Auditory neuroscience: Development, transduction, and integration

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Hearing underlies our ability to locate sound sources in the environment, our appreciation of music, and our ability to communicate. Participants in the National Academy of Sciences colloquium on Auditory Neuroscience: Development, Transduction, and Integration presented research results bearing on four key issues in auditory research. How does the complex inner ear develop? How does the cochlea transduce sounds into electrical signals? How does the brain's ability to compute the location of a sound source develop? How does the forebrain analyze complex sounds, particularly species-specific communications? This article provides an introduction to the papers stemming from the meeting.

We live in a world of sounds. Although we often attend to these signals only subconsciously, hearing constantly informs us about our surroundings: people entering and leaving the room, equipment beginning and ending its tasks, announcements and alarms alerting us to change and danger. From plainsong to Smashing Pumpkins, audition underlies one of life's chief pleasures, the enjoyment of music. Most importantly, our communication with one another rests primarily on our ability to interpret the complex sonic signals that constitute speech. The study of hearing is therefore motivated not only by intellectual curiosity but also by an appreciation of the sense's importance in daily life and an interest in restoring hearing in those deprived of its virtues.

The National Academy of Sciences colloquium on Auditory Neuroscience: Development, Transduction, and Integration, held on May 19–21, 2000, at the Arnold and Mabel Beckman Center in Irvine, CA, reviewed recent progress in auditory research. Rather than attempting a comprehensive overview of the field, the colloquium's organizers sought to elicit contemporary answers to four questions. How is the ear formed? How does it transduce sounds into electrical signals? How does the brainstem develop its capacity to compute the spatial location of sound sources? How do the upper reaches of the auditory pathway analyze complex sounds? The balance of this article establishes the motivation for each of these queries and provides a précis of our current understanding.

Development of the Inner Ear

The ear's elaborate structure—justifiably called the labyrinth—forms from a simple slab of epithelial cells, the otic placode of the embryo. Developmental biologists have begun to elucidate the steps in this process. Cellular expression of a battery of morphogenetic proteins partitions the aural primordium into precursors for six receptor organs (1). In a series of origami-like steps, the otic cyst then folds into the three toroidal semicircular canals, the ellipsoidal utricle and saccule, and the snail-like cochlea. The constituent cells meanwhile begin to adopt several fates. Cells in the sensory patch of each receptor organ hone their identities by molecular competition with one another, yielding in the mature ear a crystalline array of hair cells separated by supporting cells. Incipient hair cells then erect their elaborate hair bundles by complex manipulations of the cytoskeleton (2). Supporting cells simultaneously differentiate into several distinct types whose functions remain obscure. After neuroblasts have left the sensory epithelium, the daughters of their cell divisions coalesce into ganglia adjacent to the labyrinth. The resultant neurons innervate hair cells and extend axons along the eighth cranial nerve into the brain, where they transmit information to cells of the cochlear and vestibular nuclei.

Because hair cells in the human cochlea are not mitotically replaced, their number declines throughout life as a result of genetic abnormalities, ear infections, loud sounds, ototoxic drugs, and aging. As a consequence, about one-tenth of the population in industrialized countries suffers from significant hearing loss. Research on the development of hair cells is accordingly motivated in part by the expectation that an understanding of the factors involved in creating hair cells will suggest a means of regenerating them. There are several reasons to hope for success in this endeavor. First, it is clear that supporting cells can serve as hair-cell precursors: in fishes and amphibians, hair cells are formed throughout life by this means. Next, functional hair cells have been shown to regenerate in avian cochleas after destruction of the original receptors with loud sounds or ototoxic drugs. Finally, several growth factors have already proven effective in promoting the mitosis of hair-cell precursors in the mammalian utricle. If new hair cells can be created in the human cochlea, their potential connection to the nerve fibers surviving nearby offers an excellent opportunity for the restoration of hearing.

Transduction of Stimuli in the Inner Ear

Not only can we hear sounds of frequencies from 20 Hz to 20 kHz, but a trained musician can discriminate frequencies with a precision of $\approx 0.1\%$. An important topic of research for over a century therefore has been the mechanism by which stimulus frequency is represented along the basilar membrane. Our understanding of this process rests on three fundamental insights. First, as adduced by Helmholtz (3), each increment of the approximately 30-mm-long basilar membrane is tuned to a particular frequency by such mechanical properties as its mass and tension. Next, as demonstrated by von Békésy (4), sound energy flows through the fluids of the cochlea, producing a traveling wave along the basilar membrane. Finally, as hypothesized by Gold (5), the cochlea contains an active element that

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This paper is the introduction to the following papers, which were presented at the National Academy of Sciences colloquium ''Auditory Neuroscience: Development, Transduction, and Integration,'' held on May 19–21, 2000, at the Arnold and Mabel Beckman Center in Irvine, CA.

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amplifies mechanical inputs and allows resonant responses despite the damping effects of viscosity.

The nature of the amplifier that mediates cochlear sensitivity and frequency discrimination is a topic of lively debate. Mechanical amplification originated over 350 million years ago, for it occurs in amphibians and in all four ramifications of the amniote vertebrates (6). At least in nonmammalian tetrapods, amplification seems to result from active movements of the mechanoreceptive hair bundles (7). Mammals have evolved a distinctive amplificatory appurtenance, the outer hair cell. Electrical stimulation of this cell causes it to elongate or contract, a movement thought to effect amplification by pumping energy into the basilar membrane's oscillation (8). It remains unclear whether this electromotile mechanism has supplanted hair-bundle motility as the amplificatory mechanism in mammals, whether the two processes coexist, or whether electromotility serves another purpose altogether.

Recent studies of cochlear mechanics have used laser interferometry to provide details of the basilar membrane's elaborate motion. As a result of saturation in the cochlear amplifier, the structure's responsiveness is highly nonlinear. The peak sensitivity occurs for threshold sounds, which elicit movements of less than ± 1 nm; amplification is negligible for loud sounds (9). The waveform of oscillation suggests that, even near the threshold, dozens of outer hair cells contribute to the amplification of a pure sinusoidal input. Interferometric measurements also imply that each increment of the basilar membrane does not simply oscillate up and down, but rather that the inner and outer portions of the membrane move in opposite directions as the overlying tectorial membrane resonates independently.

Processing of Sound in the Brainstem

The auditory system is built for speed. Hair cells transduce stimuli in microseconds, a striking contrast to the tens to hundreds of milliseconds required by photoreceptors and olfactory neurons. Axons in the auditory nerve can fire action potentials at rates approaching 1,000 per second. Specialized glutamate receptors speed synaptic processing along the auditory pathways; the lavish use of K^+ channels lowers neuronal time constants and shortens the climb to threshold (10). In keeping with this intense signaling activity, histochemical staining reveals that the auditory system has the highest metabolic rate in the brain.

The rapidity and temporal precision of auditory processing underlie one of the fundamental functions of the auditory brainstem, the localization of sound sources in space. Like many other animals, we often detect a novel environmental feature by hearing it, then turn our eyes or head for closer inspection. Although quite routine, this procedure involves remarkable neural computations. Interaural time difference, the delay in the arrival of a sound at the ear farther from its source relative to that at the nearer ear, is a key clue to a sound source's position. But even a sound coming directly from one side reaches the near ear only 600 μs earlier than the far one, an interval comparable to the duration of a single action potential. Our finest discrimination of a source's position involves measurement of interaural time delay with a precision of less than 20 μs—a seemingly impossible feat that we reflexively perform dozens of times a day.

Our ability to localize sound sources is not confined to the horizontal dimension; we can also situate an aural target along the vertical axis. Here the corrugated surface of the external ear is of prime importance, for the efficiency with which the pinna captures sounds originating at different elevations depends on their frequencies. The dorsal cochlear nucleus appears to be the neural computer charged with inferring sound-source elevation from the resultant spectral clues.

For the brain's sound-localization apparatus to direct eye and head movements, it is essential that an exact correspondence exist between the sensory representations of sound sources and of visual objects. This interaction in fact occurs when a map of auditory space, created by neurons in the inferior colliculus, projects to the optic tectum or superior colliculus of the midbrain to form a bimodal, visual-auditory map (11). In both owls and ferrets, developmental studies indicate that the visual map regulates the auditory one: after derangement of the correspondence by respectively offsetting visual images with prisms or deflecting the eyes by surgery, the auditory map shifts so as to regain its congruence with the visual map. Studies of this elegant form of neural plasticity have now pinpointed the site where the shift occurs, which in owls lies in the external nucleus of the inferior colliculus.

Analysis of Complex Sounds by the Forebrain

The most important role of hearing in our daily lives is the perception of speech. Audition likewise serves many other animals in the analysis of signals from conspecifics: the alarm calls of numerous gregarious species, the territorial and mate-attracting songs of birds, and the extensive lexicon of primates. The processing of communication signals is very difficult, as attested in the instance of human speech by the fact that computers have achieved a limited degree of success only after 50 years' effort! The neuronal substrate for analysis of complex sounds, including those associated with conspecific communication, is beginning to emerge from contemporary investigations.

Although the auditory cerebral cortex of primates has been known for decades to occupy the dorsal surface of the temporal lobe, the complexity of the region has been appreciated only recently. The auditory cortex now is known to have at least 15 subdivisions, each with distinct patterns of anterograde and retrograde projection. Although neurons in the core region of the auditory cortex are responsive to pure-tone stimuli, those in the belt of surrounding cortical areas are better activated by more complex sounds, including species-specific vocalizations.

Among the most discriminating auditory areas studied to date are the telencephalic nuclei of the song system in songbirds. Neurons here respond only to species-specific song and distinguish between song syllables played in different orders. Studies on this topic, as well as on the cortical analysis of species-specific calls in primates (12), are especially exciting because they seem likely to shed light on the mechanism of our most profound auditory ability, the interpretation of speech.

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