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Cross-modal plasticity in cortical development: differentiation and specification of sensory neocortex

Mriganka Sur, Sarah L. Pallas and Anna W. Roe

Early developmental manipulations can induce sensory afferents of one modality to project to central targets of a different sensory modality. We and other investigators have used such cross-modal plasticity to examine the role of afferent inputs and their patterns of activity in the development of sensory neocortex. We suggest that the afferent rewiring can significantly influence the internal connectivity or microcircuitry of sensory cortex, aspects of which appear to be determined or specified relatively late in development, but that they cannot influence, or influence only to a minor extent, the laminar characteristics and external connectivity patterns of cortex, which appear to be specified earlier.

One of the most fundamental organizing principles of the cerebral cortex is the localization of function into different areas of representation. In recent years, a major goal of research into cortical mechanisms of sensory processing has been to define the functional role of different cortical areas within each modality. In the visual cortex of primates, for example, there are at least 17 and perhaps 30 or more areas, each of which contains a separate representation of the visual field and processes limited aspects of the visual scene[1–3]. While the organization of the auditory and somatosensory cortical areas is less well understood, it is clear that at least the main features of cortical organization in these modalities are similar to those of the visual system[4].

Cortical development may be thought of as a progressive restriction of the fate of cortical neurons, a process variously termed determination or specifi-

cation. How are the sensory cortical areas specified during development, and how do they come to represent and process specific kinds of information? The most general answer is that cortical areas are specified intrinsically by genetically determined mechanisms, and/or that specification occurs by extrinsic factors that operate epigenetically. Several kinds of experiments have addressed this issue, and excellent reviews have appeared[5–7]; here we synthesize the results of primarily one sort of experiment that addresses the issue of cortical specification directly. These experiments involve cross-modal plasticity in development, i.e. the routing of fibers that carry information about one sensory modality into structures and central pathways that normally process a different modality.

The development of a cortical area involves the specification of several features that make up the area, including the characteristics and location of its constituent cells (cytoarchitectonics), the external connections it makes with other cortical areas and subcortical structures (i.e. its inputs and outputs), and the internal connections or microcircuitry within the cortical area. Whereas other experimental paradigms can be used to address the first of these features, the induction of cross-modal plasticity provides a paradigm that is particularly suited to addressing the role of afferents in specifying the external and internal connections of a cortical area.

Similarities and differences between sensory cortical areas

Any discussion of the specification of sensory cortex requires an understanding of which attributes

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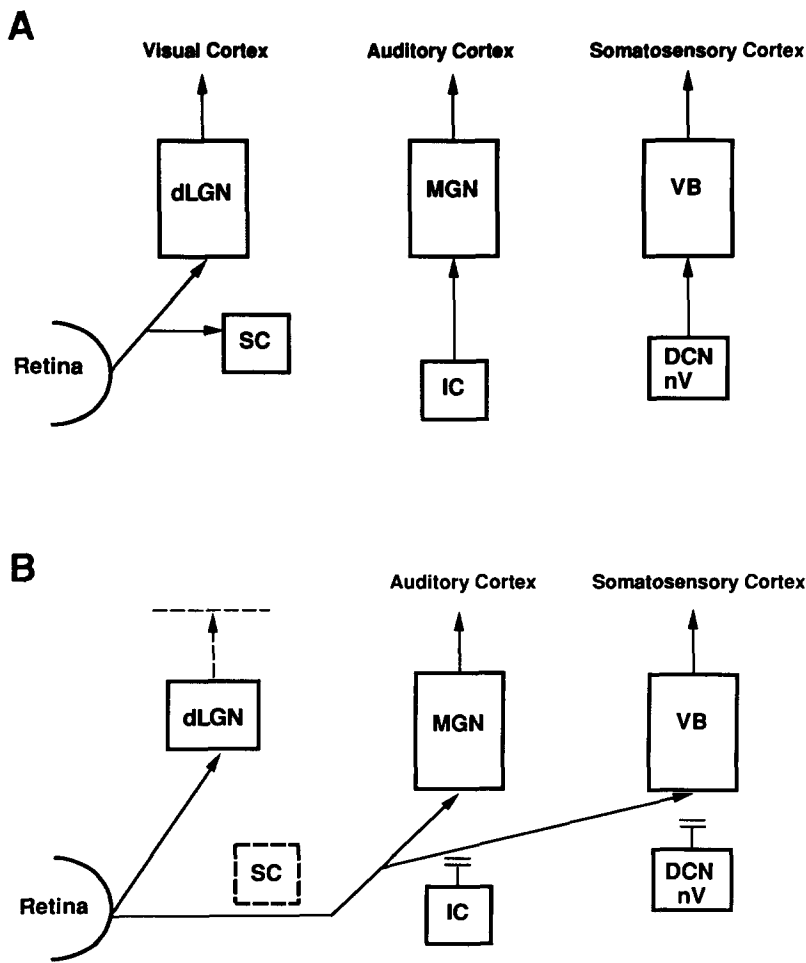
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A

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Fig. 1. *Illustration of the neonatal manipulations that lead to cross-modal plasticity of visual projections.* (A) *The normal connectivity pattern of the three sensory systems. The dorsal lateral geniculate nucleus (dLGN) and the superior colliculus (SC) are the major targets of the retina. In the auditory pathway, the cochlea projects, via intermediate relays, to the inferior colliculus (IC) of the midbrain, which projects to the medial geniculate nucleus (MGN). In the somatosensory pathway, the dorsal column nuclei (DCN) and the nuclei of the trigeminal nerve (nV), along with spinal afferents, project via the medial lemniscus to the ventrobasal nucleus (VB) of the thalamus.* (B) *This review describes the results of manipulations that route retinal projections to either the MGN in ferrets, or the VB in hamsters. On the day of birth, in either the hamster or the ferret, the SC is removed by direct ablation and the occipital cortex is ablated, causing the dLGN to degenerate. MGN or VB is deafferented by sectioning the major input pathways. The retina then invades the deafferented thalamic nucleus, which retains its normal cortical termination site. Visual responses can thus be elicited from cells in auditory cortex (AI) or somatosensory cortex (SI/SII).* (Modified from Refs 40, 44.)

are unique to each sensory cortical area in the adult brain, and which are common to all. Cortical areas were originally subdivided on the basis of cyto-architecture[8], which is quite distinct between the different areas. Factors that contribute to these cytoarchitectonic differences include the type, number, size and arrangement of constituent neurons, and the arrangement of myelinated fibers among the cortical layers. Also, areas can differ in their cortico-cortical and subcortical connectivity patterns, in their topography, in the response properties of their neurons, and in their behavioral role.

At the same time, there are many underlying similarities between different cortical areas. The

number of anatomical similarities is striking. All areas of neocortex are composed of six layers of cells, each of which contains characteristic cell types. Primary sensory cortices are often referred to as 'granular', reflecting the prominence of the small-celled layer IV. A common organizational principle is the modular organization of afferents and cortical processing circuitry of similar functional types[9]. In addition, there are gross similarities in the pattern of interlaminar connections, and in the laminar origin of extrinsic connections[10-12]. Widespread horizontal connections, appreciated relatively recently in area 17 (Refs 13, 14), may also be a feature common to most or all areas of sensory neocortex (see, for example, Ref. 15).

Apart from these anatomical similarities, there may be significant similarities in functional aspects of neurons in different areas, even between areas that represent different modalities. Neurons selective for both the velocity and direction of the stimulus are found in auditory, visual and somatosensory cortex[16-18]. Topographic maps and some form of contrast enhancement, or lateral inhibition, also seem to be universal features of sensory pathways, including those in cortex.

Thus, sensory neocortex appears to consist of a basic structure held in common by all cortical areas, on which is superimposed a number of area-specific differences. A reasonable hypothesis is that similar aspects are intrinsically determined, perhaps before interaction with extrinsic influences (via afferent input) has occurred. Conversely, differences between areas may arise from extrinsic or afferent-induced factors, presumably at a later stage of development. This would apply not only to cortical areas of different modalities, but also to areas processing different subsets of inputs within a given modality (e.g. color, form, or motion in the visual pathway). This hypothesis provides a framework for identifying intrinsic and extrinsic components for each of the features that defines the identity of an area.

Cortical differentiation and specification include at least three different processes; radial specification (the development of the laminar pattern typical of each cortical area), development of external connections (with subcortical or other cortical structures), and development of internal circuitry (i.e. the local connections, or microcircuitry within and between cortical columns). We review briefly the evidence for afferent control of each of these processes.

Radial specification of cortex

The radial development of the cortex begins with proliferation of precursor cells at the ventricular layer[6,19]. These cells then migrate out along radial glial fibers in an inside out manner; the earliest born cells reside deepest in the cortex and vice versa. Thus, the birthdate of a cortical neuron is a powerful predictor of its final laminar position. McConnell[5,20,21] has evidence from heterochronic transplants that many cells are committed early to their laminar fate.

The laminar distribution of cortical cells may also be influenced by thalamic inputs. This idea is supported by the positive correlation between the thickness of layer IV in different cortical areas and the amount of thalamic afference each area receives (see Refs 22, 23 for review). Thalamic afferents wait underneath the

cortical plate as the presumptive layer IV cortical cells migrate through them on their way to their laminar destination[24,25]. This waiting period may provide an opportunity for interaction between the afferents and their cortical target cells. Ablation of large regions of the thalamus prior to migration of layer IV neurons drastically reduces the number of neurons in layer IV (Ref. 26). However, tritiated thymidine labelling suggests that some of the cells originally destined for layer IV can be respecified into layer II–III cells in the absence of their thalamic input.

Development of external connectivity patterns

Each cortical area has a unique pattern of input and output connections. However, early in development, single cortical cells send collaterals to many targets that they later retract. Thus, motor cortex and visual cortex both project to the pyramidal tract in neonatal rats, but visual cortical cells withdraw these projections[7]. Similarly, callosal projections are initially widespread and are restricted later by collateral elimination (see Ref. 7 for review).

There is increasing evidence that at least the basic afferent and efferent connections of a cortical area are established early in development. Shatz and colleagues have shown that a population of cells in the cortical subplate, which appears before the generation of the six cortical layers, projects toward subcortical and callosal target areas at very early developmental stages[27,28]. These subplate cells largely disappear by adulthood, but the efferent projections of subplate neurons may form early guides for later corticofugal (and thalamocortical) axons[29]. In principle, at least, the subplate cell axons may pioneer the early, exuberant projections to and from cortical areas as well as the restricted projections found in the adult.

The final connectivity pattern of cortical cells is not rigidly predetermined, however, and can be influenced by outside factors. O'Leary and Stanfield[30] have reported that the development of specific cortical efferent projections can be influenced by location. They transplanted pieces of late fetal (E17) rat neocortex from visual cortex to sensorimotor cortex or vice versa, and found that the donor tissue makes final projections appropriate to the host tissue. These results suggest that some property of the surrounding host cortical tissue (such as its inputs or its location) may influence the connectivity of the donor tissue independent of its origin.

Development of internal cortical microcircuitry

At present, little is known about the role of afferents in the development of the microcircuitry responsible for the response characteristics of cortical cells. Afferents and their activity patterns clearly play an important role in the development of neuronal response properties in the cortex, and there is an extensive literature on the effects of altering activity or experience on the responses of sensory cortical neurons[31,32]. However, in the experiments we discuss below, the modality (and hence the activation pattern) of the afferents innervating a cortical area is changed without changing the thalamocortical identity of these afferents. Such experiments provide an alternative way to address the issue of afferent control of intrinsic connectivity.

Cross-modal studies: rerouting of sensory projections

In 1973, Gerald Schneider first described a series of experiments in the hamster[33] that was to open the way for a direct investigation of the role of afferent inputs in specifying cortical processing circuitry. Schneider noted that retinal axons could sprout into nearby deafferented areas if the normal retinal targets were removed by neonatal brain lesions. For example, lesions of the superior colliculus (SC) that extended into the inferior colliculus (IC), which provides the major afferent input to the auditory thalamus, resulted in abnormal retinal projections into the auditory relay nucleus of the thalamus, the medial geniculate nucleus (MGN) (Fig. 1). Kalil and Schneider[34] obtained ultrastructural evidence demonstrating that these retinal axons make synaptic connections in the MGN.

Since these pioneering studies, cross-modal rewiring has been demonstrated in a number of different preparations. Devor[35] showed that hamster olfactory afferents can regenerate after section of the lateral olfactory tract in neonates, but that they regenerate into inappropriate cortical regions. Graziadei et al.[36]
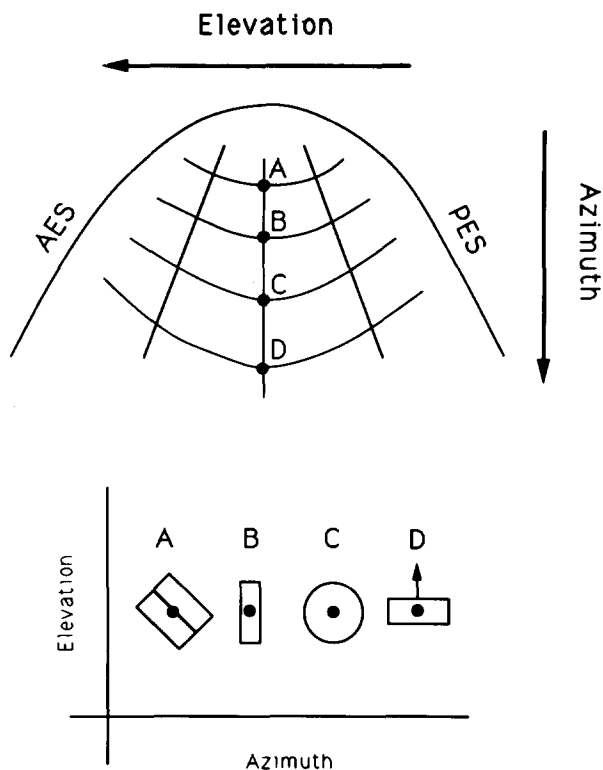

Fig. 2. Results of physiological recordings of visually responsive cells in AI of rewired ferrets. A two-dimensional visuotopic map is created in AI as a result of retinal input to the auditory pathway. Elevations of visual receptive fields recorded in AI increase in a posterior–anterior direction, and azimuths increase in a mediolateral direction on the cortical surface. As shown schematically, visual units recorded at points along a line of constant elevation from A to D in AI have receptive field locations that increase in visual field azimuth (A–D, bottom). The bottom schematic also illustrates physiological characteristics of visual units in AI. Receptive field types recorded in AI can be rectangular, with orientation and direction selectivity (indicated by an arrow on one field), and with or without subfields; many receptive fields are circular.
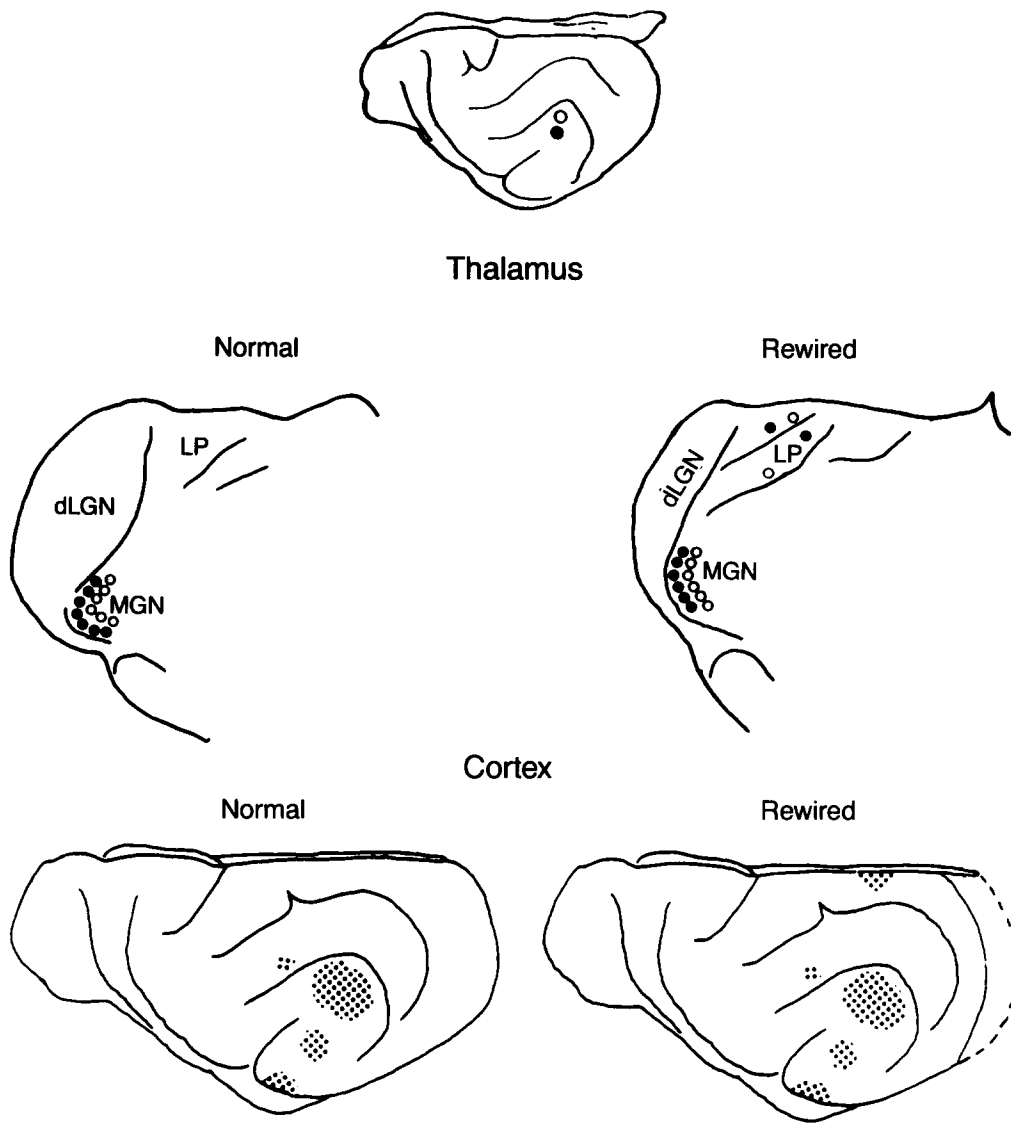
Thalamus

Normal   Rewired

Cortex

Normal   Rewired

Fig. 3. *Patterns of thalamocortical and corticocortical connections in normal and rewired ferrets.* Thalamus: *following injections of neuroanatomical tracers in AI (which lies lateral to the suprasylvian sulcus, as indicated by the dotted line), labeled cells are seen in the medial geniculate nucleus (MGN) in both normal and rewired animals. In the latter, there are a few additional labeled cells in the dorsal thalamus, particularly in the region of the lateral posterior nucleus (LP). As shown by injections of two different dyes at topographically separate locations in AI, the one-dimensional pattern of the MGN-to-AI projection is unchanged by the early lesions. See text for details.* Cortex: *cortical inputs (and outputs) of AI, shown as hatched areas along with AI, are similar in normal and operated animals (with the exception of a projection from medial cortex in rewired animals that is sparse in normal animals). Other abbreviations: dLGN, dorsal lateral geniculate nucleus.*

demonstrated that olfactory afferents regenerate following unilateral olfactory bulbectomy in neonatal mice, and that these regenerating axons can innervate neocortex rather than their normal olfactory bulb target.

Studies in mole rats *(Spalax ehrenbergi)* have taken advantage of a natural evolutionary diversion of auditory afferents into visual structures[37]. Mole rats have only vestigial eyes, and their retinal axons largely degenerate during development. As a result, the LGN and occipital cortex receive auditory input[38,39], and response properties typical of auditory cortex are recorded in occipital cortex (Heil, P. and Scheich, H., pers. commun.).

Frost has shown that the hamster retina can also be induced to project to the ventrobasal nucleus (VB),

the principal somatosensory relay nucleus of the thalamus, again by reduction or removal of normal retinal targets and transection of ascending afferent inputs to VB[40]. Unlike the retinal projection to MGN, the retinal projection to VB results in part from the stabilization of an early, exuberant projection[41].

These studies indicate that, while there may be a preference of sensory axons for their normal termination sites, they will innervate other sensory areas either within or across sensory modalities if their normal target is not available.

Visual projections induced into primary somatosensory and primary auditory cortex

Studies of cross-modal plasticity can provide information about the afferent control of cortical specification, and they can reveal inherent differences or similarities between different sensory neocortical areas. What effect, if any, does changing the modality of the information carried by the thalamic afferents have on cortical processing? Can somatosensory and auditory cortex make use of visual information, and if so, do they perform transformations on that input that are typical of normal visual cortex?

In our laboratory, we have generalized the paradigm in Schneider's early work to another mammal, the ferret *Mustela putorius furo.* Ferrets have a number of advantages for this type of study. Like hamsters, they are born in an immature state, facilitating manipulations of the developing nervous system. The organization of their visual pathway closely resembles that in cats; the ferret retina contains X and Y retinal ganglion cells, as well as a third, heterogeneous group of cells collectively termed W cells[42–44]. In ferrets, retinal afferents can be induced to project into the MGN by reducing the normal retinal targets and by providing alternative target space in the MGN (Fig. 2). We have demonstrated that retinal W cells are responsible for the aberrant projection in rewired ferrets[44].

Response characteristics of visual neurons

Our electrophysiological studies show that visually responsive cells can be recorded in the MGN of rewired ferrets. Since the pathway from MGN to auditory cortex has not been disrupted but carries visual information as a result of the lesion, cells in primary auditory cortex (AI) also respond to visual stimulation. Visual cells in AI have large receptive

fields. About one-third of the fields are orientation-selective, and a similar proportion are direction-selective[44] (Roe, A. W., Pallas, S. L. and Sur, M., unpublished observations). The oriented receptive fields have either separate or co-extensive ON and OFF zones and hence resemble receptive fields of simple or complex cells in normal visual cortex[45] (Fig. 2, bottom). A number of cells are driven binocularly.

Results from hamsters with retinal projections to somatosensory thalamus also show that responses typical of visual cortex can be elicited from non-visual cortex. Metin and Frost[46] found that neurons in somatosensory cortex (area SI/SII) have responses to visual stimuli similar to those of cells in area 17 of normal animals. As in area 17, the cells in SI/SII respond to flashing spots or bars, and their receptive fields are often organized into concentric or adjacent subfields of ON, OFF, or ON/OFF types. The percentage of cells showing orientation and direction selectivity is similar to that found in area 17.

Anatomical organization of cortical projections

Does the rewiring procedure affect the external connections of AI, and might there be other pathways for visual input to AI? To answer these questions, we have made injections of anterograde and retrograde tracers into AI in rewired ferrets. These studies reveal that, in addition to the connections with MGN and the posterior thalamic group that resemble those in normal animals, AI in the rewired ferrets makes anomalous, reciprocal connections with the dorsal thalamic area, including the lateral posterior nucleus of the thalamus (LP)[47] (Fig. 3). While there are also anomalous projections from the retina to LP in these animals, these new projections are quite sparse, and we think they are unlikely to have a major influence on visual processing in AI. Corticocortical connections of AI are similar in normal and rewired animals.

We have also examined the details of the thalamo-cortical projection from the MGN to AI in the rewired ferrets. In normal ferrets[47], as in cats[48,49], focal injections of retrograde tracers into AI label laminae or slabs of cells that are oriented dorsoventrally within the MGN and extend as sheets of projection in the rostrocaudal dimension of the nucleus. We interpret these slabs to correspond to physiologically defined isofrequency slabs in the MGN[49]. Consistent with this idea, injections of multiple tracers along the tonotopic axis in AI label non-overlapping slabs in the MGN, while injections along the isofrequency axis label overlapping slabs[47]. This pattern of essentially one-dimensional projections in the auditory pathway is fundamentally different from the pattern of two-dimensional projections that characterizes the retino-geniculocortical pathway, and the pattern remains unchanged in the rewired ferrets (Fig. 3).

Topography of visual representation

The primary auditory cortex in normal ferrets, as in other animals, contains a one-dimensional, cochleo-topic map of sound frequency[50,51]. Visual input to AI results in a two-dimensional visual field map with elevation increasing from caudal to rostral, and azimuth increasing from medial to lateral[52] (Fig. 2, top). The azimuthal axis, which corresponds to the tonotopic axis in normal animals, contains an orderly progression of visual field location. The elevational
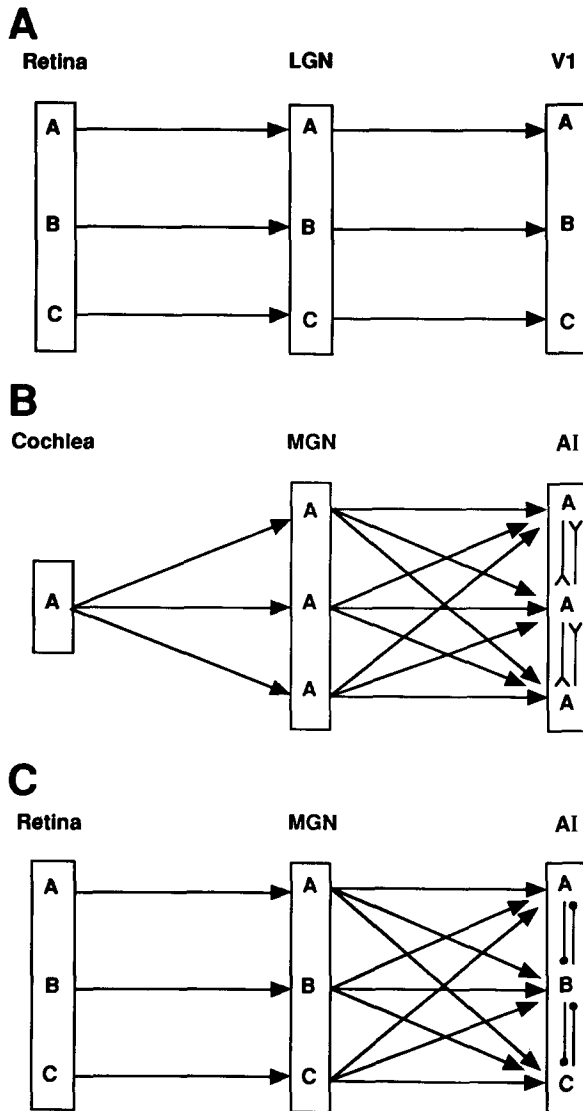

Fig. 4. Highly schematic representation and summary of thalamocortical projections in (A) the normal visual system, (B) the normal auditory system, and (C) the retina-to-MGN-to-AI projection in rewired ferrets. **(A)** Each point on the retina projects in a roughly point-to-point fashion through the lateral geniculate nucleus (LGN) onto visual cortex (V1), and each neuron in V1 'sees' a limited region of visual space. **(B)** In the auditory system, the cochlea contains a one-dimensional representation of sound frequency, and each point on the cochlea is represented in a redundant fashion along a slab of cells in the MGN[49]. Isofrequency slabs in MGN are thought to project in a highly overlapped fashion to AI, such that any neuron in AI receives input from a large number of neurons along the MGN slab representing the same frequency[48,49]. **(C)** In the rewired ferrets, we impose a two-dimensional input from the retina onto the MGN. The nature of the retina-to-MGN projection has not yet been examined in detail (but see Ref. 44), so this part of the schematic is hypothetical. Because the MGN still projects in a highly convergent and divergent fashion to AI (Ref. 47), we hypothesize here that the spatially restricted visual fields and the visual field map in AI arise from changes in the intrinsic circuitry of AI. We have schematized one possible scenario for this change by postulating changes in lateral connections along the isofrequency dimension in AI (which lies anteroposteriorly in cortex). Lateral inhibitory connections between neighboring locations in AI would have the effect of silencing a subset of the thalamic inputs, creating spatially limited receptive fields.

map, along the normal isofrequency axis, is less precise, and the maps can vary in polarity between animals. We suggest that the mapping along this dimension is created in cortex, perhaps by dynamic alterations in intrinsic connectivity during development (see below).

Somatosensory cortex in hamsters, as in other mammals, normally contains a two-dimensional map of the body surface that is transmitted from VB. However, in rewired hamsters, there is a systematic progression of visual receptive fields only from superior to inferior retina, and therefore essentially a one-dimensional visual field map in SI/SII (Ref. 53). The nasotemporal axis of the retina is apparently collapsed onto the isorepresentational axis in VB, and thus the second dimension is 'lost' in cortex.

Role of afferents in cortical specification

What do these studies of cross-modal plasticity suggest about the influence of thalamocortical afferents and their patterns of activity on the development of sensory cortex? The receptive field properties of visually responsive cells in SI/SII in hamsters and in AI of ferrets demonstrate that at least some of the transformations in stimulus representation that occur in normal visual cortex can also occur in AI or SI/SII if they receive visual input.

It is possible that there are some basic processing modules in all sensory cortices that perform stereotypical transformations on their inputs regardless of modality. Thus, visual inputs to SI/SII or to AI simply tap into these modules. The idea of similar cortical processing modules is supported by commonalities in processing between different primary sensory cortices. In the somatosensory cortex, there are straightforward parallels to two of the basic transformations that striate cortex performs on its visual inputs: direction selectivity and orientation selectivity have both been described for neurons in postcentral somatosensory cortex[17,18]. In AI, neurons that respond to the direction and rate of modulation of sound frequency have been described[16,54]. It is possible that processing modules in AI that respond to complex notes or chords[55], and hence to simultaneous stimulation of discrete regions of the sensory epithelium, would generate patterns of orientation selectivity when they receive visual input. Still, given the one-dimensional nature of the cochlea and of sound transduction, generalizing such modules to generate orientation selectivity in auditory cortex for two-dimensional visual stimuli is not straightforward. There are also significant differences between different areas of visual and somatosensory cortex in the types and proportions of neurons with various response properties[32,56]. Thus, while there may be a basic framework of similar modules in neocortical organization and development, afferents must also play a significant role in regulating intrinsic cortical microcircuitry.

We suggest that, in auditory cortex of rewired animals, those physiological features that depend on the two-dimensional nature of visual input arise as a result of alterations in the intrinsic microcircuitry of AI. The anatomy of thalamocortical projections between MGN and AI in normal and rewired animals (Fig. 3) would predict that visual fields of neurons in AI would be anisotropic (i.e. elongated along one

dimension), since single neurons in AI would receive inputs from a slab of cells in MGN (and presumably from an elongated strip of retina). However, single neurons in AI of the rewired ferrets have spatially restricted receptive fields, and AI contains a systematic two-dimensional map of visual space. One possible interpretation consistent with our anatomical and physiological observations is that local inhibition in AI, driven by correlated activity patterns between neighboring elements in the retina, physiologically sharpens the receptive fields of single neurons (Fig. 4) and thus generates the overall visuotopic map as well. Retinal activity, and hence retinal afferents, might play an instructive role in shaping intrinsic cortical connectivity, particularly those intrinsic connections that occur along the isofrequency dimension in AI (Ref. 15). It is important to emphasize that changes in internal connections or microcircuitry need not imply gross changes in intracortical connections, and may include changes in the weights of pre-existing synapses or in the balance of excitation and inhibition on cortical cells. In principle, it is also possible that retinal afferents to auditory thalamus alter the pattern of thalamocortical projections in subtle ways, directing the visual field map in AI. Addressing these issues requires more detailed anatomical and physiological experiments, and this is an important goal of our work at present.

Temporal determinants of cross-modal plasticity

Why do the early lesions in ferrets (and the consequent switch of input modality) produce changes in response properties and topography in AI so that it functionally resembles visual cortex, but no change in corticocortical connectivity and only minor changes in the thalamocortical connectivity of AI (Refs 44, 47)? One possible reason is that the external connectivity patterns of AI and visual cortex are inherently different and cannot be influenced by experimental manipulation. Alternatively, it is possible that the lesions were made too late for afferents to have an influence.

These possibilities can be examined by looking at the time course of cortical development in ferrets. On the day of birth, when the lesions to induce rewiring are made, the infragranular layers of cortex are migrating into position[57], and thalamocortical afferents have not quite reached the cortical plate[58]. Thus, thalamocortical and intrinsic connectivity patterns have not yet been established at birth. However, the cortical efferent pathways may already have been laid down by the subplate pioneers[29], and the laminar arrangement of cortex has been largely specified[5]. Our results then support a role for temporal factors in the lesion-induced effects: major changes could be induced only in those aspects of cortical development that were not already specified at the time of the lesions. The minor changes that were seen in extrinsic connectivity may be due to differential time courses for different thalamocortical projections (such as those from the lateral posterior nucleus of the thalamus).

Temporal factors are also important in retinothalamic connectivity. Projections of the retina become more stabilized and less plastic with age[59], suggesting a critical period for the induction of cross-modal

plasticity. After postnatal day 3 in the normal hamster, the transient retino-VB projections are eliminated[40], thus removing the substrate for inducing retinal projections to the somatosensory pathway. In ferrets, the small (presumably W) cells that arise last in the retina[60] may be the cells that project to the MGN following neonatal lesions, and earlier manipulations may allow retinal X and Y cells to project to the auditory pathways as well.

Concluding remarks

The specification of sensory cortex involves a progressive restriction of fate[5], or a sequential determination from 'protocortex'[7] to maturity. While these events are overlapped in time, laminar identity is apparently determined early, callosal and efferent connections next, then thalamocortical connections, and finally, the intracortical circuitry responsible for the physiological properties of neurons. Apart from intrinsic or genetic determinants, each specification event probably has a critical period when epigenetic factors may influence its outcome. Manipulations of the organism during development will thus have different results depending on how far the restriction of fate has progressed at the time of manipulation. Experiments on cross-modal plasticity suggest basic commonalities in cortical processing modules as well as a role for afferents in specifying intrinsic microcircuitry. These experiments have thus provided important new insights into the control of later stages of cortical development. In the future, earlier manipulations may allow us to address how the specification of early stages occurs as well.

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