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Detecting interaural time differences and remodeling their representation

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Interaural time differences (ITDs) represent an important cue in sound localization and auditory scene analysis. To assess this cue the auditory system internally delays binaural inputs to compensate for the outer delay, before neurons in the brainstem detect the coincident arrival of the inputs from the two ears. Different origins of internal delays have been controversially discussed and have given rise to conflicting interpretations of the ITD representation ensuing from coincidence detection. Yet, recent findings indicate that ITD representations undergo substantial transformations or remodeling after the detection step. Here we treat the detection step separately from remodeling, and explain why a similar representation of ITD across species may exist in the forebrain despite differences in detection and representation in the midbrain.

Introduction

In everyday life humans and animals effortlessly localize sound sources with their ears. They can do this much more precisely with two ears than with one [1]. This is strongly experienced by people having unilateral hearing loss [2]. It is currently a challenge to develop binaural cochlear implants that improve the user's sound-localization capabilities and sound perception [3–5]. To do so, it is necessary to understand the mechanisms underlying the representation of sound-localization information in healthy brains. In this review we discuss advances in one sound-localization cue, the ITD (see Glossary), which has received increased interest recently due to new but still controversial findings of its representation in the brain.

ITDs arise from path-length differences between the sound source and the two ears, and correlate with azimuth, the angle between a sound source and the medial plane. The physiological ITD range (gerbil, ± 120 µs [6]; barn owl, ± 250 µs [7]; human, ± 600 µs [1]) depends on the head size of the animal and the morphology of aural appendages such as the ear flaps in humans or the ruff of the barn owl. After the signal reaches the ear the temporal relationships at the ear drum are conserved throughout monaural processing and lead to a step of binaural interaction, in which tuning to and a representation of ITD emerges in the brainstem. Further processing steps then follow along the auditory processing pathways.

Current research tries to identify the mechanisms underlying the binaural interaction, to characterize subsequent processing, and to find out how the representation of ITD may interact with higher brain functions and drive motor networks.

An influential theory detailing how ITD might be computed in the brain was proposed by Jeffress in 1948 [8]

Glossary

Characteristic delay (CD) and characteristic phase (CP): parameters that describe the ITD tuning across different frequencies in a neuron. The CD reveals the frequency-independent component of tuning to ITD whereas the CP describes the frequency-dependent component. CD and CP represent slope and offset, respectively, of the linear relation between preferred interaural phase difference (IPD) and stimulus frequency, and thus are either both defined or both undefined, if the relation is nonlinear. Although they are always interlinked, we refer to pure CD or 'time delay' if the contribution of the CP is zero, and to pure CP or 'phase delay' if the contribution of the CD is zero (see Box 1).

Coincidence detector: a neuron highly sensitive to the timing of its synaptic inputs: the probability of generating a spike rises with the synchronicity of the inputs. Here, the term designates the auditory neurons that compare well-timed synaptic inputs from the two ears forming the site of binaural interaction where tuning to ITD emerges (see Box 2).

Interaural phase difference (IPD): the phase equivalent of the ITD; in other words, the product of ITD and stimulus frequency (f): IPD = ITD*f.

Interaural time difference (ITD): difference in traveling times of sound waves to the two ears of a listener. ITDs change as a function of the angle between the sound source and the midsagittal plane of the head.

ITD detection: in this article this term is defined as the earliest step in binaural auditory processing that results in neural responses sensitive to changes in ITD (Figures 1 and 2).

ITD-tuning curve: the response of a neuron depends typically in a periodic manner on ITD. The ITD eliciting the largest response is called best ITD and serves as a descriptive parameter of the curve. If several peaks have similar height, the peak closest to zero ITD is commonly chosen as best ITD and the other peaks are termed secondary peaks.

π-Limit: the empirical limit observed in many neural populations that restricts the best ITD of a neuron to not exceed half a period or π in frequency space. ITD distributions complying with this π-limit are predicted from phase delays, but not time delays (see Box 3).

Phase code: a frequency-dependent representation of ITD within a neural population. The best IPD remains constant as the frequency tuning changes in a population of neurons. This concept is analogous to the characteristic phase measured in single neurons but refers to the entire neural population. Non-zero characteristic phases may contribute to forming such a representation of ITD.

Remodeling of ITD tuning: the ensemble of transformations in the tuning to ITD that ensue after the detection step and change the code for ITD (Box 3 and Figure 3).

Time code: a frequency-independent representation of ITD within a neural population. The range of best ITDs that the neurons within a population are tuned to is unrelated to the preferred frequency they respond to and, if no other assumptions are made, should be constant across frequency space. This concept is akin to the characteristic delay measured in single neurons but refers to the entire neural population. Non-zero characteristic delays may contribute to forming such a representation of ITD.

(Box 1). His model assumes three basic elements underlying the representation of ITD: neurons acting as coincidence detectors, time delays, and an arrayed arrangement of these cells resulting in a place map of ITD. Since then vast progress has been made from the molecular to the systems level. Although several reviews on this topic are available [9,10], we want to stress here that the processing level dealt with by Jeffress is only the first step in the representation of ITD. We shall refer to this first processing step as the detection of ITD and we review recent advances regarding the diversity of proposed mechanisms as well as their strengths and weaknesses in the next section. The sensitivity to ITD extracted at the detection step does not drive motor output directly, presumably because it lacks a suitable format. Instead the signal is transformed through further processing which takes place in two main parallel pathways within the ascending auditory system. We shall refer to these further processing steps as remodeling because they may change the code underlying the representation of ITD, as we shall show in the second section of this review.

By separating the detection step from the remodeling we show that neurons on the first step reveal properties of the detection mechanism in their responses, but that this signature may be lost throughout remodeling and instead other qualities emerge that potentially reflect adaptations to behaviors that make use of ITD information.

Diversity in ITD detection

Neurons detecting ITDs by a coincidence mechanism have been found in a wide range of vertebrates, including birds, reptiles, and mammals ([9,10] for review). The site of binaural interaction is the nucleus laminaris (NL) in birds, and the medial superior olive (MSO) plus – for ITDs in the signal envelope – the lateral superior olive (LSO) in mammals, all situated in the hindbrain. While it is largely accepted that the cells in these nuclei function as coincidence detectors (Box 2), the main discussion related to ITD detection revolves around how the time-delay element of the Jeffress model may be implemented in the brain (Figure 1). Birds and reptiles on the one side and mammals on the other side seem to have evolved different solutions to detect ITD.

If we take for granted that coincidence detection is part of the mechanism, an internal time delay needs to be introduced into the system to compensate for the external ITD. Several major candidates for internal delays have been proposed (Figure 1): (A) cochlear delays generated by the traveling wave on the basilar membrane. These can be effective if the binaural input to the coincidence detectors is tuned to different frequencies [11]; (B) axonal conduction delays created by the presynaptic neurons that project to the coincidence detectors [12,13]; (C) delays generated at the coincidence detector neurons themselves through asymmetric properties of, for example, inhibition or asymmetric filtering of excitatory postsynaptic potentials (EPSPs) [14,15].

These different proposals may be discriminated experimentally, among others, based on the ITD tuning of the coincidence detectors across different frequencies: the peaks in the ITD curve, indicating the best ITD, may shift with different stimulus frequencies revealing a phase-delay component as part of the internal delay mechanism ('characteristic phase', CP). Alternatively, the peaks may occur at the same ITD independently of frequency, indicating a time-delay mechanism ('characteristic delay', CD)

Box 1. The three elements of the Jeffress model

Element 1: the coincidence detector. This functions as a time-comparison unit similar to a cross-correlator. Neurons, tuned to narrow frequency bands, from both sides of the brain provide phase-locked inputs to the coincidence detector (Figure I, panel 1D); in other words, action potentials occur at preferred phases of the fluctuating sound waves (panels 1A,B). Locking to the stimulus fine structure (carrier) is the basis for ITD detection at low frequencies. For higher frequencies, spikes remain entrained to the time-varying envelope [86], leading to so-called envelope ITD sensitivity. Cross-correlating two narrow-band input signals at the coincidence detector generates a narrow-band output signal that oscillates with the period of the input frequency. This response-versus-ITD function is called the ITD-tuning curve or ITD curve (Figure I, panels 2A,3A). Inhibitory inputs may also modulate the ITD curve. The periodic behavior implies that the ITD may well be represented by its phase equivalent, the IPD.

Element 2: an internal delay. This shifts the inputs from the two ears independently of each other, thereby compensating for the ITD at the eardrums (Figure I, panel 1C). As a consequence, the internal delay enables the coincidence detectors to be tuned to events that occur at a given external ITD. The composition of the internal delay affects the shape of the ITD-tuning curve, when wide-band stimuli are used, and thus the code for ITD (see Box 3).

Element 3: a map of ITD. This is an ordered arrangement of internal delays resulting in a topographic representation of ITD. This element is mentioned for the sake of completeness and is not further dealt with in the article.

An internal delay may consist of a frequency-dependent component termed phase delay or characteristic phase (CP), and/or a frequency-independent component called time delay or characteristic delay (CD).

The contribution of the CD and the CP to the overall delay may be computed from ITD curves for tones at different frequencies (f) (Figure I, panels 2A,3A). The IPD to which a neuron responds best is called the best IPD (IPD_b) (2B,3B). CD and CP are the slope and y-offset, respectively, of the linear IPD_b–frequency relation (2C,3C) [87]:

$$IPD_b(f) = CD * f + CP \qquad [I]$$

Rewriting this equation in terms of the best ITD (ITD_b) by dividing it by f and taking into account that IPD_b is the phase equivalent of ITD_b:

$$ITD_b = IPD_b/f \qquad [II]$$

yields:

$$ITD_b(f) = CD + CP/f \qquad [III]$$

There are two simple cases of this latter equation, CD = 0 or CP = 0. The case CP = 0 corresponds to a pure time delay (2): ITD curves recorded at different frequencies intersect at the peaks (2A), the best IPDs point to different directions in the polar plot (2B), the IPD–frequency relation intersects the y axis at zero IPD (2C), and the frequency–ITD relation is a vertical straight line (2D). The case CD = 0 corresponds to a pure phase delay (3): ITD curves intersect at lower response levels (3A), the best IPDs all point to the same direction (2B), the IPD–frequency relation is a horizontal line that intersects the y axis at a non-zero IPD (3C), and the frequency–ITD relation forms a hyperbolic curve (3D).

Jeffress originally proposed that the internal delay is created by axonal conduction times which generate pure time delays. Other sources of internal delays that may cause phase delays have been proposed later (Figure 1).