CHAPTER

# 4

# Multisensory Circuits

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## 4.1 INTRODUCTION: MULTISENSORY PERCEPTION AND BEHAVIOR

As they interact with their surroundings, humans and other animal species typically experience multiple stimuli that are registered by different sense organs. These signals may provide complementary information about the same object or event. This is likely to be the case if the stimuli occur at more or less the same time and originate from the same location in space or – in the case of more complex signals, such as the auditory and visual components of speech – if they are semantically related. The capacity of the central nervous system to merge and integrate input from different sensory modalities can have profound effects on perception and behavior. This can be seen as an improvement in an animal's ability to detect or discriminate objects, or determine where they are located, and a reduction in the time required to react to them (reviewed by Alais et al., 2010; Calvert et al., 2004).

In addition to enhancing perceptual judgments, particularly when the stimulus information supplied by one or more sensory modalities is weak or ambiguous, crossmodal interactions can induce various illusions if the different sensory inputs provide conflicting cues. These illusions provide further evidence of how the brain attempts to merge multisensory inputs so that they are perceived as if they originate from the same external event. One of the most striking examples involves the effect of vision on speech perception. Being able to view the speaker's face improves speech comprehension so long as the audiovisual cues are congruent (Ma et al., 2009; Sumby and Pollack, 1954), but watching the speaker articulate a different speech sound from the one that is being presented results in the perception of a third sound that represents a combination of what was seen and heard (the "McGurk effect"; McGurk and MacDonald, 1976). Another well-known example of the influence of vision on auditory perception is provided by the "ventriloquism effect." Although spatially aligned visual cues can improve the accuracy of auditory localization (Shelton and Searle, 1980; Stein et al., 1988), misaligned visual cues can bias or capture the perceived location of a sound source (Howard and Templeton, 1966; Slutsky and Recanzone, 2001).

In addition to their effects on the perceived identity and location of stimuli, interactions between the senses can determine when those stimuli are perceived to occur. For example, if a single light flash is accompanied by multiple auditory beeps, subjects report seeing multiple

flashes (Shams et al., 2000). Similarly, sounds can alter the perceived timing of visual events (Fendrich and Corballis, 2001; Recanzone, 2003). Thus, whereas vision tends to dominate audition in the spatial domain, the reverse is true for temporal tasks (Welch and Warren, 1980). This is because in many species, including humans, the spatial resolution of the visual system is superior to that of the auditory system, whereas temporal sensitivity is much greater for audition (King and Nelken, 2009). However, this relationship between the senses is not fixed because the ventriloquism effect can work in reverse, with audition capturing vision, if visual signals are degraded so that they become harder to localize (Alais and Burr, 2004). It seems, therefore, that the integration of different sensory cues in the brain is statistically optimal, in the sense that each cue is weighted in a task-specific way according to how reliable it is (Alais et al., 2010; Ernst and Banks, 2002).

These examples illustrate how interactions between the senses can have a considerable impact on how the world is perceived. Circuits within the brain must therefore be able to merge multisensory signals that are linked in space and time, as well as more complex cues, such as facial expressions and their associated vocalizations. Although certain brain regions such as the superior colliculus (SC) in the midbrain and the posterior parietal cortex, prefrontal cortex, and superior temporal sulcus have long been associated with specific multisensory functions, it is now clear that convergence of different modality inputs is much more widespread than previously realized. This is particularly the case in the cortex, where even those areas typically associated with modality-specific processing, such as the auditory or visual cortex, are now thought to be part of an interactive network of brain regions that are influenced by multiple sensory systems (reviewed by Alais et al., 2010; Ghazanfar and Schroeder, 2006). Inputs from other modalities to primary and secondary cortical areas may serve to amplify responses to related input from the dominant modality (Schroeder et al., 2008), but there is also evidence that they can alter the sensitivity of cortical neurons in more specific ways (e.g., Bizley and King, 2008; Ghazanfar et al., 2005). Moreover, the finding that early cortical sensory areas are engaged when crossmodal illusions, including the ventriloquism effect (Bonath et al., 2007) and the sound-induced perception of illusory light flashes (Mishra et al., 2007), are experienced indicates that these brain regions as well as the more traditional association areas are likely to contribute to perception in a multisensory world.

In spite of the widespread intermixing of sensory modalities in the cerebral cortex, surprisingly little is known about the development of those circuits. Instead, the SC has, for many years, served as a model system for investigating both the principles of multisensory integration by neurons in the adult brain and the developmental processes that allow different sensory inputs to be combined and coordinated in the first place. This chapter therefore focuses primarily on the developmental mechanisms involved in merging multisensory spatial information in this midbrain structure. Although relatively few attempts have been made to examine the maturation of multisensory processing in the cortex, valuable insights into how the different senses interact at this level during development have been obtained by investigating the crossmodal consequences of early sensory deprivation. These studies, which are based predominantly on humans and other species that have been deprived of their vision or hearing, are considered in the second part of the chapter.

## 4.2 MULTISENSORY PROCESSING IN THE SC

The mammalian SC receives visual, auditory, and somatosensory afferents from a large number of subcortical and cortical brain areas (e.g., Edwards et al., 1979; King et al., 1998a; Wallace et al., 1993). As far as we know, these inputs are all unisensory and converge, often on the same neurons, in the deeper layers of the SC. In contrast, the superficial layers contain only visually responsive neurons. Nevertheless, the sensory representations found in both the superficial and deeper layers are arranged topographically with respect to their receptive field locations (Cynader and Berman, 1972; King and Hutchings, 1987; King and Palmer, 1983; Middlebrooks and Knudsen, 1984; Stein et al., 1976; Wallace and Stein, 1996). Moreover, these maps lie in spatial register with one another so that different modality signals arising from a particular direction in space, and therefore, potentially from the same source, are represented in a corresponding region of the SC. For those deep-layer neurons that receive converging visual, auditory, and somatosensory afferents, this means that their unisensory receptive fields overlap and covary with the anatomical location of the neurons within the SC.

One of the most important and well-studied properties of SC neurons is that the number of spikes evoked by a combination of two or more stimulus modalities is often higher than that of the response to each stimulus presented by itself and may even exceed the sum of those responses. Multisensory enhancement is typically most pronounced when the individual stimuli are weakly effective in driving the neurons (Meredith and Stein, 1986) and is observed when those stimuli are presented in close temporal and spatial proximity (King and Palmer, 1985; Meredith and Stein, 1996; Meredith et al., 1987). In contrast, pairing multisensory signals that are widely separated in time or space does not enhance,

and may even depress, the response to unisensory stimulation. These interactions between the different sensory inputs reaching the SC should therefore serve to amplify the neuronal responses to a multisensory target, such as an object that can be seen and heard.

Neurons in the deeper layers also discharge prior to eye and head movements, and while the SC is implicated in different motor behaviors, its principal function is to shift an animal's gaze toward sensory stimuli located on the contralateral side of the body (reviewed by Gandhi and Katnani, 2011). Superimposing the different sensory representations in the SC therefore allows each of the spatial cues associated with a multisensory target to trigger, via a common motor output map, a gaze shift in that direction. The principles of multisensory integration exhibited by SC neurons suggest that spatiotemporally coincident stimuli will, by evoking stronger responses in SC neurons, promote more accurate orienting behavior, whereas pairing unisensory stimuli from different locations or at different times should have the opposite effect. Similarly, integration of inputs from different sensory modalities would be expected to have the greatest effect on orienting behavior when the individual cues are weak. Studies in cats (Stein et al., 1988) and humans (Corneil et al., 2002) have indeed confirmed that this is the case. Moreover, in cats, deactivation of descending projections from two association areas in the cortex, the anterior ectosylvian sulcus (AES) and the rostrolateral suprasylvian sulcus (rLS), eliminates both the multisensory integrative processes displayed by SC neurons (Jiang et al., 2001) and the behavioral benefits of synthesizing inputs from different sensory modalities (Jiang et al., 2002).

Because multisensory enhancement of the responses of SC neurons occurs only when each stimulus falls within its excitatory receptive field, the spatial registration of the sensory maps in the SC would appear to be essential if these interactions are to signal the different modality cues associated with a common source. However, maintaining map registration is problematic because spatial information is specified by each sensory modality using a different frame of reference. The visual map is coded in retinal coordinates, and so the receptive fields of SC neurons will shift relative to the head as the eyes move and therefore potentially become misaligned with the auditory receptive fields, which are centered on the head and ears, and the body-centered somatosensory receptive fields. However, electrophysiological recordings from SC neurons in awake animals have shown that somatosensory (Groh and Sparks, 1996) and auditory (Hartline et al., 1995; Jay and Sparks, 1984; Populin et al., 2004) responses are modified by changes in eye position, suggesting that these signals are partially transformed into a common eye-centered reference frame that matches the coordinates of the visual map.

Combining appropriate inputs from different sensory modalities during development is also challenging, particularly since the spatial relationship between the sense organs can change as the body grows. The following section examines the role of sensory experience in aligning the different modality maps and in the maturation of multisensory integration in the SC.

## 4.3 DEVELOPMENT OF MULTISENSORY RESPONSES IN THE SC

Each of the sensory systems appears to begin functioning at a different stage of development, with somatosensory sensitivity emerging first and visual last (Gottlieb, 1971) (see Chapter 3). This sequence has also been observed in the SC, where recordings from newborn kittens have shown that the earliest sensory responsive neurons are activated only by tactile stimuli, followed a few days later by the first acoustically responsive neurons and subsequently by responses to visual stimuli (Figure 4.1; Stein et al., 1973). The maturation of multisensory neurons follows the same order, with neurons sensitive to both tactile and auditory stimuli appearing during the second postnatal week, almost 2 weeks before the first visually responsive multisensory neurons (Figure 4.1; Wallace and Stein, 1997). However, in more precocial species, including humans and other primates, most sensory systems become functional before birth, and the SC of newborn monkeys has been shown to contain many multisensory neurons (Wallace and Stein, 2001).

Despite these differences in the postnatal age at which multisensory neurons develop, a common feature of all the species, both precocial and altricial, that have been studied is that the sensory response properties of deep SC neurons initially differ in a number of ways from those seen in older animals (Campbell et al., 2008; Stein et al., 1973; Wallace and Stein, 1997, 2001; Withington-Wray et al., 1990a). In common with other brain areas, sensory responses recorded from SC neurons in very young animals typically have longer latencies, are more sluggish, and show greater habituation to repeated stimulation than is the case in later life. They also lack at least some of the stimulus selectivity that is characteristic of the adult. The details of these age-dependent differences vary to some extent between species and stimulus modalities, but it has consistently been observed that the spatial receptive fields of SC neurons in infant animals are larger than those found in adults and that the earliest multisensory neurons lack the capacity to integrate different modality cues in ways that either enhance or depress their responses.

The key events in the maturation of the sensory representations in the SC therefore comprise a gradual contraction of receptive fields and the appearance of
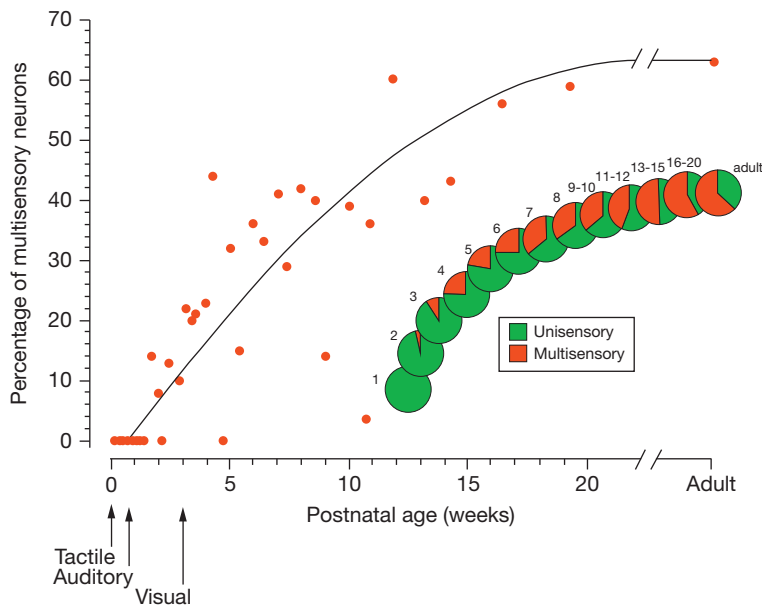
FIGURE 4.1 Postnatal development of multisensory neurons in the deeper layers of the cat superior colliculus (SC). The percentage of sensory neurons responding to stimuli in two or more modalities is plotted as a function of age. The arrows indicate the ages at which the first unisensory responses have been recorded in the deep SC layers of this species. The pie charts show how the incidence of multisensory neurons increases as development proceeds. *Adapted from Wallace MT and Stein BE (1997) Development of multisensory neurons and multisensory integration in cat superior colliculus.* Journal of Neuroscience *17: 2429–2444, with permission.*

multisensory integration. Indeed, Wallace and Stein (1997) observed that there is a clear correlation between these developmental changes, with the size of the deep-layer receptive fields in cats being a good predictor of whether the neurons will display the capacity to synthesize multisensory inputs. Although this suggests that these events may be causally related, perhaps involving maturation of the same or closely related cellular mechanisms, other aspects of sensory processing also need to be considered.

Foremost among the other factors is the sometimes overlooked fact that the development of sensory representations in the brain depends on the maturation of the relevant sense organs as well as the neural circuits involved (See Rubenstein and Rakic, 2013. Readers are also encouraged to read Chapters 2, 3, 14 within this book). Determining the relative contributions of these factors is generally not straightforward, but studies of the developing auditory representation have provided unique insights into this. Because sound frequency is mapped along the length of the cochlea in the inner ear, sound source location has to be derived by comparing the amplitude and timing of sounds reaching each ear and by sensing the spectral-shape cues produced by the direction-dependent way in which the external ears filter the incoming sound (King et al., 2001). Individual variations in the size and shape of the head and external ears are matched by differences in the binaural and monaural localization cue values corresponding to each direction in space. Consequently, the localization cues available in infancy, when the auditory receptive fields are very large and lack topographic order, are different from those provided by adult ears. But, if virtual acoustic space stimuli are used to allow infant ferrets to hear through adult ears, the auditory receptive fields immediately shrink and are

no longer any different in size from those found in adult animals (Campbell et al., 2008).

This result would seem to indicate that growth-related changes in the physical dimensions of the head and external ears can account for the contraction of auditory spatial receptive fields that occurs during postnatal development. However, whether a similar process contributes to the maturation of spatial tuning in other modalities is less clear. In the visual system, for example, the maturation of receptive fields seems to be determined more by the specificity of the afferent connections than by the resolution of the optics or the photoreceptors (Jacobs and Blakemore, 1988; Kiorpes and Movshon, 1990; Tavazoie and Reid, 2000) (see Chapter 14). Moreover, even though providing infant ferrets with adult ears removes age-dependent differences in spatial tuning, no improvement is seen in the topography of the auditory representation in the SC, which gradually emerges over the course of several weeks following hearing onset (Figure 4.2; Campbell et al., 2008). Thus, central mechanisms must also be involved in auditory map development (see Chapter 2).

As noted in the previous section, descending signals from association areas of the cerebral cortex must be available if multisensory integration is to be observed in adult cats. Those inputs also appear to be critically involved in the maturation of the multisensory integrative properties of SC neurons. Evidence for this comes from the observation that the development in these neurons of a capacity to integrate their different sensory inputs coincides with the functional maturation of inputs from the AES (Wallace and Stein, 2002). Moreover, in cats in which the AES and rLS were lesioned in infancy, no difference is seen either physiologically (Jiang et al., 2006) or behaviorally (Jiang et al., 2007) between the
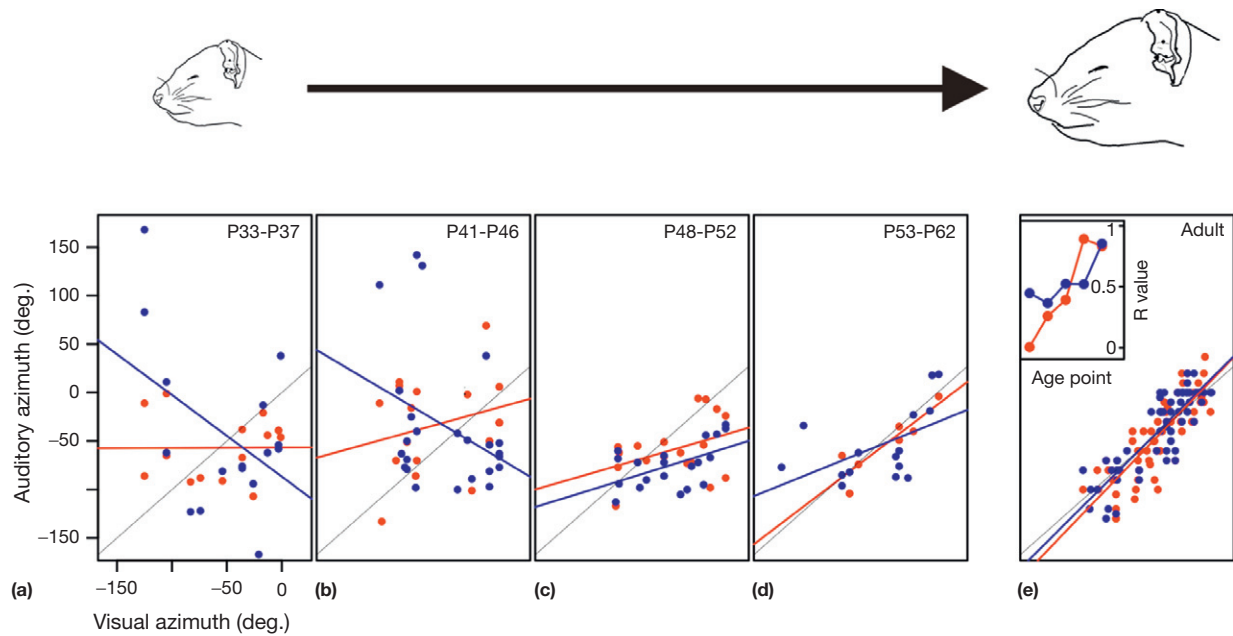
**FIGURE 4.2** Maturation of auditory spatial topography in the ferret SC. (a–e) Each panel plots the auditory best azimuth of deep-layer SC neurons as a function of the visual best azimuth of neurons recorded in the overlying superficial layers. The data were obtained at the postnatal ages indicated at the top of each panel using free-field stimuli. Because adultlike visual topography is present in the superficial SC layers throughout this developmental period, the topographic order of the auditory map is reflected in the degree to which it is in register with the visual map. Auditory responses recorded at near-threshold sound levels ($\sim$10 dB > unit threshold) are shown in red; suprathreshold levels ($\sim$25 dB > unit threshold), in blue. A linear regression was fitted to the data from each sound level at each age group (red and blue lines; the black line is the 45° diagonal indicating perfect alignment of the visual and auditory data). The inset panel in (e) plots the correlation coefficient ($R$) of each regression slope as a function of age. At both sound levels, there is a steady increase in the $R$ value during development, indicating an improvement in topographic order in the auditory representation. *Adapted from Campbell RA, King AJ, Nodal FR, Schnupp JWH, Carlile S, and Doubell TP (2008) Virtual adult ears reveal the roles of acoustical factors and experience in auditory space map development.* Journal of Neuroscience 28: 11557–11570, with permission.

responses to spatiotemporally matched visual and auditory stimuli and those made to the most effective unisensory stimuli. What signals the cortex provides that are apparently so critical for multisensory integration in the midbrain have yet to be identified.

Collectively, these studies suggest that infant animals should not be able to benefit from combining inputs across the different senses. Unfortunately, little is known about the multisensory perceptual abilities in developing animals because of the difficulty of conducting such experiments. In contrast, a great deal of research has been carried out on human infants. Although these studies have demonstrated that certain multisensory processing skills are present at birth, the ability to match or integrate particular combinations of sensory cues continues to mature over the following months and years. Of particular relevance to the maturation of multisensory spatial processing is the finding that infants only start to integrate auditory and visual localization cues toward the end of the first year of life (Neil et al., 2006), which is clearly consistent with the gradual appearance of the multisensory integrative properties of SC neurons. But while many studies point to a progressive expansion in multisensory abilities, such as the ability to perceive

more complex crossmodal relationships based on gender or affect, recent work suggests that a developmental narrowing also takes place, leading to infants losing their initial ability to match the visual and auditory attributes of nonnative social signals (reviewed by Lewkowicz and Ghazanfar, 2009). What appears to be critical for these changes in multisensory perception is exposure to appropriate sensory inputs during early life. How experience influences the maturation of multisensory circuits in the brain is considered in the following sections.

### 4.3.1 Role of Experience in Aligning the Sensory Maps in the SC

The importance of experience in merging the spatial cues provided by different sense systems has been demonstrated in a number of studies in which sensory inputs have been altered in particular ways. For example, if barn owls (Knudsen, 1985; Mogdans and Knudsen, 1992) or ferrets (King et al., 1988, 2000) are raised with one ear blocked, the auditory receptive fields in the SC (or its homolog in birds, the optic tectum) develop relatively normally and follow the topography of the visual

representation, even though the sound localization cues available are highly abnormal. A compensatory change in the developing auditory representation can also be induced by manipulating the visual inputs. This has been achieved in barn owls by mounting prisms in front of the animal's eyes, which, because these animals have very limited eye movements, results in a corresponding displacement of the visual map in the optic tectum. Prism rearing produces a corresponding shift in both the tectal map of auditory space (Figure 4.3(a) and 4.3(b); Knudsen and Brainard, 1991) and in the accuracy of sound-evoked head-orienting responses (Knudsen and Knudsen, 1990). A shift in the auditory map in the SC has also been observed in ferrets in which the orbital position of the contralateral eye was changed by removing the medial rectus muscle in infancy (King et al., 1988). As discussed,

auditory responses in the mammalian SC are modulated whenever an animal alters its direction of gaze. However, the shift in auditory spatial tuning observed in this study appeared to be caused by visual experience rather than the change in eye position itself (King and Carlile, 1995).

In barn owls, prism-induced plasticity of auditory spatial tuning has also been described in another midbrain nucleus, the external nucleus of the inferior colliculus (ICX), where a map of auditory space is first generated and then relayed to the optic tectum (Brainard and Knudsen, 1993; Figure 4.3(c) and 4.3(d)). The shift in the auditory map in the ICX is brought about by a rewiring of connections from the central nucleus of the inferior colliculus (ICC; DeBello et al., 2001) and appears to be triggered by visual signals that are transmitted from the upper layers of the optic tectum to the ICX (Hyde and
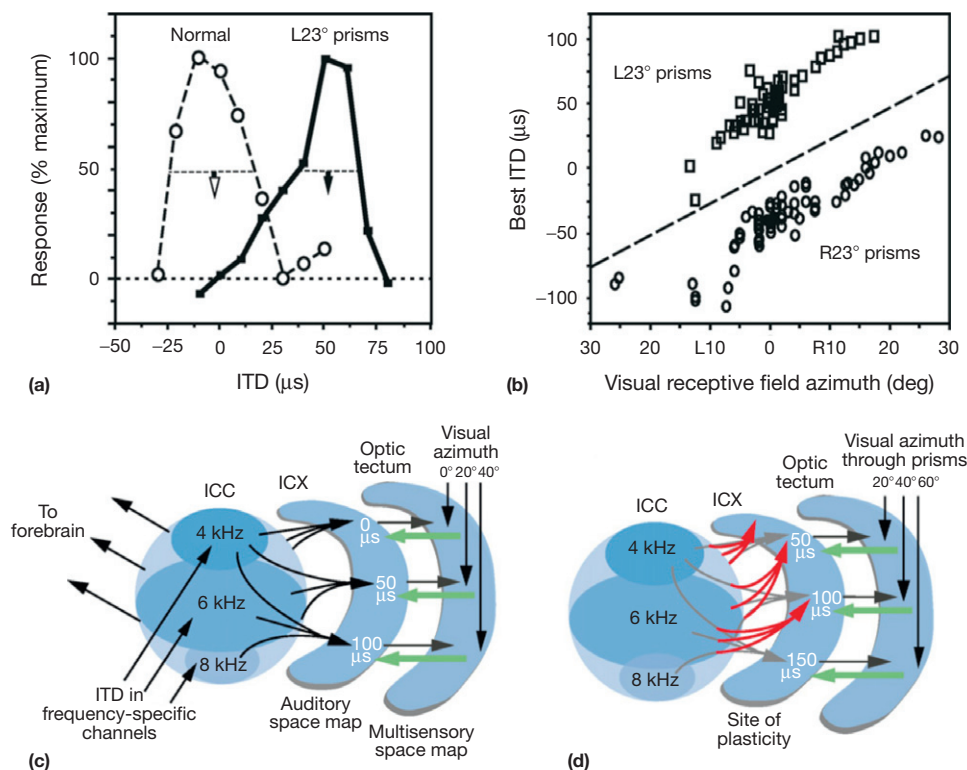


**FIGURE 4.3** Prism adaptation in the barn owl. (a) The effects of prism experience on the spatial tuning of neurons in the optic tectum. These neurons derive their azimuth sensitivity through their tuning to interaural time differences (ITDs). Before prism experience (Normal), the neuron shown is tuned to about 0° μs ITD, matching its visual receptive field, which is centered at 0° azimuth. After a young owl has experienced prisms that displace the visual field to the left by 23° (L23°) for more than 8 weeks, the ITD tuning at this site has shifted toward the values produced by sounds at the locations of the neuron's optically displaced visual receptive field (in this case, 50 μs right-ear leading). Down arrows indicate the best ITD in each case. Negative ITD values indicate left-ear leading. (b) Best ITDs plotted as a function of visual receptive field azimuth for neurons recorded in the optic tecta of owls raised with either L23° prisms (boxes) or R23° prisms (circles). The expected relationship found in normal owls is indicated by the dashed line. (c) The midbrain pathway in a normal barn owl. ITDs are mapped in frequency-specific channels in the central nucleus of the inferior colliculus (ICC). Information across frequencies is then integrated by neurons in the external nucleus of the inferior colliculus (ICX) to create space-specific auditory neurons that are organized to form a map of contralateral space. The map is conveyed to the optic tectum, where it merges with a visual map of space from the retina and forebrain. Topographic projections back from the optic tectum to the ICX (green arrows) are thought to carry visual spatial information to instruct auditory plasticity in the ICX. (d) Following a period of several weeks of prism experience during early life, a systematic change occurs in the ICC-ICX projection (red arrows), which shifts the auditory maps in both the ICX and the OT, so that they realign with the shifted visual map. *Adapted from Keuroghlian AS and Knudsen EI (2007) Adaptive auditory plasticity in developing and adult animals.* Progress in Neurobiology *82: 109–121, with permission.*

Knudsen, 2002). A similar circuit is likely to exist in mammals, where the exclusively visual superficial layers of the SC project topographically both to the deeper multisensory layers and to the nucleus of the brachium of the inferior colliculus (IC; Doubell et al., 2000, 2003), which is the principal source of auditory input to the SC (Figure 4.4; King et al., 1998a). The finding that partial lesions of the superficial SC layers in neonatal ferrets disrupt the developing topography of the underlying auditory representation suggests that they might provide a template for guiding the development and plasticity of the auditory responses (King et al., 1998b).

Therefore, vision plays an instructive role in merging multisensory spatial information during development through its influence on the maturation of the auditory space map. This resembles the visual dominance seen in studies of stimulus localization by adult humans described in the first section of this chapter and is consistent with the fact that vision generally provides more precise and reliable spatial information. Moreover, as previously discussed, a map of auditory space has to be computed in the brain by tuning neurons to spatial cues whose values depend on the physical dimensions of the head and external ears, and those dimensions often change considerably during development. The retinotopic visual map most likely guides the emergence of auditory spatial selectivity by helping to overcome the uncertainty and variability in the relationship between auditory localization cues and directions in space and thus promotes the alignment of sensory maps that are constructed in different ways (Gutfreund and King, 2012).

Early loss of vision therefore results in a partial breakdown in visual–auditory map alignment (King and Carlile, 1993; Knudsen et al., 1991; Wallace et al., 2004). Some studies have also reported that auditory neurons in the SC of visually deprived animals can have abnormally large receptive fields (Knudsen et al., 1991; Wallace et al., 2004; Withington, 1992; Withington-Wray et al., 1990b) or are ambiguously tuned to multiple sound directions (King and Carlile, 1993). Although confirming that visual inputs play a pivotal role in guiding the formation of a normal map of auditory space in the brain, accurate sound localization can develop in the absence of vision. Indeed, as discussed in more detail later
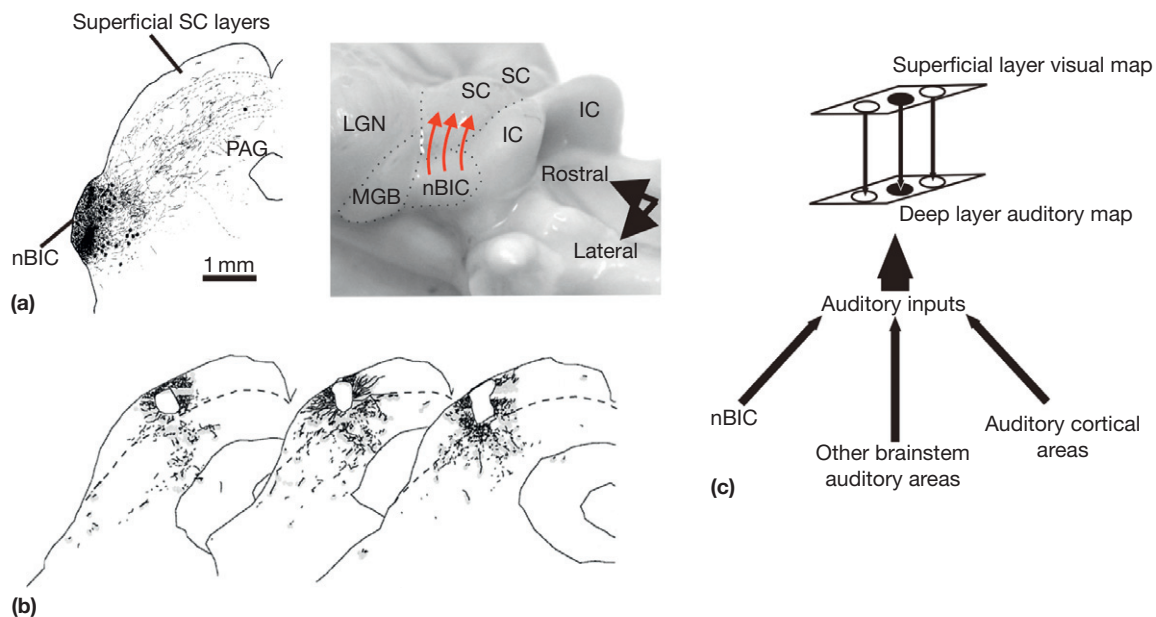


**FIGURE 4.4** Circuits underlying auditory map formation in the mammalian superior colliculus (SC). (a) The left panel shows in a camera lucida drawing of a coronal section through the ferret midbrain the distribution of retrograde and anterograde labeling following a single injection of biotinylated dextran amine conjugated with fluorescein in the nucleus of the brachium of the inferior colliculus (nBIC). Fibers and terminals are represented by lines and labeled somata by circles. The right panel shows a lateral view of the ferret midbrain, with the arrows illustrating the topographic organization of the projection from the nBIC to the deeper SC layers. (b) Series of sections from a ferret in which a single injection of biocytin had been made in the superficial visual layers of the SC. The light gray shading depicts areas containing boutons, and black stippling indicates axons. (c) Summary of visual and auditory inputs to the deeper layers of the SC. This part of the SC receives converging inputs from several auditory brainstem and cortical areas, including a spatially ordered projection from the nBIC. Neurons in the superficial layers of the SC project topographically both to the underlying deeper layers and also to the nBIC (not shown). The map of visual space in the superficial layers appears to provide an activity template that guides the development and plasticity of the auditory representation. Other abbreviations: IC, inferior colliculus; LGN, lateral geniculate nucleus; MGB, medial geniculate body; PAG, periaqueductal gray. Anatomical data from Doubell et al. (2003) and Nodal et al. (2005).

in this chapter, visually impaired or blind individuals can localize sound just as well as or even better than subjects with normal sight (Collignon et al., 2009; King and Parsons, 1999; Lessard et al., 1998; Rauschecker and Kniepert, 1994; Röder et al., 1999). Such improvements in perceptual abilities could, of course, be based on changes in other regions of the brain, particularly in the cortex. But, where multisensory spatial representations are brought together, as in the SC, concurrently available visual inputs are used to constrain the developing auditory map so that it matches the visual field representation.

Although these studies emphasize the importance of vision in coordinating multisensory inputs in the developing brain, it is not always vision that dominates intersensory spatial relations. If the somatosensory receptive fields of SC neurons are shifted by modifying the position of the vibrissae in newborn mice, a compensatory reorganization of the visual map takes place (Benedetti and Ferro, 1995). Indeed, while there is strong evidence that plastic auditory inputs are guided by a stable visual template, it has also been proposed that each of the senses is weighted during development according to the reliability of the spatial information they provide (Witten et al., 2008) in much the same way that visual and auditory spatial signals are now thought to interact when humans make localization judgments (Alais et al., 2010). In this scenario, auditory receptive fields are plastic simply because they are larger than the visual receptive fields and therefore convey less precise spatial information.

### 4.3.2 Role of Experience in the Development of Multisensory Integration in the SC

In addition to its importance in aligning the different maps in the SC, appropriate sensory experience is critical for the emergence of the multisensory integrative abilities of SC neurons. Thus, multisensory neurons in the SC of dark-reared cats have abnormally large spatial receptive fields and lack the capacity to integrate different modality cues (Wallace et al., 2004). In other words, combining spatiotemporally congruent visual and auditory stimuli did not produce the enhancement of unisensory responses that is characteristic of animals that have been raised normally.

However, while experience with objects that can be both seen and heard promotes intersensory map alignment, this is not a prerequisite for multisensory integration. Wallace and Stein (2007) showed this by raising cats in the dark and periodically presenting them with simultaneous light and sound at a fixed spatial disparity. Although most of the SC neurons recorded when the animals were fully grown again had receptive fields that had failed to contract and lacked multisensory

integration, a few had relatively small visual and auditory receptive fields whose relative locations matched the spatial configuration of the bisensory stimuli to which they had been exposed (Wallace and Stein, 2007). As in normally raised control cats, these neurons did exhibit multisensory enhancement when visual and auditory stimuli occurred together within their respective receptive fields, but this now meant presenting those stimuli from different locations in space. Provision of abnormal multisensory experience can therefore lead to neurons developing the capacity to integrate visual and auditory cues from seemingly unrelated sources. This illustrates the importance of aligning the different sensory maps in the SC, as it is presumably only then that behaviorally relevant crossmodal interactions can take place.

Behavioral observations in visually deprived humans also highlight the importance of experience in acquiring the ability to synthesize inputs from different modalities. Like the dark-reared cats, humans lacking early patterned visual experience as a result of congenital cataracts show reduced auditory–visual interactions, whereas their performance in unisensory tasks was normal (Putzar et al., 2007).

## 4.4 DEVELOPMENT OF MULTISENSORY CIRCUITS IN THE CORTEX

Early anatomical studies reported the presence in newborn animals of transient inputs from other sensory systems to areas of the cortex that are traditionally viewed as modality specific (Dehay et al., 1988; Innocenti and Clarke, 1984). However, since multisensory convergence is observed to a greater or lesser extent throughout the fully mature cerebral cortex, it is unlikely that such connections disappear altogether. Little is known about the maturation of the multisensory response properties of cortical neurons. However, Wallace et al. (2006) recorded in the AES of cats at different postnatal ages and found that responsiveness to somatosensory, auditory, and visual stimulation emerges in that order and that the capacity of the multisensory neurons to integrate crossmodal cues takes several months to mature. This sequence therefore parallels the ontogeny of sensory function in the SC.

By raising barn owls with prismatic spectacles, Miller and Knudsen (1999) found that, as in the space-mapped regions of the midbrain, visual experience shapes the developing auditory spatial receptive fields of neurons in the forebrain. However, the great majority of evidence for multisensory interactions in the cortex during development has come from studies in mammals in which experience of one modality has been restricted or eliminated altogether. In the cat AES, for example, early visual deprivation has been reported to cause an expansion

in the territory of auditory neurons (Rauschecker and Korte, 1993) and a sharpening of their spatial sensitivity (Korte and Rauschecker, 1993), as well as a change in multisensory integrative properties, which become dominated by response depression rather than enhancement (Carriere et al., 2007). These results therefore differ from those described previously for the SC, in which visual deprivation tends to either broaden or leave auditory spatial tuning unchanged and prevents the appearance of multisensory integration. Nevertheless, they show that, as in the midbrain, sensory experience plays a critical role in shaping the functional organization of cortical multisensory areas.

Many other studies have also examined the crossmodal consequences of temporary or permanent loss of one of the senses. The enhanced perceptual abilities that are often reported in those studies could result from altered processing within the neural pathways of the intact modalities (Elbert et al., 2002; Korte and Rauschecker, 1993), perhaps reflecting the greater attention paid to those modalities in the absence of the sense that has been lost. But the functional identity of an area of sensory cortex can also change if its primary input is removed, to be replaced by inputs from other modalities (Figure 4.5). Remarkably, this can happen even if existing multisensory inputs are temporarily unmasked in adulthood. Thus, wearing a blindfold for a few days leads to primary visual cortex becoming recruited for tactile processing (Merabet et al., 2008). However, the most dramatic examples of sensory substitution have been reported in humans who are congenitally deaf or blind. For example, the visual cortex appears to contribute to the superior auditory localization abilities of blind individuals (Collignon et al., 2007; Gougoux et al., 2005; Renier et al., 2010). This presumably results either from the formation of novel functional connections from auditory to visual brain areas or from the unmasking of connections that are now known to exist normally.

The capacity of a cortical area to take on the functions of a different sensory modality has been illustrated in a series of studies in animals in which visual inputs were surgically redirected into the auditory thalamus and cortex. Neonatal lesions of the midbrain (SC and IC) partially remove normal retinal targets and the main source of auditory input to the medial geniculate body. As a result, retinal afferents form connections that allow visual information to be conveyed to the auditory cortex (Kalil and Schneider, 1975; Sur et al., 1988). In 'rewired' ferrets, neurons in the auditory cortex have been shown to display receptive field properties, including orientation and direction selectivity, characteristic of the visual cortex (Roe et al., 1992), and even support limited visually guided behavior (von Melchner et al., 2000). Similar results have been obtained in hamsters in which visual afferents were redirected into either the auditory (Frost et al., 2000) or somatosensory cortex (Métin and Frost, 1989).

These studies show that the modality specificity of a given area of the cortex is determined by its inputs and can change in behaviorally relevant ways if normal inputs are replaced by those from another sense. Nevertheless, the functional specificity of different cortical areas seems to be retained following crossmodal reorganization. In early blind humans, part of the occipital cortex normally involved in visual spatial processing is more strongly activated when subjects perform auditory or tactile localization rather than identification tasks (Renier et al., 2010). Similarly, visual localization deficits are produced in deaf cats by deactivating auditory cortical areas that are known to be involved in sound localization in animals with normal hearing (Lomber et al., 2010; Meredith et al., 2011). Such crossmodal plasticity could potentially arise from an expansion or unmasking of connections that selectively link cortical areas sharing the same or related functions in different modalities. Alternatively, this reallocation of resources might be mediated via top–down pathways to different sensory areas involved in stimulus localization.

## 4.5 SENSITIVE PERIODS IN THE MATURATION OF MULTISENSORY PROCESSING

The finding that human multisensory perceptual abilities narrow during infancy (Lewkowicz and Ghazanfar, 2009) suggests that a sensitive period of development may exist during which experience is particularly effective in shaping the functional architecture of the brain. Several studies have indicated that the guiding influence of vision on the maturation of auditory space maps in the midbrain is
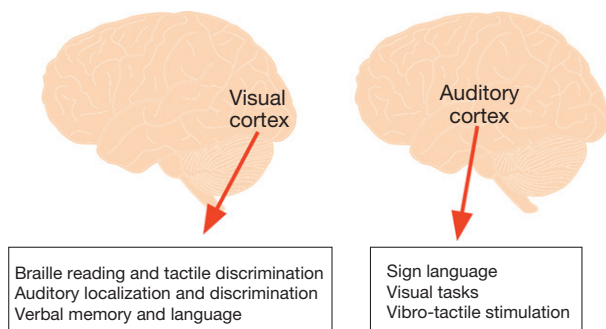


FIGURE 4.5  Crossmodal plasticity in the cortex following sensory deprivation. (a) Recruitment of visual cortex in the blind for tactile processing (e.g., Braille reading, sound localization, and verbal memory). (b) Recruitment of auditory and language-related areas in deaf people for viewing sign language, peripheral visual processing, and vibrotactile stimulation. *Reproduced from Merabet LB and Pascual-Leone A (2010) Neural reorganization following sensory loss: The opportunity of change.* Nature Reviews Neuroscience *11: 44–52.*

developmentally regulated (King et al., 1998b; Knudsen and Brainard, 1991), and similar findings have been obtained from behavioral studies (Knudsen and Knudsen, 1990). However, more recent experiments have shown that adaptive crossmodal plasticity is possible throughout life. To some extent, plasticity in later life is constrained by changes in neural circuitry that take place during the sensitive period. For example, visual experience can adjust auditory spatial tuning in the midbrain of adult barn owls if the animals were previously exposed to the same prismatic displacement, but not if adult birds are fitted with prisms that displace the visual field in the opposite direction (Knudsen, 1998). This experience-specific plasticity in adulthood can be accounted for by changes in midbrain connectivity induced by prism rearing (Figure 4.3), which leave a 'trace' that can be reactivated by appropriate experience in later life. A similar explanation likely applies to other forms of sensory plasticity that were previously thought to be restricted to a sensitive period of development (Hofer et al., 2009).

The question of whether sensitive periods exist can also be addressed in deprivation studies either by determining whether the age at which the sensory loss occurs influences the nature and extent of the changes that take place in the brain or by examining the potential for recovery if the missing function is restored. That a sensitive period is present for the acquisition of multisensory integration is suggested by studies of patients who have had congenital cataracts removed. Even after several years of multisensory experience, they lack the ability to synthesize different modality cues normally (Putzar et al., 2007). Integration of auditory and visual cues is possible, however, if sensory function is restored early enough. Congenitally deaf children fitted with cochlear implants within the first 2 ½ years of life exhibit the McGurk effect, whereas, after this age, auditory and visual speech cues can no longer be fused (Schorr et al., 2005). In contrast, recent animal studies suggest that sensitivity to crossmodal experience might be maintained in later life. Following repeated presentation of spatiotemporally congruent visual and auditory cues to anesthetized adult cats that had been reared in the dark, SC neurons start to acquire their characteristic multisensory integrative properties (Yu et al., 2010).

Most of the evidence for compensatory crossmodal changes in neural processing and behavior following sensory deprivation has come from subjects who have been blind or deaf from birth or early in life. But while functional and anatomical differences do exist between early- and late-onset blind individuals (e.g., Cohen et al., 1999; Jiang et al., 2009; Stevens and Weaver, 2009), enhanced nonvisual abilities have also been reported following late-onset blindness (Fieger et al., 2006; King and Parsons, 1999; Occelli et al., 2008; Voss et al., 2004).

Together, these studies show that the mature brain retains some capacity for crossmodal plasticity, although to a lesser extent than that seen during development. As with other aspects of sensory processing (e.g., Kacelnik et al., 2006), behavioral training is likely to be an important factor in determining the extent to which the mature brain can adapt to changes in input. Similarly, adult barn owls exhibit much greater visually induced auditory plasticity if the stimuli acquire behavioral significance for the animals (Bergan et al., 2005). This suggests that top–down regulation of sensory responses is part of the circuitry involved in integrating multisensory information in the brain.

## 4.6 CONCLUDING REMARKS

The studies reviewed in this article show that sensory experience plays a vital role during development in establishing and maintaining the neural circuits responsible for synthesizing information across different sensory modalities. Much of this evidence has come from research in animals, which provide an opportunity both to alter sensory inputs in a controlled and reproducible manner in ways that are not possible in humans and to investigate how different senses interact at the level of individual neurons. Nevertheless, many of the animal studies have examined the crossmodal consequences of depriving inputs in one sensory modality and therefore offer valuable insights into the changes that likely take place in the human brain following blindness or deafness.

The emphasis in most of the animal work has been on the development of multisensory spatial interactions, particularly at the level of the SC, where vision has been shown to play a pivotal role in aligning the different modality maps and in the maturation of multisensory integration. The SC has provided a model system for research in this area, leading to the formulation of a number of general principles that also apply to other aspects of multisensory processing. Nevertheless, most multisensory functions, at least in primates, rely on cortical activity, and it will clearly be important to extend the range of developmental studies to include other processes, such as the integration of faces and voices during infancy.

The considerable crossmodal plasticity that takes place during development, and to some extent in later life too, has clear adaptive value. This enables information from different sensory modalities to be merged in behaviorally relevant ways and allows for crossmodal compensatory changes to take place following sensory deprivation. However, these changes can potentially be maladaptive in that they may limit the capacity of the brain to utilize sensory inputs that are restored as a result, for example, of cataract surgery or cochlear implantation. The growing evidence for adult crossmodal

plasticity nevertheless holds out the promise of developing effective rehabilitation strategies in such cases for patients who are recovering from early sensory loss.

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