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Hierarchical processing of sound location and motion in the human brainstem and planum temporale

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Abstract

Horizontal sound localization relies on the extraction of binaural acoustic cues by integration of the signals from the two ears at the level of the brainstem. The present experiment was aimed at detecting the sites of binaural integration in the human brainstem using functional magnetic resonance imaging and a binaural difference paradigm, in which the responses to binaural sounds were compared with the sum of the responses to the corresponding monaural sounds. The experiment also included a moving sound condition, which was contrasted against a spectrally and energetically matched stationary sound condition to assess which of the structures that are involved in general binaural processing are specifically specialized in motion processing. The binaural difference contrast revealed a substantial binaural response suppression in the inferior colliculus in the midbrain, the medial geniculate body in the thalamus and the primary auditory cortex. The effect appears to reflect an actual reduction of the underlying activity, probably brought about by binaural inhibition or refractoriness at the level of the superior olivary complex. Whereas all structures up to and including the primary auditory cortex were activated as strongly by the stationary as by the moving sounds, non-primary auditory fields in the planum temporale responded selectively to the moving sounds. These results suggest a hierarchical organization of auditory spatial processing in which the general analysis of binaural information begins as early as the brainstem, while the representation of dynamic binaural cues relies on non-primary auditory fields in the planum temporale.

Introduction

In humans, horizontal sound localization mainly relies on the analysis of interaural differences in sound arrival time and level by comparison of the signals from the two ears. The processing of these binaural cues begins at the level of the superior olivary complex (SOC) in the brainstem. Neurones in the medial superior olive receive excitatory projections from both cochleae [excitatory–excitatory (EE) neurones] and their responses tend to be facilitated by coincident binaural input (cat, Yin & Chan, 1990). In contrast, the lateral superior olive contains neurones whose main input from one cochlea is inhibitory, the other being excitatory [excitatory–inhibitory (EI) neurones]. EE neurones are sensitive to interaural time differences (ITDs; Joris *et al.*, 1998), whereas EI neurones are sensitive to both ITDs (Joris & Yin, 1995; Batra *et al.*, 1997) and interaural level differences (Tollin, 2003).

While it is generally assumed that the brainstem plays a vital role in spatial hearing, there is still little consensus about the mechanisms underlying the processing of binaural cues in the brainstem. Part of the problem is the difficulty of investigating brainstem binaural processing in humans: So far, the sole established correlate of binaural integration in the human brainstem is the binaural difference (BD) in the brainstem auditory evoked potentials (AEPs), often referred to as binaural interaction component (see Riedel & Kollmeier, 2002, and references therein). The BD is defined as the difference between the response to a binaural sound and the sum of the responses to the corresponding monaural sounds presented separately [BD = Bin − (Left + Right)]. Any deviation from zero BD is interpreted as an indication of binaural functional coupling. In particular, the BD would be expected to be positive for EE neurones and negative for EI neurones (Gaumond & Psaltikidou, 1991). An EI neurone's binaural response would be even smaller than the response to the neurone's excitatory monaural input alone. The BD in the human brainstem AEPs is invariably negative, amounting to about 14–23% of the sum of the monaural responses (McPherson & Starr, 1993). When interpreting the sign of the BD in the brainstem AEPs, however, one needs to keep in mind that AEPs represent spatially distributed activity (Kaufman *et al.*, 1981) and so both EE and EI neurones may contribute to the BD, their respective effects partially cancelling out.

The present study investigates the BD with functional magnetic resonance imaging (fMRI). The aims were: (i) to devise a method which would enable the imaging of brainstem binaural processing in a spatially specific manner and (ii) to characterize sites of facilitatory and inhibitory binaural interaction in the ascending auditory pathway. The experiment also included a motion paradigm similar to those used in previous fMRI studies of spatial hearing (Baumgart *et al.*, 1999; Seifritz *et al.*, 2002a; Warren *et al.*, 2002), in which moving sounds

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were contrasted against appropriately matched stationary sounds. The comparison between the BD and the motion contrast was expected to reveal which of the regions that are involved in general binaural processing are specifically specialized in motion processing and thus complement the physiological data on this question (Spitzer & Semple, 1998; Malone *et al.*, 2002; McAlpine & Palmer, 2002).

Materials and methods

Listeners

Twelve right-handed listeners (six male, six female) between 23 and 32 years of age with no history of hearing disorder or neurological disease participated in the experiment after having given informed consent. The experimental procedures conform to The Code of Ethics of the World Medical Association (Declaration of Helsinki) and were approved by the ethics review board of the University of Leipzig.

Stimuli and experimental protocol

The experiment comprised two binaural and two monaural sound conditions as well as a silence condition (Sil). In the monaural conditions (Left and Right), trains of noise bursts were played either to the left or right ear separately. In the binaural conditions (Diotic and Move), the same noise bursts were played to both ears simultaneously. The two binaural conditions differed from each other only in the interaural temporal properties of the sound; in the Diotic condition the noise bursts were identical at both ears so the perception was that of a stationary sound in the centre of the head. In the Move condition, the noise bursts were presented with an ITD that varied continuously between −1000 and +1000 μs to create the perception of a sound that moves back and forth between the two ears. By convention, a positive ITD means that the sound to the left ear is lagging the sound to the right ear, whereas a negative ITD denotes the reverse situation. The ITD in the Move condition was varied according to a continuous linear function of time and the rate of the variation was 1000 μs/s, so it took 2 s for the sounds to move from one ear to the other. The starting point of the movement was randomized from trial to trial. In both binaural conditions, the noise bursts had the same energy at both ears and the energy to each ear was equal to the energy of either of the monaural noises. The noise bursts had a duration of 50 ms; they were filtered between 200 and 3200 Hz and presented at a rate of 10/s. Due to the fact that the perception of auditory motion is sluggish with a time constant of several hundreds of milliseconds (see, e.g. Blauert, 1997) the stimuli in the Move condition created the perception of a smoothly moving source, even though they were pulsed, because the pulse rate was fairly fast (10/s). The noise was continuously generated afresh (System 3; Tucker Davis Technologies, Alachua, Florida, USA) so that none of the noise bursts was ever repeated during the experiment. The sounds were presented through electrostatic headphones (Sennheiser, Wedemark, Germany) that passively shielded the listener from the scanner noise.

Cardiac triggering of image acquisitions (Guimaraes *et al.*, 1998) was used to minimize motion artefacts in the brainstem signal due to basilar artery pulsation (see next section for details). The sparse imaging technique (Hall *et al.*, 1999) was applied to avoid masking of the experimental sounds by the scanner noise and to reduce the effect of scanner noise on the recorded activity. The gaps between consecutive image acquisitions, during which the sounds or silence were presented, had a duration of about 7 s. The exact duration of the gaps, and thus also the repetition time of the image acquisitions (TR), varied slightly due to cardiac triggering. The average TR over all listeners and trials amounted to 10.5 s. The experimental conditions were presented in epochs, during which five images were acquired. Four sound epochs containing the four sound conditions in pseudo-random order were alternated with a single silence epoch. A total of 250 images (corresponding to 50 epochs) were acquired per listener.

Listeners were asked to attend to the sounds and take particular notice of their spatial attributes. To avoid eye movements in the direction of the sounds, the listeners had to fixate a cross at the midpoint of the visual axis and perform a visual control task. The task was to press a button with the left or right index finger upon each occurrence of the capital letter 'Z' in either of two simultaneous, but uncorrelated, sequences of random one-digit numbers that were shown to the left and right of the fixation cross. The numbers were presented once every 2 s for 50 ms.

Functional magnetic resonance imaging data acquisition

Blood oxygen level-dependent contrast images were acquired with a 3-T Bruker Medspec whole body scanner using gradient echo planar imaging (EPI; average TR, 10.5 s; TE, 30 ms; flip angle, 90°; acquisition bandwidth, 100 kHz). The functional images consisted of 28 ascending slices with an in-plane resolution of 3×3 mm^2, a slice thickness of 3 mm and an interslice gap of 1 mm. The slices were orientated along the line connecting the anterior and posterior commissures and positioned so that the lowest slices covered the cochlear nucleus (CN) just below the pons. They were acquired in direct temporal succession, the acquisition of each slice lasting 75 ms. Each image acquisition was triggered 300 ms after the cardiac R-wave, about 100 ms after the main cardiac pulse reaches the brain (Allen *et al.*, 1998). The benefit of this cardiac triggering was presumably greatest for those structures that were covered by slices, which were acquired before the occurrence of the next pulse artefact. This would be expected to have been the case for the CN as well as the inferior colliculus (IC) which was, on average, covered by the seventh slice (525 ms into the image acquisition). However, to the extent that the pulse rate was stable over the duration of the epochs ($\sim$ 52.5 s), later slices would also be expected to have benefited from cardiac triggering because they were effectively acquired at a roughly constant phase of the next cardiac cycle.

A high-resolution structural image was acquired from each listener using a three-dimensional Modified Driven Equilibrium Fourier Transform (MDEFT) sequence (Ugurbil *et al.*, 1993) with 128 1.5-mm slices (FOV, $25 \times 25 \times 19.2$ cm; data matrix, 256×256; TR, 1.3 s; TE, 10 ms). For registration purposes, a set of T1-weighted EPI images was acquired using the same parameters as for the functional images (inversion time, 1200 ms; TR, 45 s; four averages).

Data analysis

The data were analysed with the in-house software package LIPSIA (Lohmann *et al.*, 2001; see also http://www.cns.mpg.de/lipsia). The functional images of each listener were corrected for head motion and rotated into the Talairach coordinate system by coregistering the structural MDEFT and EPI-T1 images acquired in this experiment with a high-resolution structural image residing in a listeners' database. The functional images were then normalized and were spatially smoothed with two different Gaussian kernels (3 and 10 mm full width at half maximum) to optimize for the signals from the brainstem and cortex, respectively. The auditory structures in the brainstem are only a few millimeters long and their location with respect to macro-anatomical landmarks varies little across individuals so the chances of detecting auditory activity in the brainstem can be

increased by using a small smoothing kernel. In contrast, auditory cortical regions are comparatively large and their boundaries exhibit a considerable interindividual variability with respect to macro-anatomy (Rademacher *et al.*, 2001), which means that a larger smoothing kernel is more suitable for analysing the auditory cortical signal. The smoothed image time series of 12 listeners, comprising a total of 3000 image volumes, were subjected to a fixed-effects group analysis using the general linear model. Each of the five experimental conditions (silence and four sound conditions) was modelled as a box-car function convolved with a generic haemodynamic response function including a response delay of 6 s. The data were highpass filtered at 0.0019 Hz to remove low-frequency drifts and lowpass filtered by convolution with a Gaussian function (4 s full width at half maximum) to control for temporal autocorrelation. The height threshold for activation was $Z = 3.1$ ($P \leq 0.001$ uncorrected). In addition to the fixed effects analysis, we also performed second-level random effects and Bayesian analyses (as implemented in the LIPSIA software, see Neumann & Lohmann, 2003) to test the stability of the effects across listeners.

Results

Comparison between all sounds and silence

In order to reveal brain regions that showed a general sensitivity to the noise stimuli used in the present experiment, and thereby identify possible candidates for non-linear binaural interaction, we first compared the average activation produced by all sound conditions (Left, Right, Diotic and Move) to the activation in the silence condition. This all sounds vs. silence contrast revealed bilateral activation at four different levels of the auditory processing hierarchy (Fig. 1).

The lower two panels of Fig. 1 show activation in both cochlear nuclei (CN). The CN is the first processing stage in the auditory system and receives purely monaural input from the ipsilateral cochlea. The location of the CN activations with respect to macro-anatomical landmarks (Fig. 1) corresponds well with the location of the respective activations in the data of Griffiths *et al.* (2001; see their Figure 2) and Melcher *et al.* (1999; see their Figure 4). The Talairach coordinates of the left and right CN activations amounted to −14, −42, −30 mm and 10, −42, −30 mm, respectively. These coordinates transform to about −14, −42, −38 mm and 10, −42, −38 mm in the Montreal Neurological Institute (MNI) space, which corresponds reasonably well with the respective coordinates reported by Griffiths *et al.* (2001; −12, −40, −46 mm and 8, −34, −48 mm).

The middle panels of Fig. 1 show activation in the inferior colliculi (IC) in the midbrain and the medial geniculate bodies (MGBs) in the thalamus (right panel). The IC is the last auditory processing stage in the brainstem and contains a mandatory synapse for all ascending auditory pathways. The ICs are strongly interconnected by commissural fibres, suggesting that the IC may have profound implications in binaural processing. The MGB activation can also be seen in the upper left panel of Fig. 1. As for the CN, the Talairach coordinates of the most significantly activated voxels in the IC and MGBs (Table 1) correspond well with the coordinates of the respective activations reported by Griffiths *et al.* (2001). The upper right panel depicts a slice parallel to the Sylvian fissure showing activation in the auditory cortices (ACs).

The SOC failed to exhibit any significant activation in the all sounds vs. silence contrast, and indeed in any of the other contrasts tested, probably because it is too small to be detectable with standard-resolution fMRI sequences. In humans, the largest nucleus of the SOC, the medial superior olive, has a rostrocaudal extent of about 2.6 mm and a dorsoventral extent of 1.8–2.4 mm (Bazwinsky *et al.*, 2003), which is smaller than even a single voxel in the functional images or the width of the spatial smoothing kernel (3 mm). Thus, even in the case that the SOC completely fell into a single voxel, which is in itself improbable, the activation of this voxel would probably fail to reach statistical significance.

TABLE 1. Talairach coordinates and *Z*-values of auditory activation foci in the all sounds vs. silence contrast

Brain region	*x*	*y*	*z*	*Z*-value
Left CN	−14	−42	−30	> 3.1
Right CN	10	−42	−30	> 3.1
Left IC	−8	−36	−3	> 4.5
Right IC	4	−36	−3	> 4.5
Left MGB	−17	−30	0	> 3.1
Right MGB	13	−30	−3	> 3.1
Left STP	−47	−27	12	> 16
Right STP	40	35	25	> 19

CN, cochlear nucleus; IC, inferior colliculus; MGB, medial geniculate body; STP, supratemporal plane.

Binaural difference contrast

In order to reveal sites of facilitatory and inhibitory binaural interactions, which underlie the processing of auditory spatial information, the sum of the haemodynamic responses to the left and right monaural sounds (Left and Right) was compared with the response to the diotic binaural sound (Diotic). This comparison is analogous to the BD operation that has previously been applied to AEP data (see, e.g. Riedel & Kollmeier, 2002). The particular difficulty in applying this operation to fMRI data lies in the fact that it involves comparing a single sound condition (Diotic) with the sum of two sound conditions (Left + Right). Such a comparison would be unbalanced for any of the non-auditory processes that were also active during sound presentation, for instance the visual control task, and the corresponding contrast would be unestimable if the baseline is modelled explicitly, as was the case in the current experiment. The problem can be circumvented by referring each of the sound conditions in the BD contrast to the silence condition (Sil) yielding BD = (Diotic − Sil) − [(Left − Sil) + (Right − Sil)] which reduces to BD = (Diotic + Sil) − (Left + Right). By this means, the BD contrast was not only balanced for any non-auditory processes that were active during both sound and silence epochs but also for sound energy because the intensity and presentation rate of the left and right monaural sounds were equal to those of the left- and right-ear stimuli in the diotic sound and the silence condition did not contain any sound energy. Balancing the contrast for sound energy is the prerequisite for recording non-linear (facilitatory or inhibitory) binaural interactions. In particular, testing for a negative BD (–BD > 0) reveals regions whose binaural response is suppressed relative to the monaural responses, whereas a positive BD (BD > 0) would be associated with regions that exhibit facilitatory binaural coupling.

The BD contrast yielded a significant bilateral response in the IC, MGB and the medial and central part of Heschl's gyrus (HG), which is the site of the primary AC (PAC) in humans (Fig. 2a; Rademacher *et al.*, 2001). In contrast, the CN exhibited no significant BD response, as would be expected as the CN receives purely monaural input. In all regions which showed a significant BD contrast, the BD was invariably negative. In fact, the size of the binaural response (red bars in Fig. 2b) never exceeded 50% of the sum of the monaural

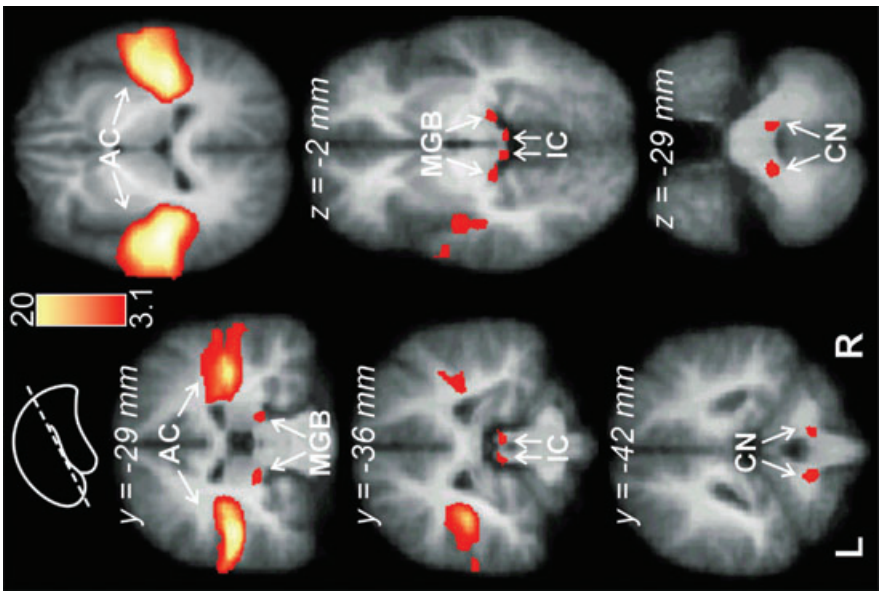

FIG. 1. Activation for the contrast between all four sound conditions (Left, Right, Diotic and Move) and the silent baseline (Sil), rendered onto the average structural image of the group. The left column depicts three coronal slices at $y = -42$, -36 and -29 mm (from bottom to top). The lower two panels in the right column show axial slices at $z = -29$ and -2 mm; the slice shown in the upper right panel is orientated parallel to the Sylvian fissure (see small inset at the top). The colour bar (top) shows the Z-values for the statistical comparison. The contrast revealed bilateral activation in the cochlear nucleus (CN), inferior colliculus (IC), medial geniculate body (MGB) and auditory cortex (AC) on the supratemporal plane.

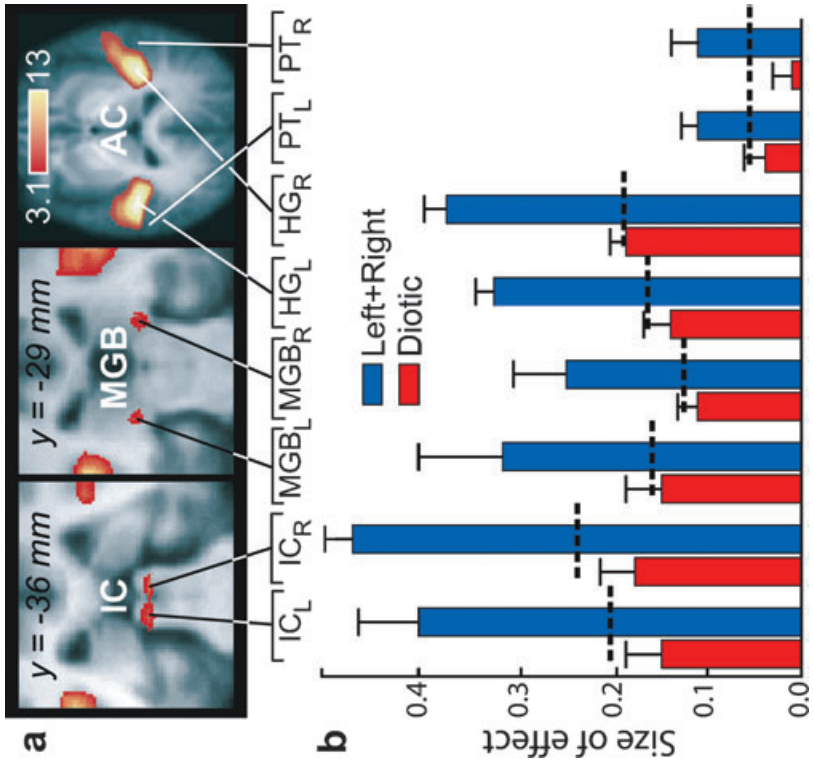

FIG. 2. Binaural difference (BD) contrast. (a) Activation to the BD contrast rendered onto two coronal slices at $y = -36$ and -29 mm (left and middle) and one oblique slice orientated parallel to the Sylvian fissure as in Fig. 1 (right). The BD contrast yielded bilateral activation in the inferior colliculus (IC), the medial geniculate body (MGB) and on Heschl's gyrus (HG) in the region of the primary auditory cortex (AC); there was no activation on the planum temporale (PT) behind HG. (b) Size of the response to the binaural stationary sounds (Diotic, red bars) and the sum of the responses to the two monaural sounds (Left + Right, blue bars) relative to the silent baseline in each of these regions. The binaural response never exceeded 50% of the sum of the monaural responses (horizontal dashed lines). The absence of BD activation in the PT (at the location of the most significant voxel in the motion contrast) was due to the fact that the responses to all of the stationary sounds (Left, Right and Diotic) on the whole were greatly reduced in this region (two right-most sets of bars).

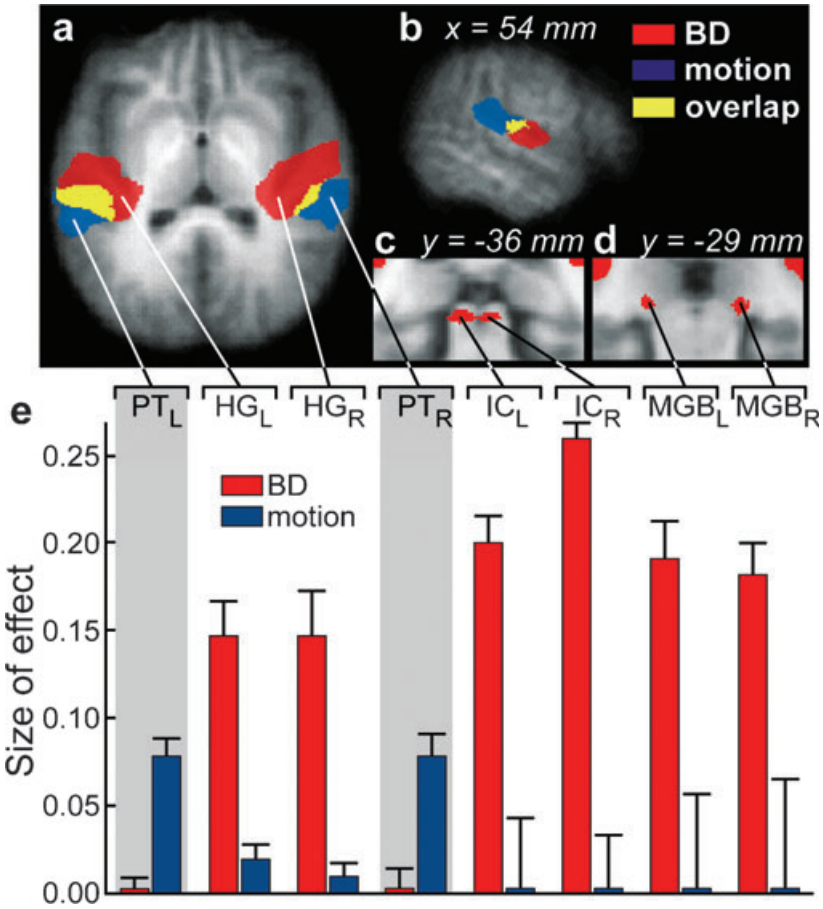

FIG. 3. Motion contrast. Upper panel: activation to the motion contrast (blue highlight) rendered onto an oblique slice orientated parallel to the Sylvian fissure (a), a sagittal slice at $x = 54$ mm (b) and two coronal slices at $y = -36$ and -29 mm (c and d). For a comparison, the red highlight shows the activation to the binaural difference (BD) contrast; the overlap between the motion and BD activations is shown in yellow. Whereas the BD produced activation in the inferior colliculus (IC), the medial geniculate body (MGB) and on Heschl's gyrus (HG), the activation to the motion contrast was largely confined to the planum temporale (PT) and the temporo-parietal junction behind HG. (e) Contrast-weighted beta-values for the motion contrast (blue bars) and the negative BD contrast (–BD; red bars) in each of these regions. The grey shading highlights those regions, where the motion response surpassed the BD response.

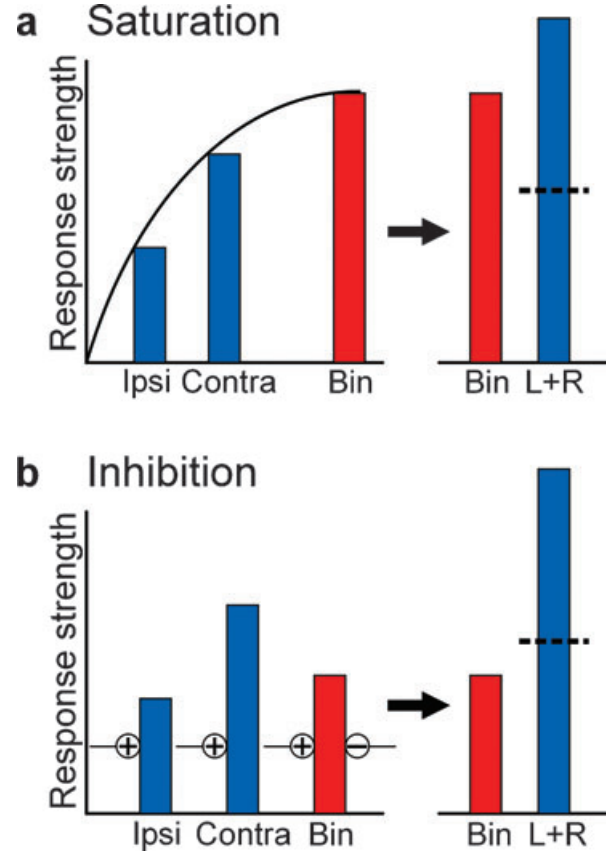

FIG. 4. Schematic representations of saturation and inhibition/refractoriness accounts of binaural suppression. The left part of each panel shows the responses to the ipsi- and contralateral monaural sounds (Ipsi, Contra) and to the binaural sound (Bin); the right part of each panel shows the binaural response (Bin) in comparison with the sum of the monaural responses (L + R). Response saturation (schematically represented by curved, solid line in a) may cause binaural response suppression even in the absence of any inhibition or refractoriness; in this case, the binaural response would be expected to be larger than the larger of the two monaural responses (Contra) and thus larger than 50% of the sum of the monaural responses (horizontal dashed lines). The fact that the binaural response was actually smaller than 50% of the sum of the monaural responses suggests that suppression was brought about by an active reduction (–) of the convergent binaural inputs, caused either by inhibition or refractoriness (b).

responses (horizontal dashed lines on blue bars in Fig. 2b). On average, the binaural response amounted to 37% of the sum of the monaural responses in the IC and 46% in both the MGB and PAC. Thus, the binaural response was not only smaller than the sum of the monaural responses but was also smaller than the larger of the two monaural responses alone. From the level of the IC upwards, contralateral monaural sounds usually produce a larger response than ipsilateral sounds, which is consistent with the notion that the majority of ascending auditory pathways cross from the ipsilateral to the contralateral side below the level of the IC (Pantev *et al.*, 1998; Melcher *et al.*, 1999, 2000; Woldorff *et al.*, 1999). In the present experiment, the average ratio of the contralateral to the ipsilateral monaural response was 153% in the IC, 124% in the MGB and 126% in the PAC. Thus, when expressed relative to the contralateral monaural response, the suppression of the binaural response averaged 38% in the IC, 17% in the MGB and 18% in the PAC.

Testing for a positive BD yielded no significant activation whatsoever anywhere in the auditory pathway.

Motion contrast

In order to assess which brain regions are specialized in auditory motion processing and whether they overlap with those regions that are involved in general binaural processing as shown by the BD contrast, we compared the activation produced by the Move condition to that produced by the Diotic condition. The Move and Diotic conditions only differed in the interaural temporal characteristics of the noise bursts, the ITD being fixed at 0 μs in the Diotic condition and varying linearly over time in the Move condition. The motion contrast (motion = Move − Diotic) revealed significant bilateral activation in the planum temporale (PT), namely the part of the supratemporal plane that lies posterior to HG and the temporoparietal junction (TPJ; blue highlight in Fig. 3a and b). The PT contains non-primary auditory fields and, like the TPJ, has previously been implicated in the processing of sound location and sound movement (Baumgart *et al.*, 1999; Warren *et al.*, 2002; Zatorre *et al.*, 2002).

Unlike the BD contrast, the motion contrast did not produce any significant activation in the IC, MGB or PAC on HG. Usually, the absence of activation is difficult to interpret as activation may still be present even if it does not meet the underlying significance criterion. In the current experiment, however, the response to the motion contrast can be directly compared with the BD response. In the IC and MGB, the motion response (blue bars in Fig. 3e) was miniscule compared with the BD response (red bars in Fig. 3e). In the PAC, the motion contrast produced a small response which did not, however, reach statistical significance. Only in the PT and the TPJ was the motion response larger than the BD response (grey highlight in Fig. 3e). Although the BD contrast produced no significant activation in the PT (at the location of the most significant voxel in the motion contrast), the response to the stationary binaural sound (Diotic) was still smaller than the sum of the monaural responses (Left + Right), as shown by the two right-most sets of bars in Fig. 2b. The absence of activation to the BD contrast in the PT was due to the fact that the responses to all stationary sound conditions were, on the whole (Left, Right and Diotic), very small in this region.

Random effects and Bayesian analyses

In order to test the stability of the observed effects of binaural and motion processing across listeners, we performed a random effects and a Bayesian analysis at the second level (Neumann & Lohmann, 2003). The Bayesian analysis is more robust against outliers than the random effects analysis (Neumann & Lohmann, 2003) and may thus be particularly suitable for analysing brainstem signals, which are small and thus difficult to detect due to the smallness of the underlying structures and whose variability would be expected to be dominated by anatomical rather than functional factors.

The results from the fixed effects analysis were, in the main, confirmed by the random effects and Bayesian analyses. The random effects analysis revealed a significant binaural suppression (–BD > 0) in the left and right IC ($Z = 2.58$, $p_{rfx} = 0.005$, uncorrected, at −7, −37, −4 mm and $Z = 4.33$, $p_{rfx} < 0.001$, uncorrected, at 5, −37, −4 mm) and the Bayesian posterior probability for binaural suppression (i.e. the probability of –BD > 0, given the data) exceeded 99.99% in the left and right IC. The random effects analysis yielded a marginally significant BD contrast in the left MGB ($Z = 1.73$, $p_{rfx} = 0.042$, uncorrected, at −21, −23, −5 mm) and the Bayesian posterior probability for binaural suppression was 99.96% in the left MGB (at −18, −26, −4 mm). Neither analysis, however, yielded any significant BD activation in the right MGB. Both the random effects and the Bayesian analysis yielded a significant BD activation in the region of the PAC on left and right HG ($Z = 5.71$, $p_{rfx} < 0.001$, uncorrected, $p_{bayes} > 99.99\%$ at −39, −26, 11 mm and $Z = 7.58$, $p_{rfx} < 0.001$, uncorrected, $p_{bayes} > 99.99\%$ at 38, −24, 13 mm). As for the fixed effects analysis, the activation to the motion contrast revealed by the random effects and Bayesian analyses was confined to the left and right superior temporal planes and was located in the region of the PT and TPJ, namely posterior to the corresponding BD activation ($Z = 5.41$, $p_{rfx} < 0.001$, uncorrected, $p_{bayes} > 99.99\%$ at −55, −31, 13 mm and $Z = 3.62$, $p_{rfx} < 0.001$, uncorrected, $p_{bayes} > 99.99\%$ at 50, −28, 16 mm).

In order to obtain an estimate of the range of the amount of binaural suppression in individual listeners, the sizes of the individual binaural and summed monaural responses were extracted from those voxels in the IC and AC that had shown the most significant BD activation in the fixed effects analysis. Only the IC and AC had shown a sizeable BD activation in the random effects analysis. The size of the binaural response ranged between 11 and 91% of the summed monaural responses in the IC and between 18 and 110% in the AC. These ranges include values that are considerably smaller than 50%, indicating greater binaural suppression. The majority of values above 50% stemmed from voxels, for which the summed monaural responses were themselves too small to reach significance and which must therefore be considered less or not reliable. In fact, only three of all 48 analysed voxels [four voxels (left and right IC and AC) in each of 12 listeners] exhibited significant monaural responses and at the same time showed a binaural response that was larger than 50% of the summed monaural responses.

Discussion

In this study, we present a new paradigm which enables the investigation of binaural processing in the human brainstem in a spatially specific manner using fMRI. The BD contrast revealed a substantial binaural interaction in the IC, MGB and PAC. Interestingly, the BD was invariably negative in these regions. In fact, the binaural response was not only smaller than the sum of the monaural responses but was even smaller than the contralateral monaural response alone. This finding suggests that the observed binaural suppression reflects an active reduction of the underlying activity due to binaural stimulation, rather than just a passive saturation. A reduction in

activity may be caused by binaural inhibitory processes as, for instance, in EI-type neurones or by refractoriness, by which the earlier of the convergent binaural inputs to a monaurally excitable EE neurone makes the neurone unresponsive to the later input. Alternatively, a binaural reduction in activity may be caused by EE neurones whose binaural response is smaller than the monaural responses if the ITD of the binaural stimulus is outside the neurone's favourable range of ITDs (Joseph & Hyson, 1993). Recent physiological data suggest that this reduction is brought about by formerly unrecognized inhibitory inputs to EE neurones (Grothe, 2000, 2003), which have been proposed to play an important part in ITD processing (guinea pig: Brandt *et al.*, 2002; Grothe, 2003; McAlpine & Grothe, 2003). While saturation may effect binaural suppression in the absence of any actual reduction in activity (Fig. 4a), the binaural response would, in this case, be larger than the larger of the two monaural responses, which is the response to the contralateral monaural sound from the level of the IC upwards (Contra in Fig. 4a). The fact that the observed binaural response was actually smaller than the contralateral monaural response, particularly in the IC, suggests that binaural suppression involves either inhibition or refractoriness (Fig. 4b; for a similar argument see Ungan & Yagcioglu, 2002). The relative size of the BD was greatest in the IC and decreased slightly towards higher levels, suggesting that the binaural suppression in the MGB and PAC was simply relayed from the IC. The current results are consistent with those of Jäncke *et al.* (2002), who found that the superior temporal response to binaural consonant–vowel syllables and tones is smaller than the sum of the responses to the corresponding monaural sounds and, in some cases, even smaller than the response to the contralateral sound alone.

Combined near- and far-field recordings of the BD potential and lesion studies in the cat suggest that binaural suppression originates in the SOC (Wada & Starr, 1983; Melcher, 1996; Ungan & Yagcioglu, 2002). The fact that the size of the BD in the human brainstem AEPs is comparatively small has been interpreted as an indication that binaural suppression is generated by EI neurones in the lateral superior olive (see, e.g. Ungan *et al.*, 1997). The lateral superior olive in humans is much smaller than in animals with more extended high-frequency hearing, in which the EI mechanism has been physiologically established (Moore, 2000). Moreover, the existence of the medial nucleus of the trapezoid body, which is the main source of inhibitory input to SOC neurones in non-human mammals (Grothe, 2003), is still disputed in humans (Moore, 2000; Bazwinsky *et al.*, 2003). However, the size and extent of the BD response in the current data as well as in the cortical potentials and magnetic fields (Pantev *et al.*, 1986; Tiihonen *et al.*, 1989; McPherson & Starr, 1993) indicate that binaural suppression in humans is not just an unimportant relict of past high-frequency hearing but a fundamental characteristic of binaural integration in general. On the assumption that the observed binaural suppression is brought about by inhibitory processes in the SOC, the present data would thus suggest that a structure functionally and phylogenetically equivalent to the medial nucleus of the trapezoid body also exists in humans. In any case, however, the present data raise the question of where, if not in the medial nucleus of the trapezoid body, binaural suppression may originate in humans. The fact that the BD in the human brainstem AEPs is comparatively small is probably due to contributions from monaurally responsive neurones or neurones whose binaural responses are roughly equal to the sum of their monaural responses. Contributions from such neurones would not affect the size of the BD potential but they would increase the amplitude of the monaural AEPs to the sum of which the BD potential is referred.

Is the suppression exerted by the ipsilateral or the contralateral signal?

Physiological data indicate that the vast majority of EI-type neurones in and above the IC are excited by contralateral and inhibited by ipsilateral input (Imig & Adrián, 1977; Middlebrooks & Zook, 1983; Reser *et al.*, 2000; Tollin, 2003), suggesting that the binaural suppression observed in the present study reflects inhibition that the ipsilateral signal exerts on the contralateral signal. In contrast, accounts of the right ear advantage in dichotic listening (Tervaniemi & Hugdahl, 2003) are generally based on the assumption that the stronger contralateral signal suppresses the weaker ipsilateral signal before reaching the left-hemisphere speech system (Kimura, 1967). It is difficult to reconcile the notion of contralateral suppression with the ipsilateral inhibition effected by EI neurones in the IC and AC other than by assuming that the two processes are functionally unrelated and that any contralateral suppression possibly occurs above the level of the AC.

Recently, Fujiki *et al.* (2002) reported evidence for contralateral suppression within AC using the so-called frequency-tagging method and magnetencephalography (see also Kaneko *et al.*, 2003). However, the validity of their conclusions is challenged by the fact that a good part of the putatively 'binaural' suppression obtained with the frequency-tagging method may actually be an entirely monaural effect (Picton *et al.*, 1987; Lins & Picton, 1995; Draganova *et al.*, 2002). If binaural suppression was exerted mainly or exclusively by the contralateral signal, the net binaural response would be expected to be at least as large or larger than the contralateral monaural response, which is contrary to the current data and, indeed, also to previous magnetencephalography data obtained with the conventional BD paradigm (Reite *et al.*, 1981; Pantev *et al.*, 1986; Tiihonen *et al.*, 1989).

Absence of binaural facilitation

The absence of any evidence of facilitatory binaural interaction in the current data is surprising from the point of view of the prevalent theories of binaural processing (Colburn, 1996). According to the model of Jeffress (1949), which is still the basis of most of the current models of interaural temporal processing (Joris *et al.*, 1998; see, however, Fitzpatrick *et al.*, 2002), ITDs are processed by EE-type neurones that are tuned to narrow ranges of ITDs by virtue of a coincidence mechanism. This mechanism would be expected to produce strongly facilitated binaural responses at each neurone's best ITD, namely the ITD producing maximal discharge. The best ITD is assumed to vary parametrically across neurones to create a topographic map of ITD, with a concentration of best ITDs around the midline (0 μs) where ITD perception is most accurate (Durlach & Colburn, 1978). Midline sounds with a large proportion of low-frequency energy, like the diotic noise bursts used in the current experiment, would thus be expected to elicit a strongly facilitated response in Jeffress-type coincidence neurones and the complete absence of any facilitation in the current data calls the model into question. Many medial superior olive neurones actually behave like coincidence detectors, in that they are strongly sensitive to ITDs and exhibit facilitated binaural responses at their best ITD (Joris *et al.*, 1998). However, in small rodents, the majority of best ITDs in the medial superior olive and IC have been found to be concentrated around a mean of 200–300 μs, well away from the midline and outside the range of ITDs that these animals encounter in natural sounds (McAlpine *et al.*, 2001; Brandt *et al.*, 2002; McAlpine & Grothe, 2003). If these physiological results generalize

to humans, the absence of any facilitatory responses to the midline sounds used in the current experiment would be unsurprising. In that case, one may expect to observe facilitatory responses to strongly lateralized sounds with ITDs of several hundred microseconds.

Nonetheless, the absence of any evidence for binaural facilitation in the current data remains surprising in view of the fact that binaural sounds are perceived as about twice as loud as the corresponding monaural sounds (Hirsch, 1948) and the finding that activity in the PAC increases with increasing loudness (Hart *et al.*, 2002). Our observation that the binaural response was less than half as large as the sum of the monaural responses on the entire HG suggests that binaural loudness summation is represented other than by an increase in discharge rate in the PAC.

Hierarchical processing of binaural cues

Whereas the BD contrast revealed activation in the brainstem (IC), the thalamus (MGB) and the PAC on HG, activation to the motion contrast was largely confined to non-primary auditory fields in the PT and TPJ, posterior to HG. This suggests that the BD paradigm and the motion paradigm yield largely complementary measures of auditory spatial processing, which appear to be associated with different levels in the processing hierarchy. The stationary and moving binaural sounds produced similar activations up to the level of and including the PAC. In contrast, in the PT, the activation to all stationary sounds was greatly reduced relative to the lower levels, whereas the moving sounds still produced a sizeable response. The reduction of the responses to the stationary sounds may be due to the fact that non-primary auditory fields exhibit largely phasic responses to prolonged, perceptually unchanging auditory stimuli, whereas responses in and below the PAC are more tonic (Giraud *et al.*, 2000; Harms & Melcher, 2002; Seifritz *et al.*, 2002b). Phasic responses would be expected to produce a lesser activation than tonic responses in the blocked sparse imaging design used in the current experiment. The fact that the activation to the BD contrast extended onto the anterior part of the PT, partly overlapping the motion-related activation (see yellow highlight in Fig. 3a and b), suggests that the shape of the haemodynamic response to prolonged, unchanging sounds changes gradually across anatomical boundaries rather than abruptly. The current results suggest that the processing of motion conveyed by time-varying interaural cues (ITDs) starts in the PT and that motion sensitivity in the PT is established by adaptation to invariant sound features. The fact that motion sensitivity appears to emerge so late in the processing hierarchy suggests that auditory motion processing is based on the analysis of successive instantaneous binaural representations relayed from lower processing centres.

In summary, this study shows that the BD paradigm enables the measurement of brainstem binaural processing with fMRI. Comparing the BD and motion paradigms revealed a hierarchical organization of binaural processing in humans, with binaural integration starting below the IC and motion sensitivity emerging only above the level of the PAC, in the PT.

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Abbreviations

AC, auditory cortex; AEP, auditory evoked potential; BD, binaural difference; CN, cochlear nucleus; EE, excitatory–excitatory; EI, excitatory–inhibitory; fMRI, functional magnetic resonance imaging; HG, Heschl's gyrus; IC, inferior colliculus; ITD, interaural time difference; MGB, medial geniculate body; PAC, primary auditory cortex; PT, planum temporale; SOC, superior olivary complex; TPJ, temporo-parietal junction; TR, image repetition time.

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