteristics were corrected for such differences in brain sensitivity by dividing the response levels in individual voxels by the respective averages over the active brain regions as a whole. Although this procedure influences the outcomes of the analysis, it cannot introduce any bias towards the presence of topographic mappings or spatial gradients because all voxels will be affected in exactly the same way.

Response lateralization

Relative preferences for left or right stimulus presentation were analyzed and visualized at the level of individual voxels. Activation occurred most strongly in response to stimulation of the contralateral ear. This observation was especially valid for the HG and the anterior bank of HS, where the primary processing centers of the auditory core regions are approximately located (Leonard et al., 1998; Morosan et al., 2001; Rademacher et al., 2001). The primary auditory cortex is the first cortical stage of auditory processing, and receives input from the brainstem via the thalamus. The contralateral cortical response patterns in the primary auditory cortex reflect similar contralateral preferences that have been found in the inferior colliculi in the midbrain and the thalamic medial geniculate nuclei (Langers et al., 2005b; Melcher et al., 2000).

Previous studies have suggested that the auditory cortices as a whole are predominantly involved in the processing of stimuli from the opposite auditory hemifield (Lipschutz et al., 2002; Pantev et al., 1986; Scheffler et al., 1998; Suzuki et al., 2002; Woldorff et al., 1999), similar to and compatible with the functioning of the visual and somatosensory systems. Our findings for the primary auditory cortex are in general agreement with these reports. However, such contralateral preferences were not as systematically observed for activation situated in the planum temporale (PT) and the planum polare (PP). These parts of the upper temporal lobe contain secondary areas involved in higher auditory processing. Here, a more random distribution of voxels responding preferentially to the left and/or right ear was found, even in the group analysis. Although this might reflect a fine parcellation into various specialized sub-areas, it can also be the result of an absence of a clear preference regarding stimulus lateralization in secondary auditory cortex.

Tonotopic organization

A low-to-high frequency gradient was prominent in the (antero) lateral to (postero)medial direction along the HG and HS. This part of the auditory cortex contains the primary processing areas. The frequency dependence of brain activation patterns that was found in this study is consistent with the presence of tonotopic gradients, and this finding is compatible with previous investigations by others (Bilecen et al., 1998; Howard et al., 1996; Romani et al., 1982; Schmid et al., 1998; Wessinger et al., 1997; Yetkin et al., 2004). Gradients in the left primary auditory cortex were less pronounced than in the right, but still noticeable.

Hemispheric differences have been found before in relation to frequency selectivity and tonotopic organization (Liegeois-Chauvel et al., 2001; Rosburg et al., 1998; Wessinger et al., 1997; Yetkin et al., 2004), possibly related to an asymmetry in the anatomy and function of both hemispheres. It has been suggested that the right hemisphere is most responsive to acoustic sound features like pitch, such as found e.g. in music, whereas the left hemisphere is more or less specialized in the processing of temporal dynamics, like the phonological aspects of speech-like stimuli (Binder et al., 1997; Gage et al., 2002; Hickok and Poeppel, 2000; Josse et al., 2003; Palomaki et al., 2002; Specht and Reul, 2003; Tervaniemi and Hugdahl, 2003). A compatible interpretation would be that the right half of the brain specializes on spectral resolution and the left half on temporal resolution (Zatorre et al., 2002). Our results are consistent with an emphasis on spectral analysis in the right hemisphere as opposed to the left hemisphere.

On a more detailed level it is much more difficult to discern the relevant substructures in the brain, to objectify their existence on the basis of functional criteria, and to establish their organizational principles. Various studies have shown multiple sub-areas with mirror-symmetric tonotopic representations in non-human mammals (Kaas et al., 1999; Linden et al., 2003), and more recently evidence was also found for similar tonotopic representations in humans (Formisano et al., 2003; Scarff et al., 2004). Our results are not inconsistent with such findings since some of the most laterally located voxels did show a response preference for high frequencies. However, definite conclusions about the presence and nature of a second mirrored gradient on the far medial side of Heschl's gyrus do not seem justifiable on the basis of our findings alone.

In comparison with primary auditory cortex, systematic gradients were less obvious in secondary and higher processing areas located in the PT and the PP. While the primary auditory cortex receives thalamic input from the ventral subdivision of the medial geniculate body which has been reported to display a tonotopic organization, the secondary cortex receives thalamocortical projections from the dorsal subdivision which does not show distinct tonotopic progressions (Jones, 2003). Therefore, similar to the organization in primates and other mammals, the presence of a tonotopic principle in the human auditory cortex presumably is a direct reflection of such a presence in the thalamic nuclei from which it receives its input (Kosaki et al., 1997; Velenovsky et al., 2003).

Nevertheless, some recent results in literature report the existence of tonotopic gradients between various low- and high-frequency endpoints posterior to the primary auditory cortex, i.e., on the PT (Talavage et al., 2004). Our study shows small-scale variations in optimal stimulus frequency in the PT that are reminiscent of these findings. Since tonotopic gradients in the secondary areas cannot result from tonotopic input from the dorsal subdivision of the medial geniculate body, such frequency preferences might for instance be mediated by connections from primary to secondary areas. However, we are unable to assess whether these patterns reflect a uniform organizational principle, or whether they are caused by coincidental variations. Nor is it clear whether they involve gradual tonotopic gradients or discrete differences in the frequency sensitivity between neighboring functional sub-areas (Schönwiesner et al., 2002).

Neural representation of auditory signals

Obviously, our data show a difference in the neural representation of the attributes of sound between primary and secondary auditory processing regions. While the response strengths in the HG and HS were found to depend closely on the lateralization and frequency of the incoming sound, these sound parameters appeared to have a less systematic influence on the response patterns in the PT as well as the PP. This may be regarded as evidence for a transition in the neural code between the primary and secondary auditory cortices in humans.

This may bear relation to the existence of a type of auditory scene analysis based on auditory objects. Auditory objects are the perceptual entities in the auditory environment that can be distinguished, categorized and integrated with object information from other sensory modalities (Binder et al., 2004; Griffiths and Warren, 2004; Nelken, 2004; Zatorre et al., 2004). Perhaps, the transition in neural representation that is visible in our data concurs with the emergence of auditory object processing streams (Micheyl et al., 2005). This explanation is compatible with the proposed existence of ‘what’ and ‘where’ processing streams in primates, that have also been suggested to diverge in the secondary auditory cortex (Kaas and Hackett, 2000; Rauschecker and Tian, 2000). Our data are consistent with the view that in humans similar streams arise in the transition from primary to secondary auditory areas (Arnott et al., 2004; Brunetti et al., 2005).

The construction of an auditory scene representation with multiple streams may have been further stimulated in this experiment by the use of a tone-in-noise detection task. In this task, a foreground tone stimulus needs to be differentiated from a background noise stimulus, which might be facilitated by internally segregating the foreground and background stimuli into separate streams. In this experiment, both the foreground and background stimuli were identically lateralized and restricted to a narrow frequency band. Nevertheless, in our data the representation of stimulus lateralization and frequency was much less systematic in secondary auditory cortex than in primary cortex. This suggests that other sound features than frequency or lateralization are neurally encoded in stream representations.

We hypothesize that basic acoustic signal features (like frequency and lateralization, but probably also other relevant features like harmonicity, onset time synchronicity, modulation coherence, loudness, or interaural correlation) are detected and extracted in the primary auditory cortex, and that these are used in the secondary auditory cortex as clues for the construction of separate object streams (Carlyon, 2004; Gutschalk et al., 2005). These streams no longer encode the original acoustic features that underlie their segregation, but likely contain representations of perceptually more relevant sound attributes that are related to the object that they represent (like the identity and location of the sound source).

Inter-subject variability

The significance of the detected activation showed some variation across subjects. Such variation may arise from numerous causes (e.g., task-related attention levels, perceptual stimulus loudness, subject head motion, susceptibility artifacts, individual cerebro-vascular characteristics, etc.) and will lead to variable volumes of activation if the statistical threshold for significance is held constant. Because this would complicate a comparison of activation patterns and topographic mappings across subjects in this study, statistical thresholds were adjusted to obtain equal activation volumes across subjects. In all cases the resulting thresholds were sufficiently stringent to restrict the influence of falsely positive voxels to negligible levels ($p<0.02$, and typically much better).

To determine general response characteristics, a group model was designed involving the data of all subjects simultaneously. Because error levels according to this model were substantially lower due to the larger amount of available data, a much more stringent statistical threshold could be obtained. At the same time, the estimated activation level AL equaled the average of the ALs of all subjects and was therefore representative for the average response behavior in the subject group as a whole. By averaging out inter-subject variability in this way, the interpretation of activation images and the detection of lateralization preferences and tonotopic gradients were greatly simplified. However, we emphasize that conclusions that apply to the group obviously do not necessarily extend to every individual subject, as the variance between subjects appeared considerable. For this reason, in this report both individual and group results were listed throughout.

Conclusion

In summary, we found that at the first stages of cortical auditory processing both hemispheres respond most strongly to the contralateral ear. Also, we provided further evidence for a tonotopic organization in the primary auditory cortices. In contrast, at higher processing levels in the auditory cortex (i.e., in secondary and higher cortical auditory areas) no systematic preferences with regard to stimulus lateralization and frequency were obvious. Our findings support the hypothesis that the transformation of the physical characteristics of sound into information about objects in the auditory scene takes place in the transition from primary to secondary auditory cortex.

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