

Processing of sound location in human cortex

Jörg Lewald,^{1,2} Klaus A. J. Riederer,^{3,4} Tobias Lentz⁵ and Ingo G. Meister^{6,7}

¹Leibniz Research Centre for Working Environment and Human Factors, Institute for Occupational Physiology at the University of Dortmund, Ardeystr. 67, D-44139 Dortmund, Germany

²Department of Cognitive Psychology, Faculty of Psychology, Ruhr University Bochum, D-44780 Bochum, Germany

³Laboratory of Acoustics and Audio Signal Processing, Helsinki University of Technology, FI-02015 HUT, Finland

⁴KAR, Isokaari 40, FI-00200 Helsinki, Finland

⁵Institute of Technical Acoustics, RWTH Aachen University, Neustr. 50, D-52066 Aachen, Germany

⁶Department of Neurology, RWTH Aachen University, Pauwelsstr. 30, D-52074 Aachen, Germany

⁷Department of Neurology, University Hospital Cologne, Kerpener Str. 62, D-50924 Cologne, Germany

Keywords: auditory space perception, functional magnetic resonance imaging, sound localization, spatial hearing

Abstract

This functional magnetic resonance imaging study was focused on the neural substrates underlying human auditory space perception. In order to present natural-like sound locations to the subjects, acoustic stimuli convolved with individual head-related transfer functions were used. Activation foci, as revealed by analyses of contrasts and interactions between sound locations, formed a complex network, including anterior and posterior regions of temporal lobe, posterior parietal cortex, dorsolateral prefrontal cortex and inferior frontal cortex. The distinct topography of this network was the result of different patterns of activation and deactivation, depending on sound location, in the respective voxels. These patterns suggested different levels of complexity in processing of auditory spatial information, starting with simple left/right discrimination in the regions surrounding the primary auditory cortex, while the integration of information on hemispace and eccentricity of sound may take place at later stages. Activations were identified as being located in regions assigned to both the dorsal and ventral auditory cortical streams, that are assumed to be preferably concerned with analysis of spatial and non-spatial sound features, respectively. The finding of activations also in the ventral stream could, on the one hand, reflect the well-known functional duality of auditory spectral analysis, that is, the concurrent extraction of information based on location (due to the spectrotemporal distortions caused by head and pinnae) and spectral characteristics of a sound source. On the other hand, this result may suggest the existence of shared neural networks, performing analyses of auditory 'higher-order' cues for both localization and identification of sound sources.

Introduction

Despite the multitude of neuroimaging studies dealing with sound localization, the issue of where in the human cortex the coding of sound location takes place is still a matter of debate. The current discussion on this topic has been strongly influenced by the auditory dual-pathway model, that states that beyond the primary auditory cortex spatial information is preferably processed within a dorsal stream and non-spatial information preferably within a ventral stream (Hackett *et al.*, 1999; Romanski *et al.*, 1999a,b; Rauschecker & Tian, 2000; Tian *et al.*, 2001; Romanski & Goldman-Rakic, 2002). Several previous imaging studies thus focused on the question of auditory spatial vs object-feature processing by contrasting tasks of localization and spectral analysis (e.g. Bushara *et al.*, 1999; Alain *et al.*, 2001; Maeder *et al.*, 2001; Zatorre *et al.*, 2002; Barrett & Hall, 2006). In a meta-analysis of 36 functional magnetic resonance imaging (fMRI) and positron-emission tomography studies, in which subjects completed either 'spatial' (e.g. discrimination of sound location) or 'non-spatial' auditory tasks (e.g. pitch discrimination), Arnott *et al.* (2004) argued that more 'spatial' than 'non-spatial' studies reported activation in the

inferior parietal lobule (IPL) and in the region around the superior frontal sulcus (SFS); activation in the anterior regions of the temporal lobe (aT) and the inferior frontal gyrus (IFG) was obtained in more 'non-spatial' than 'spatial' studies, and activation in posterior regions of the temporal lobe (pT) was observed in both types of studies equally.

It has, however, to be emphasized that previous studies indicated relative, not absolute, functional segregation of dorsal and ventral pathways, with some evidence for spatial processing also in the ventral stream (cf. also Cohen *et al.*, 2004; Gifford & Cohen, 2005). An important point to be noted in this context is the evident functional duality of spectral content in auditory spatial and object-feature analyses. Under the realistic conditions of a complex free-field sound source, auditory localization is based not only on analysis of interaural differences in sound pressure level (ILDs) and time of arrival (ITDs), but also on spectral localization cues. These latter cues are distortions in the overall spectral shape of the incoming sound and differences in the frequency spectra between the ears, produced by the listener's body, head and pinnae. Their existence is crucial for emergence of a natural sound image in external space (Blauert, 1997; Kulkarni & Colburn, 1998). Thus, it seems reasonable to assume that regions specialized in spectral analysis, namely those in the ventral auditory stream, may be shared by object-feature processing and spatial processing of realistic sound sources.

Correspondence: Dr J. Lewald, ²Department of Cognitive Psychology, as above.
E-mail: joerg.lewald@rub.de

Received 11 July 2007, revised 20 December 2007, accepted 14 January 2008

The present fMRI study aimed to reveal ‘genuinely spatial’ cortical areas, in due consideration of the abovementioned points. For this purpose, firstly, we used a methodological approach that most effectively took into account all localization cues available to the auditory system under natural conditions. Secondly, we deliberately refrained from contrasting ‘spatial’ and ‘non-spatial’ stimuli, but rather focused on the separate analysis of activations evoked by different sound directions and the computation of contrasts between these conditions.

Materials and methods

Subjects

Eleven right-handed, normal-hearing male subjects (20–44 years, mean 28.7 years) participated in this study. Data from three further participants were excluded because of head motion during the experiment. Written informed consent was obtained from all participants, in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and the guidelines of the local ethical committee of the University Hospital Aachen. All subjects reported normal hearing. Normal sound localization ability was assessed in all subjects by a psychoacoustical test conducted outside the fMRI scanner (see below).

Audio stimulator system

Because real sound sources (loudspeakers) can not be used inside the headcoil of an fMRI scanner, virtual sound sources were presented over headphones. Normal (electrodynamic/electrostatic, circum-/supra-aural) headphones may not be used with magnetic brain imaging techniques [fMRI, magnetoencephalography (MEG)], as they all create spurious electric and magnetic fields causing artefacts to the neuroimaging data (Hytönen, 2005). In the case of electrodynamic headphones the sound stimuli themselves, including the embodied subtle spectral localization cues, would be distorted due to the magnetic fields in fMRI scanner (Baumgart *et al.*, 1999). Piezoelectric insert headphones, which are commonly used in MEG experiments, yield a very limited and uneven frequency response (about 0.1–3 kHz) with notable harmonic distortions non-suitable for realistic sound reproduction.

The present experiment applied custom-made high-quality insert-type headphones (UD ADU2a, Unides Design, Helsinki, Finland), with plastic tubes conveying the sound stimulus over air into the subject’s ears, thus avoiding any magnetic or electric disturbance to the fMRI scanner (empirically verified in Hytönen, 2005). The complex acoustics and perception involved with insert-type headphones is investigated in detail in Riederer & Niska (2002) and Riederer (2005). The 5.25-m-long plastic tubes were firmly fitted to the ear canals of the subject by disposable polyurethane foam ear-tips (ER1–14A, Etymotic Research, Elk Grove Village, IL, USA). Vibrations caused by the fMRI scanner and other equipment were suppressed by wrapping the tubes around isolating plastic foam. In order to obtain maximum hearing protection from scanner noise, the subjects wore plastic circum-aural earmuffs (mean attenuation 20 dBA; Bilsom 717, Bilsom, Sweden) on top of the ear-tips that yield average ambient noise cancellation of about 20 dBA. The frequency response of the headphone system was 0.1–9 kHz (± 10 dB; smoothed 1/3 octave and measured with an artificial ear at the end of the tubes) and equalized flat for the stimuli (see below). Sound-pressure level (SPL) was adjusted to about 80 dB re 20 μ Pa. This somewhat high SPL was necessary in order to provide clear

perception of the stimulus against the strong ambient noise caused by the fMRI scanner. Nevertheless, the stimuli were perceived at a comfortable loudness level due to their wide-spread (non-peaking) energy spectrum.

One may note that animal studies have indicated increases of receptive field size in space-specific auditory neurons with SPL, while ‘best directions’ remained constant (Sterbing *et al.*, 2003). Also, human precision in localization of elevation may exhibit some decrease with higher SPLs (Vliegen & Van Opstal, 2004). However, the real concern is to have a flat and wide-range frequency response by the headphones, as this is needed for creating sounds appearing in external space. The usage of head-related transfer functions (HRTFs) gets complicated above about 7–9 kHz, where the idiosyncratic pinna acoustics can no longer be measured and reproduced very reliably (Wightman & Kistler, 1989a; Møller, 1992; Blauert, 1997; Riederer & Niska, 2002; Riederer, 2004, 2005). This affects mostly virtual elevation perception, and is a problem for all reproduction equipment, not only the used custom insert-type headphone. Further complications arise from the equalization of the device. Unfortunately, the insert headphones can not be equalized individually for each listener, which degrades the elevation and externalization perception, but only to a small extent with untrained listeners (Riederer, 2005).

Sound stimuli

Unlike any other previous fMRI study, sound stimuli were convolved with individual HRTFs. These measurements are idiosyncratic responses from a real sound source to the ear canals of the subject in the free-field. HRTFs embody all the spectral and temporal auditory localization cues caused by individual anatomy: the body, head and pinnae (Wightman & Kistler, 1989a,b; Møller, 1992; Blauert, 1997; Kulkarni & Colburn, 1998; Jin *et al.*, 2004). The neural representation of auditory space is well known to be highly adapted to the individual spectral properties of the subject’s ears, and any perturbation of this correlation results in deficits in localization (e.g. Van Wanrooij & Van Opstal, 2005). Only few earlier studies employed stimuli that were convolved with non-individualized (generic) HRTFs (e.g. Alain *et al.*, 2001). On the other hand, individual binaural recordings (Palomäki *et al.*, 2005) or individual HRTFs (Fujiki *et al.*, 2002), that most reliably reproduce the complete set of localization cues, have already been used in MEG experiments on spatial hearing.

The virtual auditory stimuli, involving sound source locations in three-dimensional space, were created using individual HRTFs measured in a semi-anechoic chamber (interior dimensions 6 \times 11 \times 5 m³; concrete floor) at the Institute of Technical Acoustics, RWTH Aachen University. All HRTF measurements were done with the same microphones (KE4-211-2, Sennheiser, Wedemark, Germany) located at the entrance of the blocked ear canals (Riederer, 2004, 2005). The subject was seated on a comfortable chair mounted on a turntable, with the subject’s ears about 2 m above the floor level. A head rest was used in order to avoid spatial inaccuracies due to head movements. The measurement signal, a sweep of 16 384 samples, was delivered via a full-range cone driver (FR 8 R, Visaton, Haan, Germany; diameter 8 cm) in an enclosed box (volume 0.25 m³) mounted on a lightweight pendant at a distance of 2 m from the subject’s head. Sound azimuth (θ) was varied by rotating the turntable. For each azimuth, measurements from different sound elevations (δ) were obtained by changing the vertical position of the pendant in successive order, while the source distance was kept constant from the subject’s head. HRTFs for each subject were measured over ranges of

$\theta = \pm 90^\circ$ and $\delta = \pm 30^\circ$, all in steps of 10° . All positioning devices were servo-driven and controlled by software, and the HRTF measurements took approximately 20 min per subject.

All measured individual HRTFs were post-processed identically, as described in the following. A more detailed discussion of the stimulus generation can be found in Riederer (2005), which applied similar general guidelines for behavioural and MEG experiments. The first-order reflection from the concrete floor in the semi-anechoic chamber had a delay of 6 ms (260 samples at 44.1 kHz sampling frequency) to the direct signal at $\delta = -30^\circ$. The system measurement, needed for the compensation (removal) of the loudspeaker response, was measured at the position of the centre of the subject's head using a $\frac{1}{2}$ -inch free-field microphone (Type 4190, Brüel & Kjær, Nærum, Denmark). The impulse response (IR) of the headphone was measured using an artificial ear Type II (Type 4157, Brüel & Kjær), as recommended for insert-type headphones in IEC 60711. The 0.1-octave smoothed frequency response was calculated from the windowed and minimum-phased IR. The same was done for the loudspeaker (system) response for each elevation angle, after which the headphone and loudspeaker responses were convolved. The result (per elevation) was then inverted, with dynamics limited to 24 dB, and this outcome was further filtered with a 28th order finite infinite response low-pass digital filter (6 dB cutoff frequency set at 9 kHz). This filtering was necessary so that non-linear distortion caused by uncontrollable higher-order wave propagation inside the headphone tubes was avoided.

The particular HRTF (both ears, per sound incident angle) was likewise windowed, minimum-phased and 0.1-octave smoothed. The ITD was calculated using the so-called leading-edge method and added as zero-valued samples to the contralateral ear response. Then, the processed HRTF was convolved with the above-described elevation-specific headphone-system-inverse response. Finally, the outcome was windowed into 256 samples, removing any possible remains from the floor reflections in the processed IRs. This is how the processed HRTF, system compensated and headphone equalized, involved only all the idiosyncratic spectral and temporal cues needed for proper virtual sound synthesis.

The base stimulus, a 150-ms white noise burst with 20-ms rise and fall times, was re-calculated for each sound incident angle (and subject). This base was convolved (filtered) with the processed HRTF explained above, and finally a 40-Hz sinusoidal amplitude modulation was added. This stimulus type was chosen on the basis of wide-ranging informal experiments done on multiple listeners, as well as previous listening tests (Riederer, 2005), and it yielded the optimal clarity in spatial perception.

Eight virtual sound locations were presented to the subjects. Stimuli were located in frontal space, at horizontal positions of 20° or 80° to the left ($\theta = -20^\circ, -80^\circ$) or right ($\theta = +20^\circ, +80^\circ$), and with elevations of 30° above ($\delta = +30^\circ$) or below ($\delta = -30^\circ$) the horizontal plane of the subject's head.

All 11 subjects performed a psychoacoustical test outside the scanner, using the same sound reproduction equipment and stimuli used for the fMRI measurements. This was done in order to obtain an estimate of the subjects' localization ability. On average, the percentage of correct discriminations between two neighbouring azimuthal locations was 94.1% (SE 1.7%; $P < 0.0001$; binomial test). Because perception of up/down alteration (although statistically significant for all subjects; $P < 0.01$) seemed to be reversed by some subjects and was even absent in two of the subjects, we refrained from any analyses of potential activations evoked by changes in elevation, but concentrated on azimuthal sound localization (see below).

Imaging procedure

The cerebral activation was studied with fMRI employing the blood oxygen level-dependent contrast on a 1.5 T Philips Gyroscan scanner (Philips, Best, the Netherlands) in a standard headcoil. The fMRI sessions comprised six dummy scans, followed by 360 whole-brain scans, using single-shot gradient-refocused echo-planar imaging (EPI; TR = 2.8 s, TE = 50 ms, flip angle = 90° , 24 slices). We used a fast event-related design with 30 events per sound location in pseudorandom order; as there were eight different stimulus locations, the probability of each stimulus type was 12.5%. In addition, 66 null events were included, which prolonged several interstimulus intervals to allow recovery of the BOLD response. During the rest condition between these sound events no acoustic stimuli were presented. The stimulus-onset asynchrony was varied between 2.3 and 8.7 s (mean 3.3 s).

Unlike most related studies, we employed a methodological approach in which subjects listened passively to the sound stimuli rather than performing any active task of localization. This was deliberately done in order to exclude contamination of the imaging data by activations resulting from the subject's responses and to minimize the effects of attention and/or arousal, as our focus was on genuinely sensory processes rather than sensorimotor or higher-order cognitive functions (cf. Brunetti *et al.*, 2005; Zimmer *et al.*, 2006). As suggested by recent single-unit recordings in the monkey primary auditory cortex, responses observed during passive listening may provide a valid representation of neuronal spatial tuning properties (Scott *et al.*, 2007). Subjects were instructed to fixate on a white crosshair on black background located in the median sagittal plane. The crosshair was continuously presented during the whole experiment via high-resolution MRI-compatible three-dimensional glasses (Resonance Technology, Van Nuys, CA, USA). No specific instruction was given with respect to auditory stimuli.

Data analysis

The fMRI data were analysed using Statistical Parametric Mapping software (SPM2, <http://www.fil.ion.ac.uk/spm>, London, UK). Dummy scans were discarded. The remaining scans were realigned and spatially normalized to the standard stereotactic space, using the EPI-template of the Montreal Neurological Institute (MNI). The voxel size was $3 \times 3 \times 3$ mm. Subsequently, the normalized data were smoothed using a Gaussian kernel ($9 \times 9 \times 9$ mm), in order to improve the signal-to-noise ratio. For the following parameter estimation, an appropriate design matrix was specified. As regressors, the stimulation time points for each of the eight different stimulus classes were used. The voxel-by-voxel parameter estimation for the smoothed data was carried out according to the general linear model. First, functional brain activations for each stimulus location vs rest were computed. A conjunction analysis then was carried out revealing areas commonly activated by all sound locations; furthermore, fMRI activations during sound perception from the main stimulus directions were computed, including all stimuli comprising a given direction. For all these analyses, the statistical threshold was set to $P < 0.05$, corrected (false discovery rate, FDR). The main effects and interactions depending on sound locations were determined using one-way within-subjects ANOVA comprising contrasts of single subject data for the different sound locations vs rest. These constituted a 2×2 factorial design (azimuth eccentricity: 20° and 80° ; hemisphere: left and right). As we aimed to focus on azimuthal sound localization (see above), data obtained from different sound elevations were collapsed for each azimuth. The ANOVA included analysis of the main factors azimuth

eccentricity and hemisphere, as well as the interactions between the main factors. These analyses compared relatively similar networks; to increase sensitivity, therefore the statistical level was primarily set to $P < 0.001$, uncorrected, with a cluster size of 10 voxels or more considered. To rule out false positive fMRI activations, these data then were further analysed using a small volume correction (SVC) with spherical volumes with a radius of 3 cm. The centres of the small correction volumes were chosen according to the five brain regions of interest described by the meta-analysis of Arnott *et al.* (2004). On this basis, we tested the hypothesis that variation of sound location results in changes of activation in the 'spatial' (IPL; SFS) and mixed 'spatial/non-spatial' regions (pT) of the dual-pathway model, but not in the 'non-spatial' regions [aT; inferior frontal lobe (IFL)]. The coordinates of the centres of the small correction volumes were: (i) $x = \pm 50$, $y = -40$, $z = +10$ (pT); (ii) $x = \pm 45$, $y = -50$, $z = +45$ (IPL); (iii) $x = \pm 35$, $y = +5$, $z = +50$ (SFS); (iv) $x = \pm 50$, $y = -5$, $z = -10$ (aT); and (v) $x = \pm 40$, $y = +25$, $z = -10$ (IFL). The statistical threshold for the SVC was set to a level of $P < 0.05$, corrected (FDR).

Results

On the basis of a preceding study that used pure-tone stimuli with various ILDs (Zimmer *et al.*, 2006), we hypothesized that acoustically evoked activity in cortical areas regarding the analysis of spatial auditory cues would show co-variation with the sound location. Activations evoked by different sound directions were thus analysed separately, and contrasts between these conditions were computed.

A conjunction analysis ($t > 3.20$) was carried out in order to identify those areas that were activated in common by sound stimuli from all directions (Fig. 1A). The main clusters of activation were located in the superior temporal cortices, including bilaterally the auditory areas BA (Brodmann area) 22 and 42, left BA 41, and right BA21. We further identified those areas that were activated by stimuli from any location (Table 1; Fig. 1B–E). These analyses indicated more widespread clusters of activation, comprising inferior parietal cortex (right BA 7, right BA 40, left BA 39), frontal (bilateral BA 6, left BA 9, left BA 45) in addition to the regions mentioned above. Activation foci, as revealed by the main effects for stimuli located either left, right or central (Fig. 1B–D), were identical. However, as confirmed by the ANOVA performed, stimuli from the right hemisphere elicited higher fMRI activations than left-sided stimuli (Fig. 1E).

All 11 subjects showed similar patterns of activation for the main effects of each sound location ($P < 0.05$, corrected, FDR; not shown), with the same positions of clusters as were obtained in the group analyses. Bilateral superior temporal cortices were strongly activated in each individual subject, and the vast majority of subjects exhibited activations in the frontal and parietal regions as described above.

In a one-way within-subjects ANOVA, we computed main effects and interactions of the factors azimuth eccentricity and hemisphere. This was performed by contrasting central stimuli ($\theta = \pm 20^\circ$); eccentric stimuli ($\theta = \pm 80^\circ$); stimuli on the right ($\theta = +20^\circ, +80^\circ$); stimuli on the left ($\theta = -20^\circ, -80^\circ$). For each sound azimuth, data obtained from different elevations were collapsed. As summarized in Table 2 and Fig. 2, significant activation clusters were obtained for: (i) the main effect of hemisphere (contrast of right vs left sound locations); and (ii) the interaction of the factors hemisphere and azimuth eccentricity. The effect of hemisphere (right vs left stimuli) revealed larger clusters of activation mainly in the region around the left TPO junction (the junction area between the temporal, parietal and occipital lobes): the posterior parts of the superior temporal (BA 22, 41) and

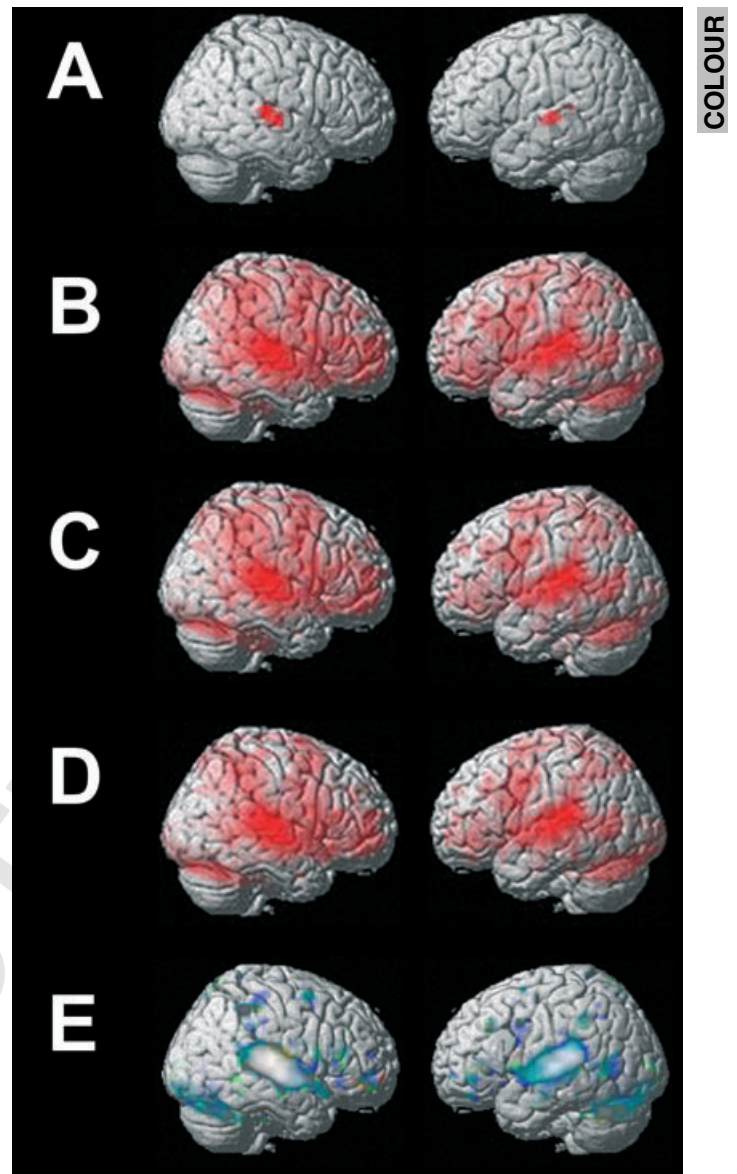


FIG. 1. Brain regions activated by different sound positions. (A) Areas activated in common by sound stimuli from all locations, as revealed by conjunction analysis. (B–D) Areas activated by left (B), central (C) or right (D) sound stimuli. Left stimuli include azimuths 20° and 80° to the left ($\theta = -20^\circ, -80^\circ$), central stimuli include azimuths 20° to either side ($\theta = \pm 20^\circ$), and right stimuli include azimuths 20° and 80° to the right ($\theta = +20^\circ, +80^\circ$), with data obtained from different elevations collapsed for each azimuth angle. (E) Colour-coding of the areas activated by left (red), central (green) or right (blue) sound stimuli (same data as shown in A–C). The statistical threshold was set to $P < 0.05$, corrected (FDR).

middle temporal gyri (BA 37); the IPL (BA 40); left and right extrastriate cortices; and left parahippocampal gyrus (Fig. 2A). The interaction hemisphere \times azimuth eccentricity revealed a more widespread bilateral network of activations (Fig. 2B), which were clearly distinct from those of the main effects. This network included anterior regions of the left superior temporal and middle temporal gyri (BA 21, 38); right insula; right superior, middle and medial frontal gyri (BA 8, 9); right superior and IPL (BA 7, 39); the left IFG (BA 47); and left parahippocampal, and left and right posterior cingulate gyri. All other possible interactions were non-significant at the chosen level of $t < 3.20$ ($P < 0.001$; uncorrected).

TABLE 1. Peak values of clusters activated by at least one of the sound locations

Region	BA	Talairach coordinates (mm)			<i>t</i> -value
		<i>x</i>	<i>y</i>	<i>z</i>	
Right hemisphere					
Frontal					
Right medial frontal gyrus	6	6	-18	72	5.12
Parietal					
Right IPL	40	54	-45	45	8.99
	7	6	-67	59	5.93
Temporal					
Right STG	22	51	-18	0	20.29
	42	66	-24	9	16.07
	21	66	-18	-3	12.07
Left hemisphere					
Frontal					
Left middle frontal gyrus	9	-36	27	36	7.68
Left IFG	45	-57	15	24	5.19
Left superior frontal gyrus	6	-9	9	60	4.55
Parietal					
Left angular gyrus	39	-51	-60	6	8.67
Temporal					
Left STG	41	-48	-24	3	23.39
	42	-51	-36	12	15.19
	22	-66	-18	6	13.90

Analysis was conducted with a threshold of $P < 0.05$, corrected (FDR) for each sound stimulus vs baseline. BA, Brodmann area; IFG, inferior frontal gyrus; IPL, inferior parietal lobule; STG, superior temporal gyrus.

TABLE 2. Peak values of regions showing significant contrasts or interactions of the main factors azimuth eccentricity and hemispace, as was computed by contrasting: (i) central stimuli ($\theta = \pm 20^\circ$); (ii) eccentric stimuli ($\theta = \pm 80^\circ$); (iii) stimuli on the right ($\theta = +20^\circ, +80^\circ$); and (iv) stimuli on the left ($\theta = -20^\circ, -80^\circ$; $P < 0.001$, uncorrected; minimum cluster size 10 voxels)

Contrast and region	BA	Talairach coordinates (mm)			SVC		Dual-pathway model region
		<i>x</i>	<i>y</i>	<i>z</i>	Z-score	<i>P</i> -value	
Hemispace (right vs left sound locations)							
Left postcentral gyrus	40	-57	-30	18	4.28	0.007	IPL
Left STG	22	-48	-21	0	4.27	0.007	pT
Left STG	41	-60	-27	9	4.06	0.007	pT
Left middle temporal gyrus	37	-54	-66	6	3.75	0.007	pT
Left parahippocampal gyrus	30	-12	-48	3	3.97	-	-
Left lingual gyrus	19	-15	-60	-3	3.5	-	-
Right middle occipital gyrus	19	30	-84	-18	3.63	-	-
Right cerebellum, culmen		9	-63	-12	3.63	-	-
Right cerebellum, declive		48	-60	-27	3.63	-	-
Hemispace \times azimuth eccentricity interaction							
Right middle frontal gyrus	9	33	36	42	5.56	< 0.001	SFS
Right superior frontal gyrus	9	21	48	39	3.42	-	-
Right superior frontal gyrus	8	18	24	54	3.9	0.012	SFS
Right medial frontal gyrus	9	6	42	21	4.04	-	-
Left IFG	47	-45	24	-9	3.45	0.046	IFG
Right superior parietal lobule	7	3	-57	51	4.2	-	-
Right angular gyrus	39	54	-72	30	4.08	0.05	IPL
Left STG	38	-33	18	-24	3.76	0.033	aT
Left middle temporal gyrus	21	-54	-6	-18	3.94	0.033	aT
Right insula	13	42	-3	3	3.69	-	-
Right posterior cingulate gyrus	31	12	-42	30	3.95	-	-
Left posterior cingulate gyrus	23	-9	-63	15	3.77	-	-
Left parahippocampal gyrus		-27	-39	-3			

The two columns on the right show the outcome of a SVC (voxel-level) that was conducted using coordinates derived from a meta-analysis (Arnott *et al.*, 2004) on functional imaging studies on the auditory dual-pathway model (aT, anterior temporal lobe; BA, Brodmann area; IFG, inferior frontal gyrus; IPL, inferior parietal lobe; pT, posterior temporal lobe; SFS, superior frontal sulcus; STG, superior temporal gyrus; see Materials and methods). The statistical threshold for the SVC was set to a level of $P < 0.05$, corrected (FDR).

On the basis of the recent meta-analysis of Arnott *et al.* (2004), who reviewed 'spatial' and 'non-spatial' auditory functional imaging studies in order to determine the reliability of the dual-pathway model in humans (see above), we then performed a SVC. As this method relies on *a priori* hypotheses on fMRI activations, the centres of the small correction volumes were chosen according to the five brain regions of interest mentioned above (for coordinates, see Materials and methods). As shown in Table 2, the SVC revealed significant activations in areas described as 'spatial' (IPL, SFS), those referred to as 'non-spatial' (aT, IFL) and in the 'mixed' area pT. The main effect of hemispace resulted in activation of IPL and pT, and the hemispace \times azimuth eccentricity interaction indicated aT, IFG, IPL and SFS to be activated, that is, both the putative 'non-spatial' and 'spatial' regions of the dual-pathway model.

Discussion

The contrasts and interactions between sound locations revealed by our analyses suggest at least two segregated networks to be involved in different aspects of auditory spatial functions. (i) Hemispace (left/right) discrimination seems to take place primarily in the region around the TPO junction, including posterior superior temporal gyrus (STG), IPL and BA 37 (Fig. 2A). (ii) The integration of information on hemispace and azimuth eccentricity of the sound is apparently performed by adjacent regions in the more anterior parts of the temporal lobe and more dorsal parts of the posterior parietal lobule, as well as by more distant areas in IFG and dorsofrontal cortex (Fig. 2B).

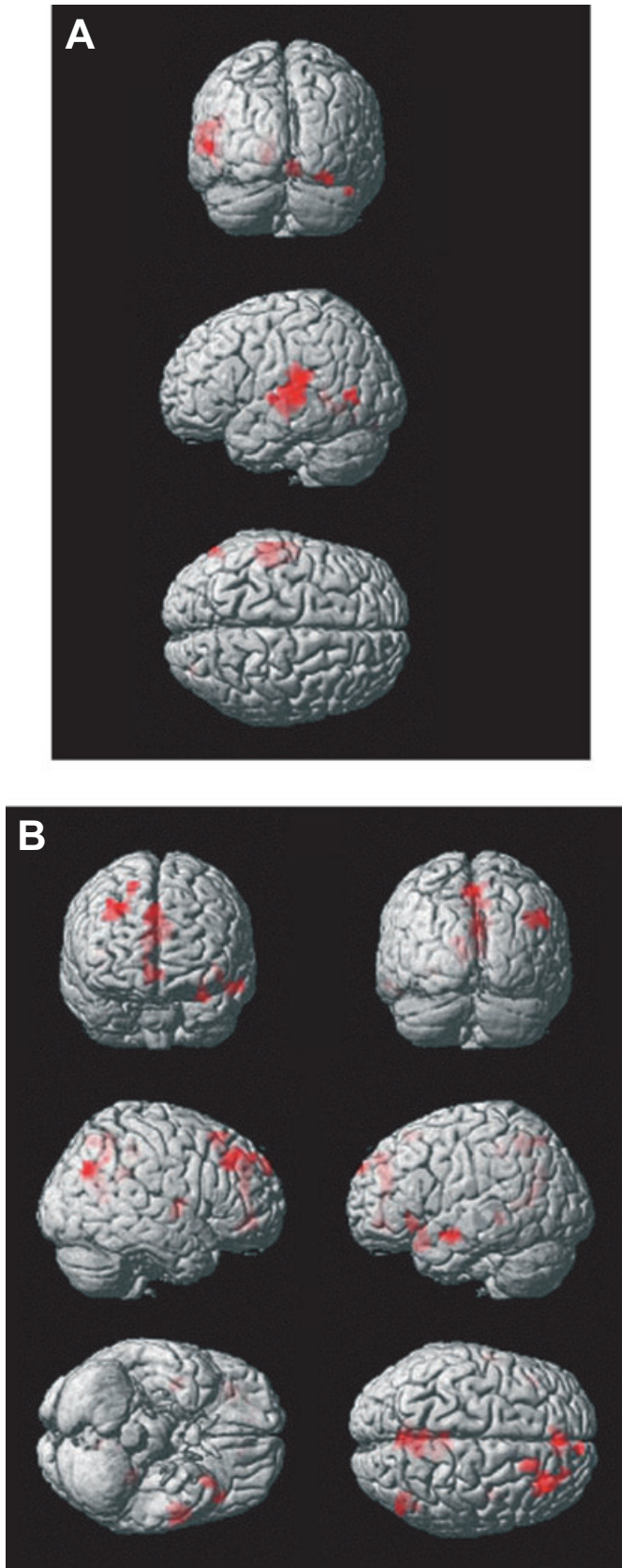


FIG. 2. Activations of brain regions as revealed by the main effect of the factor hemisphere of sound locations (A), and from the interaction of the factors azimuth eccentricity and hemisphere (B). Contrasts and interactions are as given in Table 2.

As illustrated in Fig. 3, the distinct topography of these networks is the result of different patterns of activation and deactivation, depending on horizontal sound location, in the respective voxels. Recently, Mukamel *et al.* (2005) showed that the fMRI signal measured in human auditory cortex is highly correlated with the firing rates of single neurons. Thus, it seems reasonable to assume that the activation/deactivation patterns obtained here reflect the sum of the single-unit responses as a function of stimulus location at the respective brain coordinates. That is, the networks described above may actually represent regions in which the majority of space-specific auditory neurons is selective for the hemisphere of the sound (Figs 3A and D, and 2A), or 'mixed' regions containing various combinations of neurons responding predominantly depending on either hemisphere or azimuth eccentricity of the sound (Figs 3B, C, E and F, and 2B). Given the above, it seems as if in these cortical networks auditory spatial information is processed at different levels of complexity, starting with simple left/right discrimination in the regions surrounding the primary auditory cortex, up to a stage where hemisphere and azimuth eccentricity information are equally present.

When only the hemisphere contrast is considered (Fig. 2A; Table 2, upper panel), the finding by our SVC analysis of significant activations in pT and IPL regions might agree with the idea of a dorsal 'spatial' stream, as proposed in the dual-pathway model (Rauschecker & Tian, 2000; Arnott *et al.*, 2004). However, when the factors azimuth eccentricity and hemisphere were combined in the interaction analysis (Fig. 2B; Table 2, lower panel), the SVC revealed significant activations in both the dorsal (putative 'spatial') stream (IPL, SFS) and the ventral (putative 'non-spatial') stream of the dual-pathway model (aT, IFG). Thus, it seems as if the neural analysis of more complex spatial features (compared with those sufficient for left/right discrimination) may involve both dorsal and ventral auditory regions.

Sound localization incited with natural-like stimuli appearing in external space, as was approached in the present experiment, must necessarily involve areas processing both binaural and spectral cues. As already mentioned above, the distinction of spatial and spectral sound features, as assumed by most previous imaging studies, is highly artificial, as it neglects the fundamental significance of spectral localization cues in perception of sound sources in the extrinsic space (Blauert, 1997; Kulkarni & Colburn, 1998; Jin *et al.*, 2004). Even though our data generally confirm the locations of the regions involved in auditory analysis proposed by the dual-pathway model, they apparently argue against a strict dichotomy, with spatial processing being confined to the dorsal-stream regions only.

Of the activation clusters obtained by the contrasts and interactions summarized in Table 2, the locations in the inferior and superior parietal lobules (BA 7, 39, 40) may generally confirm earlier neuroimaging studies that have concurrently shown IPL activity with auditory spatial tasks. Also, one of these studies (Zatorre *et al.*, 1999) reported activity immediately nearby in the superior parietal lobule, as was the result of the hemisphere \times azimuth eccentricity interaction here. Moreover, there is evidence from repetitive transcranial magnetic stimulation (rTMS), indicating a role of the human IPL in localization of both sound azimuth and elevation (Lewald *et al.*, 2002, 2004a, b). Also, specific deficits in auditory spatial functions have consistently been reported in human subjects with lesions including the parietal cortex (Bisiach *et al.*, 1984; Pinek *et al.*, 1989; Vallar *et al.*, 1995; Tanaka *et al.*, 1999; Bellmann *et al.*, 2001; Maeder *et al.*, 2001; Clarke *et al.*, 2002; Zimmer *et al.*, 2003). In the monkey, spatially selective responses to auditory stimuli have been demonstrated in single neurons of the posterior parietal cortex (Mazzoni *et al.*, 1996;

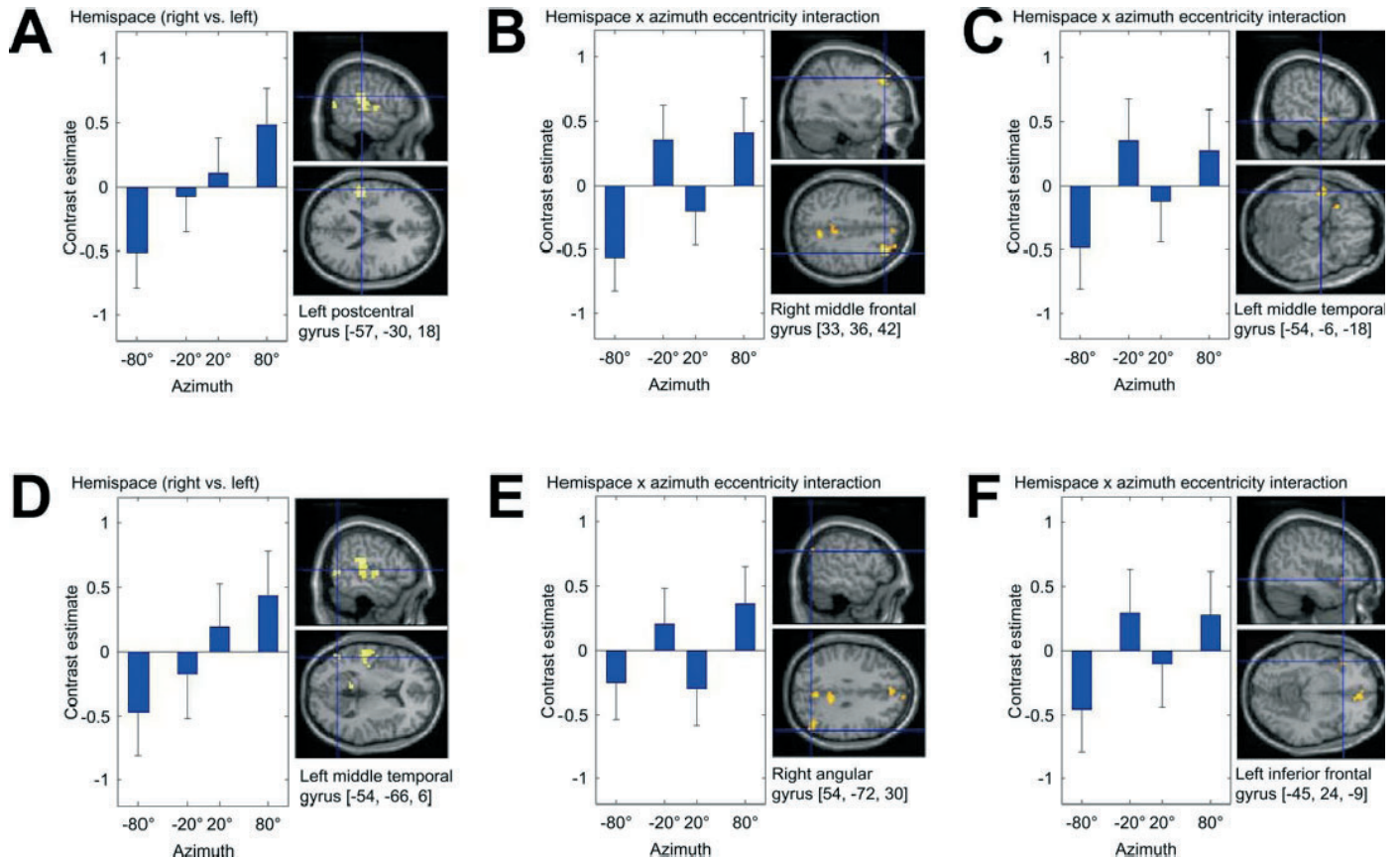


FIG. 3. Contrast estimates plotted as a function of sound location for six brain areas (A–F), as revealed by different conditions of contrasts and interactions. For the voxel with maximum activation in each of the clusters, the plots show the mean as a function of sound azimuth (error bars, 90% confidence intervals). Coordinates given in brackets indicate x, y, z Talairach coordinates of the maximum activation of the clusters, as are shown in sagittal and horizontal slices. Areas are as in Table 2 and Fig. 2.

Stricanne *et al.*, 1996). Finally, this region was shown to receive afferent input from the caudolateral regions of the auditory cortex that process spatial information (Romanski *et al.*, 1999a,b).

Similarly, our finding of activations in the dorsofrontal cortex (BA 6, 8, 9) may be related to observations in the monkey. The posterior parietal cortex, the caudal principal sulcus and periacuate regions (caudal area 46 and area 8a) in the monkey frontal lobe receive afferent input from the caudolateral auditory cortex belt region, and have thus been proposed to represent the anterior target region of the dorsal pathway (Hackett *et al.*, 1999; Romanski *et al.*, 1999a,b). Also, space-specific neurons have been found in this region of the monkey cortex (Vaadia *et al.*, 1986). According to Arnott *et al.* (2004), the human homologue of the frontal ‘spatial’ region may be located anterior to the frontal eye fields, encompassing the caudal SFS ($x = \pm 20$ to ± 40 , $y = 0$ – 20 , $z = 40$ – 60 mm). Even though the clusters obtained here in the superior and middle frontal gyri are lying slightly more anterior or dorsal (cf. Table 2), these activations are immediately nearby, and may certainly exhibit some overlap with the region related to the ‘spatial’ aspects of area 46 in the monkey (see fig. 3 in Romanski *et al.*, 1999b). Also, our finding confirms most of the previous imaging studies that reported activity in the dorsal frontal cortex with auditory spatial tasks in human subjects (Arnott *et al.*, 2004).

In the context of the previous literature, the locations of the ventral activation foci in anterior regions of middle and STG and in IFG, as were revealed by the hemispace \times azimuth eccentricity (Table 2),

appear rather unexpected. The temporal activation clusters lie in the anterolateral aspects of the middle temporal (BA 21) and STG (BA 38), surrounding the lower bank of the superior temporal sulcus (STS). In the monkey, the rostral STS has been referred to as the superior temporal polysensory cortex, and suggested to subservise functions of auditory–visual spatial integration (Kaas & Hackett, 2000). Also, the STS has dense reciprocal connections with the caudal parabelt region of the monkey auditory cortex, that receives input from the caudolateral and caudomedial fields of the auditory cortex belt, regions that are thought to be part of the ‘spatial’ auditory pathway (Kaas & Hackett, 2000). On the other hand, the anterior STG is in the dual-pathway model part of the ventral (‘non-spatial’) stream (anterolateral belt of the monkey auditory cortex), and is assumed to be involved in the analysis of sound identity, such as species-specific vocalizations (in monkeys) or speech (in humans), rather than spatial information (Rauschecker & Tian, 2000; Tian *et al.*, 2001). Consistent with this view is that almost all previous ‘spatial’ imaging studies failed to find activations in the anterior ($y > -10$ mm) temporal lobe (Arnott *et al.*, 2004).

The same applies to the inferior frontal activation cluster in BA 47. The IFG with BA 45 and BA 47 has been associated with the ventral (‘non-spatial’) stream on the basis of findings in the monkey, that indicated connectivity of IFG with anterior STG (Romanski *et al.*, 1999b; Rauschecker & Tian, 2000; Arnott *et al.*, 2004). Accordingly, ‘spatial’ imaging studies did not report activations in IFG (Arnott *et al.*, 2004).

Why have most previous 'spatial' imaging studies failed to find activation in these putative 'non-spatial' areas? Noteworthy is at first that, unlike other approaches, we introduced sound stimuli convolved with individual HRTFs by using custom-designed insert headphones that reproduced adequately the critical high-frequency components of the signal (for details, see Materials and methods). This stimulation method took into account the individual shapes of the subjects' pinnae, which is critical for the generation of the spectral localization cues. The possibly most important methodological difference to previous studies, however, is that we based our conclusions on analyses of contrasts and interactions between genuinely spatial main factors, that is, contrasts were computed exclusively between different virtual sound locations. Opposite to the above, previous studies have usually analysed single contrasts between an active task of sound localization (often involving a motor response) and either silence, passive listening or 'non-spatial' tasks such as pitch discrimination (for review, see Arnott *et al.*, 2004). Those imaging results may involve contamination with unspecific factors that are quite difficult to control, and results may thus be generally less reliable with respect to the identification of 'spatial' auditory brain areas. In particular, it has to be emphasized that analyses contrasting 'spatial vs non-spatial' tasks (involving spectrotemporal processing), as were used in several previous studies, may necessarily cancel any activations related to the neural analysis of spectrotemporal localization cues. Thus, it seems rather likely that those 'spatial vs non-spatial' contrasts actually reflect the contrast between: (i) binaural spatial (ITD/ILD) cues; and (ii) both the spatial and non-spatial aspects of spectrotemporal processing.

In accordance with these considerations, the clusters activated by at least one of the sound locations (Table 1) as well as the right vs left contrast (Table 2) largely equal the activation patterns found in previous studies, with the most prominent activations in bilateral posterior planum temporale, including primary and adjacent non-primary auditory cortex areas (BA 22, 41, 42). As obtained here for the main effect of hemispace, left BA 37 was found to be activated in the study by Zimmer *et al.* (2006), with contrast of left vs right sound positions (implemented by ILDs). Also, right BA 40 was revealed in the central vs eccentric contrast, an area activated here in the left hemisphere with hemispace \times azimuth eccentricity interaction.

Interestingly, we also found activations in extrastriate visual areas in addition to the temporo-parieto-frontal areas that are traditionally thought to be auditory or multimodal regions. The possibility that these occipital activations resulted from the subjects' mental visualization of stimulus position, as was demonstrated for tactile tasks (Zangaladze *et al.*, 1999), seems doubtful because the present experiment did not involve any specific auditory task. More likely may be relations to recent studies that showed an effect of rTMS of the human occipital lobe (with the focus in BA 18 and 19) on sound lateralization (Lewald *et al.*, 2004a, b), and occipital activation clusters (largely overlapping those obtained here in BA 19), as revealed by human fMRI with a task of sound lateralization when eccentric and central eye positions were contrasted (Zimmer *et al.*, 2004). One can not completely exclude that effects of incorrect fixation played any role in the present study. However, in the study by Zimmer *et al.* (2004), specific effects of eccentric eye position on auditory activations have been demonstrated exclusively in occipital cortical areas (V1/V2). Thus, it seems rather likely that such potential effects would be limited to occipital cortex only. Even though single-unit recordings in non-human primates have indicated eye-position effects on auditory responses also in parietal areas (Mazzoni *et al.*, 1996; Stricanne *et al.*, 1996), and even in primary auditory cortex (Werner-Reiss *et al.*, 2003; Fu *et al.*, 2004), human fMRI studies have, until present, failed to find any related effects.

Earlier neuroimaging data mostly suggested general right hemisphere superiority or dominance for the processing of both auditory azimuth (Griffiths *et al.*, 1998; Kaiser *et al.*, 2000; Palomäki *et al.*, 2000) and elevation cues (Fujiki *et al.*, 2002). In partial opposition to this view, Pinek *et al.* (1989), employing a task of hand-pointing, obtained errors in azimuthal sound localization, but no deficits in vertical localization, in patients with right temporo-parietal damage. Patients with left-sided lesions showed deficits also in vertical localization and front/back discrimination (which decisively depends on spectral cues as perception of elevation), thus rather arguing in favour of a left-hemisphere superiority in spatial hearing when one accounts for the use of spectral localization cues in addition to binaural cues. As shown in Fig. 2B, the present interactions of spatial factors revealed largely bilateral networks, without any obvious advantage of one hemisphere. In accordance with that, studies that investigated callosal or callosotomy subjects suggested that transfer of auditory spatial information via the corpus callosum plays a significant role in sound localization (Poirier *et al.*, 1993; Hausmann *et al.*, 2005). Also, investigations with brain-damaged subjects indicated that total inability of sound localization or lateralization can occur in individual patients with left-hemispheric lesions and those with right-hemispheric lesions, even though severe deficits are usually observed more frequently in the latter group (Ruff *et al.*, 1981; Bisiach *et al.*, 1984; Zatorre & Penhune, 2001; Hausmann *et al.*, 2005). However, when the locations of the activations are considered in detail, our data suggest a bilateral asymmetry of heterotopic activation foci, with a tendency of the dorsal parieto-frontal activations to be located in the right hemisphere and ventral (anterior temporal and inferior frontal) activations in the left hemisphere (see Fig. 2B).

We conclude that the activation foci revealed in inferior parietal and dorsolateral prefrontal cortex for the hemispace \times azimuth eccentricity interaction (Table 2) are identical with those believed to be the two target regions of the dorsal 'spatial' auditory stream in the dual-pathway model. The anterior temporal and inferior frontal activation foci revealed by the same analyses partly overlap the two target regions of the ventral auditory stream. Until now, these regions have been thought to be concerned primarily with processing of 'non-spatial' sound features. Against the earlier belief, our data indicate that these ventral-stream areas are activated depending on the alteration of the sound location. This finding may reflect the well-known functional duality of auditory spectral analysis, that is, the concurrent extraction of information based on location (due to the spectrotemporal distortions caused by head and pinnae) and spectral characteristics of a sound source. In accordance with this functional point of view, our results argue in favour of a model in which functions of sound identification and spatial analysis are colocalized in the ventral and dorsal auditory streams (cf. also Zatorre *et al.*, 1999). Notable is that such an assumption of shared networks for both these auditory functions perfectly fits the more recent studies in the monkey, which reported similar spatial and non-spatial sensitivities of neurons in ventral prefrontal and lateral intraparietal cortex (Cohen *et al.*, 2004; Gifford & Cohen, 2005). In a more general context, our conclusion may also be in alignment with recent neuropsychological findings suggesting that in human brain spatial processing is strongly linked with functions of pitch perception (Douglas & Bilkey, 2007).

Acknowledgements

We are especially grateful to Dorotee Bülte and Oliver Strauch for their help in running the experiments, and to Hans-Otto Karnath for valuable comments on an earlier draft of the manuscript. This work was supported by the Deutsche Forschungsgemeinschaft (Fa211/17-1; Fa211/17-2; Bo1576/7-1).

Abbreviations

aT, anterior temporal lobe; BA, Brodmann area; EPI, echo-planar imaging; FDR, false discovery rate; fMRI, functional magnetic resonance imaging; HRTF, head-related transfer function; IFG, inferior frontal gyrus; IFL, inferior frontal lobe; ILD, interaural level difference; IPL, inferior parietal lobule; IR, impulse response; ITD, interaural time difference; MEG, magnetoencephalography; pT, posterior temporal lobe; rTMS, repetitive transcranial magnetic stimulation; SFS, superior frontal sulcus; SPL, sound-pressure level; STG, superior temporal gyrus; STS, superior temporal sulcus; SVC, small volume correction.

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5	Tiitinen et al. 2006 has not been found in the text	

	E	J	N	6	0	9	4	B	Dispatch: 19.2.08	Journal: EJM	CE: Blackwell
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MARKED PROOF

Please correct and return this set

Please use the proof correction marks shown below for all alterations and corrections. If you wish to return your proof by fax you should ensure that all amendments are written clearly in dark ink and are made well within the page margins.

<i>Instruction to printer</i>	<i>Textual mark</i>	<i>Marginal mark</i>
Leave unchanged	... under matter to remain	Ⓟ
Insert in text the matter indicated in the margin	∧	New matter followed by ∧ or ∧ [Ⓢ]
Delete	/ through single character, rule or underline or ┌───┐ through all characters to be deleted	Ⓞ or Ⓞ [Ⓢ]
Substitute character or substitute part of one or more word(s)	/ through letter or ┌───┐ through characters	new character / or new characters /
Change to italics	— under matter to be changed	↵
Change to capitals	≡ under matter to be changed	≡
Change to small capitals	≡ under matter to be changed	≡
Change to bold type	~ under matter to be changed	~
Change to bold italic	≈ under matter to be changed	≈
Change to lower case	Encircle matter to be changed	≡
Change italic to upright type	(As above)	⊕
Change bold to non-bold type	(As above)	⊖
Insert 'superior' character	/ through character or ∧ where required	Υ or Υ under character e.g. Υ or Υ
Insert 'inferior' character	(As above)	∧ over character e.g. ∧
Insert full stop	(As above)	⊙
Insert comma	(As above)	,
Insert single quotation marks	(As above)	Ƴ or ƴ and/or ƶ or Ʒ
Insert double quotation marks	(As above)	ƶ or Ʒ and/or ƹ or Ƹ
Insert hyphen	(As above)	⊥
Start new paragraph	┌	┌
No new paragraph	┐	┐
Transpose	└┐	└┐
Close up	linking ○ characters	Ⓞ
Insert or substitute space between characters or words	/ through character or ∧ where required	Υ
Reduce space between characters or words		↑