NEUROSCIENCE

What's the Best Sound?

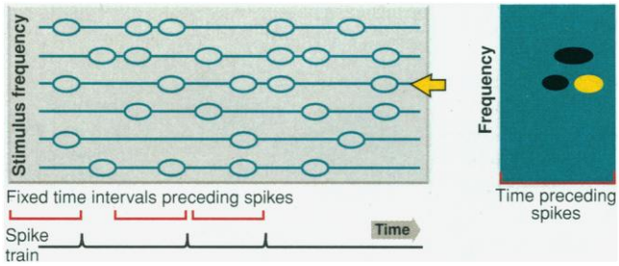
Eric D. Young

We are constantly bombarded with stimuli from the environment. How does the brain make sense of this complex input? Each of the senses feeds information to the brain's cerebral cortex, where neurons respond to important features of the stimulus; these responses are then relayed to higher order processing centers, which respond to more elaborated features of the stimulus. In the visual system, for example, neurons in the primary visual cortex respond best to oriented bars and to moving bars (*1*), thought to represent an analysis of edges. The edges, in turn, define shapes, as the next stage in interpretation of the visual scene (*2*). In the auditory cortex, however, we lack this kind of understanding. There is no agreement as to which sounds maximally stimulate auditory cortical neurons, and as a result it is not clear how auditory perception translates into cortical neural processes. The paper by deCharms and colleagues on page 1439 of this issue describes a promising approach to this problem and begins to define acoustic features for processing by the auditory cortex (*3*).

Most attempts to understand auditory processes have depended on ad hoc assumptions about what the critical auditory features should be, and these have often been chosen on the basis of their importance in auditory perception. In some cases, the sensitivity of cortical neurons to a particular sound feature varies across the surface of the auditory cortex, that is, the feature is mapped onto the cortex, reinforcing the assumption that it is an elementary unit of analysis of the acoustic signal. This method has been most successful in the bat (*4*), where parts of the auditory cortex are organized according to sound features clearly necessary for operation of the animal's sonar, which it uses to locate objects in space while flying. For example, certain cortical regions are specifically sensitive to the delay between the sonar pulse emitted by the bat and the returning echo, providing a key piece of information for the bat's perception of its distance from the obstacle or prey.

Like the research on the sonar-using bat, most other analyses have also been special cases, and the features that have emerged have not been sufficiently general to support a broad theory of auditory perception. One exception is the work of Shamma and colleagues (*5*), in which static and moving sinusoidal spectral shapes define the neurons' response characteristics. This method produces a spectral weighting function, which shows how the neuron weights energy in the stimulus at different frequencies, and has been used to describe the cortical responses to complex stimuli such as speech.

In their new work, de Charms *et al.* use a technique called reverse correlation to determine the features of sound used by the auditory cortex. The method allows the neuron to define its own feature set; no a priori assumptions about the importance of specific features are made. In traditional reverse correlations, the neuron is exposed to random noise, which contains a wide variety of stimulus features, and signals its response preferences by discharging action potentials when exposed to a stimulus resembling the neuron's ideal feature. The neuron's selectivity can then be determined by averaging the stimulus during intervals of time preceding action potentials (*6*). Versions of this method have been applied to the visual and somatosensory systems (*7*), as well as to the auditory system. The particular version of reverse correlation applied by deCharms *et al.* is an extension of this original method. It estimates the optimal response of the neuron as a function of time and frequency—the spectrotemporal receptive field (STRF) (see the figure).



The neuron picks its favorites. To determine the optimal stimulus for a neuron with the reverse correlation method, a sequence of chords consisting of several tones of randomly chosen frequencies is played to the neuron (**left**); the neuron responds with a spike train (**bottom**). The time-frequency patterns of tones during fixed time intervals (brackets) preceding spikes are averaged to produce the spectrotemporal receptive field (STRF) (**right**). Frequencies that excite (yellow) or inhibit (black) the neuron are shown as a function of time preceding spikes. In this case, the neuron is excited by the frequency indicated by the arrow and inhibited by a higher frequency.

In the past, reverse correlation has not worked well in auditory cortex. Auditory neurons are usually not responsive to the broadband noise that is the typical stimulus. To get around this problem, deCharms and colleagues used a more defined stimulus—a sequence of chords made up of a randomized selection of tones of different frequencies (see the figure). The resulting responses, expressed as STRFs, show how often a neuron responds (or does not respond, which indicates inhibition) after stimulation with a particular frequency. The STRFs also capture such subtleties as temporal sequences of frequencies that are excitatory or inhibitory for the neuron.

The time-frequency pattern of the STRF is interpreted by deCharms and colleagues to be the optimal stimulus for the neuron. That is, the neuron should respond most strongly to a stimulus with a time-frequency pattern that resembles the STRF. This expectation is borne out for most of the neurons that they studied. In this sense, the components of the STRFs are indeed auditory features to which the neurons are specifically sensitive. An impressive aspect of the results is that neurons respond with relatively high discharge rates to optimal stimuli constructed from their own STRFs; similar rates are not obtained for simple auditory stimuli such as single tones, clicks, or noise.

Reverse correlation captures only linear interactions among stimulus components. A neuron that responds only when simultaneously exposed to two specific tones of different frequencies—as opposed to simply responding to a sum of the energy at the two frequencies—would not be detected by reverse correlation. This limitation of the method, which is shared by most current methods for analyzing neural receptive fields, is a significant drawback. In higher cortical areas, its application may not give a full picture of a neuron's responses. As neurons are activated by more and more specific aspects of the environmental scene [as, for example, in the neurons of the primate inferotemporal area that respond to faces and other body parts (*8*)], their nonlinear response characteristics would increase and could not be detected by reverse correlation.

Nevertheless, these results set the stage for unraveling the neural representation of auditory stimuli in terms of acoustic features. The feature set promises to be complex, as might be expected from the extensive synaptic processing that occurs in the

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brainstem auditory system before the information even reaches the auditory cortex. The STRFs are clearly useful in defining responses to relatively simple stimuli, like noise bands and frequency sweeps. But is this method up to the job of finding the relevant stimuli in complex natural scenes? Can the neural representation of complex real-world auditory stimuli be adequately understood in terms of a temporal sequence of acoustic features? The inability of reverse correlation to detect nonlinear computation may limit its ability to solve this ultimate problem. But in the process, it will define the extent to which nonlinear computations contribute to auditory processing, in proportion to the failure of reverse correlation methods to adequately account for the stimulus selectivity of a neuron (9).

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UPDATE: HUMAN GENETICS

More Deafness Genes

Karen P. Steel and Steve D. M. Brown

New genes underlying genetic deafness have appeared in a rash of reports that continues apace [see previous commentary (*1*)]. In *Nature Genetics*, moderate but dominantly inherited hearing impairment in two large families is shown to be a result of a mutation in the *TECTA* gene, on chromosome 11 (*2*). In addition, on pages 1444 and 1447 of this issue, Probst *et al.* and Wang *et al.* report that the unconventional myosin gene *MYO15* is mutated in the *shaker-2* mutant mouse and in three human families with recessive, nonsyndromic deafness linked to chromosome 17, *DFNB3* (*3*, *4*).

The first new gene implicated in deafness, *TECTA*, encodes the protein α-tectorin, one component of the tectorial membrane, an extracellular matrix that hangs over the hair cells. Each hair cell projects about 100 stereocilia from its upper surface, and the tectorial membrane just touches the tallest of these. During sound stimulation, shearing between the tectorial membrane and the hair cells leads to the deflection of stereocilia bundles. The bending of the stereocilia during sound stimulation pulls on delicate tip links between adjacent stereocilia, which in turn directly opens a transduction channel at the end of the tip link, triggering the response (*5*). This arrangement must be precisely maintained for normal hearing.

The discovery of α-tectorin mutations in people with hearing impairment suggests that the properties of the tectorial membrane are critical for delivering an appropriate stimulus to the hair cells. It also opens up a new class of candidate molecules for the dozens of deafness genes yet to be identified.

The other new gene, *MYO15*, encodes the third myosin molecule implicated in deafness, out of only a handful of deafness-associated genes so far identified. It was found by bacterial artificial chromosome (BAC) rescue, a process in which a nonmutated DNA clone was introduced into the genome of a *shaker-2* mutant homozygote to see whether *shaker-2*'s characteristic deafness and hyperactive behavior could be eliminated. When a BAC clone did succeed in rescuing the phenotype, it was sequenced and the myosin gene identified. Mutations in the gene were found in the *shaker-2* mouse as well as in human families.

The first gene found to affect the sensory hair cells directly also encoded a myosin, myosin VIIA, in the *shaker-1* mouse mutant and Usher syndrome type 1B (*6*, *7*), and this was followed rapidly by the discovery of a second myosin, myosin VI, as responsible for the deafness in the *Snell's waltzer* mouse mutant (*8*). What function of these myosins makes them so critical for hearing? A myosin is believed to be responsible for adjusting the tension on the tip link, but it is myosin 1B that is the favored candidate for this role. Unconventional (non–muscle-like) myosins act as actin-based motors, and are generally thought to use actin filaments as tracks along which to transport their cargos such as intracellular vesicles. Sensory hair cells have an abundance of actin for the unconventional myosins to act on; the stereocilia are filled with actin and are anchored in a dense actin-rich network inside the cell. Thus, the three unconventional myosins that underlie mammalian deafness may help to move vesicles or other cargo around the hair cell, using the abundant actin as a substrate, as in other cell types.

However, these unconventional myosins may have another role. The earliest abnormalities seen in the mouse mutants all involve the actin-rich stereocilia: *shaker-1* mutants show disorganization of the stereocilia bundle (*9*), stereocilia are fused in *Snell's waltzer* mutants, and now *shaker-2* mutants are reported to have abnormally short stereocilia (*3*). These defects all suggest that these unconventional myosins may anchor or otherwise control the actin-based architecture that is vital to hair cell function, in contrast to simply using actin as a substrate for moving cargo. The recent report that diaphanous, a protein that assists in establishing an actin scaffold, is also implicated in progressive hearing loss emphasizes the critical importance of the actin network in hair cell function (*10*). Now the difficult bit begins: establishing exactly what these molecules do in hair cells, and why each one has such a different effect on the ultrastructure of the developing cell.

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