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CHAPTER

18 Cross-Modal Plasticity in the Mammalian Neocortex

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Abstract

Cross-modal plasticity refers to how the loss of sensory activity within one modality affects the development of the remaining modalities at cortical and subcortical levels. Two approaches are used to understand how this plasticity is generated. A comparative approach is used to determine how aspects of cortical organization are altered across species with natural enhancement of a sensory system, whereas a developmental approach is used to determine the factors that contribute to sensory domain allocation as well as the functional assignment of cortical fields. Together, comparative and developmental studies suggest that a cortical field is a combination of the sensory-driven input each sensory system receives during development and the genes that contribute to basic aspects of cortical field emergence including location, size, and connectivity.

Keywords: Sensory-driven activity, congenital sensory loss, development, multimodal plasticity, cortical fields, sensory domains, evolution

Introduction

The neocortex is a highly dynamic structure, particularly during development. In fact, recent studies in humans and other animals indicate that a substantial amount of the neocortex can be reorganized following the early loss of sensory inputs. Specifically, neurons in the deprived cortex become responsive to stimulation of the remaining sensory modalities. Even in adults, the functional organization of cortical areas can be significantly modified by sensory experiences (e.g., Merzenich & Kaas, 1982; Recanzone, Merzenich, Jenkins, Grajski, & Dinse, 1992). This remarkable plasticity throughout the life of an animal seems to be at odds with recent developmental studies, which demonstrate that highly conserved patterns of gene expression play a pivotal role in the emergence and development of cortical fields in mammals. Further, the precise nature of the spatial and temporal patterns of gene expression, as well as the developmental cascades upon which their expression depends, must constrain the types of changes that can be made to the developing and evolving neocortex. While a number of studies have demonstrated that sensory experience or sensory-driven activity can influence the development of cortical fields in terms of their connections and functional properties, most studies have only focused on limited portions of the nervous system and have not explored how sensory activity within one modality affects the other sensory systems (e.g., see Majewska & Sur, 2006; O'Leary & Nakagawa, 2002; Pallas, 2001, for review). This phenomenon, in which changes in one sensory system alter the development of the remaining sensory systems, is called cross-modal plasticity. In this chapter, we will discuss the cross-modal plasticity of the neocortex, particularly in terms of functional organization and connectivity.

The relative contributions of sensory experience and genetic factors to the development of cortical fields continue to be debated. For example, some believe that genetic factors play the leading role in establishing the location, size, and connectivity of cortical fields (e.g., Sur & Rubenstein, 2005; O'Leary, Chou, & Sahara, 2007). By contrast, others believe that sensory experience not only refines existing organization, but also plays an equal role with genetic factors in the development of cortical fields (e.g., Krubitzer & Kahn, 2003; Krubitzer, 2007). While one must concede that genes do control many processes, it is hard to isolate their exact role because genes do not work in a vacuum; there is an ongoing interaction between the expression of genes intrinsic to the cortex, intrinsic to the animal, and the environment that an animal inhabits. Nevertheless, there are aspects of the developmental process that seem to be invariant from one generation to the next regardless of alterations in the body or the environment. This indicates that certain developmental processes are intrinsically regulated by genes, whereas other processes are based on the sensory experience of the individual animal.

In some ways, it seems intuitive that the physical parameters of the environment should play a fundamental role in shaping the structure that will ultimately enable an animal to detect, perceive, and execute appropriate behaviors in their unique and dynamic environment. However, like genes, the physical stimuli that impinge on sensory receptor arrays, although variable in their distribution in time and space, are invariant in nature. For example, there are invariant forms of physical energy that obey fundamental, physical laws that control how energy moves, such as how photons travel, how sound waves propagate, and how molecules combine and interact with each other. Consequently, these fixed features of the world limit the way in which sensory receptors, such as photoreceptors, mechanoreceptors, and chemoreceptors, can be modified. These limitations have shaped the evolution of sensory transduction, which in turn constrains the patterns of sensory-driven activity that can be delivered to the developing brain. Thus, as with genes, the physical parameters of the environment constrain brain development and evolution (Krubitzer, 2009).

Given these genetic and environmental constraints, how is cross-modal plasticity generated in the neocortex? There are two general approaches to address this question. First, one can adopt a comparative approach and examine neocortical organization in species with naturally modified sensory receptor arrays and peripheral morphology, and determine if and how the neocortex was altered in different lineages that have evolved extreme modifications in their sensory periphery. Alternatively, one can adopt a developmental approach and examine the effect of altered sensory array activity on cortical field organization. In this chapter, we utilize a combined comparative and developmental approach. First, we begin by discussing the primary subdivisions of the neocortex and how aspects of cortical organization are altered across species. We then describe the development of the neocortex and factors that contribute to cortical field emergence and organization. Finally, we discuss the organizational changes to the neocortex that occur following congenital loss of sensory arrays or impairment of sensory-driven activity in human and nonhuman animals.

Sensory Neocortex in Mammals: Evolutionary Cross-Modal Plasticity

As noted above, one way to understand the role of sensory-driven activity on neocortical organization is to examine mammals with naturally modified sensory systems. This has been done for a variety of mammalian species, and a strong relationship has been observed between peripheral sensory morphology and the two major features of neocortical organization: cortical fields and sensory domains.

Cortical Fields

Traditionally, the neocortex is divided into cortical fields or areas, which are defined using a number of criteria including architectonic appearance, neuronal response properties, and cortical and subcortical connections (Kaas, 1982, 1983). While all mammals possess a basic plan of cortical organization that is composed of several cortical fields with specific patterns of connections, different species have different relative sizes of cortical areas, numbers of cortical fields, functional organization, and connectivity (Figure 18.1). This variability in cortical field organization is thought to generate the behavioral diversity exhibited by various mammals. Cortical areas common to all mammals include the primary visual area (V1; Rosa & Krubitzer, 1999), the primary somatosensory area (S1; Johnson, 1990; Kaas, 1983), and the primary auditory area (A1; Ehret, 1997; see Krubitzer & Kaas, 2005, for review).

Comparative studies indicate that in all mammals, V1 is always located caudally on the cortical

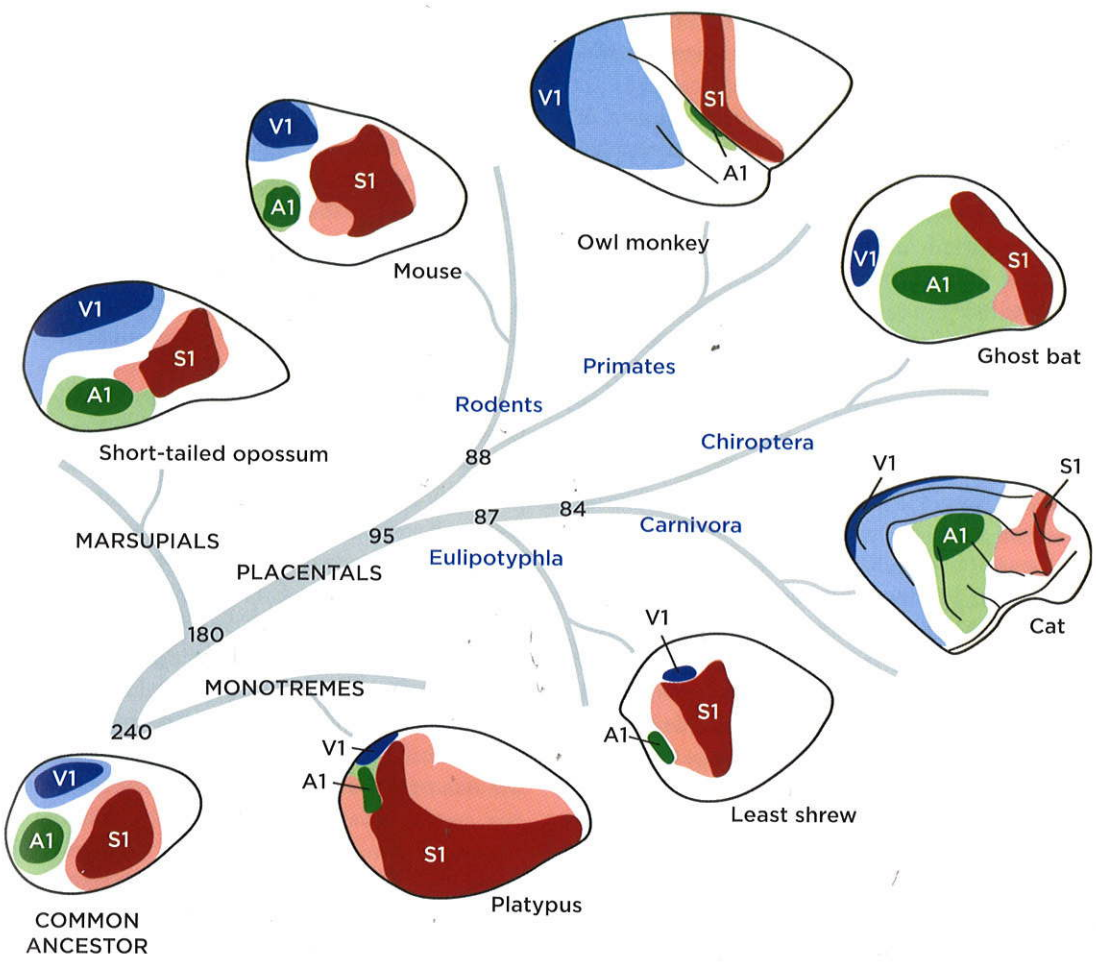

Figure 18.1 All mammals studied possess a primary visual area (V1; dark blue), a primary somatosensory area (S1, dark red), and a primary auditory area (A1, dark green). These primary areas contain a complete representation of the sensory epithelium that is coextensive with a unique architectonic appearance and pattern of connectivity. In addition, most animals possess other cortical fields devoted to processing information from a single sensory system. Combined, these larger subdivisions of the neocortex are termed sensory domains. Shown here is the visual domain depicted in light and dark blue, the somatosensory domain in light and dark red, and the auditory domain in light and dark green. While all mammals possess a basic plan of cortical organization, different species have different relative sizes of cortical areas and sensory domains, and this variability is thought to generate the behavioral diversity exhibited by various mammals. Short-tailed opossum (Huffman, Nelson, Clarey, & Krubitzer, 1999; Kahn, Huffman, & Krubitzer, 2000); mouse (Carvell & Simons, 1986; Woolsey, 1967); owl monkey (Kaas, 2004); ghost bat (Krubitzer, 1995); cat (Scannell, Blakemore, & Young, 1995); least shrew (Catania, Lyon, Mock, & Kaas, 1999); platypus (Krubitzer et al., 1995); phylogeny (Murphy, Pevzner, & O'Brien, 2004); timescale in millions of year ago. Medial (M) is up; rostral (R) is to the right.

sheet, S1 is always located rostral to V1, and A1 is always located lateral to V1 (Figure 18.1). Each of these primary areas contains a complete representation of the corresponding sensory epithelium that is coextensive with a unique architectonic appearance and pattern of connectivity. Regardless of the morphological and behavioral specializations of many mammals (e.g., Catania, 2000; Henry, Marasco, & Catania, 2005; Krubitzer, 1995), the conserved constellation of fields is always present, even in the absence of apparent use. For example, the blind mole rat (*Spalax ehrenbergi*) still has a "visual" cortex even though this species is functionally blind (Bronchti et al., 2002; Cooper, Herbin, & Nevo, 1993; Heil, Bronchti, Wollberg, & Scheich, 1991). The ubiquity of these fields, their consistent patterns of corticocortical and thalamocortical connectivity, and their conserved geographic arrangement on the cortical sheet across all mammals indicate that the primary cortical fields were present in the common

ancestor, cannot be eliminated under most or all circumstances, and reflect the genetic constraints imposed upon the evolving neocortex.

On the other hand, there are a number of alterations that have been made to this basic plan of cortical organization in different mammals, and to a large extent, these evolutionary changes reflect alterations in peripheral morphology, sensory receptor arrays (such as number and distribution of receptors), and patterns of behavior. For example, in the short-tailed opossum (*Monodelphis domestica*), an arboreal, highly visual marsupial, the size of V1 is large in relation to other primary sensory areas (Figure 18.1; Kahn, Huffman, & Krubitzer, 2000). By contrast, in the least shrew (*Cryptotis parva*), a small insectivore that lives in subterranean burrows, the size of S1 is large in relation to V1 and A1 (Figure 18.1; Catania, Lyon, Mock, & Kaas, 1999). This is consistent with the least shrew's reliance on its somatosensory system for exploring the environment and detecting prey. Finally, in the ghost bat (*Macroderma gigas*), which uses echolocation for navigating its environment and catching prey, the size of A1 is large in relation to other primary fields (Figure 18.1), similar to the organization observed in other echolocating bats (e.g., Suga, 1984, 1994).

In addition to these alterations in the overall size of primary cortical fields, some species have expanded representations within a cortical field of behaviorally important morphological structures. For instance, the duck-billed platypus (*Ornithorhynchus anatinus*) uses its bill for many activities including navigating in water, prey capture, predator avoidance, and mating, and approximately two-thirds of the cortex is involved in processing input from the bill (Krubitzer, Manger, Pettigrew, & Calford, 1995). Similarly, in the star-nosed mole (*Condylura cristata*), much of the cortical sheet is devoted to processing input from the 22 appendages that surround the nose and are used for navigating and foraging (Catania, 2000; Catania & Kaas, 1995). Finally, in the naked mole rat (*Heterocephalus glaber*), the representation of the upper and lower incisors, which are used for foraging, digging, and moving objects, occupy over 30% of S1 (Henry, Remple, O'Riain, & Catania, 2006). These examples serve to illustrate that species with highly specialized body morphology have expanded representations of these behaviorally relevant structures within a cortical field.

Although the size of primary fields can vary dramatically among species, the expansion (or contraction) of individual primary fields does not occur in isolation. Rather, cortical fields that increase their relative size seem to do so at the expense of other fields. This change in the size of cortical fields is directly related to peripheral morphology, the types and distribution of sensory receptor arrays, and the unique sensory-driven behaviors of an animal. We term these types of changes to the neocortex that occur in different mammalian lineages across time *evolutionary cross-modal plasticity*.

Sensory Domains

Recently, we have considered larger divisions of the cortex when making cross-species comparisons. These larger subdivisions of the neocortex are termed sensory domains and are defined as the amount of cortex allotted to each sensory system. As with cortical fields, some aspects of sensory domain allocation are similar across species. For example, the visual domain is located in the occipital lobe, the auditory domain in the temporal lobe, and the somatosensory domain in the parietal lobe. Further, as with cortical fields, the size of sensory domains can vary across species, and this variability is related to the sensory systems that are most behaviorally relevant to the animal. For instance, in the highly visual short-tailed opossum, a large proportion of the neocortex is devoted to the visual system (Figure 18.1), which includes several cortical fields such as V1, second visual area (V2), and caudotemporal area (CT). Similarly, mice (*Mus musculus*) and other rodents rely more on their vibrissae than on their visual system, and relatively more of the neocortex is devoted to processing information from this sensory system (Figure 18.1), which includes S1, second somatosensory area (S2), and parietal ventral area. Finally, chiroptera, such as ghost bats, are echolocating mammals that rely heavily on their auditory system and a large proportion of their neocortex is devoted to processing auditory information (Figure 18.1), which includes A1 and surrounding auditory fields.

We have purposely described extreme examples of sensory domain allocation to emphasize our point that cortical organization in mammals can vary dramatically and, moreover, that this organization reflects and supports peripheral morphology, receptor array distribution, and behavior. However, in most instances, animals do not depend exclusively on a single sensory system. For example, cats (*Felis catus*) rely on both vision and audition,

which is reflected by the functional organization of their neocortex (Figure 18.1; Scannell, Blakemore, & Young, 1995). Similarly, prairie voles (*Microtus ochrogaster*) rely on both somatosensation and audition, and the neocortex in this species primarily processes information from these two modalities (Campi, Karlen, Bales, & Krubitzer, 2007). Finally, owl monkeys (*Aotus trivirgatus*) and other primates rely on both vision and somatosensation, and they have a large proportion of their neocortex devoted to processing input from both modalities (Figure 18.1; Kaas, 2004). Thus, the amount of the cortical sheet that is allocated to each sensory domain closely reflects the sensory systems that are most behaviorally relevant to the animal.

As with the organization of individual cortical fields, these studies demonstrate that sensory domain allocation also varies across lineages, and suggests that cross-modal plasticity within the neocortex is related to alterations in peripheral sensory morphology, sensory-driven activity, and use. However, the extent to which these cortical field and sensory domain differences between species are genetically mediated, and thus heritable, or are due to sensory-driven activity during development, and not directly heritable, is not known.

Development of the Neocortex

Traditionally, developmental mechanisms involved in parceling the neocortex into separate fields have been broken down into intrinsic and extrinsic factors. Intrinsic factors are defined here as features of development that occur solely within the neocortex, such as changes in cell division and cell death, shifts in the global patterns of gene expression, and variations in protein translation and posttranslational modifications. Extrinsic factors influence neocortical development but do not originate within the cortex, such as shifts in circulating hormonal levels, changes in thalamocortical connectivity, and variations in the pattern of activity received from the external environment and relayed through sensory receptors. Extrinsic factors, as defined here, refer to the more limited set of features, such as sensory-driven activity patterns that occur outside of the cortex entirely, but directly influence the developing neocortex. There is strong evidence that both intrinsic and extrinsic factors play a role in neocortical development and that both contribute to the differences observed across species, although extrinsic factors are likely to play a larger role in cross-modal plasticity within the lifetime of an individual.

Intrinsic Factors That Shape Cortical Field Development and Evolution

There is ample evidence indicating that intrinsic factors, such as genes expressed within the developing neocortex, play a significant role in specifying the gross geometric, anatomical relationships of the neocortex. Early in development, positional information is provided to the cortical primordium by signaling centers that produce secreted molecules, such as fibroblast growth factor (FGF) proteins that are involved with patterning of the anterior/posterior axis and other molecules that pattern the dorsal/ventral axis, such as bone morphogenetic proteins (BMPs) and Wingless-Int (Wnt) proteins (e.g., see Grove & Fukuchi-Shimogori, 2003; Monuki & Walsh, 2001; Rash & Grove, 2006; Sur & Rubenstein, 2005, for review). These patterning centers are highly conserved across lineages (see Barembaum & Bronner-Fraser, 2005, for review).

Secreted proteins, such as FGF, BMP, and Wnt, interact to generate graded expressions of transcription factors in the ventricular and subventricular zones of the neocortex, which in turn regulate different aspects of cortical development. For example, FGF8 has been shown to play a role in establishing the anterior–posterior axis of the neocortex (Fukuchi-Shimogori & Grove, 2001), and Wnt signaling has been shown to be involved in patterning the dorsal–ventral axis (Grove, Tole, Limon, Yip, & Ragsdale, 1998). Changes in FGF8 and Wnt signaling interact to regulate the expression of two transcription factors important for the regionalization of the neocortex, *Emx2* and *Pax6*, which are expressed in opposing gradients (see O'Leary & Nakagawa, 2002; Rash & Grove, 2006; O'Leary et al., 2007, for review). By changing the graded expression of these transcription factors, the size and location of cortical fields on the cortical sheet can be altered. For example, *Emx2* is expressed in a low-rostral/high-caudal and low-lateral/high-medial gradient, whereas *Pax6* is expressed in a low-caudal/high-rostral and low-medial/high-lateral gradient (Figure 18.2) (Bishop, Goudreau, & O'Leary, 2000). In *Emx2* knockout mice, rostral cortical areas, such as somatosensory cortex, expand while caudal areas, such as visual cortex, contract (Figure 18.2). *Pax6* mutants show shifts in cortical areas in the opposite direction from *Emx2* mutants, as predicted by their complementary expression patterns, with caudal areas showing expansion and rostral areas showing contraction (Bishop et al., 2000). In addition, when *Emx2* is overexpressed, using nestin-*Emx2* transgenic mice, an expansion

of visual cortex is observed (Figure 18.2; Hamasaki, Leingartner, Ringstedt, & O'Leary, 2004).

These transcription factors regulate the region-specific expression of other genes that appear to be directly related to the emergence and further development of cortical fields into the adult phenotype, as well as in the development of thalamocortical and corticocortical connections. For example, *cadherin 6* (*Cad6*), *Cad8*, and *Cad11* are cell adhesion molecules that are regionally expressed in both the neocortex and thalamus; furthermore, there is a matching expression pattern between the primary sensory areas in cortex and their corresponding thalamic nuclei (Nakagawa, Johnson, & O'Leary, 1999; Suzuki, Inoue, Kimura, Tanaka, & Takeichi, 1997). Similarly, the Eph family of receptors, in conjunction with the ephrin ligands, act as axon guidance molecules for incoming thalamocortical axons in both the visual and somatosensory systems (e.g., see Bolz et al., 2004; O'Leary & Nakagawa, 2002; Vanderhaeghen & Polleux, 2004, for review).

Taken together, these studies in developing animals indicate that several of the ubiquitous features of cortical organization, such as the presence of primary sensory fields and their location are intrinsically regulated and predominantly under the influence (control) of genes. The size and connectivity of primary sensory areas can be intrinsically regulated as well, but they are also shaped by extrinsic influences as well (described below). What is not clear is how alterations in the features of cortical organization are accomplished during the life of an individual, given the control that genes have on the formation of cortical areas and patterns of connections during development.

Extrinsic Factors That Shape Cortical Field Development and Evolution

During development, genes do not function in isolation, but are influenced by a number of extrinsic factors present in the internal and external environment of the developing neocortex. For example, the physical properties of the environment are necessarily conveyed through sensory receptors, which transmit patterns of activity to the developing neocortex via thalamocortical afferents. Historically, studies have addressed the role of patterned activity in cortical field development within a single sensory system. For example, Wiesel and Hubel (1963, 1974; Hubel, Wiesel,

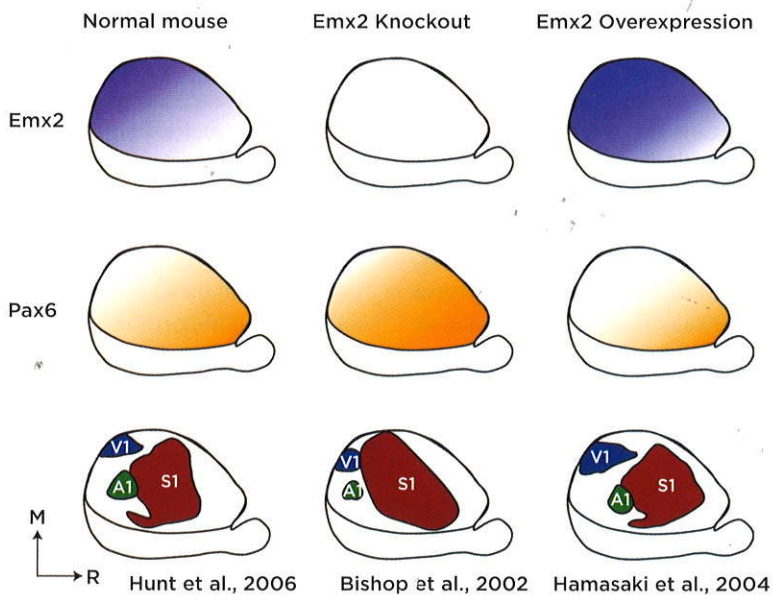

Figure 18.2 Genes intrinsic to the neocortex play a substantial role in determining cortical field size and location. By changing the graded expression of transcription factors, the size and location of cortical fields on the cortical sheet can be altered. Shown here is *Emx2* (purple) expressed in a low-rostral/high-caudal and low-lateral/high-medial gradient, while *Pax6* (orange) expressed in a low-caudal/high-rostral and low-medial/high-lateral gradient (Bishop et al., 2000). In *Emx2* knockout mice, rostral areas, such as S1 (red), expand while caudal areas, such as A1 (green) and V1 (blue), contract. Conversely, when *Emx2* is overexpressed, using nestin-*Emx2* transgenic mice, V1 expands more rostrally, and S1 and A1 are shifted forward (Hamasaki et al., 2004). Conventions as in previous figure; abbreviations defined in Table 18.1.

& LeVay, 1977) demonstrated that experience-dependent mechanisms were involved in normal ocular dominance column development in cats and monkeys. Specifically, they found that monocular deprivation led to a larger cortical representation of the nondeprived eye. Similarly, Rakic (1981) demonstrated that when rhesus monkeys (*Macaca mulatta*) were monocularly enucleated before birth, they failed to develop ocular dominance columns, which suggested that binocular competition is necessary for ocular dominance column formation. Further studies on ocular dominance columns have shown that both sensory-driven activity and spontaneously generated activity are critical for the normal development of visual cortex (e.g., see Katz & Shatz, 1996, for review; Shatz, 1990; Stryker & Harris, 1986). Similarly, Chapman and Stryker (1993) have demonstrated that visually driven activity is necessary for the maturation of orientation-selective responses in visual cortex (see Chapman, Godecke, & Bonhoeffer, 1999, for review).

In the somatosensory system, multiple studies in mice have demonstrated that lesions of vibrissae follicles early in development lead to the absence of the corresponding barrels in the adult neocortex (Rice & Van der Loos, 1977; Van der Loos & Woolsey, 1973) and in strains of mice with supernumerary vibrissae, the barrel field in S1 exhibits extra barrels that correspond to the location of the additional vibrissae (Van der Loos & Dorfl, 1978; Van der Loos, Dorfl, & Welker, 1984; Van der Loos, Welker, Dorfl, & Rumo, 1986). In the auditory system, Zhang and colleagues (2002) examined developmental plasticity by introducing white noise pulses during rat pup development (P9–P28) and found that in the adult rat the A1 tonotopic representation was disordered and frequency-response selectivity was degraded.

Together, these studies demonstrate the effects of extrinsic factors on the development of a single cortical field; however, the effect that a loss or enhancement of sensory-driven activity in one sensory system has on the organization, connections, and functions of the neocortex associated with the remaining sensory systems is less understood. As discussed below, recent studies in both humans and other animals have begun to address this issue of cross-modal plasticity within the life of an individual.

Cross-Modal Plasticity Resulting from Congenital Sensory Loss in Humans

Psychophysical studies have demonstrated cross-modal plasticity following early sensory loss in humans (see Bavelier & Neville, 2002, for review). For example, blind individuals exceed sighted individuals in monaural sound source localization (Doucet et al., 2005; Lessard, Pare, Lepore, & Lassonde, 1998), particularly in peripheral auditory space (Roder, Rosler, & Neville, 1999). Further, early blind subjects perform better than normal subjects on self-localization when auditory cues are used to define the space in which the subject is tested (Despres, Boudard, Candas, & Dufour, 2005). They also exceed sighted individuals in auditory memory for verbal encoding and retrieval tasks (Raz, Amedi, & Zohary, 2005; Roder, Rosler, & Neville, 2001), and auditory memory for environmental sounds (Roder & Rosler, 2003). Moreover, blind subjects have shorter reaction times for tactile and auditory spatial attention tasks (Collignon, Renier, Bruyer, Tranduy, & Veraart, 2006).

Similarly, psychophysical studies have shown that deaf subjects are significantly faster than hearing subjects at detecting a visual stimulus in the periphery, although the reaction time of deaf and hearing subjects is the same for stimuli presented in the central visual field (Loke & Song, 1991; Neville & Lawson, 1987). Further, deaf subjects experienced in American Sign Language show greater right visual field sensitivity for motion processing than hearing subjects (Bosworth & Dobkins, 2002). Finally, deaf subjects are more accurate than hearing subjects in detecting suprathreshold tactile changes, although frequency discrimination is not significantly different between the two groups (Levanen & Hamdorf, 2001). Thus, in humans with early visual or auditory loss, sensory-driven abilities mediated through the remaining sensory systems exceed those of normal individuals and the underlying source of these psychophysical differences appears to be due to functional changes in the neocortex.

Noninvasive functional imaging and electrophysiological studies in both early blind and deaf humans indicate that cortex normally activated by the lost sensory system becomes activated by the remaining sensory systems. For example, positron emission tomography (PET) studies in blind humans indicate that auditory localization tasks activate occipital cortex in regions normally involved in visual localization and motion detection (Weeks et al., 2000). Similarly, functional magnetic resonance imaging (fMRI) studies in blind individuals indicate that Braille reading activates occipital cortex (Burton et al., 2002; Gizewski, Gasser, de Greiff, Boehm, & Forsting,

2003; Sadato et al., 1996; Sadato, Okada, Honda, & Yonekura, 2002), and vibrotactile stimulation elicits activation throughout "visual" cortex (Burton, Sinclair, & McLaren, 2004). Even for high-level perceptual and cognitive tasks, such as language processing, fMRI and repetitive transcranial magnetic stimulation (rTMS) studies indicate that the occipital cortex is activated (Amedi, Floel, Knecht, Zohary, & Cohen, 2004; Burton, Snyder, Diamond, & Raichle, 2002).

Functional MRI studies have also shown that "visual" cortical areas, including V1, process auditory information (Kujala et al., 2005), although not all auditory stimuli have been found to elicit a response in the "visual" cortex. Similarly, event-related potential (ERP) studies demonstrate that for auditory stimulation, the N1 and P3 waves peak over occipital cortex (Leclerc, Saint-Amour, Lavoie, Lassonde, & Lepore, 2000). For higher-level processing, such as auditory memory, ERP and fMRI studies have shown that the occipital cortex is activated in blind individuals, as compared to normal controls (Raz et al., 2005; Roder, Rosler, & Neville, 2000). Finally, a desynchronization of the electroencephalogram (EEG) has been found over the occipital lobe in congenitally blind subjects, as compared to normal adults (Noebels, Roth, & Kopell, 1978). Together, these studies demonstrate that the regions of cortex, normally activated by visual stimulation, become responsive to auditory and tactile stimulation in congenitally blind individuals.

There are only a handful of studies that have examined the anatomical substrate for this cross-modal plasticity in humans. In one study, rTMS over S1 generated significantly higher levels of activity, as measured by PET, in area 17 of early blind individuals as compared to late blind individuals (Wittenberg, Werhahn, Wassermann, Herscovitch, & Cohen, 2004). This suggests that S1 provides input to "visual" cortex through corticocortical connections in early blind individuals. Similarly, a study by Shimony and colleagues (2006) found a decrease in geniculocortical projections in early blind individuals as compared to normally sighted individuals using diffusion tensor imaging (DTI) and diffusion tensor tractography (DTT). These results indicate that the observed functional reorganization is mediated by alterations in corticocortical connections, although no additional projections were detected in the blind individuals as compared to sighted individuals (Shimony et al., 2006).

Cross-modal cortical plasticity has also been demonstrated in congenitally deaf subjects. For instance, functional imaging studies indicate that "auditory" areas are active during a variety of visual tasks in congenitally deaf individuals (e.g., Catalan-Ahumada et al., 1993; Finney, Clementz, Hickok, & Dobkins, 2003; Finney, Fine, & Dobkins, 2001; Nishimura et al., 1999). Further, congenitally deaf individuals exhibit enhanced ERP N1 amplitudes, which are associated with the processing of visual motion (Armstrong, Neville, Hillyard, & Mitchell, 2002) when attending to the peripheral visual field (Neville & Lawson, 1987). Finally, using magnetoencephalographic (MEG) techniques, Levanen and colleagues (1998) found that vibrotactile stimuli applied to the palm and fingers activated "auditory" cortex in congenitally deaf subjects.

While the studies noted above in humans represent only a few of the many studies that demonstrate cross-modal plasticity with early sensory loss, the data clearly indicate that following the loss of one sensory modality, behaviors mediated by the remaining modalities are enhanced. This is likely due to an increase in the amount of cortex devoted to the remaining sensory systems (Bavelier & Neville, 2002; Shimony et al., 2006), alterations in the development of the attentional system (Bavelier, Dye, & Hauser, 2006; Forster, Eardley, & Eimer, 2007; Loke & Song, 1991; Poirier et al., 2006), as well as changes in connectivity along the entire neuroaxis. The details of the functional and anatomical changes that occur both in the neocortex and at subcortical levels following early sensory loss have been recently described in nonhuman animals.

Cross-Modal Plasticity Resulting from Early Sensory Loss in Other Mammals

Sensory compensation has been demonstrated behaviorally following early visual loss in a variety of nonhuman animals. For example, bilateral lid suture at birth in cats results in enhanced precision for sound localization, especially for lateral and rear positions, as compared to normal animals (Rauschecker & Kniepert, 1994). Further, ferrets that were deprived of early visual experience by binocular eyelid suture have enhanced sound localization as compared to normal animals when tested in the lateral field; however, there is no clear difference when they are tested at the midline (King & Parsons, 1999), a finding similar to the results of psychophysical studies in humans. Finally, in bilaterally enucleated hamsters, an unconditioned

orienting reflex paradigm was used to examine the direction of orientation and habituation to an auditory stimulus (Izraeli et al., 2002). This study found that bilaterally enucleated hamsters performed like normal animals in terms of correctly orienting toward the stimulus, but they were slower to habituate to the stimulus than normal animals. Although there was no difference in sensory ability, the blind animals were more responsive to auditory stimuli. As in human studies, the cause of these behavioral differences can be traced to functional changes in the nervous system.

In the visual system, there are a number of studies in cats and ferrets that examine the functional and anatomical changes that occur with early visual deprivation via either binocular lid suture or dark rearing. In cats deprived of early visual experience, the majority of neurons in areas 17 and 18 show no orientation selectivity or directional selectivity (Blakemore & Price, 1987; Blakemore & Van Sluyters, 1975). Dark rearing in cats also decreases contrast sensitivity of neurons in area 17 (Gary-Bobo, Przybyslawski, & Saillour, 1995). In ferrets, dark rearing decreases direction selectivity (Li, Fitzpatrick, & White, 2006) and decreases or disrupts orientation selectivity (Chapman & Stryker, 1993; Coppola & White, 2004; White, Coppola, & Fitzpatrick, 2001). Early visual deprivation also decreases the volume, surface area, cortical thickness, and numerical density of neurons in area 17 (Takacs, Saillour, Imbert, Bogner, & Hamori, 1992). When responsiveness to other modalities was specifically investigated in these animals, it was found that 6% of cells in area 17 responded to auditory stimulation (Sanchez-Vives et al., 2006; Yaka, Yinon, & Wollberg, 1999). Further, when higher-order "visual" areas in the suprasylvian sulcus (areas, anterolateral lateral suprasylvian area [ALLS] and anteromedial lateral suprasylvian area [AMLS]) were examined in bilaterally enucleated or lid-sutured cats, most neurons were responsive to auditory stimulation (Yaka et al., 1999).

Similar findings have been reported in areas of the anterior ectosylvian region of early visually deprived cats. In cats with early binocular lid suture, neurons in the anterior ectosylvian "visual" area, which are normally only responsive to visual stimulation, contain neurons that respond predominantly to auditory stimulation (Rauschecker, 1996; Rauschecker & Korte, 1993). Finally, not only are visual areas affected by early loss of vision, but neural responses in nonvisual areas are also modified with early visual deprivation. For example, in cats with early binocular lid suture, a higher proportion of neurons in auditory fields, including the anterior auditory field (AAF) and the anterior ectosylvian auditory field (AEA), are spatially tuned to a particular direction and are more sharply tuned (Korte & Rauschecker, 1993; see Rauschecker, 1995, for review). These findings are similar to those seen in naturally blind animals, like the blind mole rat, in which neurons in "visual" cortex respond to auditory stimuli (Heil et al., 1991).

Since spontaneous visual activity still occurs in dark-reared animals and in those with eyelids bilaterally sutured, as well as in congenitally blind animals, like the blind mole rat, bilateral enucleation experiments have been used to prevent the effects of both spontaneous and sensory-driven activity on cortical field development. In bilaterally enucleated cats, Yaka and colleagues (1999) found that 6% of neurons in area 17 (Figure 18.3), as well as roughly 65% of neurons in extrastriate "visual" areas ALLS and AMLS, respond to auditory stimuli. Further, they found that substantially more cells were responsive to auditory stimulation in bilaterally enucleated cats than in bilaterally eyelid-sutured cats (Yaka et al., 1999). Similarly, about 63% of cells in "visual" cortex responded to auditory stimulation in bilaterally enucleated hamsters, whereas no auditory responsive cells were found in V1 in normal hamsters (Figure 18.3; Izraeli et al., 2002). In rats that were enucleated later in development, about one-third of the cells in "visual" cortex responded to auditory stimulation, although the tuning properties differed from auditory cells in the auditory cortex of normal and enucleated rats, and no tonotopic organization could be identified (Piche et al., 2007).

Finally, in our laboratory, we have found that bilaterally enucleated short-tailed opossums show functional reorganization of visual cortex such that neurons in area 17 as well as extrastriate cortex respond to auditory, somatosensory, or auditory and somatosensory stimulation (Figure 18.3; Kahn & Krubitzer, 2002; Karlen, Kahn, & Krubitzer, 2006). Which sensory system dominates the invaded area varies between animals and is most likely due to differences in strategies implemented by individual animals to explore their surroundings (see Karlen et al., 2006, for more detail).

The differences between these studies in the extent to which "visual" cortex is reorganized (see Figure 18.3) could be due to species differences, but are more likely due to the progressively later developmental ages at which the bilateral enucleations

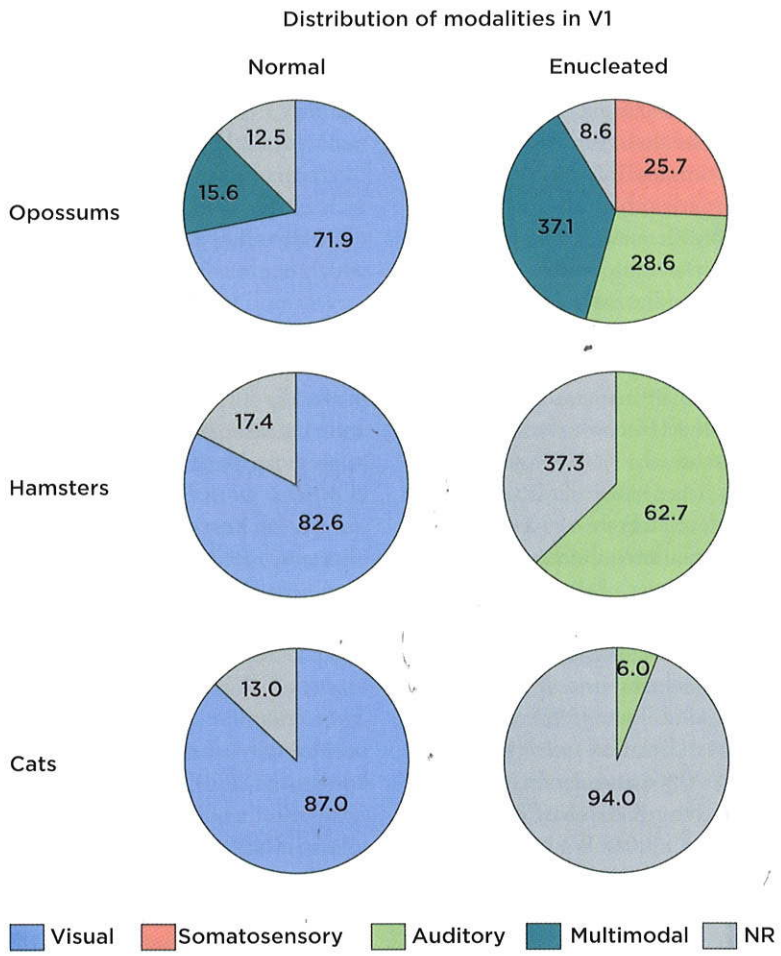

Figure 18.3 Bilateral enucleations early in development result in the functional reorganization of "visual" cortex. Shown here are the percentage of recording sites in architectonically defined V1, which contain neurons that respond to visual (light blue), somatosensory (light red), auditory (light green), and multimodal (teal) stimuli. Lack of response to stimuli from any modality is indicated in gray. The differences between these three studies could be due to species differences, but are more likely due to the progressively later developmental ages at which the bilateral enucleations took place. In enucleated short-tailed opossums, which were enucleated very early in development before retinal axons reach the diencephalon and well before thalamic axons reach the cortex, the majority of recording sites contain neurons that respond to auditory and somatosensory stimulation (Kahn & Krubitzer, 2002; Karlen et al., 2006). In enucleated hamsters, which were enucleated later in development when retinal axons had reached the LGd and thalamocortical axons had reached the subplate but before the formation of cortical layers, most of the cells responded to auditory responses (Izraeli et al., 2002). Finally, in enucleated cats, which were enucleated at the latest developmental timepoint after the retinal axons innervated the LGd and thalamocortical axons innervated layer IV of the cortex, very few of the cells responded to auditory responses (Yaka et al., 1999).

took place. Specifically, opossums were enucleated at an age before retinal axons reach the diencephalon and well before thalamic axons reach the cortex; hamsters were enucleated later in development when retinal axons had reached the dorsal lateral geniculate nucleus (LGd) and thalamocortical axons had reached the subplate but before the formation of cortical layers; and cats were enucleated only after the retinal axons innervated the LGd and thalmocorical axons innervated layer IV of the cortex. Thus, future research in these and other species should consider the timing of sensory loss relative to other important developmental events.

The functional reorganization that occurs in the neocortex with the early loss of a sensory system (Figure 18.3) appears to be driven by dramatic changes in cortical and subcortical connectivity. For example, Asanuma and Stanfield (1990) showed that in both congenitally blind mice and those bilaterally enucleated at birth, ascending

somatosensory projections from the dorsal column nuclei innervate the LGd. Further, in bilaterally enucleated hamsters (Izraeli et al., 2002; Piche, Robert, Miceli, & Bronchti, 2004) and in naturally blind animals, such as the blind mole rat (Doron & Wollberg, 1994), the inferior colliculus has been shown to be the major source of input to the LGd. Likewise, in bilaterally enucleated short-tailed opossums, area 17 receives input from thalamic nuclei associated with somatosensory (ventral posterior nucleus [VP]), auditory (medial geniculate nucleus [MG]), motor (ventrolateral nucleus [VL]), and limbic/hippocampal systems (anterior dorsal nucleus [AD], anterior ventral nucleus [AV]) (Karlen et al., 2006). Finally, there are alterations in corticocortical connections. The callosal pathway between areas 17 and 18 was significantly altered in bilaterally enucleated rats (Olavarria & Li, 1995) and cats (Berman, 1991; Innocenti & Frost, 1980), and in bilaterally enucleated macaque monkeys area 18 had significantly more callosal projections than in normal animals (Dehay, Horsburgh, Berland, Killackey, & Kennedy, 1989). Izraeli and colleagues (2002) did not find any changes in corticocortical connections in bilaterally enucleated hamsters; however, in short-tailed opossums that were bilaterally enucleated very early in development, we found substantial changes in the density of cortical projections as well as the cortical fields projecting to area 17 (Karlen et al., 2006). Specifically, bilaterally enucleated opossums exhibit projections to area 17 from S1, A1, and frontal cortex, in addition to normal cortical projections to V1 from V2, CT, multimodal area (MM), and entorhinal cortex.

There are only a few studies that have examined the functional organization of "auditory" cortex in congenitally deaf animals. In congenitally deaf cats, Kral and colleagues (2003) were unable to find any evidence of cross-modal plasticity in A1 (Figure 18.4). From these results, they concluded that only higher-order auditory areas undergo substantial reorganization following congenital sensory loss. This differs from our own work in congenitally deaf mice, where we have seen extensive cortical reorganization of A1 and the surrounding auditory cortex in adult animals (Figure 18.4; see Hunt, Yamoah, & Krubitzer, 2006, for more detail). Specifically, we found that cortex, which would normally contain neurons that respond to auditory stimulation, contained neurons that responded to somatosensory (36%), visual (15%), or somatosensory and visual (24%) stimulation. In addition to changes in A1, the other primary fields, V1 and S1, were also functionally reorganized in congenitally deaf animals such that there were more bimodal responses. Further, V1 was significantly larger and A1 was significantly smaller in congenitally deaf mice compared to normal animals, as measured using myeloarchitecture (Hunt et al., 2006). The results of these studies indicate that cortical domain territories shift dramatically in congenitally deaf mice such that "auditory" cortex is taken over by the visual and somatosensory system.

The difference in the extent to which "auditory" cortex is reorganized (see Figure 18.4) between our findings and those of Kral and colleagues could be due to species differences, but are more likely due to methodological differences in the timing of sensory loss in the two studies. Specifically, in the deaf cat study, the organ of Corti progressively deteriorates postnatally (Heid, Hartmann, & Klinke, 1998), whereas in the congenitally deaf mouse study, there is never any sensory-driven activity from the cochlea (Delpire, Lu, England, Dull, & Thorne, 1999; Kozel et al., 1998). Despite this lack of patterned activity in the deaf cats, the brief exposure to spontaneous activity, which occurs normally during development and precedes the onset of hearing, could be sufficient to establish normal auditory connections and prevent the more substantial changes observed in the congenitally deaf mice.

Very few anatomical studies have examined the effect of early auditory loss on neocortical and subcortical development. However, the studies that have been done demonstrate that the loss of auditory stimulation also leads to changes in cross-modal connectivity. For example, in congenitally deaf mice, the loss of auditory activity results in aberrant projections of the retina into nonvisual auditory structures, such as the MG and the intermediate layers of the superior colliculus (Hunt et al., 2005).

Animal models of cross-modal plasticity following early sensory loss are consistent with the results described in humans in that the data clearly indicate that with the early loss of one sensory modality, behaviors mediated by the remaining modalities are improved. As in human studies, there seems to be a negative correlation between the age of sensory loss and the amount of cortical reorganization (Figures 18.3 and 18.4); however, the relationship between the age of sensory loss and the amount of cortical reorganization may not be straightforward. For example, in ferrets deafened as adults, 84% of neurons recorded in auditory cortex responded to

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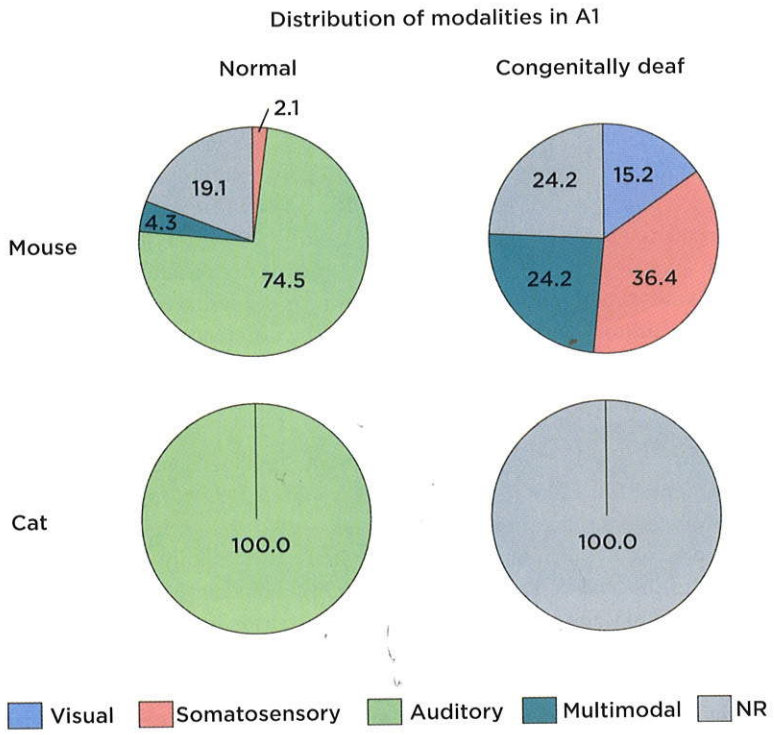

Figure 18.4 Congenital deafness early in development results in the functional reorganization of "auditory" cortex. In mice, congenital deafness results in the functional reorganization of "auditory" cortex. Shown here are the percentage of recording sites in architectonically defined A1 that contain neurons, which respond to visual (light blue), somatosensory (light red), auditory (light green), and multimodal (teal) stimuli. Gray indicates a lack of response to any stimulus. The differences between these two studies could be due to species differences, but are more likely due to the timing of auditory loss in the two experiments. In congenitally deaf mice, which never have any sensory-driven activity from the cochlea, the majority of recording sites in A1 contain neurons that responded to somatosensory and visual stimulation (Hunt et al., 2006). In congenitally deaf cats, Kral and colleagues (2003) were unable to find any evidence of cross-modal plasticity in A1 and concluded that only higher-order auditory areas undergo substantial reorganization following congenital sensory loss; however, in these animals, the organ of Corti progressively deteriorates postnatally, so the animals do have a brief exposure to spontaneous activity during early development.

somatosensory stimulation (Allman, Keniston, & Meredith, 2009). These changes in neuronal response properties did not seem to be due to unmasking or the formation of new cortical connections; instead the authors hypothesize that these changes may be due to subcortical alterations (Allman et al., 2009). Although the mechanisms generating cross-modal plasticity in the neocortex may differ between early development and adults, the data indicate that the loss of one sensory system can lead to changes in the remaining modalities. Further, these changes in functional organization likely result from alterations in cortical and/or subcortical connectivity.

How is Cross-Modal Plasticity Generated in the Neocortex?

Given the examples above, it is clear that the neocortex can be globally affected by changes in sensory-driven activity during early development, regardless of which modality is deprived of activity. For example, both in bilaterally enucleated and congenitally deaf individuals, not only do we observe reorganization of the neocortical area directly affected by the lost modality, but substantial portions of the remaining cortical sheet also reorganize (Figure 18.5). In some ways, this is analogous to a pebble thrown in the water. The largest displacement (ripple) occurs at the point of entry, which in terms of the neocortex, would be the sensory modality directly affected by the loss. But, successive alterations in neocortical organization can occur a good deal away from the cortical area directly associated with the lost modality. Although the changes do not disperse in a uniform fashion, like ripples in a pond, changes in the affected modality induce alterations in the remaining,

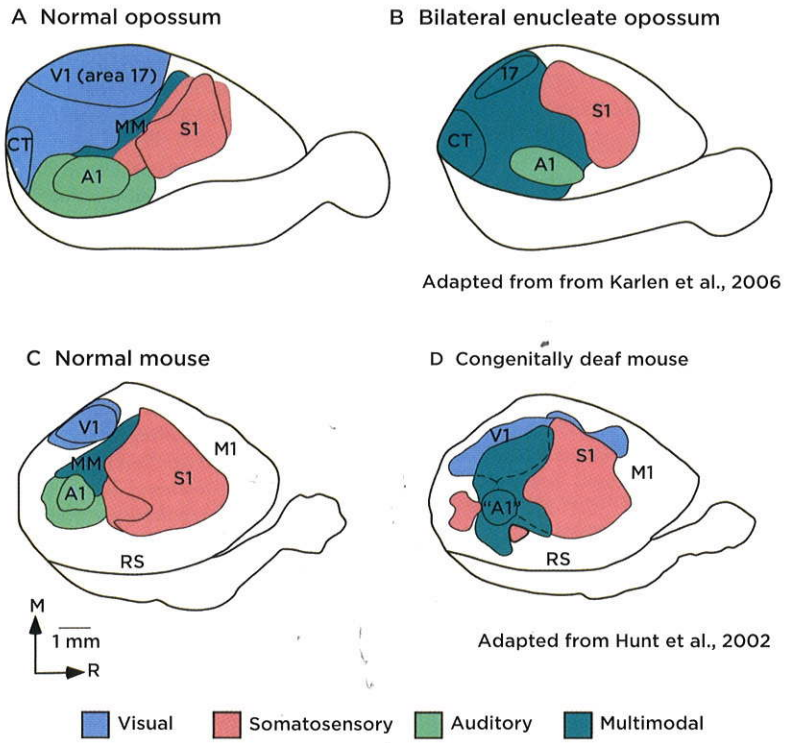

Figure 18.5 In both bilaterally enucleated and congenitally deaf animals, not only is the cortical area that is directly affected by the lost modality reorganized, but substantial portions of the remaining cortical sheet also reorganize. The cortical fields (outlined) and sensory domains (colored) are illustrated for a normal opossum (A), bilaterally enucleated opossum (B), normal mouse (C), and congenitally deaf mouse (D). In the bilaterally enucleated opossum (B), the entire cortex, which would normally be devoted to visual processing, contains neurons responsive to somatic, auditory, or both somatic and auditory stimulation. In the congenitally deaf mouse (D), the entire cortex, which would normally be devoted to processing auditory inputs, contains neurons responsive to somatic, visual, or both somatic and visual stimulation. In both these examples, the cross-modal plasticity is substantial such that all of cortex that is deprived of normal inputs is responsive to new types of sensory stimulation. In opossums and mice, sensory-specific cortical areas can be identified architectonically, although in sensory-deprived animals (B,D), the fields are smaller. (Modified from Krubitzer & Hunt, 2006.) Conventions as in previous figures; abbreviations defined in Table 18.1.

intact sensory systems. In essence, what happens at one point in a fluid, highly dynamic structure like the neocortex affects the development of adjacent points.

The patterns of cortical and subcortical connections provide insight into the neuroanatomical substrates underlying the observed cross-modal plasticity. The fact that normal patterns of connections are intact in both experimental and naturally modified sensory systems suggests that these connections are inherently specified and not easily affected by changes in activity. Conversely, the presence of abnormal wiring, such that normally unimodal structures receive inputs from more than one sensory system, suggests that other connections are greatly affected by sensory-driven activity during development. Whether these are exuberant connections that fail to be pruned or new connections that sprout during development is not known. Regardless, these activity-driven changes in connections most likely drive the changes in functional reorganization of the neocortex following early sensory loss, which in turn contributes to the observed behavioral changes.

Data from both comparative and developmental studies indicate that sensory systems do not develop or evolve in isolation. Instead, they develop in the presence of other sensory systems, each transmitting some form of patterned activity from a unique environment that governs the combinatorial patterns of activity across sensory systems. While genes appear to determine the global organization of the neocortex, the ultimate adult cortical phenotype (which includes sensory domain allocation and cortical field size, organization, and connectivity) can be altered significantly. Thus, despite the

Table 18.1 Abbreviations

A1	Primary auditory area
AAF	Anterior auditory field
AD	Anterior dorsal nucleus
AEA	Anterior ectosylvian auditory field
ALLS	Anterolateral lateral suprasylvian area
AMLS	Anteromedial lateral suprasylvian area
AV	Anterior ventral nucleus
BMP	Bone morphogenetic protein
Cad	Cadherin
CT	Caudotemporal area
DTI	Diffusion tensor imaging
DTT	Diffusion tensor tractography
EEG	Electroencephalogram
ERP	Event-related potential
FGF	Fibroblast growth factor
fMRI	Functional magnetic resonance imaging
LGd	Dorsal lateral geniculate nucleus
M	Medial
MEG	Magnetoencephalograph
MG	Medial geniculate nucleus
MM	Multimodal area
PET	Positron emission tomography
R	Rostral
rTMS	Repetitive transcranial magnetic stimulation
S1	Primary somatosensory area
S2	Second somatosensory area
V1	Primary visual area
V2	Second visual area
VL	Ventrolateral nucleus
VP	Ventral posterior nucleus
Wnt	Wingless-Int

formidable constraints imposed by genes and the invariant nature of physical energy on the development and evolution of the neocortex, the patterns of sensory activity set up across sensory systems allow for a wide range of cortical phenotypes within the lifetime of an individual and across evolutionary time.

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