

Sensory experience and the formation of a computational map of auditory space in the brain

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Summary

The basic wiring of the brain is first established before birth by using a variety of molecular guidance cues. These connections are then refined by patterns of neural activity, which are initially generated spontaneously and subsequently driven by sensory experience. In the superior colliculus, a midbrain nucleus involved in the control of orienting behaviour, visual, auditory, and tactile inputs converge to form superimposed maps of sensory space. Maps of visual space and of the body surface arise from spatially ordered projections from the retina and skin, respectively. In contrast, the map of auditory space is computed within the brain by tuning the neurons to different localization cues that result from the acoustical properties of the head and ears. Establishing and maintaining the registration of the maps in the face of individual differences in the size and relative positions of different sense organs is an activity-dependent process in which the synaptic circuits underlying the auditory representation are modified and calibrated under the influence of both auditory and visual experience. *BioEssays* 1999;21:900–911. © 1999 John Wiley & Sons, Inc.

Introduction: representing sensory information in the brain

One of the most important functions of the nervous system is to obtain information about events in the external environment. This information is used for the control of movement and to generate, on the basis of previous experience, our perception of the world. The sensory analysis of the environment begins with receptor cells that are specialized for detecting particular physical or chemical stimuli such as mechanical displacements, light, certain molecules, or

changes in temperature. The receptor cells, which may be housed in sense organs, such as the eyes or the ears, transduce these various forms of energy into the electrical potential changes that are used by nerve cells for transmitting signals. The information carried by the receptor cells is then fed into the sensory pathways, which consist of distinct subcortical and cortical areas within the central nervous system.

In the visual, auditory, and somatosensory systems, the receptor surface is topographically organized in that neighbouring cells signal adjacent sensory stimuli. For example, the optical properties of the eye allow each region of the retina to receive an image from a different part of the visual world, giving rise to a neural map of visual space. Similarly, each location on the body surface is represented by the activity of mechanoreceptors in that part of the skin. The response selectivity of the auditory receptor cells also varies systematically along the length of the cochlea in the inner ear. In contrast to the visual and somatosensory systems, however, neighbouring cochlear hair cells are tuned to slightly different sound frequencies rather than positions in space.

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Abbreviations: AMPA, α -amino-3-hydroxy-5-methyl-4-isoxazole propionate; BIN, nucleus of the brachium of the inferior colliculus; ICX, external nucleus of the inferior colliculus; ILD, interaural level difference; ITD, interaural time difference; NMDA, *N*-methyl-D-aspartate; SC, superior colliculus.

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In these sensory systems, the neural pathways that transmit signals from the receptor cells to their targets exhibit the same spatial order as that of the receptor cells within the sense organ. This is also the case for most of the ascending and descending connections that exist between successive levels of processing within the central nervous system.^(1,2) Consequently, sensory information is represented in the brainstem, thalamus, and at least the primary sensory areas of the cerebral cortex in the form of neural maps that mirror the functional organization of the receptor surface.

In principle, the axons of neurons in the projection nucleus could maintain their neighbourhood relationships as they grow toward the target nucleus and therefore arrive there in a topographically organized manner. However, this is frequently not the case. For example, the ordered arrangement of axons in the optic nerve of certain species is lost and then recreated at the target structure.⁽³⁾ The organization and polarity of the maps at successive levels of processing may also differ, as is the case between the thalamus and some sensory areas of the cortex.⁽⁴⁾ This will determine whether a systematic exchange of neighbours is required for neurons in the two areas are to be connected appropriately.

Within the framework of these projectional receptor maps, so named because they arise from the spatial order in the afferent projections that leave the sense organs, neurons integrate converging inputs to compute other sensory qualities. Progressive levels of processing can give rise to new representations that are no longer isomorphic with those found at the level of the sensory receptor cells, but which are instead topographically related to other biologically relevant features. These higher-level representations are often referred to as computational maps because they are generated as a result of integrative processes that take place within the brain.

Computational maps provide a means by which more complex and sophisticated sensory information can be encoded. In some brain areas, computational maps are superimposed on a projectional map. For example, the primary visual cortex is organized “retinotopically” so that each point in visual space is analyzed by a restricted region of cortical neurons. Within these regions, other functional properties, such as selectivity for lines or edges of a particular orientation and the extent to which neuronal responses are dominated by either eye, are organized in an orderly manner.⁽⁵⁾ In the auditory system, the one-dimensional sound frequency map of the ear is expanded within the central auditory structures, so that a band or sheet of neurons that are tuned to the same frequency represents each point on the cochlea. Within these so-called isofrequency regions, which lie approximately orthogonal to the cochleotopic or “tonotopic” axis, clustered distributions or topographic representations of several other stimulus features have been found.^(6–9)

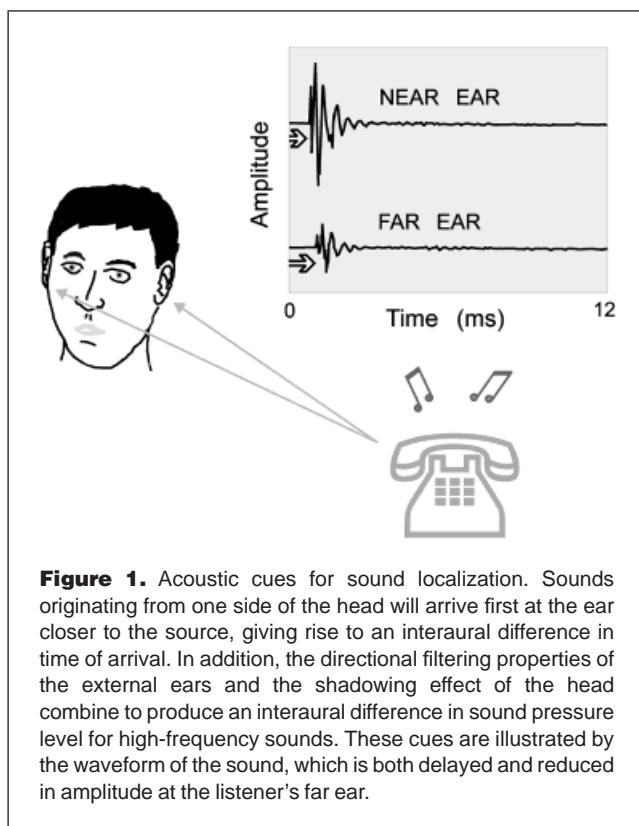
In other parts of the brain, the emergence of higher-level response properties involves the replacement of the topographic representation of the receptor surface by a computational map. A good example of this is found in echolocating bats, which navigate by emitting ultrasonic vocal signals and listening for the returning echoes due to reflections from objects in the animal’s flight path. As in other mammals, sound frequency is mapped out across the surface of the bat’s primary auditory cortex. This area is surrounded by other auditory cortical fields that are not tonotopically organized. Instead, they contain neurons that respond best to pairs of sounds that mimic different components of the animal’s biosonar pulse and its returning echo. The tuning of these neurons to particular pulse-echo combinations varies systematically in different parts of the cortex to form neural maps of important stimulus features such as target range and relative velocity.⁽¹⁰⁾

One of the most fundamental tasks performed by the auditory system is sound localization. Identifying the location of a sound source plays a key role in the ability of animals to direct attention toward novel stimuli in the environment and, therefore, is particularly important when seeking prey or trying to avoid potential predators. Sound source location is another feature that must be derived computationally because this involves the synthesis of neuronal stimulus selectivities that are not present at the level of the receptor epithelium.

This review focuses on the integrative steps involved in sound localization that lead to the mapping of auditory space within the brain and on the mechanisms that underlie their formation and plasticity during development. The development of the tonotopic organization of the auditory system and of neuronal sensitivity to other complex stimuli, including the neural circuitry responsible for song learning in birds, has been the subject of other recent reviews.^(11–13)

Localizing sounds in space

The location of a sound source is determined by using spatial cues that arise from the way in which sounds interact with the head and the external ears (Fig. 1). The most thoroughly studied are known as binaural cues, because they are based on differences between the sounds reaching the two ears.^(14,15) Sounds emanating from a source located on the midline will arrive simultaneously and with equal amplitude at the two ears. For a source located to one side of the midline, however, the difference in the path length to each ear gives rise to an interaural difference in the time of arrival (ITD). Low-frequency tones (up to 1,500 Hz in humans) can be localized by using the differences between the phases of the sound at the two ears, which result from the sound arriving



slightly later at the ear farther from the source. Interaural differences in sound level (ILD) are generated by a combination of the acoustic shadow cast by head, which acts as an obstacle for high-frequency sounds, and the direction-dependent filtering produced by the external ear, the visible part of the ear on the side of the head. As sounds pass through the external ear, the amplitude of different frequency components may be increased or decreased according to their direction of incidence. These filtering effects give rise to spectral cues for sound location, which actually provide sufficient directional information to allow broadband sounds to be localized reasonably well by using one ear alone.⁽¹⁵⁾

Neural circuits for sound localization

The first step in constructing a neural map of auditory space involves establishing the sensitivity of neurons to specific values of these localization cues. The auditory pathways to the midbrain, where a map of space is first put together, have been most thoroughly investigated in the barn owl.⁽¹⁶⁾ Unusually, this animal can use ITDs and ILDs for sound localization over the same frequency range. Because of the asymmetry in its ears, barn owls can use ILDs to determine the vertical location of a sound source, whereas ITDs are used for localization in the azimuthal or horizontal plane. To establish sensitivity to binaural cues, neurons must receive converging

signals from the two ears. ITDs and ILDs are processed initially in different tonotopically organized brainstem nuclei and topographic maps of both cues are found within frequency-specific channels.^(6,8) At subsequent levels of processing within the owl's brainstem, inputs are combined across different frequency channels and the ILD and ITD pathways merge. As a result, neurons along this pathway become less selective for sound frequency, but more selective for sound location. In the external nucleus of the inferior colliculus (ICX), individual neurons possess spatially restricted receptive fields that vary systematically to form a two-dimensional map of auditory space.⁽¹⁷⁾ This map is, in turn, transmitted by means of a topographic projection to the optic tectum, where it is integrated with a projectional map of visual space.⁽¹⁸⁾

In mammals, the initial coding of different types of auditory localization cue also takes place to a large extent within separate, parallel pathways in the mammalian brainstem.⁽¹⁹⁾ ITDs and ILDs are processed primarily in the medial and lateral divisions of the superior olivary complex, respectively. However, in contrast to barn owls, these binaural cues are used to determine sound azimuth over different frequency ranges. Much less is known about the neural pathways that encode monaural spectral cues, which are particularly important in mammals for making elevation judgments and for distinguishing between sound directions in front of and behind the head.^(15,20) Regardless of whether the information is derived from monaural spectral cues or from binaural difference cues, the problem of constructing a map of auditory space, in which neurons are unambiguously tuned to specific sound directions, is essentially the same and involves the appropriate merging of spatial information derived from different brainstem circuits.

Topographic representations of sound azimuth have been described in the ICX⁽²¹⁾ and in the nucleus of the brachium of the inferior colliculus (BIN)⁽²²⁾ of the mammalian midbrain. Along with other auditory brainstem and cortical areas, both the ICX and the BIN project to the superior colliculus (SC),^(23,24) the mammalian homologue of the optic tectum. Like the owl's tectum, the SC contains a computational map of auditory space (Fig. 2), which is topographically aligned with maps of visual space and of the body surface.^(25–28) These sensory inputs converge on motor output pathways that control orienting movements of the eyes, head, and, in some species, the external ears.⁽²⁹⁾ The registration of the maps in the SC, therefore, allows any of the sensory cues associated with a target in space to evoke orienting movements that help to redirect attention toward that location.

Many of the neurons in the deeper layers of the SC receive converging inputs from more than one sensory modality and their responses depend on the spatiotemporal relationship between the different stimuli.⁽²⁹⁾ Facilitatory interactions are observed when stimuli of different modalities are presented in close temporal and spatial proximity, whereas response

Figure 2. Representation of auditory space in the mammalian superior colliculus (SC). **A:** The spectral localization cues generated by each external ear for a sound source in the anterior hemifield are illustrated by the amplitude spectra (gain in sound pressure as a function of frequency) recorded by means of a microphone placed in the external ear canal. Both monaural and binaural cues are used in the synthesis of the neural map of auditory space. **B:** Representation of the azimuthal dimension of auditory space in the ferret SC. The hatched areas represent spatial response profiles, plotted in polar coordinates centered on the head, for different neurons recorded in the right SC at the positions indicated by the corresponding numbers on the surface view of the midbrain. Each response profile indicates how the action potential firing rate varies with the azimuthal angle of the loudspeaker. Neurons in rostral SC (recording site 1) respond best to sounds located in front of the animal, whereas the preferred sound directions of neurons located at progressively more caudal sites (1 → 5) shift systematically into the contralateral hemifield. IC, inferior colliculus. **C:** Relationship between the visual and auditory space maps in the ferret SC. For each vertical electrode penetration, the auditory best azimuths (loudspeaker direction at which maximal response was recorded) of neurons recorded in the intermediate and deep layers of the SC are plotted against the corresponding visual coordinates of neurons recorded in the overlying superficial layers. 0° refers to the anterior midline, and negative numbers denote positions in the hemifield contralateral to the recording site. A similar correspondence between the visual and auditory maps is also found for stimulus elevation, which is mapped mediolaterally across the surface of the SC.

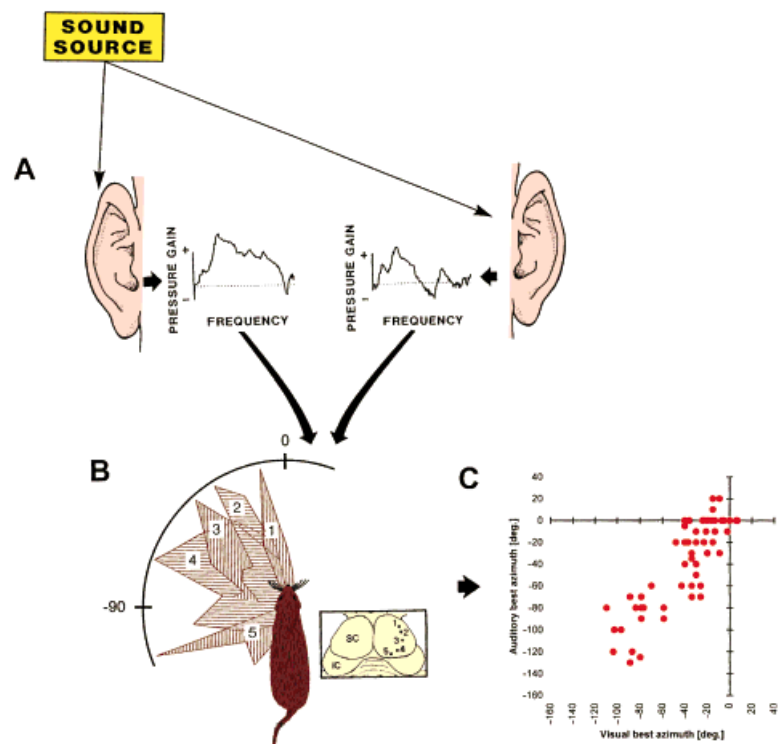
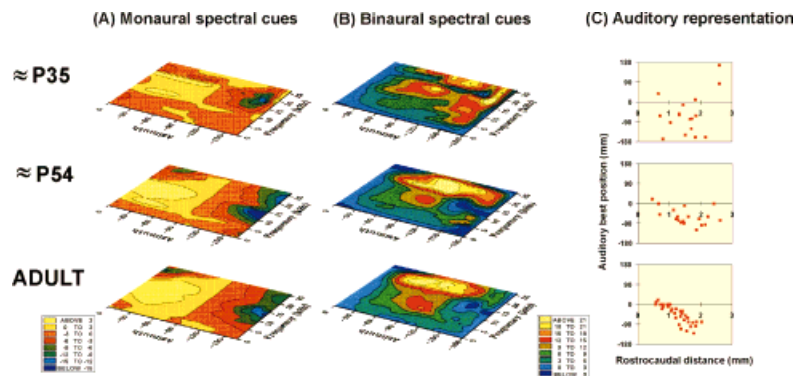


Figure 3. Time course of development of sound localization cues and the representation of auditory space in the ferret superior colliculus (SC). **A:** Monaural spectral cues recorded by means of a probe microphone implanted across the wall of the ear canal in juvenile ferrets at postnatal day 35 (P35), P54, and in adult animals (see refs. 14, 20 for details). The gains in transmission (in decibels) are indicated by the contour colors as a function of both the azimuthal direction (in the hemisphere ipsilateral to the ear from which the recordings were made) and the frequency of the sound source; warmer colors indicate higher gains. The anterior midline is at 0° azimuth. **B:** Interaural spectral differences calculated for the same animals. These contour plots illustrate how the interaural difference in sound pressure level varies with azimuth and frequency. **C:** The preferred sound directions of auditory neurons are plotted against the rostrocaudal location of the recording electrode in the SC. By the end of the eighth postnatal week, the azimuth spectral localization cues are similar to those found in adult ferrets. At the same stage, the topographic order in the auditory representation, which is initially very imprecise, is approaching that seen in adult animals.



depression or occlusion tends to occur with stimuli that are widely separated in space, time, or both. These effects appear to increase the salience of stimuli that activate more than one sense organ, making them easier to detect and localize. Because multisensory facilitation in SC neurons is observed only when each stimulus falls within its excitatory receptive field, the registration of the sensory maps would appear to be essential if response enhancements are to signal multisensory cues associated with a common source.

Wiring the brain during development

The processing of sensory information, and most other aspects of brain function, relies on the specificity with which connections are formed between neurons in the central nervous system. Studies of the visual system in particular have shown that several mechanisms are used during development to guide axons to their appropriate targets.⁽¹⁾ The early wiring of the brain appears to be determined genetically during embryonic life by using a variety of attractant and repellent molecules that influence the navigation of growth cones.⁽³⁰⁾ The initial circuits are then remodelled, a process that involves both structural and functional changes in synaptic connections, in response to the patterns of electrical activity produced by the neurons themselves.^(31,32) It has been established, at least for the visual system, that spontaneous neural activity, generated internally within the developing neural pathways, can direct the anatomic rearrangement of presynaptic axons and the formation and elimination of synaptic contacts.⁽³²⁾ But with the maturation of the sense organs and the onset of stimulus-evoked activity, sensory experience assumes an increasingly important role in shaping the neural circuits that underlie adult brain function. This is particularly the case for the higher-level response properties that are generated within the brain by serial stages of neural computation.

In the mammalian visual cortex, several functional response properties emerge as a result of specific patterns of afferent connectivity and local cortical circuits. These characteristics include binocularity, which underlies stereoscopic depth perception, and sensitivity to the orientation and direction of moving stimuli. Despite some conflicting reports, these response characteristics have been demonstrated in young, visually inexperienced animals, suggesting that they are programmed in an experience-independent manner.^(33–36) Nevertheless, the anatomic, physiologic, and behavioral consequences of altering visual inputs in various ways indicate that experience can modify and refine cortical circuitry well into postnatal life.⁽³⁷⁾

Although the influence of sensory experience on the developing brain has been most thoroughly investigated for vision, other sensory systems also show considerable developmental plasticity.^(13,14,38) In the auditory system, the role of sensory experience has been extensively examined for the development of neural circuits involved in sound localization.

In particular, studies in mammals and barn owls have demonstrated the importance of both auditory and visual experience in shaping the map of auditory space in the SC so that it matches the neural representations of the other sensory modalities.

Development of visual and auditory maps in the superior colliculus

The superficial layers of the mammalian SC are involved exclusively in visual processing and are innervated by topographically organized projections from the retina and the visual cortex.⁽²³⁾ The development of the retinocollicular projection has been studied extensively in a range of species and involves a combination of molecular guidance cues and spontaneous activity patterns.^(1,31,32) Early retinal projections exhibit targeting errors, the extent of which depends on the species in question.^(39,40) It seems likely that correlated bursts of activity in retinal ganglion cells, which have been demonstrated well before the functional onset of vision,^(41,42) contribute to the subsequent maturation of retinofugal projections. Thus, blocking either retinal activity⁽⁴³⁾ or the activity of the NMDA subclass of excitatory amino acid receptors in the target neurons^(44,45) produces an abnormal distribution of presynaptic arbors. By the time of eye opening, the refinement in the topographic precision of the retinocollicular projection is essentially complete and an adult-like map of visual space can be recorded in the superficial layers.^(14,46)

The sensory representations in the deeper layers of the SC mature more slowly. In cats, deep SC neurons first respond to visual stimuli about 2 weeks after eye opening and their receptive fields become smaller with increasing age.⁽⁴⁷⁾ This probably reflects the maturation of descending corticocollicular pathways. The first acoustically responsive neurons similarly respond to sounds presented over very large regions of space and show little sign of any topographic order.^(14,47–49) Over the next few weeks, these neurons become progressively more selective for sound direction and the map of auditory space gradually emerges. This protracted period of postnatal development is seen in both guinea pigs,⁽⁴⁹⁾ a precocial species in which the onset of hearing begins in utero, and ferrets, which are altricial animals that are unable to hear until approximately 4 weeks after birth.^(14,48)

Both peripheral and central factors contribute to the development of sensory representations in the brain. A major challenge, particularly for the auditory system, is to determine the extent to which the processing of sensory stimuli reflects the maturation of the peripheral sense organs rather than that of the afferent connections and synaptic properties of the central neurons. Airborne sounds are conducted to the receptor hair cells of the cochlea by the external ear and the middle ear. Developmental changes take place in all three parts of the ear, which will limit the effectiveness with which auditory signals are transmitted to the brain. Because the formation of a neural map of auditory space is based on the differential sensitivity of neurons to localization cues gener-

ated by the acoustical properties of the ears and head, growth-related changes in the size and shape of those structures will progressively alter the cue values that correspond to particular sound directions.^(14,50) A comparison of the development of auditory localization cues with that of the auditory space map in the ferret, reveals that the spatial tuning properties of SC neurons mature at approximately the same stage that the monaural spectral cues and ILDs reach their adult values (Fig. 3).⁽¹⁴⁾ This result would seem to indicate that the neural mechanisms underlying the map of auditory space are not adjusted continuously to adapt to the changing cues and that it is only when those cues assume their adult values that the normal topographic order in the representation becomes apparent.

The range of sound frequencies encoded by the cochlea expands toward higher values during the course of early development.⁽¹²⁾ Because the axons leaving the cochlea are topographically ordered, this tonotopic shift is closely mirrored by changes in the frequency organization of the auditory areas of the brain. The relationship between the auditory localization cue values and directions in space depends on the frequency of the sound. Consequently, developmental changes in the frequency tuning of central auditory neurons are also likely to alter their spatial response characteristics.

However, in addition to these peripheral factors, there is plenty of evidence showing that the maturation of auditory processing involves changes at different levels of the central auditory pathways in the specificity of the terminal arbors and dendritic morphology of central neurons, in the distribution of the neurotransmitter receptors they express, and in their synaptic and sound-evoked response properties.⁽¹³⁾ For example, it is possible to bypass the peripheral auditory system by direct, electrical stimulation of the afferent pathways to a particular central nucleus. This approach has demonstrated that the synaptic transmission of both excitatory and inhibitory inputs and the way in which they are integrated by neurons in the lateral superior olive, the principal brainstem nucleus that processes ILDs, is immature in neonatal gerbils.⁽⁵¹⁾

Because the SC receives inputs from several auditory nuclei and cortical fields,^(23,24) there are potentially many different levels of processing that could limit the rate at which the auditory space map matures. In ferrets, the largest inputs arise from the BIN, which appears to be particularly involved in the construction of a topographic representation of sound azimuth.^(22,24) The projection from the BIN to the ipsilateral SC is spatially ordered in both adult⁽²⁴⁾ and neonatal ferrets.⁽⁵²⁾ It also seems certain that, before the onset of hearing, some synaptic transmission is possible in the circuits that lead to the SC.⁽¹³⁾ Indeed, spontaneous activity is probably present throughout the central auditory pathway during early postnatal life⁽¹³⁾ and

presumably plays an equivalent role in modelling patterns of afferent connectivity to that postulated for the visual system.

Role of auditory experience in shaping maps of auditory space

Once the ear becomes capable of transducing sounds and the central nervous system is capable of encoding information with adequate precision, stimulus-evoked activity becomes available for making further refinements in the neural circuitry underlying the auditory space map. As with other systems, the contribution of experience to auditory map development has been assessed by observing the physiologic consequences of raising animals with altered sensory inputs. The binaural cues used to derive sound source location can be altered in a reversible manner by occluding one ear. In adult barn owls⁽⁵³⁾ and ferrets⁽⁵⁴⁾ that have been raised with one ear occluded, a near-normal map of auditory space is found, as long as the recordings are made with the ear plug still in place. It has been shown in owls that this finding is based on a compensatory change in the binaural cues to which the SC neurons are tuned,⁽⁵⁵⁾ a process that begins at the first level of binaural convergence in the brainstem.⁽⁵⁶⁾ This is an example of developmental plasticity because a similar period of monaural occlusion in adult animals does not produce an equivalent change in auditory spatial tuning in SC neurons.^(14,53)

Attempts have also been made to examine the consequences for the auditory representation in the SC of altering the localization cues provided by the external ears. Like monaural occlusion, removal of the preaural flap and facial ruff feathers in owls will change the binaural cue values that correspond to particular sound directions. Auditory neurons in the tectum of both juvenile and adult owls respond to this procedure by shifting their sensitivity toward the abnormal cue values.⁽⁵⁷⁾ In contrast, removal of the pinna and concha of the external ear in juvenile ferrets disrupts the formation of the auditory space map, as many neurons exhibit spatially ambiguous responses or tuning to inappropriate sound directions.⁽⁵⁸⁾ This is likely to be a developmental change, because a topographic representation of space is still apparent after acute removal of these structures in adult animals, even though many SC neurons exhibit spatially ambiguous tuning to two different sound directions.⁽²⁰⁾ Pinna and concha removal eliminates much of the directional information available in the spectral cues and, despite the availability of residual binaural cues, appears to interfere with the developmental process by which neurons in the mammalian brain “learn” to compute the location of sound sources. Because of self-produced sounds, complete deprivation of auditory spatial cues is technically very difficult. One way around this is to raise animals in an environment of constant, omnidirectional white noise in an attempt to mask any location-specific

information. Exposing juvenile guinea pigs to these conditions prevents the normal, age-related sharpening of auditory receptive fields and their assembly into a map of space.⁽⁵⁹⁾

These experiments indicate that the postnatal maturation of the auditory space map requires auditory experience and that the spatial tuning of individual neurons can be moulded in response to alterations in the acoustic cues generated by the animal's head. Where measured, the visual topography in the SC was reported to be unaffected by changes in auditory spatial cues. The compensatory adjustment in the auditory space map that occurs when animals are reared with one ear occluded will tend to preserve the alignment with the visual map. That visual information may be used to guide this process is suggested by the finding that much smaller changes in auditory tuning occur if the owls are visually deprived at the same time.⁽⁶⁰⁾

Role for vision

Because different sensory systems derive spatial information in different ways, establishing and maintaining the registration of the sensory maps in the SC is not straightforward. It is now clear that extensive interactions take place between visual and auditory inputs during development and that visual experience can influence the mapping of auditory space in the midbrain.

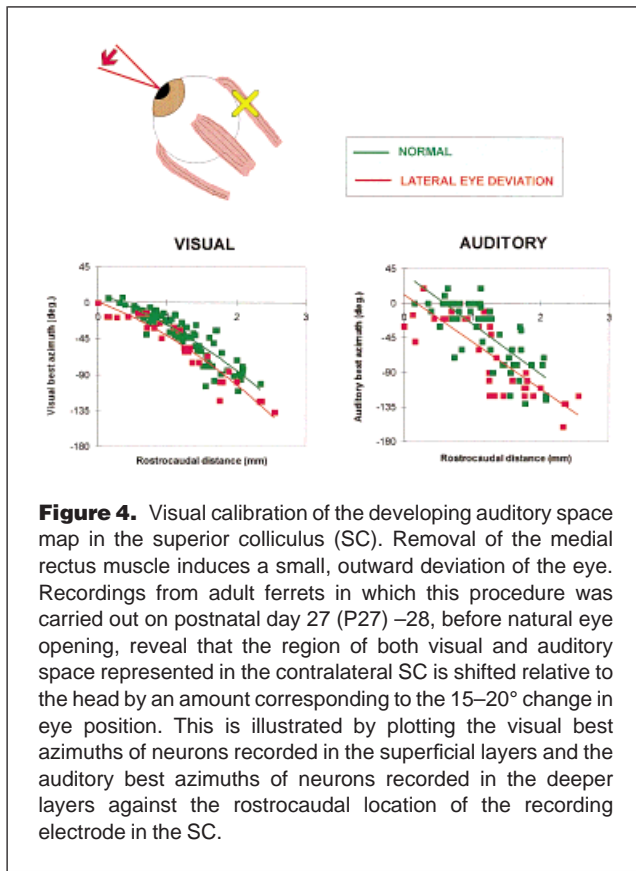
The effects on the developing map of auditory space of either altering or depriving animals of visual cues have been examined extensively. Because the visual map in the SC is retinotopic, a change in eye position will alter the coordinates of the visual field representation with respect to the head. Consequently, the visual and auditory maps should become misaligned. Indeed, this becomes a problem whenever animals move their eyes (or, in some species, their external ears) and appears to be at least partially resolved by modulating the auditory responses as eye position changes.⁽¹⁴⁾

A compensatory remapping of the auditory representation has also been observed by manipulating visual cues during development. For example, if the eye is deviated laterally in juvenile ferrets by removal of one of the extraocular muscles, the auditory representation in the contralateral SC undergoes a corresponding shift so that the visual and auditory maps continue to share the same topographic organization (Fig. 4).^(54,61) In this case, the change in auditory spatial tuning appears to be due to the shifted visual responses rather than the change in eye position per se.⁽¹⁴⁾ A matching shift in the auditory representation can also be induced by raising barn owls with prisms mounted in front of their eyes to displace the visual field optically.⁽⁶²⁾ However, the capacity of the auditory representation to undergo this adaptive realignment appears to be strictly limited as the spatial tuning of these neurons becomes somewhat disordered if the polarity of the visual map is radically altered by rotating one eye in young ferrets.^(14,54)

Because shifts in auditory topography may follow an experimentally induced alteration in the visual map, it might be expected that a loss of patterned visual signals would disrupt the process by which the auditory map is elaborated. Indeed, although topographically ordered, the auditory representation is somewhat altered by degrading the pattern of visual input by binocular eyelid suture in young owls,⁽⁶³⁾ guinea pigs,⁽⁶⁴⁾ and ferrets.⁽⁶⁵⁾ The reported errors include tuning to aberrant sound directions or to two different angles and even maps that possess the wrong polarity. However, some spatial information does pass through the closed eyelids,⁽⁶⁶⁾ and if visual inputs are eliminated altogether by rearing guinea pigs in the dark, the auditory neurons remain broadly tuned and fail to develop any topographic order.⁽⁶⁷⁾ This latter, perhaps surprising, result suggests a potential role for visual activity in auditory map development that goes beyond the retuning of auditory spatial responses after a mismatch between the two modalities. Dark rearing extends the period of developmental plasticity in the visual cortex⁽⁶⁸⁾ and, possibly by altering the expression or functional properties of neurotransmitter receptors, may delay or prevent the synaptic changes that would normally take place in the SC.

The maturation of the auditory space map is altered not only by peripheral manipulations of visual inputs but also by experimentally induced changes to the visual map in the superficial layers of the SC. In ferrets, partial neonatal lesions of this exclusively visual region disrupt the emergence of order in the underlying auditory representation.⁽⁶⁹⁾ This effect is localized to the region of the deep SC that lies below the lesion, which is consistent with the presence of topographically organized connections between the superficial and deeper laminae.⁽⁷⁰⁾ Consequently, the superficial layers of this midbrain nucleus may provide the source of the visual signals that guide the refinement of the underlying auditory representation.

These experiments highlight the importance of correlated visual and auditory activity in the physiological maturation of the auditory representation. The more accurate and reliable spatial cues provided by visual inputs seem to play an instructive role in adjusting the sensitivity of SC neurons to acoustic localization cues. As a consequence, the alignment between the visual and auditory maps can be achieved, despite individual differences in the size, shape, and relative position of different sense organs. Because topographic precision in the auditory representation appears only once the monaural and binaural cues have approached their adult values,⁽¹⁴⁾ it seems unlikely that a continuous, visually guided readjustment in the tuning of SC neurons to those cues takes place during the course of postnatal development. Moreover, these neurons may show an innate predisposition toward the typical cue values that correspond to positions in visual space. Recordings from owls raised wearing prismatic spectacles have shown that tectal neurons are initially tuned to

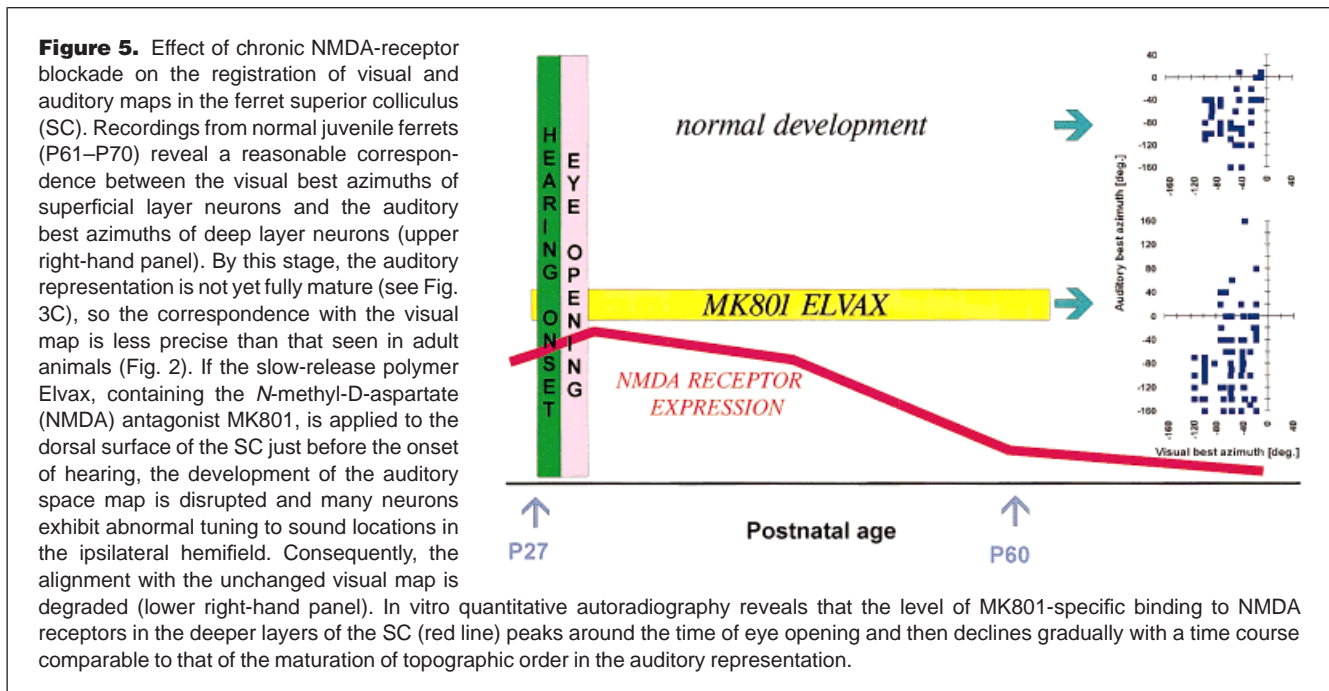


normal ITD values and that it is only after several weeks that these responses are replaced by tuning to ITD values that correspond to the optically displaced visual map.⁽⁷¹⁾ These changes are relatively slow compared with those reported for the visual cortex after monocular deprivation.⁽³²⁾ The time course over which vision calibrates the auditory representation may also be related to the ontogeny of bimodal interactions within the SC. In the cat, for example, deep layer neurons begin to show enhanced or depressed responses to bimodal stimulation several weeks after the appearance of the first unimodal responses.⁽⁴⁷⁾

Studies in the visual cortex have shown that the relationship between activity-dependent changes in physiologic response properties and the anatomic connections of those neurons are often not straightforward.⁽³²⁾ Nevertheless, in owls, visually guided changes in ITD tuning are first observed at the level of the ICX,⁽⁷²⁾ which projects topographically to the SC, and are brought about as a result of an anatomic reorganization of the projection to that structure from the central nucleus of the inferior colliculus.⁽⁷³⁾ How visual signals feed back into what is apparently a purely auditory nucleus is unclear. In ferrets, however, the BIN, the principal source of auditory input to the SC,^(22,24) does receive a topographically ordered visual input from the superficial layers of the SC.⁽⁷⁴⁾

Basis for activity-mediated changes in auditory spatial tuning

The cellular mechanisms responsible for matching the sensitivity of SC neurons to corresponding values of different auditory localization cues and to positions in visual space are



not well understood. In other systems, especially the developing visual pathways, it is widely postulated that the activity-dependent steps that lead to the reorganization of neural circuits conform to Hebbian principles of synaptic plasticity. The essential idea is that synapses are strengthened if presynaptic and postsynaptic activity are correlated but weakened when this is not the case. The probability of coordinating of presynaptic and postsynaptic activity and, therefore, of strengthening the synapse is thought to increase if converging inputs, e.g., from neighbouring axons or from the two eyes, are simultaneously active.⁽⁷⁵⁾ The same principle could apply to converging visual and auditory inputs that convey signals relating to events that are both seen and heard.

The search for the molecular trigger for the events that lead to the activity-dependent refinement of neural circuits has focused primarily on NMDA receptors. Because of the voltage-dependent Mg^{2+} block of NMDA channels, presynaptically released glutamate will open these channels and allow Ca^{2+} entry only if the postsynaptic membrane has already been sufficiently depolarized. Consequently, the activation of NMDA receptors depends on the correlation of presynaptic and postsynaptic activity, a key feature of a Hebbian synapse. Evidence from many studies in which NMDA receptor activation has been altered chronically, supports the notion that these receptors may be critically involved in the developmental refinement of connections within the brain.^(31,32)

In keeping with the effects of altered sensory experience, blockade of NMDA receptors has a particularly marked effect on the development of the map of auditory space in the SC. Chronic application of NMDA receptor antagonists to the SC by means of Elvax, a slow-release plastic, prevents the elimination of inappropriately positioned retinal arbors in rats⁽⁴⁵⁾ and the maintenance of topographic order in developing visual afferents in tadpoles.⁽⁷⁶⁾ However, studies in ferrets suggest that once the retinocollicular projection is mature, NMDA-receptor blockade has no effect on the visual map in the superficial layers.⁽⁷⁷⁾ In contrast, the auditory topography fails to develop properly in ferrets reared with Elvax implants from before the onset of hearing until after the age at which the map normally emerges.⁽⁷⁷⁾ Consequently, the registration with the unchanged visual map is much less precise than in normal animals (Fig. 5). In a similar vein, the activity-dependent matching of binocular maps in the optic tectum of *Xenopus* frogs is prevented by NMDA receptor blockade.⁽⁷⁸⁾

In contrast to the effects seen in juvenile animals, no change in auditory topography or in auditory-visual receptive field alignment is found after chronic application of NMDA-receptor antagonists to the SC in adult ferrets.⁽⁷⁷⁾ This finding would appear to be consistent with previous observations that, for most experimental manipulations, experience-induced changes in auditory spatial tuning are restricted, at least primarily, to a sensitive period during development.

Nevertheless, the relationship between NMDA receptors and the plasticity of the auditory space map is still far from clear as recent work in owls suggests that the duration of the period within which changes can be induced depends on prior experience.^(79,80)

If NMDA receptors do contribute to the developmental plasticity of sensory circuits, the reduced capacity of the maturing system to respond to altered inputs should be correlated with changes in their distribution or properties (or both). In the ferret SC, quantitative autoradiographic studies have shown that the number of NMDA receptor binding sites falls over the same time course as the maturation of the auditory space map (Fig. 5; J. Baron, A.L. Smith, and A.J. King, unpublished observation) The contribution of NMDA receptors to the synaptic currents of superficial layer neurons in the rat SC has also been reported to decline with age,^(81,82) a process that appears to be related to developmental changes in the subunit composition of the receptor channel and to the reduction in anatomic plasticity in those layers.⁽⁸²⁾ In the frog optic tectum, the first synaptic responses are mediated only by NMDA receptors and are functionally silent, whereas mature synapses also involve transmission by the AMPA subclass of glutamate receptors.⁽⁸³⁾ The addition of the AMPA component and, therefore, the selection of functional synapses may be induced by converging activity provided by other, more mature synapses that are already processing visual signals.⁽⁸³⁾

These and other results suggest that the conversion of silent synapses to functional ones may contribute to the activity-dependent refinement of synaptic connections. Moreover, developmental alterations in NMDA receptor function have been linked to synaptogenesis and other changes in neuron morphology.⁽⁸⁴⁾ It would clearly be of interest to know whether these events are correlated with the initial interaction between visual and auditory signals in the midbrain. In owls, subsequent visually guided changes in auditory spatial tuning may be mediated by synapses that also transiently exhibit a high NMDA/AMPA current ratio, raising the possibility that molecular mechanisms of plasticity can re-emerge at different stages of development.⁽⁸⁵⁾

The interpretation of experiments in which NMDA receptor antagonists have been found to affect the plastic changes that take place in the developing brain is complicated, because these receptors contribute to the excitatory currents that mediate normal synaptic transmission, particularly in young animals^(81–83) and after visually guided changes in auditory spatial tuning.⁽⁸⁵⁾ Rather than specifically interfering with a process that involves the detection of temporal correlations among converging inputs, blocking these receptors may simply reduce synaptic currents to levels below those required to induce plasticity. Nevertheless, the increasing evidence for a correlation between developmental changes in NMDA receptor function and the plasticity of different sensory

systems does support an involvement of NMDA receptors in the activity-dependent remodelling of neural circuits.

Concluding remarks

The structural and functional organization of the central nervous system is, to a large extent, programmed genetically. However, it is also the case that electrical signals generated by neurons as a means of communicating with one another play an important role in the specification of their connections. This provides a means by which experience can shape the characteristics of neurons and their assemblies, both during development and, at least for some aspects of brain function, throughout life.

Experience-dependent plasticity has been studied in many brain regions and at levels that range from molecular mechanisms to behaviour. One of the useful model systems for assessing the importance of sensory experience during development is the sound localization pathway that leads to the construction of a map of auditory space in the SC. In this midbrain nucleus, visual, auditory, and tactile inputs converge to form topographically aligned maps of space, providing different sensory signals with access to the motor pathways that control goal-directed orientation behaviour. Neural maps of visual space and of the body surface arise from topographic projections from the receptor epithelium in their respective sense organs. Because sound source location is not mapped along the auditory receptor cells in the cochlea, a representation of auditory space must be synthesized or computed within the brain by tuning neurons to appropriate combinations of acoustic localization cues that vary with the size and shape of the head and ears.

As with other complex neuronal response properties, sensory experience plays a critical role in calibrating the auditory representation so that it develops in register with the maps of the other sensory modalities. To allow for individual variations in the size and shape of the head and ears, auditory experience is needed to match the tuning of SC neurons to monaural and binaural localization cues that correspond to the same direction in space. The more accurate and reliable information provided by the visual system, however, plays the dominant role in aligning the sensory maps in the SC. Progress is now being made in identifying the origin of these visual signals and the site at which they influence the development of auditory responses (Fig. 6). Moreover, as more of the underlying circuitry becomes established, it should be possible to determine the extent to which synaptic reorganization in this system involves a remodelling of axonal connections as opposed to changes in the efficacy of individual synapses.

Key areas for future study will include the molecular and cellular mechanisms that underlie both the initial matching of visual and auditory signals and the experience-dependent adjustment of auditory spatial tuning that can be induced at

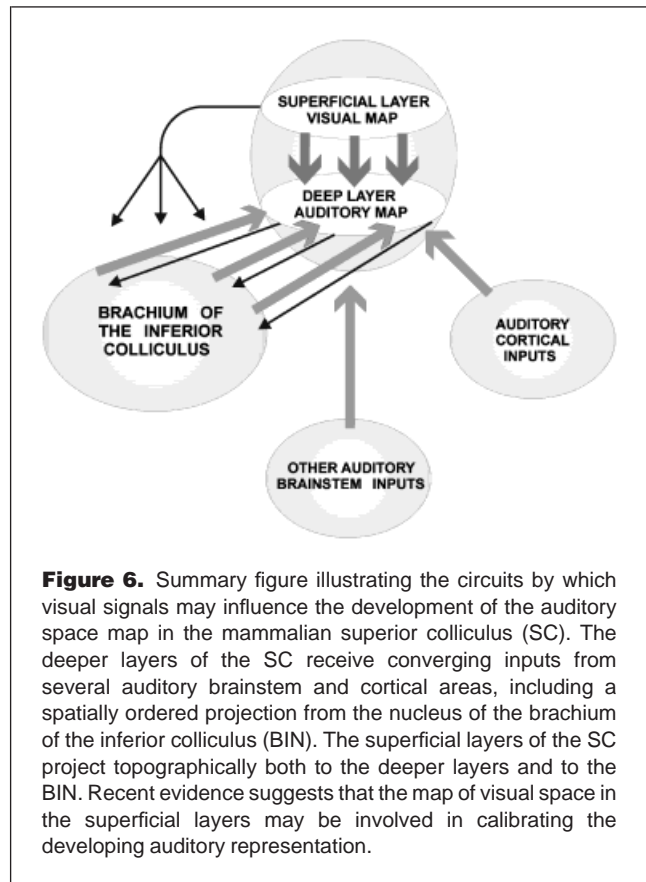


Figure 6. Summary figure illustrating the circuits by which visual signals may influence the development of the auditory space map in the mammalian superior colliculus (SC). The deeper layers of the SC receive converging inputs from several auditory brainstem and cortical areas, including a spatially ordered projection from the nucleus of the brachium of the inferior colliculus (BIN). The superficial layers of the SC project topographically both to the deeper layers and to the BIN. Recent evidence suggests that the map of visual space in the superficial layers may be involved in calibrating the developing auditory representation.

later stages of development. As in other aspects of brain development and plasticity, the NMDA class of glutamate receptors appears to contribute to the steps that mediate adaptive changes in auditory response properties. The precise function of these receptors and which of their constituent subunits are involved remain to be elucidated, however. Moreover, it is likely that other excitatory and inhibitory neurotransmitters as well as developmentally regulated growth factors play a direct or modulatory role in neuronal plasticity. Finally, if we are to understand fully the functional significance of the effects of sensory experience on the developing brain, it will also be necessary to examine the extent to which the plasticity of neural circuits is accompanied by changes in behaviour.

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