

Representation of interaural time delay in the human auditory midbrain

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Interaural time difference (ITD) is a critical cue to sound-source localization. Traditional models assume that sounds leading at one ear, and perceived on that side, are processed in the opposite midbrain. Using functional magnetic resonance imaging we demonstrate that as the ITDs of sounds increase, midbrain activity can switch sides, even though perceived location remains on the same side. The data require a new model for human ITD processing.

The main cue used by humans to determine the horizontal position of low-frequency (<1,500 Hz) sound sources is the ITD. Owing to its finite travel time, sound can arrive at one ear slightly before arriving at the other, and sounds with ITDs of just a few tens of microseconds are perceived as originating away from the midline. For sounds of sufficient bandwidth (> ~300 Hz), human listeners always report the sound to be originating from the side at which the sound is leading^{1,2}.

ITD sensitivity is achieved by coincidence-detecting neurons in the superior olive, the earliest site of binaural convergence in the auditory pathway³. It has been proposed that these neurons are innervated by a series of delay lines, axons of differing path length from the two ears⁴. Different neurons are maximally excited by different interaural time delays, creating a topological map of preferred ITDs. The activity of these neurons can be approximated by the cross-correlation of the sound at each ear following spectral filtering by the cochlea³, and a cross-correlogram is thus a common way of portraying the neural representation of ITDs (Fig. 1a,b and refs. 5,6). The cross-correlogram plots the cross-correlation function of the sound at each ear for each frequency channel; the abscissa denotes the internal delay difference, τ , and the ordinate the frequency channel, f . This ' τ - f plane' can be read as a plot of the activation of a sheet of coincidence detector neurons (ovals in Fig. 1) with various axonal delay differences and best frequencies.

It has generally been assumed that although there exist neurons that code both short and long ITDs (refs. 6,7), there are fewer of them for long ITDs than there are for short ITDs. Current models incorporate this assumption with a 'centrality' weighting function⁶. The general form of these models is illustrated for 400-Hz-wide bands of noise centered at

500 Hz for ITDs of $-500 \mu\text{s}$ (Fig. 1a) and $-1,500 \mu\text{s}$ (Fig. 1b). Although $-1,500 \mu\text{s}$ lies beyond the range usually experienced by humans under natural listening conditions, a broadband sound with an ITD in this range is accurately perceived and presents an interesting test case for theories of sound localization. Because of the centrality weighting, the peaks of the cross-correlograms at $-1,500 \mu\text{s}$ produce less activation than do the peaks at positive values of τ that are closer to 0. To account for the correct localization of such long ITDs, current models propose a second processing level (gray curve on top of each panel), putatively residing in the inferior colliculus⁸, that gives weight to the vertical alignment of peaks across frequency channels (black arrow at $-1,500 \mu\text{s}$ in Fig. 1b, and ref. 1). This process has been referred to as "straightness weighting" (refs. 1,7) and produces the expected peak in brain activation opposite the side at which the sound is leading and perceived.

Recent physiological findings in small mammals, however, suggest that this sort of model may be implausible, even with the inclusion of straightness weighting. These findings suggest that the range of ITD detectors in the mammalian brain is tightly restricted⁹⁻¹¹, with a complete absence of neurons tuned to ITDs beyond approximately half a cycle of their best frequency. We refer to this restricted representation of ITDs as the π -limit (red curves in Fig. 1c,d). In essence, it constitutes a frequency-dependent weighting for centrality that is even sharper than previously assumed. One possible justification for the absence of detectors beyond the π -limit is that they are redundant; the periodicity and relative magnitudes of the peaks in the cross-correlation function beyond the π -limit are inherent in the center frequency and bandwidth of the auditory filters.

When ITD detectors are constrained to lie within the π -limit, the straightness weighting model no longer produces a peak at $-1,500 \mu\text{s}$, as the relevant detectors for that delay are no longer present (Fig. 1d). Further, with this restricted set of ITD detectors, the maximum activation is now on the same side as the lateralized sound image (gray curve at top). This reversal of lateralization presents a key signature of the π -limit and suggests that if the π -limit holds, new models are needed to account for sound localization at long ITDs.

To test for the π -limit in humans, we used functional magnetic resonance imaging (fMRI) optimized (Supplementary Methods online) to assess the activity of the inferior colliculus in response to binaural stimulation. The inferior colliculus is located in the midbrain and is also the earliest stage at which fMRI can reliably demonstrate binaural sensitivity in humans¹². We tested the presence of a π -limit by using 400-Hz bands of noise, centered at 500 Hz. ITDs corresponding to either one-quarter (500 μs) or three-quarters (1,500 μs) of the period of the center frequency (Supplementary Methods) were imposed on the ongoing waveform. Although human listeners reliably perceive the sound on the leading side for both these stimuli^{1,2,6,13-15}, a π -limit

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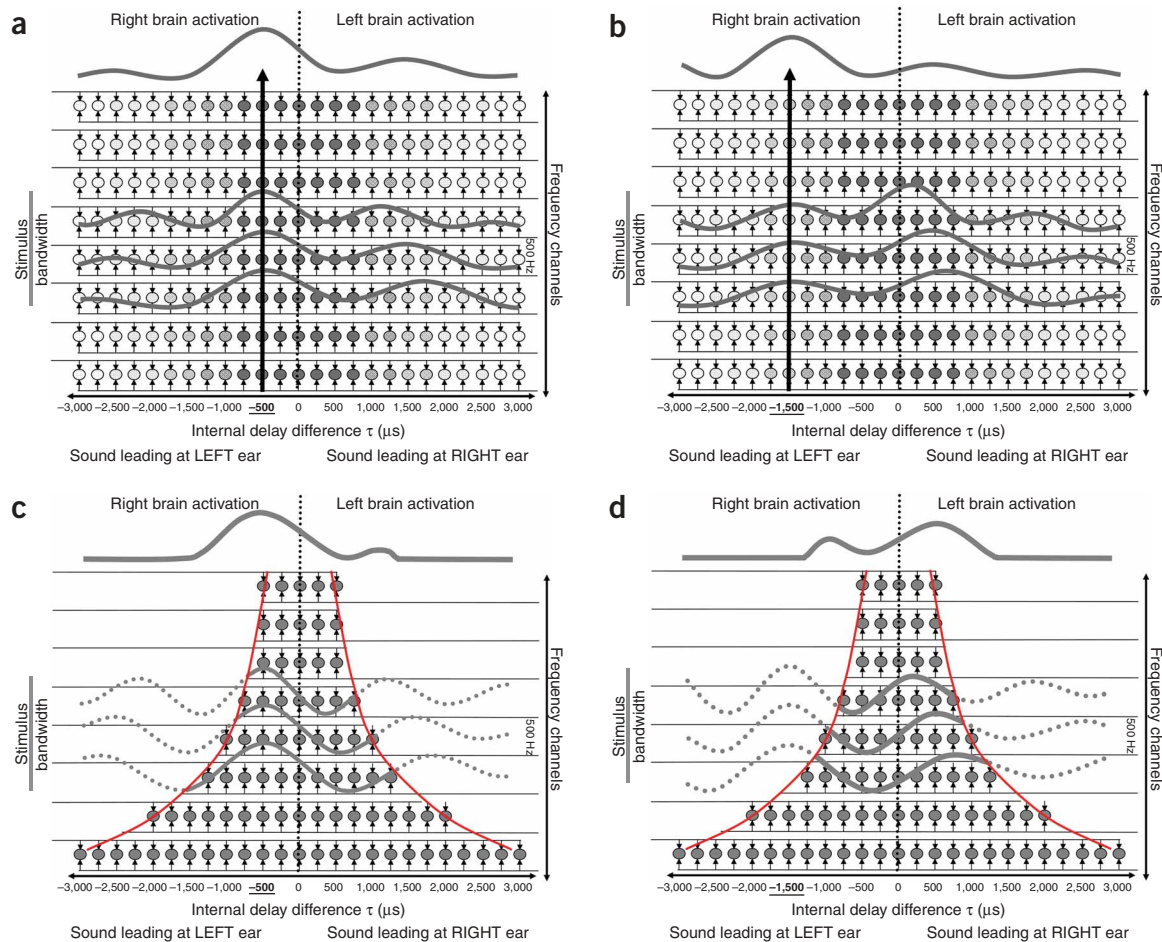


Figure 1 Cross-correlogram as a model of neural ITD representation. **(a,b)** Cross-correlogram including centrality and straightness weighting. **(c,d)** Cross-correlogram restricted to the π -limit. Gray lines, activation by 400-Hz band-pass stimuli centered at 500 Hz and ITDs of $-500 \mu\text{s}$ (**a,c**) and $-1,500 \mu\text{s}$ (**b,d**). Dashed parts of the cross-correlation functions indicate a lack of neural representation for ITD beyond the π -limit. Gray curves at top of panels, overall activation as a function of internal delay difference at a second level of processing. Note that the two ITD representations (**a,b** versus **c,d**) make the same prediction about the location of the peak activity for $-500 \mu\text{s}$ ITD (**a,c**) and opposing predictions for $-1,500 \mu\text{s}$ ITD (**b,d**). Details in text.

would cause the peak activation to occur on different sides for the two ITDs (**Fig. 1c,d**).

The experiment included five conditions with different ITDs ($-1,500, -500, 0, +500, +1,500$) and a silent baseline. Contrasting the sum of all noise conditions with activity in the silent baseline activated the inferior colliculus in all 14 subjects (**Supplementary Fig. 1** online). A group level (random effects) analysis of this contrast was used to functionally map both inferior colliculi ($P < 0.05$, family-wise error corrected; **Fig. 2a**). A second analysis (**Supplementary Methods**) examined activity within the inferior colliculi relative to the stimulus lateralization, to define activity that was on the same (ipsilateral) or opposite side (contralateral) to the percept (**Fig. 2b**). An ITD of $500 \mu\text{s}$ produced activity in the contralateral inferior colliculus (**Fig. 2b** and **Table 1**), as expected. For an ITD of $1,500 \mu\text{s}$, in contrast, the activity switched to the ipsilateral inferior colliculus (**Fig. 2b** and **Table 1**). This is in accordance with what would be predicted if a

π -limit were in effect and contrasts with the perception of such stimuli, which does not vary with ITD magnitude.

In addition to the change in the location of peak activity, the data also indicated less difference in activity between the sides for longer ITDs than for short ones (**Fig. 2c**). This is consistent with the fact that

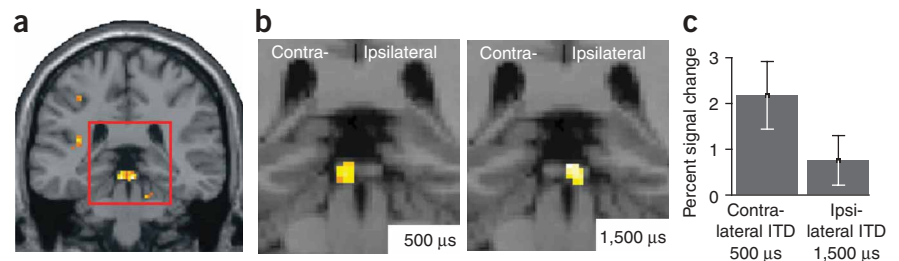


Figure 2 Representation of ITD in the inferior colliculus. **(a)** Coronal slice showing the mapping of the inferior colliculus for the group by contrasting the sum of all noise conditions with the silent baseline. **(b)** Magnified view of area marked by red square in **a**. Group statistical parametric maps for the contrasts between ipsi- and contralateral delays at different ITDs ($500 \mu\text{s}$ versus $1,500 \mu\text{s}$) within the functionally mapped inferior colliculus. Note that the contralateral inferior colliculus is shown on the left of the figure and ipsilateral inferior colliculus on the right, as in **Figure 1**. **(c)** Plots of percent signal change for the contrasts in **b**. Error bars represent 95% confidence interval of the mean.

Table 1 Effects of ITD at 500 and 1,500 μ s in right and left inferior colliculus (IC) for contra- and ipsilateral delays

ITD	IC	Contralateral		Ipsilateral	
		<i>T</i>	<i>P</i>	<i>T</i>	<i>P</i>
500 μ s	Right	6.28	0.00001	-6.28	1
	Left	5.74	0.00003	-5.74	1
1,500 μ s	Right	-2.3	1	2.3	0.02
	Left	-2.13	1	2.13	0.03

at long ITDs, equivalent to three-fourths of the period of the center frequency (1,500 μ s in the case of 500 Hz), only the smaller side-peaks of the cross-correlation functions reside within the π -limit (Fig. 1d).

These data show that the peak of activity in the human midbrain can switch from the contralateral to the ipsilateral side, relative to the leading ear, when the ITD is increased beyond the π -limit. Lateralization of the percept is thus not necessarily brought about by a lateralization at the neuronal level, at least at the level of the inferior colliculus. The basis for this fixed lateralization of the percept is, as of yet, unexplained. A new model of sound localization is required to relate the perception of lateralization to its neural instantiation.

Note: Supplementary information is available on the Nature Neuroscience website.

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AUTHOR CONTRIBUTIONS

K.v.K. contributed to brain imaging, data analysis and development and editing of the manuscript. S.K.T. contributed to brain imaging, data analysis and stimulus construction. A.D.-P. contributed to stimulus design and construction, and to initial brain imaging experiments. R.D. developed the fMRI sequence optimized for imaging the inferior colliculus. T.M. contributed to the development of the experimental hypothesis, stimulus design and development of the π -limit model. T.D.G. contributed to data analysis and to development and editing of the manuscript. D.M. contributed to the development of the experimental hypothesis, stimulus design, development of the π -limit model and development and editing of the manuscript.

COMPETING INTERESTS STATEMENT

The authors declare that they have no competing financial interests.

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