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Sound localization: Jeffress and beyond

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Abstract

Many animals use the interaural time differences (ITDs) to locate the source of low frequency sounds. The place coding theory proposed by Jeffress has long been a dominant model to account for the neural mechanisms of ITD detection. Recent research, however, suggests a wider range of strategies for ITD coding in the binaural auditory brainstem. We discuss how ITD is coded in avian, mammalian, and reptilian nervous systems, and review underlying synaptic and cellular properties that enable precise temporal computation. The latest advances in recording and analysis techniques provide powerful tools for both overcoming and utilizing the large field potentials in these nuclei.

The Jeffress model, its variants and alternatives

How can an animal tell the direction a sound is coming from? In 1948, American psychologist Lloyd Jeffress published a germinal paper [1], in which he proposed that the time difference of low frequency sounds arriving at the two ears (interaural time difference, ITD) can be represented as a “place” in an array of nerve cells. The place theory (hereafter also referred to as the Jeffress model) depends on three fundamental assumptions: (1) orderly arrangement in conduction times of ascending nerve fibers, which serve as “delay lines”, (2) conversion of input synchrony into output spike rates by “coincidence detectors”, and (3) systematic variation in spiking rates within the cell array to form a neuronal “place map”. It was only after his death that the first reports appeared, demonstrating anatomically and physiologically the presence of the neuronal ITD maps in the barn owl [2,3]. In contrast to the success in the owl, however, two decades of research in mammals and reptiles have concluded that “Jeffress is not the only answer” for sound localization. In this short review, we look first at various ITD coding schemes, then discuss their underlying synaptic and cellular properties, and briefly review recent advances in recording and analysis techniques.

Birds

Chickens and owls are the most common birds used for the study of neuronal ITD coding. In these species, axons from the nucleus magnocellularis (NM) provide the delay lines, while the neurons in the nucleus laminaris (NL) serve as coincidence detectors and change their spike rates periodically with ITD (Fig. 1A, B). In chickens, NL is a monolayer structure with cells tonotopically arranged mostly along the rostrocaudal axis. Within each single

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Conflict of interest statement

The authors declare that they have no conflict of interest.

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frequency band, the best ITD of the cell (i.e., the ITD to which the spike rate of the cell is maximal) gradually changes along the mediolateral positions [4], therefore forming a single ITD map (Fig. 1A). A three-dimensional reconstruction of the chick NM fibers revealed that both axonal diameters and internodal distances, as well as the axonal length, play a fundamental role in creating the proper neural delays [5*]. In contrast to chickens, owls NL neurons are sparsely distributed in the nucleus without forming a layered structure, resulting in multiple ITD maps in the dorsoventral dimension ([3] and Fig. 1B). Anatomical and *in vitro* physiological evidence suggests that the emu also has a mono-layered place map in NL [6]. It is still unknown, however, whether the chicken-like single ITD map is prevalent among the bird species.

Mammals

In contrast to birds, the existence of ITD maps in mammals has been controversial [7–10]. Neurons in the medial superior olivary nucleus (MSO) change their spike rates in an ITD-dependent manner, but the peaks of the ITD-rate curves often lie outside the physiologically relevant time range (Fig. 1C; see [9] for more detailed discussion). Moreover, most MSO cells in each hemisphere show similar ITD tuning, which suggests that the average spike rate of many MSO cells codes ITDs, using the “slope” rather than the “peak” of the tuning curves [11]. In the slope coding framework, unlike the place codes found in birds (Fig. 1AB), sounds coming from the contralateral and ipsilateral sides, respectively, result in higher and lower average spiking rates of MSO neurons (Fig. 1C). Note that this slope coding theory is mostly based on the anatomical and physiological results in gerbils. Since recording from the MSO is highly challenging (we will discuss it later), only a limited amount of direct data in other species are available. Findings in guinea pigs seem to be in line with the slope coding scheme [9]. Recent re-examination of the axons from the ventral cochlear nucleus (VCN) to the MSO in cats, however, confirmed a delay-line-like structure, which is compatible with the Jeffress-type model [10]. More evidence would be necessary to conclude to what extent the gerbil-like slope-coding scheme is valid among various mammalian species.

Reptiles

In addition to birds and mammals, reptiles have also been studied recently. In the alligator, bitufted NL neurons are tonotopically arranged in a compact layer, and change their spike rates periodically with ITD, in line with the Jeffress-type model observed in chickens and consistent with their phylogenetic position [12]. In geckos, however, ITD sensitivity appears in the auditory nerve, where there is no binaural neural convergence [13*]. Instead, geckos have pressure gradient receiver ears, and the vibration amplitude of the two eardrums, internally coupled through the mouth cavity, varies with ITD [14,15]. Consequently, firing rates in the gecko auditory nerve change in an ITD-dependent manner (Fig. 1D), providing yet another strategy for ITD detection. How this ITD dependent activity of auditory nerves affects the central nervous system is still under investigation. Binaural comparisons are still necessary in geckos, since monaural directional responses are ambiguous with respect to level and location.

Synaptic and cellular properties

In spite of their different ITD coding strategies, the avian and mammalian auditory brainstems have a great deal in common, including very similar synaptic [16] and cellular [17] mechanisms. This convergence in functional organization reveals basic design features in species that possess unique evolutionary histories but use similar algorithms to solve basic computational problems [18].

Glutamatergic excitation

Excitatory synaptic input in the auditory brainstem, which is primarily mediated by AMPA receptors [19,20], is one of the fastest transmission in the central nervous system. The half peak width of an EPSC is usually below 1 ms [21,22,23**]. The time scales (rise times and half peak widths) of the glutamatergic excitatory inputs in the chicken NL vary along the tonotopic axis [20–22], presumably optimizing the synaptic filtering effect [22]. High frequency NL neurons tend to have faster input time scales than low frequency neurons, enabling transmission of faster signals [20–22]. In the gerbil MSO, the excitatory synaptic input originating from the contralateral ear shows faster rise time than that from the ipsilateral ear, partially compensating the longer conduction time through contralateral axons [24**]. A recent study on the gerbil MSO [23**] found that an MSO neuron receives a very small number of excitatory inputs (estimated as 4–8 per cell), in contrast to the owl NL (100–300 afferents per cell)[25]. How these differences in the numbers of excitatory inputs are related to ITD coding remains to be a subject of future studies.

Glycinergic inhibition

Glycinergic inhibition has been shown to play a fundamental role in coding ITDs in the gerbil MSO [26,27]. The bipolar shaped MSO neuron [28] gradually confines glycinergic receptors solely to the somatic area in an experience dependent manner [29]. The number of inhibitory inputs is estimated as 2–4 per cell [23**]. The glycinergic inhibition has a time scale of about 1 msec [30], only slightly slower than the exceptionally fast excitatory input [23**]. This fast inhibition, which is assumed to arrive slightly earlier than the contralateral excitatory input, has been proposed to shift the ITD tuning curve such that the steepest slope of the curve lies within the physiological ITD range (Fig. 1C and [26,27,31]). The balance of excitatory and inhibitory inputs in gerbil MSO, showing similar strength and short term synaptic depression, is thought to be crucial for the slope coding scheme [23**]. Unlike gerbil's MSO, chicken's NL (and NM) lacks glycinergic synaptic currents, although NL neurons do coexpress GABA and glycine [32**]. Further investigation is necessary to determine whether (and how, if any) glycinergic activity affects ITD detection in birds.

GABAergic inhibition

Whereas the fast glycinergic inhibition directly affects the position of the ITD tuning curve of the gerbil MSO neuron, effects of slower GABAergic inhibition in the chicken appear more subtle and indirect. GABAergic inhibition has been suggested to improve phase-locking in NM and ITD tuning in NL, by reducing the membrane time constant, shunting and sharpening excitatory synaptic input, counteracting the increase in the input rate due to increasing sound intensity, and balancing ipsi- and contralateral input strengths [33–38]. One of the most intriguing characteristics of the GABAergic inhibition is its depolarizing nature even in mature NM and NL cells [38–41]. A recent study combining experiment and modeling suggested that the depolarizing inhibition narrows the “coincidence detection time window” of the cell by recruiting low-voltage-activated potassium current and inactivating sodium channels [42].

The source of the GABAergic inhibition to the avian NM and NL is the superior olivary nucleus (SON)[34]. A cautionary note - do not confuse the avian SON with the mammalian MSO - although they share the name, they have different roles and may not be homologous. SON neurons *in vivo* are broadly tuned to frequency, show several response types, and phase-lock to low frequency tones [43**]. More interestingly, SON neurons receive both GABA- and glycine-mediated inputs [43**]. How these detailed response properties of SON are related to ITD coding in NL remains to be investigated.

Low voltage activated potassium channels

Neurons in the auditory brainstem express a variety of voltage-gated potassium channels [44]. The low-voltage-activated potassium (KLVA) conductance mediated by the Kv1 family is prominent in the ITD coding circuit, and accounts for the robust onset spiking to constant current injection, or the so-called class 3 excitability [45,46]. The KLVA conductance, activated at the resting membrane potential, reduces the input resistance and the membrane time constant, and consequently accelerates the membrane response to facilitate temporal processing in NL and MSO neurons. In addition to this passive property, recent studies have focused on how active properties of the KLVA conductance dynamically affect ITD coding [24**,47,48,49*]. Unlike the conventional method of pharmacological blockade of the KLVA current, these studies use MSO models to virtually “freeze” the KLVA conductance to examine its dynamical effects. In their “frozen KLVA” model, the KLVA conductance is fixed to the resting level, as if it were a constant leak, while in the “active KLVA” model, the KLVA conductance dynamically modulates in a voltage-dependent manner. Model neurons with an active KLVA conductance are more sensitive to rapidly varying input [47] and to the rising phase of slowly varying input with the existence of noise [48]. In the gerbil MSO, active KLVA conductance compensates the distortion of the synaptic input due to dendritic cable filtering [49*], and underlies the selectivity to the temporal ordering of asymmetric excitatory inputs [24**].

Fast sodium channels

In addition to the KLVA channels, fast sodium channels have also received increasing attention, now that improved techniques for recording fast conductance changes have become available (see [50], for discussion on the effect of series resistance compensation on the measurement of fast EPSCs). Somatic recorded action potentials in MSO and NL neurons are exceptionally small (typically 10–20 mV) indicating axonal spike initiation in these neurons [51,52]. Separating the sites of synaptic integration and spike generation is advantageous both computationally and metabolically [53] and enables high frequency firing [54]. In the gerbil MSO, sodium channels, which are distributed in the perisomatic and axonal regions but not in dendrites, are mostly inactivated around the resting potential [55*]. Modeling results indicated, however, that the remaining active channels could amplify subthreshold EPSPs [55*]. Distribution of the sodium channels in chick NL have been shown to be regulated by presynaptic activity [56].

Recordings from MSO and NL *in vivo*

Sound-induced extracellular field potentials are commonly found in many auditory stations in various animals. This field potential is termed the “neurophonic” since it replicates the waveform of the stimulus tone (see [57] for a review). In NL and MSO, the amplitude of the neurophonic often lies in the millivolt range, hiding small somatic spikes (discussed above) in the background. This makes extracellular single unit recording in these nuclei particularly difficult [58]. There are two types of approach to the neurophonic potential.

Neurophonic

The first approach is to carefully characterize it, in order to extract information about the underlying neural activity. In the barn owl’s NL, the neurophonic potential is temporally very precise and robust [59,60]. The neurophonic amplitude depends on ITD, and its peak position shifts along the ITD map in the nucleus [61]. Therefore, like other local field potentials [62], the neurophonic is presumed to reflect information processing in the nucleus. The biggest problem, however, is the unknown origin of the neurophonic. In the cat MSO [58] and chicken NL [4], where cells are aligned in a thin flat structure, synaptic inputs to the bipolar cells are assumed to be the primary source of neurophonic. In the barn

owl, however, oval-shaped NL cells have only short stubby dendrites, and are sparsely distributed in the nucleus [57]. Signal-to-noise ratio analyses and theoretical modeling suggested that the neurophonic in owls NL should originate from either presynaptic NM axons or their excitatory synaptic input to NL, or both [57]. Further investigation is required to identify the source of the neurophonic in owl's NL.

It has been suggested that field potentials may affect spike timing via ephaptic coupling [63,64]. These studies indicate that hypersynchronized activity of neurons in hippocampus and cortex could strongly entrain neural firing, increasing spike field coherence. If this is also the case for the much faster oscillation in the auditory brainstem nuclei, characterizing the neurophonic potential will be of increasing importance in understanding ITD computations.

Advanced recording techniques

The second approach to the neurophonic is to overcome it using advanced recording procedures. Recent progress in patch-clamp techniques has enabled *in vivo* whole-cell recordings from the inferior colliculus in mice [65-67], rats [65], and bats [68], and the medial nucleus of the trapezoid body (NMTB) in mice [69], to directly examine subthreshold membrane responses and spike generation mechanisms. The loose-patch/juxtacellular recording techniques [70], which enables hours of stable “quasi-intracellular” recording, has also been used to characterize synaptic transmission in the mouse NMTB [71] and gerbil VCN [72]. Preliminary *in vivo* recording results that characterize synaptic inputs of owl's NL (K. Funabiki & M. Konishi, 2005, Assoc Res Otolaryngol Abstr #116) and gerbil's MSO (M. van der Hijden et al., 2011, Assoc Res Otolaryngol Abstr #695) have also appeared as conference abstracts.

Concluding remarks

Beginning with the Jeffress model, recent studies of sound localization have revealed the presence of multiple ITD coding strategies in birds and mammals. Notwithstanding these differences, all ITD coding depends on the accurate representation of temporal information, which is mediated by similar or identical synaptic and cellular properties. Furthermore, the different ITD coding strategies are not always mutually exclusive; for example, owls may use slopes of the ITD tuning curves in the inferior colliculus (see [73*] for a review).

More evidence is necessary to conclude if there is a unifying ITD computing strategy in mammals. Temporal coding in the ventral cochlear nucleus is very similar among different mammals (e.g., dogs [74], monkeys [75]), but not all mammals show refined ITD tuning in the MSO. Behavioral assessment shows that rats are unlikely to use ITDs [76*], in line with the poorly developed structure of their MSO [29]. Thus, temporal coding is consistent and fairly invariant among species, but may not always be used for computation of ITD. Recent advances in recording and analysis techniques should provide powerful tools for future comparative studies on how NL and MSO compute ITD cues for sound localization.

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Abbreviations

GABA gamma-aminobutyric acid

ITD	interaural time difference
KLVA	low voltage activated potassium
MNTB	medial nucleus of the trapezoid body
MSO	medial superior olive
NL	nucleus laminaris
NM	nucleus magnocellularis
SON	superior olivary nucleus
VCN	ventral cochlear nucleus

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[*] of special interest

[**] of outstanding interest

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Highlights

- New theories have emerged to describe neural coding of interaural time differences.
- Birds, mammals, and lizards use various coding strategies for locating sound.
- Nevertheless, the underlying synaptic and cellular properties are very similar.
- Advanced techniques enable overcoming and utilizing the large field potentials.

Figure 1. Various ITD coding strategies

A. Chicken's ITD coding circuit. **(Left)** Schematic drawing of the chicken's brainstem. Axons from the ipsilateral NM enter NL dorsally, while those from contralateral NM enter ventrally. NL neurons are aligned in a thin flat layer. **(Center)** Jeffress-type organization of the chicken's NM-NL circuit. Axonal conduction times lead to a place map in NL. Neurons near the lateral border of NL (marked as C) respond maximally to sounds coming from the far contralateral side, and cells located close to the medial edges of NL (marked as F) fire maximally to sounds originating from in front of the animal's head. **(Right)** Example ITD-response curves of NL cells tuned at 1 kHz. As stated above, the peak position of the tuning curve depends on the location of the neuron in the place map. Positive ITD values mean contralateral ear leading (i.e., sound arrives earlier at the contralateral ear than at the ipsilateral ear).

B. Owl's ITD coding circuit. **(Left)** Schematic drawing of the owl's brainstem. Similar to the chicken brainstem, axons from the ipsilateral NM enter NL dorsally, while those from contralateral NM enter ventrally. Owl NL neurons, however, are not aligned in a layered structure, but are distributed sparsely throughout the nucleus. **(Center)** Multiple Jeffress-type place maps of the owl's NM-NL circuit. Gradual changes in axonal conduction times along the dorsoventral dimension result in multiple place maps of NL cells. Neurons near the dorsal border of NL (marked as "C") respond maximally to sounds coming from the far contralateral side, and cells located close to the ventral edges of NL (marked as "F") fire

maximally to sounds originating from in front of the animal's head. **(Right)** Example ITD-response curves of NL cells tuned at 5 kHz. As in chickens place map, the peak position of the tuning curve depends on the location of the neuron in the place map.

C. Gerbil's ITD coding circuit. **(Left)** Schematic drawing of the gerbil's brainstem. Spherical bushy cells in the VCN provide excitatory inputs to the MSO, while LNTB and MNTB neurons, which receive outputs of the globular bushy cells in the ipsi- and contralateral VCN, respectively, send glycinergic inhibitory inputs to MSO. **(Center)**

Schematic picture of a gerbil MSO neuron. The principal neuron of the MSO has bipolar dendrites segregating ipsi- and contralateral excitatory inputs from the VCN. Inhibitory inputs from LNTB and MNTB are confined to the cell body region. **(Right)** Example ITD-response curves of MSO cells tuned at 1 kHz. In contrast to chicken's NL cells, the tuning curves of MSO neurons are very similar. Peak positions of the tuning curves can lie out of the physiological ITD range (i.e., ITDs encountered naturally) shown by the shaded area.

D. Gecko's ITD coding. **(Left)** Schematic drawing of the gecko's head. The inner ears of the gecko are interconnected through the mouth cavity. **(Center)** Gecko's ear as a pressure gradient receiver. Sound wave arriving at one ear travels through the mouth cavity to reach the tympanic membrane (eardrum) of the other ear, resulting in binaural sound interactions. The motion amplitude of the eardrum changes with the phase difference between the two sounds from inside and outside the ear. **(Right)** Example ITD-response curves of auditory nerves tuned at 2 kHz. ITD-dependent changes in the motion amplitude of the tympanic membrane results in the spike rate modulation of the auditory nerve in an ITD-dependent manner. Note that the trough of the ITD-response curve at around 200–250 ms corresponds to the conduction delay of sound through the mouth cavity.

Abbreviations: AN, auditory nerve; NA, nucleus angularis; NM, nucleus magnocellularis; NL, nucleus laminaris; VCN, ventral cochlear nucleus; LNTB, lateral nucleus of the trapezoid body; MNTB, medial nucleus of the trapezoid body; MSO, medial superior olive.

A (left and center), **B** (left and center) modified from [77]; **C** (left and center) modified from [9]; **D** (left) modified from [13*].