Inhibition in the Brain Plays a Key Role in Sound Localization

New experiments demonstrate that processing interaural timing differences entails more than just delay lines.

Localizing sounds and making sense of our acoustic surroundings from the sounds that our ears register are essential but complicated tasks. The brains of humans and other animals exploit a number of cues to meet these challenges (see "How We Localize Sound," by William Hartmann in PHYSICS TODAY, November 1999, page 24).

At low frequencies—below a few kilohertz for most mammals—the biggest localization cues come from interaural time differences (ITDs), that is, differences in a sound's arrival times at the two ears. For more than 50 years, the standard paradigm for explaining ITD processing in the brain has been a model developed by Lloyd Jeffress.[1] According to that model, there is an array of neurons that serve as cross-correlators or coincidence detectors, each one firing maximally when it receives inputs simultaneously from the two ears. The signal paths to the neurons vary in transmission delay, so that neurons receive the inputs at different times. The peak response occurs at those neurons for which the neural delay exactly offsets the acoustic delay. In essence, the brain forms a topographical map of azimuthal sound directions.

Support for such a model of ITD processing has been sought experimentally in both mammals and birds, especially the barn owl (see, for example, PHYSICS TODAY, June 2001, page 20). In the barn owl and chicken, researchers have found physical evidence for the existence of neuronal delay lines of varying lengths in the portion of the avian brain—the nucleus laminaris—that has been identified with ITD processing.[2] Similar evidence for delay lines has been reported in cats,[3] but some researchers find that evidence less convincing. "While many experiments are consistent with the Jeffress model, there's no actual proof that neural conduction delays are the sole or even primary basis for the physiological observations," says Boston University's Steven Colburn.

Now, Benedikt Grothe of the Max Planck Institute of Neurobiology, David McAlpine of University College London, and their colleagues have shown that, in Mongolian gerbils, the neuronal response to ITDs is determined by fast inhibitory inputs within the brain.[4] "These findings throw a monkey wrench into the Jeffress model," comments Tom Yin of the University of Wisconsin—Madison.

Role of inhibition

Although the Jeffress model provides a simple, effective framework for thinking about ITDs, it has been known for some time that the actual workings of sound localization are more complicated. Consider the medial superior olive (MSO), the part of the mammalian brain stem at which ITD processing begins. Neurons in the MSO receive spectrally decomposed inputs from both cochlear nuclei, each of which receives its input from the cochlea (part of the inner ear) via the auditory nerve (figure 1). Such binaural processing is fully consistent with the Jeffress coincidence model.

But MSO neurons also receive inputs from two other processing centers in the brain stem, the medial and lateral nuclei of the trapezoidal body (MNTB and LNTB). And those MSO inputs are different. The signals from the cochlear nuclei are excitatory: They depolarize the neuron, making the potential of the cell's membrane less negative; once the neuron is sufficiently depolarized—say, by receiving simultaneous excitations from each ear—it generates a voltage spike, called an action potential, that propagates along the neuron's axon to the next neurons in line. In contrast, the inputs from the MNTB and LNTB are inhibitory: They hyperpolarize the cell, making the membrane potential more negative and thereby suppressing the firing of action potentials.

Because of the inhibitory inputs to the MSO, some role for inhibition in the MSO had long been suspected. Grothe and McAlpine have provided the first direct evidence for inhibition's effect by recording the consequences of turning off the inhibition at individual MSO neurons.

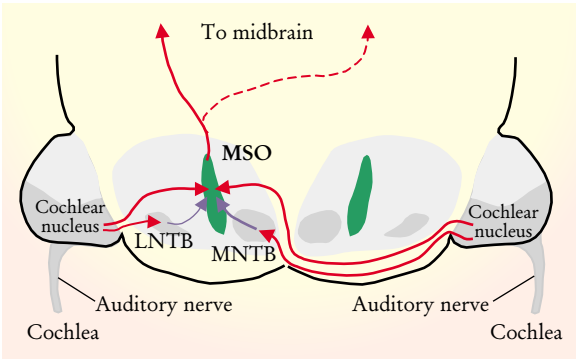

FIGURE 1. INTERAURAL TIME DIFFERENCES in mammals are first processed in the medial superior olive (MSO, shown in green) in the brain stem. The signal pathways are shown here for one of the two MSOs. MSO neurons receive excitatory inputs directly from both cochlear nuclei, which process auditory signals from the cochlea in the inner ear. In addition, the MSO receives inhibitory inputs from two other centers in the brain stem, the lateral and medial nuclei of the trapezoidal body (LNTB and MNTB), which also get their inputs from the cochlear nuclei. The MSO's inhibitory inputs, precisely timed to the excitatory inputs, appear to tune the timing sensitivity of the MSO neurons. (Adapted from ref. 4.)

Difficult measurements

Probing the MSO is notoriously difficult. Not only is it a small, dense region located deep at the base of the brain, but the signal from a single neuron can be overwhelmed by the background signal from surrounding neurons. An extra complication is that the neurons in the MSO are tuned to specific frequencies, and their firing is phase-locked to the auditory inputs from the ears. Recording the activity of an individual neuron is like isolating a single voice in a choir singing in unison.

The experimenters looked at two dozen individual neurons in a gerbil MSO; 20 of those neurons showed a strong ITD response when tones were played through headphones in the gerbil's ears. One neuron's response is plotted in blue in figure 2. The peak response of

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this neuron occurred when the sound signal—in this case a sine wave near 1 kHz—reached the contralateral ear (the one farther from the MSO) 200 μs before it reached the ipsilateral or same-side ear.

To examine the role of the inhibitory inputs, which are mediated by the neurotransmitter glycine, the researchers measured the firing rates of this neuron following the injection of strychnine near the electrode used to record the neuron's response. Strychnine blocks the glycine receptors; with the inhibition thus turned off, the peak in the ITD response curve shifted toward zero, as shown in red in figure 2. Similar shifts were seen for the four other ITD-sensitive neurons the researchers examined. Thus, say the researchers, inhibition plays a vital role in determining the ITD response of MSO neurons.

The MSO's inhibitory inputs themselves are not sensitive to ITDs. The researchers therefore conclude that the inhibition is precisely timed—that is, phase-locked—to the excitatory inputs. And it is the timing between the inhibitory and excitatory inputs that determines the position of the peak response of the MSO neurons to ITDs. The inhibition is likely dominated by input from the MNTB that reaches the MSO ahead of input from the contralateral cochlear nucleus. In support of that conclusion, Grothe notes that the MNTB receives signals from the contralateral ear through thicker, and hence faster, axons than does the MSO. McAlpine sees advantages to tuning the ITD response through inhibition: It would, for example, allow a mammal's auditory system to adjust to such changes as increasing head size during growth.

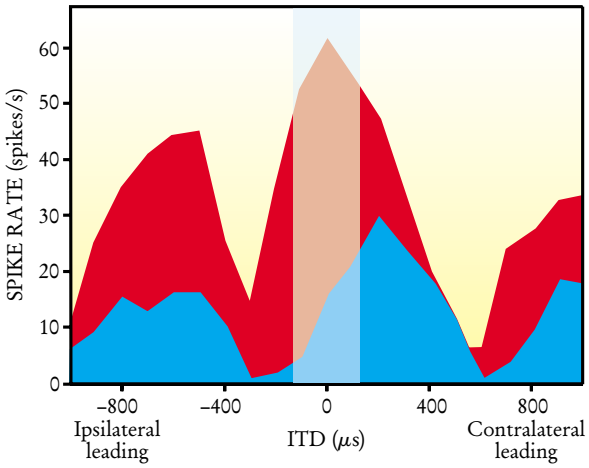

FIGURE 2. INHIBITION IS IMPORTANT for establishing the sensitivity to interaural time differences (ITDs). The firing rate, shown in blue, of a sample neuron in the medial superior olive (MSO) of a Mongolian gerbil depends on the difference in sound arrival times at the near (ipsilateral) and far (contralateral) ears. (The side peaks correspond to cross-correlations between different cycles of the input sine wave.) When inhibitory inputs to the neuron are blocked, the cell's response to ITDs shifts to the red curve. The shaded band is the range of physiologically relevant ITDs, and corresponds to the distance between the gerbil's ears. (Adapted from ref. 4.)

Unanswered questions

In addition to demonstrating the role of inhibition in ITD coding, these new results fan an ongoing debate about the nature of ITD processing in the mammalian auditory system. Grothe and McAlpine note that, for most of the neurons they examined, the peak firing rate was found at ITDs outside the so-called physiologically relevant ITD range, given by the spacing between the gerbil's ears divided by the speed of sound and indicated by the shaded band in figure 2. Such tuning seems at odds with the Jeffress model, which holds that the peak firing from coincident inputs encodes the ITD. Instead, the peak location places the steepest part of the response function within the physiological range. And, curiously, the peaks in the responses of MSO neurons are not widely distributed in ITD, as would be expected for a full Jeffress-type map; rather, the peaks all occur at roughly 1/8 of a period of each neuron's so-called best frequency, the frequency at which the neuron generates its largest response. That observation supports similar results found by McAlpine and colleagues in the guinea pig auditory system.[5] With only one peak position for neurons sensitive to a given frequency range, comparisons between the responses from the auditory processing centers on each side of the brain would be required to fully determine the ITD.

Not all hearing researchers are ready to abandon the Jeffress model. Inhibition-mediated ITD tuning could provide an alternative to physical delay lines for realizing a Jeffress-type map. For example, Doug Fitzpatrick (University of North Carolina, Chapel Hill) and his coworkers have shown, in a model, that inhibition can yield sensitivity to large ITDs when only short delay lines are present.[6] Shigeyuki Kuwada of the University of Connecticut Health Center notes that, in most other mammals, particularly larger-headed mammals that might be expected to better exploit ITD cues, peak ITDs do fall within the physiological range. McAlpine counters that in most of the experimental studies to date, the correlation between peak ITD and best frequency, especially at lower frequencies where ITDs dominate, was not determined.

For now, clearer answers to how ITDs are processed in the brain will have to wait for data from more neurons and from more species.

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Do Atomic Force Microscope Arrays Have the Write Stuff?

IBM researchers have developed an array of 1024 cantilevers, called Millipede, as a high-density alternative to magnetic recording. Moving across a polymer film, Millipede leaves footprints that encode information.

The information age has been facilitated by the exponentially growing capacity of such storage media as magnetic disks. As demand has soared, the information-storage industry has crammed more and more bits into ever shrinking areas. Significant innovations have already pushed magnetic storage densities well beyond the limits forecast by pundits just a few years ago. Developments now on the horizon promise to raise the densities from values of 30–50 gigabits per square inch (Gb/in^2), which are typical today, to double or triple those