Review TRENDS in Neurosciences Vol.30 No.2

A matter of time: internal delays in binaural processing

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As an animal navigates its surroundings, the sounds reaching its two ears change in waveform similarity (interaural correlation) and in time of arrival (interaural time difference, ITD). Humans are exquisitely sensitive to these binaural cues, and it is generally agreed that this sensitivity involves coincidence detectors and internal delays that compensate for external acoustic delays (ITDs). Recent data show an unexpected relationship between the tuning of a neuron to frequency and to ITD, leading to several proposals for sources of internal delay and the neural coding of interaural temporal cues. We review the alternatives, and argue that an understanding of binaural mechanisms requires consideration of sensitivity not only to ITDs, but also to interaural correlation.

Introduction

Spatial hearing offers a unique window on temporal processing in the nervous system. In contrast to the receptor organs for vision and touch, the cochlea does not have an explicit representation of the spatial position of sound sources, because this organ performs frequency analysis rather than spatial analysis. The spatial position of a sound source is computed in the CNS from implicit information sent downstream by the cochlea. It has long been known that the computation of azimuth (horizontal position of a source) is predominantly based on temporal differences between the two ears, but the underlying mechanisms are currently a matter of much controversy.

Sound sources off the midsagittal plane travel different distances to the two ears and thereby generate interaural time delays (ITDs), both in the arrival time of the stimulus wavefront ('onset ITD') and throughout the stimulus ('ongoing ITD') (Figure 1d). In humans, ongoing ITDs of low frequencies are the main source of information used to determine horizontal localization of sound [1–3]. Even the largest ITDs, which occur for sound sources that face one ear, are tiny. Their extreme values (henceforth referred to as the 'ecological range') are ± 700 μs in humans and ± 400 μs in cats, but ITDs can be discriminated at values of 10–20 μs [4]. Considering that the duration of an action potential is ~50 times longer, this acuity is an intriguing biological feat.

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Available online 22 December 2006.

Neural sensitivity to ITDs was discovered in the 1960s [5,6] in the midbrain inferior colliculus and brainstem medial superior olive (MSO), which have binaural neurons whose average firing rate depends on ITD (Figure 1a). Each neuron is tuned to a 'best delay' (BD), at which its response is maximal. Neurons differ in their BD, and are maximally excited by sound sources at correspondingly different positions in space. A general finding across studies is a clear bias for tuning to the contralateral hemifield: BDs are mostly at 'positive' ITDs, defined as ITDs at which the ear that is contralateral to the neuron is the first to receive the sound. For example, a sound source directly in front of a cat maximally excites neurons on both sides the brain that have a BD of 0 μs, whereas a source placed to the extreme right will excite neurons on the left (i.e. contralateral) side of the brain that have BDs near 400 μs. For each intermediary horizontal position between extreme right and the midline, there are neurons on the left side that are maximally excited.

These physiological observations, in combination with psychophysical work and an influential qualitative model [7], led to a general framework that seemed congruent with general neurobiological principles and that is commonly referred to as 'the Jeffress model'. This model holds that populations of binaural neurons are tuned both to frequency and to ITD, and that there is a neural 'display' in which these neurons are arranged topographically in terms of the frequency by which they are maximally excited (best frequency, BF) and BD. Sound sources cause activity patterns on this BD–BF plane according to their spatial location and frequency characteristics.

In various incarnations, this general model has dominated the field [8] and is the basis of most models of binaural hearing, even though not all of its components are equally well established. However, new data have spawned alternative ideas, for which we here review the evidence. The existence of a BD–BF plane has been questioned, and there are several competing proposals for the physiological mechanisms that underlie the existence of BDs. Because these controversies mostly concern mammals, we do not cover the extensive work on binaural hearing in barn owls [9].

The Jeffress model and axonal delay lines

ITD sensitivity (Figure 1a) is found throughout the central auditory system, and there is evidence that the sensitivity

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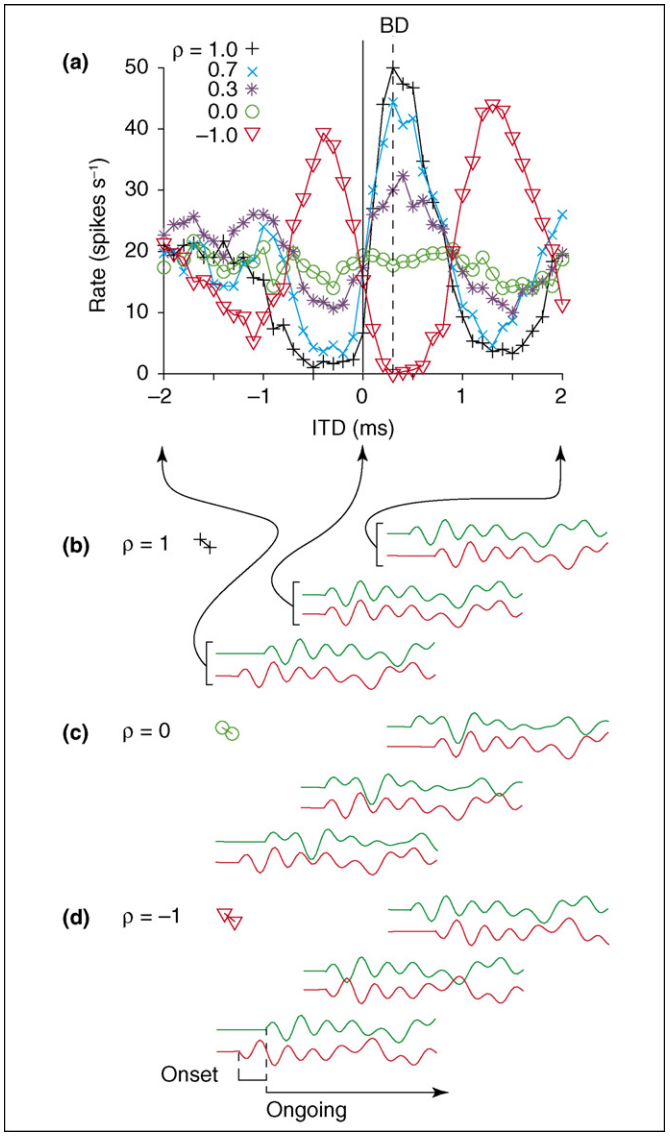

Figure 1. Sensitivity of an inferior colliculus (IC) neuron to interaural time differences (ITDs) and correlation (ρ). **(a)** Firing rate of inferior colliculus neuron was measured while broadband noise with an ITD that varied in steps of 100 μs was played through earphones. The black crosses show the rate–ITD function for identical stimuli at the two ears (ρ = 1), illustrated in panel **(b)** for the three indicated ITDs. The ITD consists of a transient-onset ITD and an ongoing ITD between corresponding parts of the waveforms at the two ears (red and green waveforms illustrate the stimulus waveforms as they would appear at the points in the left and right cochlea that are ultimately compared by the binaural neuron). Cochlear filtering induces a pseudoperiodicity in the waveforms, making the rate–ITD function also pseudoperiodic. The ITD that causes maximal firing is the best delay (BD) and is here at +0.3 ms (by convention, a positive ITD indicates that the stimulus leads at the ear contralateral to the recording site, as would occur for a sound source in the contralateral acoustic hemifield). The other curves in panel (a) are obtained in response to noise that has decreasing similarity between the ears, indicated by the interaural correlation ρ. The response to uncorrelated noise (ρ = 0; green circles) is flat, indicating no sensitivity to ITD. The response to anti-correlated noise (ρ = −1, obtained by inverting the waveform to one ear; red triangles), is out of phase with that to correlated noise. The waveforms for ρ = 0 and ρ = −1 are illustrated in panels **(c)** and **(d)**, respectively. Note that at ITD = 0 the firing rate is little affected by changes in correlation, whereas at the BD there is maximal sensitivity to ρ. The best frequency (BF) of the cell was 430 Hz. Modified, with permission, from Ref. [65].

sharpens between the superior olivary complex and the auditory cortex [10,11]. How does ITD-sensitivity arise, and why is the BD at a positive ITD for most neurons? A low-frequency sound source off the midline (Figure 2a) induces a temporal spike pattern that encodes the stimulus waveform, first in the near ear, followed by a similar pattern in the far ear with a delay that depends upon the spatial location of the sound and the head size. According to the Jeffress model, coincidence detectors receive convergent input from the two sides of the head, and discharge maximally when the external delay (the ITD) is exactly compensated by an internal delay that arises as a consequence of differences in the lengths of axons from the two sides to the detector. If, as in Figure 2, this axonal delay is longer for the contralateral afferent, the binaural neuron discharges maximally when the stimulus is closer to the contralateral ear.

There is much evidence that this scheme applies to a brainstem circuit that converges on the MSO, which receives excitatory input from spherical bushy cells in the cochlear nucleus of both sides [12]. Unfortunately, it is difficult to record activity in the MSO, probably due to low-voltage-activated K^+ channels, which electrically isolate soma and dendrites from the axon [13]. Instead, most binaural studies are conducted in the inferior colliculus, which receives a direct input from the ipsilateral MSO. Nevertheless, some ingredients of Jeffress' model are well documented. Phase-locking of activity in the auditory periphery has been documented amply since the earliest single-cell recordings [14,15] and is enhanced in bushy cells relative to the auditory nerve [16,17]. That MSO neurons operate on these inputs as coincidence detectors was elegantly demonstrated for tones [6] and other stimuli [18]. The presence of internal delays is also universally accepted. BDs in the MSO are predominantly at positive ITDs [18–20], so that MSO neurons respond maximally to sound sources in the hemifield on the other side (Figure 2a). This indicates that it takes longer for the afferents from that side to conduct the signal to the MSO neuron than for afferents from the ear on the same side as the MSO neuron. This seems logical because the MSO is not at the midline and, therefore, its contralateral inputs traverse a greater distance than its ipsilateral inputs (Figure 2a).

The recent controversies concern the origin of internal delays and the nature of ITD coding. Jeffress [7] proposed that internal delays are derived from axonal 'delay lines' (Figure 3b) – collateral branches that form a pattern graded in length to an array of coincidence detectors. As a result, the internal delay to these detectors differs, and the ITD in the acoustic signal is encoded as a spatial gradient of neural activity in the array. The essence of this model is a time-to-place conversion: horizontal sound position is encoded by the activity profile of an array of binaural cells that are tuned to different ITDs by virtue of axonal delay lines.

What is the evidence for delay lines and for a topographical map of BDs? Surprisingly, these questions have received little experimental attention. In two anatomical studies, the axonal projections of bushy-cell afferents to the MSO were reconstructed [21,22]. The findings were remarkably consistent and showed a delay pattern for the contralateral afferents, with a shorter path to the rostral MSO than to its caudal pole. The pattern of ipsilateral afferents was less clear-cut and indicated at most a weak (and opposite) spatial gradient. Thus, two independent studies provide anatomical evidence for axonal delay lines in the contralateral afferents. Although Jeffress proposed

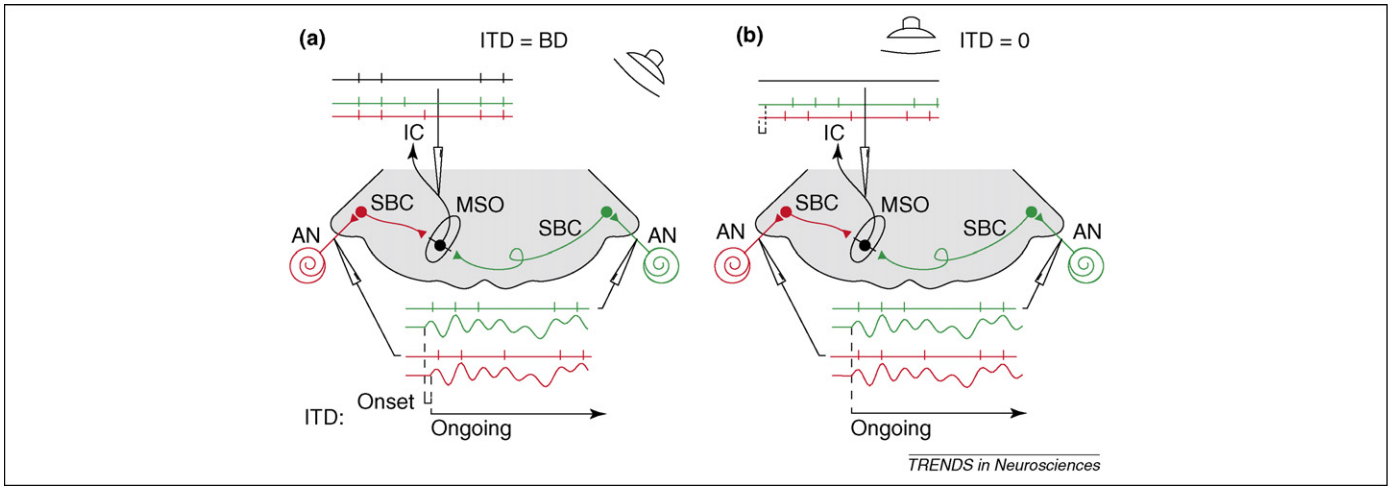

Figure 2. Common ground: components in the binaural circuit that are generally accepted. **(a)** Sound from a source to the right of the midline reaches the near ear first and the far ear after a delay that depends on speaker position and head size. The sound waveform is encoded by the temporal spike pattern in the auditory nerve (AN; spike trains and waveforms are shown for the left and right auditory nerves, in red and green, respectively, beneath a schematic coronal section of the cat auditory brainstem). The spike trains are transmitted to spherical bushy cells (SBC) of the cochlear nucleus, and reach coincidence detectors in the medial superior olive (MSO) with a delay. The internal delay is the difference in the right and left side delays, which are accrued between the eardrum and the target MSO neuron. Its exact source is controversial (note that the 'loop' in the ipsilateral afferents is only symbolic). If the internal delay exactly cancels the external delay (the ITD), the spike trains (in red and green above the brainstem section) arrive in temporal register, resulting in many coincident spikes and a high output rate of the MSO neuron (black spike train at the top). The ITD at which this occurs is the best delay (BD). **(b)** For the same neuron, a sound source at the midline generates a poor response. There is no external delay (ITD = 0), and the stimuli are coincident at the two ears. However, the afferent inputs to MSO are not coincident, owing to the internal delay. This results in fewer spikes from the binaural MSO neuron.

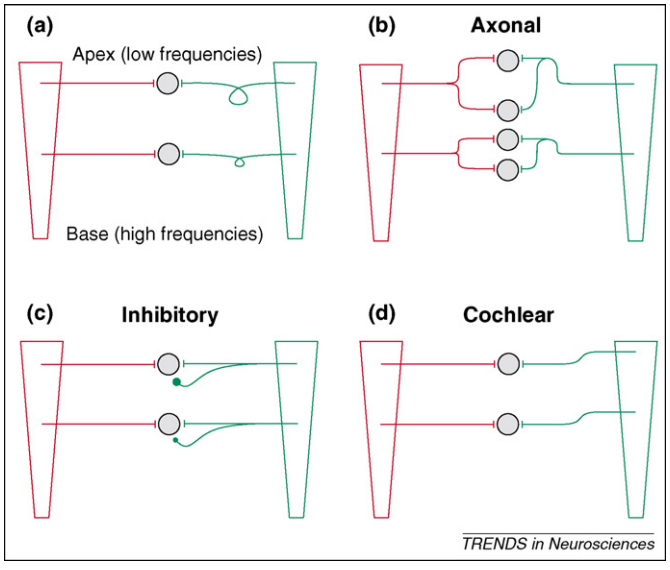

Figure 3. Different proposals for the origin of internal delays. **(a)** The empirical findings show that internal delays (symbolized by loops) increase in size with decreasing BF. Trapeziums represent the uncoiled cochlear basilar membrane, with the apex at the top and base at the bottom. Medial superior olive (MSO) neurons (grey circles) are shown receiving input from both ears (details of synaptic stages and laterality have been omitted, for simplicity) with a longer delay on the right than on the left. This left–right difference generates an internal delay. The internal delays are observed to be larger for MSO neurons that receive input from the more apical (lower frequency) part of the cochlea, symbolized by the larger size of its 'loop'. **(b)** Axonal delays invoked by the Jeffress model. Each pair of afferents supplies an array of neurons that act as coincidence detectors, here symbolized by only two neurons per pair. The length of the axonal paths to the top neuron in the pair is equal for the two sides; thus, this neuron has zero internal delay and its best delay (BD) = 0 ms. The neuron at the bottom of each pair has non-zero internal delay because of the longer pathlength on the right. **(c)** Inhibitory delays. Excitatory inputs from the right ear are preceded by inhibitory inputs from the same side. **(d)** Cochlear delays. Inputs from the right ear are derived from a more apical position of the basilar membrane than inputs from the left ear. This cochlear disparity introduces delays by virtue of the slowness of the traveling wave on the basilar membrane, which starts at the base and moves towards the apex.

that there are delay lines on both sides, their presence on one side is sufficient to generate a spatial map of BDs, even if the afferents on the other side show no length gradient (Figure 3b). The only physiological study that looked for a spatial gradient of BDs for single MSO neurons showed a positive correlation between BD and rostrocaudal position in the MSO [18], in that BDs were small at the rostral pole and increased more caudally. Importantly, the anatomical and physiological data are consistent at a qualitative level: the axon-length differences and estimated axonal conduction times are compatible with the sign and gradient of BDs present in the MSO. Nonetheless, these studies are not definitive. The size of the estimated axonal delays seems insufficient to account for the largest BDs encountered (~1 ms), and the relationship between anatomical branching pattern and physiology is inferential. As regards the map, the rostrocaudal gradient of BDs showed considerable scatter, and a limited multiunit study concluded that, if a rostrocaudal ITD map is present in the MSO, it is coarse at best [23].

In summary, the available evidence largely supports Jeffress' model. But evidence is weakest for its main feature, the topographic arrangement of BDs.

Distribution of best delays

A bias of BDs to positive ITDs (i.e. tuning to contralateral space) has been a consistent finding in many species and at many anatomical levels. In the cat, the range of BDs is largely restricted to ITDs within the ecological range (0–400 μs, with the full range of ± 400 μs subserved by having a left and right MSO) [18,24]. Surprisingly, the overall distribution of BDs in guinea pigs is similar to that of cats, even though their ecological range is much smaller because of head size [25]. Even more surprisingly, studies in guinea pigs revealed a relationship between BD and BF [26,27], which was confirmed in cats [28,29]. Instead of having the

same range of internal delays at all frequencies, as commonly assumed in the Jeffress model (Figure 4a, rectangular yellow patch), the distribution observed shows a wide range of internal delays at low BFs and a small range at high BFs (Figure 4b, tapering yellow patch).

The relationship between BD and BF was not predicted by the Jeffress model, but does it contradict it? Again, we need to distinguish the central tenet of that model (a spatial map of BDs) from its underlying mechanisms. Do the recent data contradict the mechanism of axonal delay lines? The BD–BF relationship is easily accommodated by postulating longer delay lines at progressively lower BFs (Figure 3b). Being an *ad hoc* assumption, this is not appealing but it is a testable possibility. There is, however, a deeper problem. Intriguingly, the tapering border of the range of BDs approximates the value $(2BF)^{-1}$, the 'π boundary' indicated by the hyperbolas in Figure 4b. What this means in terms of responses is illustrated with the red curves. Rate–ITD functions have multiple peaks separated by BF^{-1} – that is, the period corresponding to BF. For neurons at the π boundary (Figure 4b, red dots), the main peak is exactly half a period away from 0 ITD. By contrast, if the rectangular distribution of Figure 4a were present, high-BF neurons would show responses with a smaller side-peak closest to 0 ITD ('slipped cycle' in Figure 4a), but this is rarely observed. Because the oscillatory shape of rate–ITD functions reflects the frequency selectivity of the cochlea, somehow the source of internal delays seems to 'know' the frequency or waveform conveyed by the afferent channel and to restrict the range of delays so that slipped cycles do not occur. There is nothing inherent in axonal delays that explains the π boundary.

The recent data do not directly address the existence of a spatial map, but obviously such a map requires the availability of a range of BDs at any given BF. This requirement is contradicted by descriptions [30,31] of the BD distribution as narrow, scattered around $(8BF)^{-1}$. However, these descriptions do not capture the actual data. In cats, BDs occur throughout (and beyond) the ecological range of ITDs at all BFs, except above ~1.5 kHz (Figure 4b), where the fine-structure of the temporal waveform no longer determines ITD sensitivity [32]. Similarly, guinea pigs show a

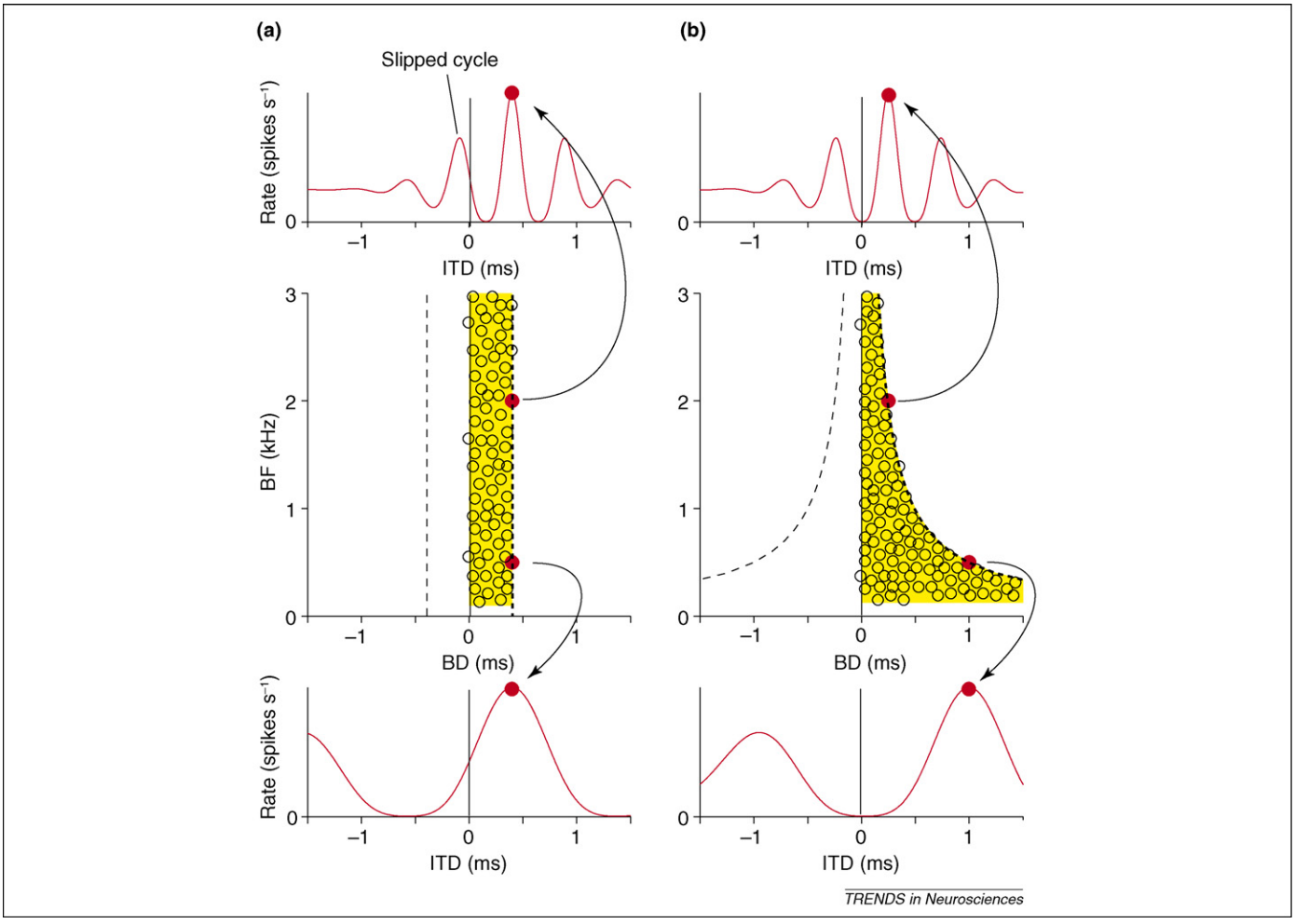

Figure 4. Schematic distributions of best delays (BDs), as predicted by the Jeffress model **(a)** and as observed experimentally **(b)**. The yellow patches indicate the range of BDs at different best frequencies (BFs) for one side of the brain. Broken lines in (a) indicate the maximal ecological range for the cat (±400 μs); the distance between the broken lines in (b) (the π boundary) gives the width of the period at BF (e.g. 1 ms at 1 kHz). Circles symbolize individual neurons. Examples of rate–ITD functions for two neurons with BDs at the upper edge of the distributions (red dots) are shown above and below the main distributions, for best frequencies of 0.5 kHz and 2.0 kHz. The Jeffress model does not predict a dependence of BDs on BF. With the rectangular distribution of BDs depicted, 'slipped cycles' would occur in neurons with BF higher than ~1.5 kHz, so that the peak closest to ITD = 0 would be a secondary peak rather than the largest peak (red curve, top panel). The distribution actually observed is wide at low BFs and narrow at high BFs. The BDs are largely within the π boundary, so that the main peak is at most half a period removed from ITD = 0.

large spread of BDs covering the ecological range [26], except possibly at very low BFs (<300 Hz) [27]. The BD–BF distribution in rabbits is not known, but for any given low-frequency stimulus, rate–ITD curves span a large range of BDs [33]. Thus, the distribution of BDs in itself does not contradict (nor does it prove) the existence of a topographic map. The only exception reported is for the MSO of the gerbil [20], which shows a radically different distribution (be it for a small sample of 16 neurons), with no BDs inside the ecological range < 800 Hz.

A complete account of internal delay would explain the decrease in both the mean and the spread of BD with increasing BF, in addition to the boundaries of the BD–BF distribution. The recently reported distributions do not invalidate Jeffress' model but make it seem incomplete. It offers no rationale for the π boundary and the large number of neurons tuned to ITDs that the animal will not naturally encounter, particularly in small-headed animals [26]. It is possible that axonal delay lines are longer at low than at high BFs, but this has not been studied.

The inhibitory model

It is well-documented that inhibition can underlie or shape ITD sensitivity [34–43]. The MSO also receives bilateral inhibition [44], which is tightly phase-locked for the contralateral ear [39,45]. Brand *et al.* [20] blocked inhibition of both sides *in vivo*, by iontophoretic application of strychnine. This gave an increase in response rate and a shift of the BD to 0 ms (Box 1). From these observations, Brand *et al.* concluded that precise inhibition is essential for ITD coding and that internal delays are not present in the excitatory inputs; rather, they are generated by inhibitory input from the contralateral ear, which precedes the excitatory input from that side and causes an effective delay in the excitatory response.

Unfortunately, the published results [20] do not support these conclusions, at least not for ongoing ITDs. For the one neuron individually reported, strychnine time-shifted the response at the BD but not at the secondary peaks. This indicates that inhibition affects onset ITDs rather than ongoing ITDs (Box 1). Whether this is also the case for the four other neurons studied cannot be evaluated from the published data. Aside from the lack of experimental support, it is also doubtful that the inhibitory mechanism could in principle explain the BD–BF distribution. In a computational model of a neuron with BF of 500 Hz [20], the leading inhibition shifted BF by ~200 μs for different tonal frequencies, whereas the actual range of BDs at 500 Hz is ~0.5 ms in guinea pigs and ~1 ms in cats. Moreover, the inhibitory parameters of this model were criticized as being unphysiologically fast and precise [46–48]; use of more physiological parameters results in delays <200 μs [46]. Physiological data point in the same direction. An appealing (but understudied) model for testing the effect of inhibition on timing directly is the other main binaural nucleus in the superior olivary complex: the lateral superior olive (LSO). Its main sources of excitatory and inhibitory input are identical to the MSO, but they are segregated so that the excitatory input is derived from the ipsilateral and the inhibitory input from the contralateral ear. Therefore, the timing and strength of inhibition can be experimentally varied independently of the excitatory input. *In vivo* data indicate that the response to the excitatory ear can indeed be delayed by the inhibitory ear [38], but only by a few hundred microseconds. Leading inhibition not only causes a delay, but also suppresses the lagging excitatory postsynaptic potential.

A variant on the inhibitory model, which does not require unrealistically fast and precise inhibition, is asymmetric placement of the axon [46]. MSO cells have a striking bipolar dendritic morphology, which is thought to be important for the process of coincidence detection [49]. It has been observed anatomically that the axon sometimes originates not from the soma but from the dendrite that receives the ipsilateral inputs [48]. Zhou *et al.* [46] propose that interplay of somatic Na^+ channels with glycine-mediated inputs enables dynamic modulation of internal delay. Again, the range of delays obtained is too small and the required anatomical asymmetries are too infrequent to make this a viable model for the experimentally observed range of BDs. However, as stressed by Zhou *et al.*, the mechanism might provide a means to fine-tune ITD sensitivity over a limited range.

In summary, physiological and computational studies do not support the inhibitory delay mechanism proposed by Brand *et al.* Moreover, it has not been specified how this mechanism would explain any of the three features of the BD–BF distribution (decrease in average BD and spread of BD with BF, and presence of the π boundary).

Cochlear disparity

Sound vibrations of the eardrum and middle-ear generate a vibration pattern of the cochlear basilar membrane in the shape of a wave that travels from cochlear base to apex. This traveling wave generates delays, so that low-frequency (apical) nerve fibers are activated later than high-frequency (basal) fibers. If binaural neurons receive a perfectly symmetrical tonotopic innervation, these cochlear delays are inconsequential. Schroeder [50] first proposed that asymmetries in frequency tuning of ipsilateral and contralateral inputs generate internal delays and shift the BD of a binaural neuron. Modeling studies [51,52] support this idea and suggest that relatively small cochlear disparities cause appreciable delays. Moreover, there is indirect evidence for mismatches in frequency tuning in the cat inferior colliculus [24], although not in the barn owl [53]. A cross-correlation analysis of auditory nerve fibers showed that BF asymmetries generate internal delays with the same frequency-dependent pattern observed in the inferior colliculus [54]. At low BFs, a small mismatch causes a large delay in spike times between fibers, whereas the same mismatch (in terms of cochlear distance) at higher BFs causes a smaller delay. Although these data suggest that cochlear disparities are important or even crucial, it remains to be tested with binaural recordings whether such disparities are actually present.

The attraction of this model is that it can account for all features of the BD–BF distribution: the decrease in both average value and spread of BD with BF, and presence of the π boundary. Also, it suggests a simple basis for the similar BD distribution in mammals that have different head sizes: perhaps an unattainable precision in wiring is required to match exactly the frequency tuning of inputs to

Box 1. Does inhibition contribute to internal delay?

Sensitivity to ongoing and/or onset interaural time differences (ITDs)
The ITD curve of a binaural neuron that is purely sensitive to *ongoing* ITDs of tones (Figure Ia) is perfectly periodic at the frequency of the stimulus: it lacks the prominent central peak seen in responses to broadband stimuli (compare with Figure 1 of the main text). This is expected because the cells are sensitive to the interaural phase difference that repeats itself at the stimulus frequency – that is, the interaural phase is the same at ITD of 0 and at ± 1 cycle, as illustrated with the partial stimulus waveforms at the bottom of Figure I. Note that actual stimuli contain many more stimulus cycles than shown here.

A neuron that has pure onset-ITD sensitivity (Figure Ib) responds to only a restricted range of ITDs, at which the onset between the waveforms is within certain limits. Such sensitivity would be obtained if the inputs to a coincidence detector were of the 'onset' variety, for example with only a transient response to sustained tones. Neurons that have combined sensitivity (Figure Ic) show a mixture of the two forms of ITD-sensitivity. These three examples (Figure Ia–c) are drawn with an internal delay that favors the contralateral ear.

The role of inhibition
If a neuron receives a mixture of excitatory and inhibitory inputs, their relative strength and timing can affect not only the strength but also the timing of the resulting response (Figure Id). For example, the response to a suprathreshold excitatory postsynaptic potential (EPSP) might be delayed if it is preceded by an inhibitory postsynaptic potential (IPSP). Brand *et al.* [20] measured the ITD sensitivity of five medial superior olive (MSO) neurons while blocking inhibition, and found an average shift of the central peak of the rate–ITD functions to 0 μs (arrow in Figure Ie). They propose that EPSPs reach binaural neurons without internal delay – that is, with the same latency for ipsilateral and contralateral inputs – and that leading inhibition from the contralateral ear is the basis of internal delay. Two main features of the response shown by Brand *et al.* [20] indicate that it is shaped by onset ITDs rather than ongoing ITDs. First, the response displayed a large central peak and smaller peaks on either side, indicating a combined sensitivity to both onset and ongoing ITDs (as in Figure Ic). Second, if internal delay is due to inhibition, its removal should cause a shift of the entire curve, including the secondary peaks (as indicated by the arrows in Figure If), rather than the observed shift of only the central peak (Figure 1e).

Inhibition might thus have a role in the coding of onset ITDs, but is not relevant for the internal delays that affect ongoing ITDs. Onset ITDs do not have a prominent role in the localization of low-frequency sounds [3]. Whether inhibition has any role in the latter process thus remains unclear.

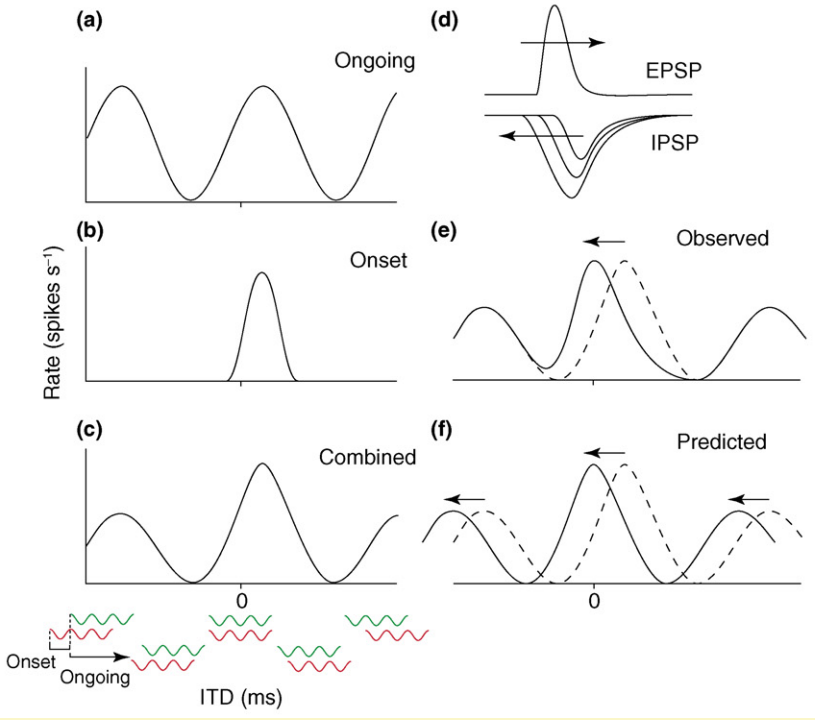

Figure I. Sensitivity to ongoing and/or onset ITDs and the role of inhibition. **(a)** ITD curve of a binaural neuron that is purely sensitive to ongoing ITDs of tones. **(b)** A neuron that has pure onset-ITD sensitivity. **(c)** A neuron that has combined sensitivity. **(d)** Increasing the strength and lead of an IPSP (left arrow) can delay the timing of an EPSP (right arrow). **(e)** ITD sensitivity of an MSO neuron before blocking of inhibition (broken line) and after blocking inhibition (solid line), as observed by Brand *et al.* [20] **(f)** ITD sensitivity of MSO neurons as would be predicted if the internal delay was due to inhibition. Part (d) modified, with permission, from Refs [34,38].

binaural neurons. Limits on this precision (e.g. in the formation of precise connections during development) might be similar across mammals, resulting in similar BD–BF distributions.

The main drawback of the cochlear disparity hypothesis is the requirement for a systematic tonotopic offset. Random wiring errors generate a BD–BF pattern that is symmetrical around the delay axis (compare the two hyperboles in Figure 4). The asymmetrical distribution actually observed in the inferior colliculus requires an additional systematic tonotopic offset between the inputs, so that the ipsilateral input is systematically derived from a more basal cochlear location (and thus higher BF) than the contralateral input (Figure 3d). Alternatively, the average BD–BF trend might be due to another mechanism (e.g. axonal delay lines), whereas the decrease in spread of BDs with increasing BF and the π boundary reflect cochlear disparities.

Localization versus detection

In the debate on internal delays, teleological arguments are often used. Such arguments are difficult to put to

experimental test but are important because they touch on the nature of ITD coding. The existence of large BDs in small-headed animals led to the 'two-channel' proposal [26] that horizontal sound position is encoded by the overall activity of one side of the brain relative to the other. In this scheme, BDs are positioned such that the steeply sloping part of the ITD-tuning function is within the physiological range. At low BFs, this requires BDs outside the physiological range. Changes in ITD then give rise to monotonic changes in firing rate, which are opposite for the right and left MSO. Comparison of the activation of the two sides gives a code of lateral position independent of other stimulus variables (e.g. stimulus intensity).

This model substitutes the vector coding inherent in the Jeffress model with a scalar code [55]. This is appealing for several reasons. Scalar coding seems to apply to interaural level differences (ILDs, the other main binaural cue), although this issue is not settled [56]. More importantly, as has been emphasized in various systems, the slopes of tuning functions rather than their peaks are important for discrimination of the stimulus variable to which tuning is present, because they represent the stimulus range that gives large changes in firing rate [55]. A theoretical study [30] on coding of ITDs in experimental mammals found narrow BD distributions to be the optimal strategy at low BFs, with two distinct and opposing subpopulations tuned to BDs outside the physiological range. This 'optimum coding model' thus supports the two-channel proposal.

A drawback of the two-channel model is the need for integration across hemispheres, for which lesion studies offer little support: transections of the commissure of the inferior colliculus or of the corpus callosum have little effect on localization performance in cats [57] or humans [58] and unilateral lesions of the inferior colliculus or auditory cortex produce deficits in localization in the contralateral sound field [59–61]. A scalar coding model that would not require hemispheric comparison would be more plausible. Perhaps a more serious concern is that the BD distribution can be characterized as 'scalar' only by ignoring much diversity in the experimentally observed BD distributions. With the exception of the gerbil MSO [20], these distributions show a spread in the position of rate–ITD functions (Figure 4b) that is not captured by the optimal coding model [30]. In fact, for the cat, the distribution observed is nearly opposite of that predicted by this model: at >1500 Hz, the range of BDs observed becomes restricted relative to the ecological range, to a 'subpopulation' tuned near 0 ms, whereas at lower BFs all BDs occur (by contrast, the optimum coding model predicts restricted subpopulations at <1500 Hz and a homogenous distribution above).

The most serious problem with the aforementioned proposals, and a probable reason why the experimental data deviate from the model predictions, is that the binaural system is crucial not only for sound localization but also for spatial hearing in general (e.g. for detection of signals in a noisy environment). In real sound fields, that have reflections and multiple sound sources, the waveforms at the two ears differ not only in their time of arrival (ITD) but also in their similarity, measured by the interaural correlation (ρ). We experience this in concert halls, where decorrelation leads to the desirable perceptual quality of 'spaciousness' [62]. Human sensitivity to interaural correlation is extremely acute ($\Delta\rho$ thresholds of $\sim$0.006 [63,64]), enabling us in noisy and reverberant environments to hear signals that are very weak – indeed so weak that they are not detectable with only one ear [63,64]. Binaural neurons are sensitive to changes in ρ [65], particularly at the peak of the noise-delay function and not at the steep slope (near 0 ITD in Figure 1a). By positing that restricted channels have their steepest slopes at 0 ITD, the two-channel model is rendered insensitive to decorrelation at that ITD. The delay requirements for optimal detection of changes in ITD and correlation are orthogonal to each other: for the ITD at which neurons are most sensitive to changes in ITD, they are poorly sensitive to changes in correlation, and vice versa [65–69]. In humans, detection and ITD discrimination both have their lowest thresholds at small ITDs and increase with increasing ITD [70], which is inconsistent with the two-channel model.

Concluding remarks: the quest for internal delays

The nature of internal delays and coding of ITDs are still uncertain, and the debate about them touches on many key neurobiological issues. None of the current proposals for the source of internal delay can satisfactorily explain the relationship between BD and BF, which has now been described in several mammals. The multitude of alternatives reflects the facts that extremely small binaural temporal differences can be detected behaviorally and that many processes that have comparatively slow time courses intervene between acoustic stimulation and the spike output of binaural neurons.

Many observations support the Jeffress model, but it clearly needs amendment to account for all data. The key prediction of Jeffress' model – a topographic map of BDs – has not been experimentally addressed by any of the recent studies. The main question regarding axonal delay lines is not whether they exist but, rather, whether they are sufficient to account for the range and pattern of observed BDs. Cochlear disparities are an attractive possible source of internal delays, but their relative importance is unclear and might be minor. Frequency tuning of binaural neurons should be compared for ipsilateral and contralateral stimulation and its role in binaural sensitivity assessed. The role of inhibition in ITD processing remains enigmatic: a contribution to internal delay in ongoing ITDs is currently a theoretical possibility that has little experimental support. The effect of blocking inhibition to the MSO on sensitivity to ongoing ITDs should be examined. Finally, it is important to study the system not only as a processor of static ITDs but also to reflect on its performance in natural environments, including multiple sound sources and reflections. Fortunately, these questions are all within experimental reach, so that future studies can sort out which mechanism, or mixture of mechanisms, underpin the remarkable binaural performance.

Acknowledgements

We thank the anonymous reviewers and the following readers for their comments: S. Kuwada, E. Monzack, M. McLaughlin, J. Ruhland

and D. Tollin. P.X.J. is supported by the Fund for Scientific Research – Flanders (G.0392.05 and G.0633.07), and Research Fund K.U. Leuven (OT/01/42 and OT/05/57). T.C.T.Y. is supported by NIH grants DC02840 and DC07177.

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