Rewiring cortex: Cross-modal plasticity and its implications for cortical development and function

Mriganka Sur
Department of Brain and Cognitive Sciences
Picower Center for Learning and Memory
M.I.T.
Cambridge, MA 02139

Short title: Cross-modal plasticity and cortical development

No of text pages: 37

No of figures: 5

Please address correspondence to:

Mriganka Sur
Dept of Brain and Cognitive Sciences
MIT, E25-235
Cambridge, MA 02139

Tel: 617-253-8784
Fax: 617-253-9829
Email: msur@ai.mit.edu

Introduction

How do individual cortical areas come to process unique kinds of information and contribute to particular behaviors? This question lies at the heart of understanding how the cortex develops and acquires its functional capacities - yet there have been few direct approaches to answering it. In particular, it has proven difficult with the classical models of cortical development to separate intrinsic aspects of developmental programs from those that are influenced by extrinsic factors. A different paradigm for examining the question comes from cross-modal plasticity – such plasticity, induced by rewiring the brain early in life, utilizes inputs of one modality to drive cortical areas that normally process information from a different modality. These experiments provide important evidence that several aspects of cortical development and function are crucially influenced by the nature of input activity. This chapter reviews the logic of rewiring experiments in which visual inputs are induced to drive the auditory cortex, the physiological and behavioral consequences of rewiring, and the implications of these findings for mechanisms by which cortical areas acquire unique identities and processing functions or are able to carry out multisensory integration.

Development of cortical networks for vision

An area of the cortex is characterized by specific inputs, processing networks, and outputs, and these together enable the area to play a particular role in behavior. Traditional approaches to understanding the role of environmental influences on the development of cortical connections and networks involve reductions of activity (Sur et al. 1999; Angelucci et al. 2000). For example, the development and plasticity of ocular dominance columns in primary visual cortex (V1) has been an important proving ground for examining whether and how thalamocortical patterning and connections are regulated by visual inputs (Katz and Shatz 1996).

Ocular dominance columns in V1 arise by the segregation of inputs from the two eyes relayed through eye-specific layers of the lateral geniculate nucleus (LGN). A vast body of evidence demonstrates that visual deprivation regimes such as suturing the lids of one eye during a critical period early in life reduces the proportion of cells driven by the sutured eye (Wiesel and Hubel 1965), and also reduces the size of ocular dominance columns related to the sutured eye (Shatz and Stryker 1978; Antonini and Stryker 1993). These experiments demonstrate ocular dominance plasticity, whereby the open or untreated eye dominates the cortex both physiologically and anatomically, presumably by a dynamic mechanism of competition between axons from the two eyes for cortical territory and synaptic linkage with target cells. Activity in not only the presynaptic axons but also in the target cells has a role in regulating the outcome of the competition, for inhibiting cortical cells causes the less active axons to dominate cortex (Reiter and Stryker 1988; Hata and Stryker 1994). But the issue of whether or not the *initial formation* of ocular dominance columns uses the same mechanisms as those required for their *maintenance* remains open (Katz and Crowley 2002; Sur and Leamey 2001).

Until recently, it was thought that the mechanisms of ocular dominance column formation and maintenance are similar. This view requires that axons from the two eyes are initially overlapped in cortex, and subsequently segregate due to correlated activity in one eye and uncorrelated activity between the two eyes (Miller et al. 1989). Indeed the activity of adjacent retinal ganglion cells is correlated (Galli and Maffei 1988), and “waves” of activity sweep across the retina during early life (Meister et al. 1991), consistent with hypothesis that correlated retinal activity has a role in the patterning of inputs from the two eyes in the LGN and subsequently in the cortex. Altering retinal waves reduces the degree of segregation of fibers from the two eyes in the LGN (Stellwagen and Shatz 2002). Furthermore, the spontaneous activity of LGN cells appears to be correlated within one eye-specific layer but not across eye-

specific layers (Weliky and Katz 1999). Interestingly, however, the correlations depend on input from the cortex rather than from the retina, because ablating the cortex abolishes the correlations whereas enucleation of the eyes does not. Thus, if correlations are important for setting up ocular dominance columns, these must arise from a thalamocortical and corticothalamic loop (Sur and Leamey 2001) rather than from retinal sources – a situation facilitated by the early development of pathways from the thalamus to cortex (Johnson and Casagrande 1993; Hermann et al. 1994) and from the cortex back to the thalamus (Clasca et al. 1995).

An alternative possibility is that the initial formation of ocular dominance columns is determined by matching molecular cues between LGN axons and target regions in V1. It turns out that ocular dominance columns can form very early in life, even when LGN axons first grow into layer 4 of V1, so that axons from each eye-specific layer project to non-overlapping zones from the outset (Crowley and Katz 2000; cf Crair et al. 2001). This is different from previous findings that the early innervation of cortex by LGN axons includes a significant overlap of terminations from the two eyes. It has been argued (Katz and Crowley 2002) that the previously used technique of intraocular injection of tritiated proline for labeling the retinogeniculocortical projection (via transsynaptic transport of label from retinal axons through the LGN to geniculocortical axon terminals in V1) caused spillover in the LGN and in the cortex and thus obscured the segregation. Consistent with the finding that the initial targeting of LGN axons is specific to ocular dominance zones, it has been shown that they develop even in the absence of retinal input, for removing the eyes does not immediately degrade the patchy geniculocortical termination zones (Crowley and Katz 1999). Similarly, monocular deprivation very early in life has no effect on eye-specific driving in V1 for a time immediately after the deprivation, followed by a reduction in responses from the closed eye (Crair et al. 1998). Thus, the initial development of ocular dominance projections appears to follow an intrinsic developmental program, and it

would seem unlikely that activity instructs their formation. While specific molecules related to left and right eye regions have not been discovered, the available evidence is consistent with the possibility that such molecules exist and have a role in setting up at least an initial scaffold of terminations. Yet activity can, in certain situations, play an instructive role in the formation of eye-specific domains in retinal targets: in frogs implanted with a third eye, axons from two retinae innervate a single tectum and form eye-specific stripes there (Constantine-Paton and Law 1978). An instructive role for patterned activity in shaping the cortical columns is indicated by experiments that involve artificially induced strabismus, which causes V1 neurons to become almost exclusively monocular (Hubel and Wiesel 1965; Van Sluyters and Levitt 1980) and ocular dominance columns to sharpen and alter their spacing (Shatz et al. 1977; Lowel 1994). Since strabismus simply creates a spatial mismatch between the two eyes (thus reducing the spatial correlation between activity from the two eyes), these findings indicate that instruction by correlated input activity has a role in at least sculpting the final size and shape of ocular dominance columns.

A second system for examining the role of activity in the development of visual cortex connections involves orientation selectivity. Orientation selective cells and orientation columns in V1 involve a more complex network than the termination of thalamocortical axons into eye-specific regions. Orientation selectivity arises in V1 cells by inputs from the LGN that are aligned along the axis of orientation (Hubel and Wiesel 1968; Ferster and Miller 2000), though considerable evidence indicates that thalamic inputs are amplified by local intracortical connections that sharpen orientation tuning and contribute to contrast gain control (Somers et al. 1995, 2001). Orientation-selective cells in at least the superficial layers of V1 are organized into an orientation map (Bonhoeffer and Grinvald 1991). Columns of cells that prefer a particular orientation are preferentially linked by long-range horizontal connections in V1 that are intrinsic

to the superficial layers and are important for generating the orientation map (Gilbert and Wiesel 1989).

Like ocular dominance, the development of orientation selectivity in V1 has been extensively studied, and its plasticity examined with visual deprivation regimes. Orientation selectivity is present in V1 of monkeys at birth (Wiesel and Hubel 1974), and in cats and ferrets at eye-opening, though selectivity sharpens a great deal with visual experience (Sherman and Spear 1982; Fregnac and Imbert 1984; Chapman and Stryker 1993). Visual deprivation impairs, but does not completely prevent, the development of orientation selective responses (Sherman and Spear 1982; Fregnac and Imbert 1984; Chapman and Stryker 1993). While long-range horizontal connections are present in cats and ferrets just before eye-opening, the connections are refined after the onset of vision and visual deprivation prevents the refinement (Callaway and Katz 1990, 1991; Ruthazer and Stryker 1996). The orientation map in V1 develops alongside the sharpening of horizontal connections, but the size and distribution of orientation domains remains stable while development proceeds (Chapman et al. 1996). Visual deprivation does not alter the layout of the map, though it causes the map driven by a deprived eye to have weaker signals and less order (Crair et al. 1998). In cat V2, short-term monocular lid suture after the orientation map has formed causes the map driven by the closed eye to deteriorate, but reverse suture (so that the formerly closed eye is now opened) restores the map (Kim and Bonhoeffer 1994). Alternating suture, in which one eye or the other are sutured alternately so that the two eyes never have common visual experience, nonetheless causes the maps from the two eyes to be in close register (Godecke and Bonhoeffer 1996). Electrical stimulation of an optic nerve in ferrets with patterned bursts for a few hours each day, starting close to the time of eye-opening, broadens orientation selectivity of single neurons but does not change the layout of the orientation map (Weliky and Katz 1997). These findings have been taken to indicate that

orientation selectivity and orientation maps in V1 depend on an intrinsic scaffold of connections and depend little on visual influences.

The weight of evidence on a role for activity in the formation of ocular dominance columns – and hence on whether activity influences thalamocortical connectivity - indicates that the initial formation of the columns requires at most the presence of thalamocortical activity, though visually driven activity is required for sharpening the columns and to maintain them. The evidence in the case of orientation column formation – and hence on the role of activity in generating intracortical connectivity – is more complicated to interpret. Most of the experiments on examining activity-dependent effects on orientation maps suffer from two drawbacks. First, they commonly involved lid suture to block visual inputs, or infusion of tetrodotoxin into the eyes to block all retinal activity, both of which reduce afferent activity in visual pathways nonspecifically. The experiments hence largely addressed the effect of manipulating the *amount* rather than the *pattern* of activity on development, and were thus not suited for addressing an instructive role for activity. Second, it is now clear that in many instances the manipulations were initiated relatively late in development, after thalamocortical axons were already in place and even after much of the intracortical connections had started to organize (cf. Sur and Leamey 2001). Thus, the experiments addressed the role of activity in the maintenance of columns rather than in their development. In general, classical paradigms such as lid suture starting near the time of eye opening are not adequate for examining whether or not the pattern of input activity instructs extrinsic aspects of cortical developmental programs.

Routing visual inputs to the auditory pathway: why and how

A powerful way to address whether the pattern of input activity has a role in the development of cortical connections is to route axons that convey information about one sensory

modality into central structures that normally process a different modality (Sur et al. 1990; Sur and Leamey 2001). An early discovery by Schneider (1973; see also Frost 1982) demonstrated that axons from the retina could be directed into the auditory thalamus in hamsters if the auditory thalamus was deafferented in newborn animals. We chose to work with ferrets, which have a well-developed visual pathway and are born at a very early stage in development, when axons from the retina are still developing projections to the thalamus and thalamic axons have not yet innervated the cortical plate. The goal of the experiments was to route retinal axons into the auditory thalamus in neonatal animals, thereby providing a pathway for visual inputs to drive the auditory thalamus and subsequently the auditory cortex (Figure 1). Importantly, we reasoned that: (1) because the pattern of electrical activity due to vision had a different spatial and temporal structure than that due to audition, so that auditory structures would develop with a very different pattern of input activity than normal; (2) such re-routing would leave intact the anatomical pathways leading away from the auditory thalamus, such as the thalamocortical projection from the auditory thalamus to primary auditory cortex, but cause them to convey a different pattern of activity; and (3) the change in input activity to the auditory cortex, without altering the anatomical identity of thalamocortical projections, would occur at a very early stage in development, and thus address whether and how activity influenced the initial formation of intracortical connections (rather than just their maintenance). If the auditory cortex in rewired animals developed networks similar to those in visual cortex, it would provide powerful evidence that the formation of visual processing networks in cortex are influenced in instructive fashion by vision and are not simply due to the passive presence of activity or intrinsic developmental programs.

Retinal projections can be induced to innervate the medial geniculate nucleus (MGN) of the auditory thalamus following extensive surgical deafferentation of the MGN in newborn

ferrets (Sur et al. 1988). The procedure involves sectioning the brachium of the inferior colliculus in order to remove ipsilaterally projecting ascending auditory fibers to the MGN, combined with ablating the superior colliculus down to the deep layers in order to remove contralaterally projecting ascending fibers (Angelucci et al. 1998). Molecular factors contribute to making the re-routing possible – one key molecule that has a role is the EphA system of receptor tyrosine kinases and their associated ephrin-A ligands, which have been implicated in topographic mapping of retinal projections to central targets (Feldheim et al. 2000). The ligands are expressed in a gradient in the MGN, with high expression along the border of the MGN and the optic tract, and they normally repel receptor-bearing retinal axons of the optic tract (Lyckman et al. 2001). Mutant mice in which genes for two of the ephrin-A ligands, ephrin-A2 and -A5, are deleted show a significant increase in the extent of retino-MGN projections compared to wild-type mice (Lyckman et al. 2001), due primarily to a major enhancement of projections from the ipsilateral retina (Ellsworth et al. 2001). The likely reason for this result is that fibers from the temporal retina, which give rise to the ipsilateral projection, normally project to low Ephrin-A expressing regions of the MGN. Removing the expression of the ligands by deleting the genes that make them expands the potential target space for axons from temporal retina (Ellsworth et al. 2002). Thus, molecules that regulate topography can also regulate confinement of retinal projections to normal targets, and altering their expression can alter the specificity of retino-thalamic projections. At the same time, other molecular systems are likely to be also involved in target specificity and plasticity: mice lacking Ephrin-A ligands do not develop aberrant retinal projections to the MGN without deafferentation of the MGN, implying that other molecules, including those possibly upstream of the ephrins, have a role in confining retinothalamic projections.

The retinal projection to the MGN in ferrets arises from most of the major retinal ganglion cell types (Vitek et al. 1985), prominently including W cells (Roe et al. 1993) as well as other retinal ganglion cell classes (Angelucci et al. 1998). It is reasonable to propose that the key aspect of retinal ganglion cells that induces them to project to the MGN is the timing of axon outgrowth in the optic tract. Retinal ganglion cells which are generated around birth in ferrets, when the rewiring procedure is carried out, are likely to target novel locations; these include W cells from most of the retina as well as other cell classes from more peripheral regions of the retina (Angelucci et al. 1998).

Physiological and anatomical consequences of rewiring: visual networks in auditory cortex

Rewired ferrets form a unique model for examining how the pattern of electrical activity in space and time shapes processing networks and the role in behavior of a cortical area. The projection from the retina is chiefly to the ventral or principal division of the MGN, and provides secure driving of MGN neurons (Figure 2). MGN neurons in rewired ferrets have center-surround visual receptive fields (Roe et al. 1993). Retinal axons also map systematically to the ventral division of the MGN, with central retina represented medially, peripheral retina laterally, the ventral retina dorsally and the dorsal retina represented ventrally within the MGN (Roe et al. 1991). Retinal axons have focal terminations within the MGN (Pallas et al. 1994), though the arbors are represented within MGN lamellae and are aligned along them (Pallas and Sur 1994). Furthermore, retinal axons from each eye start out occupying overlapped territories but then segregate into eye-specific clusters within the MGN, though each cluster is smaller than the eye-specific layers that characterize the normal LGN (Angelucci et al. 1997). These findings indicate that afferent axons have a significant effect on the structure of sensory pathways through the thalamus, but the target also regulates key aspects of the projection.

The ventral division of the MGN projects heavily to primary auditory cortex (A1), and in rewired ferrets the thalamocortical projections convey visual drive to A1 rather than auditory drive. A map of visual space arises in rewired A1 (Roe et al. 1990); the map provides important clues to how the pattern of input activity shapes the strength of thalamocortical synapses during development. In normal ferrets, A1 contains a one-dimensional map of sound frequency, with low frequencies represented laterally and high frequencies medially in cortex. The orthogonal (anteroposterior) axis is one of iso-frequency, that is, the same frequency is remapped along it. Consistent with this mapping, the terminal arbors of single axons from the MGN to A1 are narrow along the variable-frequency axis but widespread along the iso-frequency axis (Pallas et al. 1990). The anatomical pattern of thalamocortical projections is not altered in rewired ferrets, and it predicts that visual receptive fields along the anteroposterior axis of rewired A1 would be highly overlapped and elongated in size and shape. Yet the physiological receptive fields, and the map itself, indicates otherwise: receptive fields are restricted in size, and there is a systematic progression along the anteroposterior dimension of A1. Thus, not all parts of thalamocortical axon arbors convey equal drive to postsynaptic neurons in rewired A1 – either the weights of thalamocortical synapses are altered, or there is an increase of cortical inhibition, so as to cancel the widespread excitation supplied by the thalamus (Sur et al. 1990). Whereas altering the nature of input activity to A1 early in development does not seem to significantly alter the anatomical structure of thalamocortical arbors, the functional consequence of the projection is significantly changed, presumably due to correlated inputs from adjacent retinal and MGN loci that provide the substrate for focal functional connections within rewired A1.

Rewired A1 also develops visual orientation selective cells and an orientation map. Single neurons within A1 are less responsive to visual stimuli compared to V1 in normal animals (Roe et al. 1992), but have orientation and direction tuning that is comparable in degree to that in

V1 (Sharma et al. 2000). In particular, the orientation selectivity arises in rewired A1 itself, just as it does within V1, because neurons in the rewired MGN exhibit significantly less selectivity (Figure 2). Thus, it seems that the same mechanisms operate within rewired A1 as in normal V1 in order to generate orientation selectivity. These mechanisms include feedforward excitation from the thalamus combined with recurrent connections in the cortex to amplify the tuning (Somers et al. 1995, 2001). The intracortical connections may be a ubiquitous feature of A1 that is common to cortical areas, whereas the feedforward projections are likely to be shaped by the nature of visual input – visual edges in natural scenes and other visual stimuli can provide correlated inputs to the MGN and to A1 in rewired animals, which may be used by cortical neurons to generate orientation selectivity. The development of orientation selectivity in rewired A1 implies strongly that a similar mechanism could be used to generate orientation selectivity in V1 in normal animals, where the influence of activity has been difficult to resolve with other experimental models.

The strongest evidence that the pattern of input activity can shape intracortical networks is provided by the orientation map and the structure of long-range horizontal connections within rewired A1 (Sharma et al. 2000). Optical imaging of intrinsic signals demonstrates that domains of neurons in rewired A1 respond to the same preferred orientation; these domains are organized systematically around pinwheel centers to form a map of orientation selective cells (Figure 3). The pinwheel organization of the map is similar to that in V1, and indicates that the pinwheel structure is an important means by which the mapping of orientation selectivity relates to other maps and representations within V1. Long-range connections within rewired A1 connect domains that have the same orientation preference, and hence obey the same principle as do connections in V1. However, the orientation maps in rewired A1 and V1 also have differences: the orientation domains are larger in size in rewired A1 and seem to be less orderly in their

spacing. Similar to the orientation map, horizontal connections in rewired A1 also seem to be less orderly than those in V1. Still, the pattern of horizontal connections in rewired A1 is significantly different from that in normal A1, and resembles in essential aspects the connections in V1 (Figure 4). In V1, the connections are patchy and periodic, and often elongated along the orientation axis of the injection site. In A1, the connections are band-like and extend along the isofrequency axis of the cortical sound frequency map. In rewired A1, the connections form patches that are much smaller than the bands in normal A1 (cf Gao and Pallas 1999), and the patches tend to extend along the orientation axis of the injection site. Thus, input activity has a significant role in shaping horizontal connections within the cortex. In rewired A1, input correlations driven by visual stimuli of the same orientation influence horizontal connections that come to interconnect cells responsive to the same visual orientation. In normal A1, the correlations are driven by auditory stimuli of the same frequency, and horizontal connections interconnect cells responsive to the same sound frequency (Read et al. 2001).

The behavioral consequences of routing visual projections to the auditory pathway

The routing of retinal inputs to the auditory thalamus and the shaping of networks in the auditory cortex raises the question: what is the role in behavior of the rewired projection? In other words, is visual activation of the rewired projection interpreted by the ferrets as a visual stimulus or as an auditory one? If the behavioral role of a cortical area is set independent of its inputs, then activation of the auditory cortex by any stimulus (auditory or visual) would be interpreted as auditory. But if the nature of inputs has a role in determining the function of a cortical area, rewired animals would interpret visual activation of the cortex as a visual stimulus.

This is a fundamental question about cortical function, yet there are few ways of answering it outside of a paradigm such as rewiring. Von Melchner et al (2000) used a selective

training and stimulus presentation procedure in rewired ferrets to address the issue. Ferrets were rewired in the left hemisphere, and were trained to discriminate between light and sound (Figure 5). Sound stimuli (clicks or tone bursts) were presented at a range of locations and animals received juice reward for correct identification at a particular reward spout. Light stimuli (red LEDs) were presented in the left monocular segment, and hence were seen only by the right, normal, hemisphere; animals received juice reward for correct identification at a different reward spout. Thus, animals eventually learned to associate one reward location with sound and another with light. After training was complete, the response of animals was tested with light stimuli presented in the right monocular segment; these stimuli were projected into the left, rewired, hemisphere. Reward was given indiscriminately at either reward spout for light or sound stimuli. (Visual stimuli were also presented at other locations for comparison; however, the critical part of the experiment involved the right monocular segment). In the first stage of testing, animals responded overwhelmingly at the visual reward spout, indicating that the visual stimulus was seen. This was not surprising, because the rewired hemisphere contained two parallel pathways from eye to brain: the normal projection from the retina to the LGN and lateral-posterior nucleus (LP) to visual cortex, and the rewired projection from the retina to the MGN to auditory cortex. In the second stage of testing, the LGN/LP in the rewired hemisphere was ablated with ibotenic acid and animals were tested after a period of recovery. In this instance, the only projection from the retina was that to the MGN; animals still responded overwhelmingly at the visual reward spout, indicating that the visual stimulus was again seen. In the third stage of testing, the auditory cortex was lesioned, and animals were tested after a period of recovery. In this instance, animals responded at chance levels at the visual reward spout, indicating that the animals were blind in the right visual field and the visual stimulus was not seen (Figure 5).

Several kinds of control experiment demonstrated that rewired ferrets indeed perceived the visual stimuli with their rewired projection. In one control, normal animals were trained in the identical way to discriminate visual stimuli presented in the left monocular segment and auditory stimuli. In the testing phase, they were presented visual stimuli in the right monocular segment, and they responded overwhelmingly at the visual reward spout, indicating that the stimuli were seen. In the second phase of the control experiment, the LGN/LP and the SC in the left hemisphere were lesioned with ibotenic acid; animals now responded at chance levels at either reward spout, indicating that they were blind in the right visual field. In contrast to these animals, however, rewired ferrets had their SC lesioned at birth (as part of the procedure to induce rewiring), and the LGN/LP was lesioned prior to the second phase of testing. They were still able to perceive the visual stimuli with their rewired projection, and were functionally blind only when their *auditory cortex* was ablated. Thus, the rewired projection from the retina through the MGN to auditory cortex is able to mediate visual behavior.

What is the quality of visual sensation ("qualia") evoked in the rewired projection, and does it resemble normal vision? To ascertain how different the perception of light was from sound in the rewired animals, another set of control ferrets were trained to respond to light stimuli alone or sound stimuli alone. That is, they were trained to associate one reward spout with their training stimulus, and were then presented the other stimulus. Animals trained on sound alone never responded at the sound reward spout when a light was presented to their rewired projection, indicating that the representation of the light was substantially different from sound (at least the training set of sounds). Animals trained on light alone always responded at the light reward spout when light was presented to the rewired projection, indicating that the representation of the light was similar in their normal and rewired projections. Furthermore, the representation of sound was generalized substantially by the rewired ferrets. While they were

trained with a restricted set of sounds, they routinely responded at the sound reward spout when they were tested with a broad range of sounds. Thus, it is unlikely that the quality of representation of visual stimuli was simply another form of audition in rewired ferrets. Rather, the available evidence indicates that light stimuli were indeed perceived as visual, and as different from sound.

A final line of evidence that rewired ferrets can use their rewired projection for visual function comes from examining their ability to detect gratings of different contrasts and spatial frequencies. Animals with only the rewired projection from the retina to MGN to auditory cortex (that is, with the LGN/LP lesioned) were trained to respond at a reward spout only if a grating was visible in the right monocular field but not otherwise (Von Melchner et al. 2000). Contrast-response functions were derived, and these demonstrated that the response of animals scaled with contrast: the higher the contrast, the greater was the visibility of the grating via the rewired projection as measured by the accuracy of response. This was similar to the response of normal animals and of the normal hemisphere in rewired animals. While the spatial acuity of the rewired pathway was lower than that of the normal visual pathway (likely due to the fact that retinal W cells form the primary source of inputs to the MGN), these findings indicate that the rewired projection is competent to mediate vision. Similarly, rewired hamsters can discriminate visual patterns with their rewired projection (Frost et al. 2000).

One explanation for these results is that the capacity for visual or auditory function resides in some later, as yet unspecified, location in the brain, and routing visual inputs to the auditory thalamus causes a switch in this location so that it now interprets visual activation of auditory pathways as vision. For example, higher cortical areas in the ferret brain might be critically involved in perceptual specification, and rewiring might induce a change in the projection from the auditory cortex to such area(s) that then leads to the perception of vision.

However, a more parsimonious explanation of these results, that invokes induction of function, is that vision is a distributed property of networks that receive inputs from the retina. Thus, visual inputs routed to the auditory thalamus induce visual function in subsequent "auditory" pathways and networks; pathways central to the MGN in rewired animals, including the pathways to auditory cortex, networks within auditory cortex, intracortical pathways between auditory areas, and descending projections from the auditory cortex, are all induced to be visual and thus mediate vision. That is, brain pathways and networks derive function from their inputs.

Cross-modal plasticity in humans, and the lack of perceptual plasticity associated with "phantom limbs"

The conclusion that cortical areas derive function from their inputs is consistent with evidence from congenitally blind humans indicating involvement of visual cortex in non-visual tasks. Visual cortex in such individuals shows activation in somatosensory tasks (Sadato et al. 1996; Kujala et al. 1997) as well as, under different conditions, in auditory tasks (Neville et al. 1983; Weeks et al. 2000; Bavelier et al. 2001). Conversely, auditory cortex in congenitally deaf individuals can be activated by visual tasks (Neville et al. 1983; Finney et al. 2001; Bavelier and Neville 2002). Importantly, the quality of sensation associated with activating the visual cortex in congenitally blind individuals, or the auditory cortex in congenitally deaf individuals, appears to derive from the nature of inputs. That is, visual inputs are perceived as visual even when auditory cortex is activated, just as auditory (or somatosensory) inputs are perceived as auditory (or somatosensory) in spite of activating visual cortex. Furthermore, even in normal, non-deprived, humans, there is evidence for extensive cross-modal interactions, whereby primary sensory areas of the cortex can be activated in a task-specific manner by stimuli of other modalities (Bavelier and Neville 2002). Common to these findings is the principle that inputs

recruit pathways, cortical areas, and networks within and between areas that process the information, and the sensory-perceptual modality associated with the input is driven by the nature of the input rather than by the cortical area activated per se. Of course, under normal conditions, the primary sensory areas are the first and most consistently activated cortical regions associated with the vast majority of modality-specific processing, and it is reasonable to conclude that their activity might intrinsically process a given modality. It is situations where other modalities are adaptively processed by a cortical area without altering qualia that provide the strongest evidence for input based functions of cortex.

One important instance where the nature of the input *does not* adaptively change the perceptual role of a cortical area is in the "phantom limb" percept. Here, sensory stimulation of a forelimb stump or the skin on the face leads to a percept of the missing limb being touched (Ramachandran and Rogers-Ramachandran 2000). Removal of peripheral input causes a remapping of the cortical territory associated with the remaining skin, and this remapping is thought to underlie the phantom percept. Thus, removing the digits of the hand or deafferenting the arm causes an expansion of the cortical territory representing the face (Merzenich et al. 1984; Pons et al. 1991). The mechanism for this expansion is likely to be both an unmasking of divergent projections to cortex from peripheral receptors relayed through brainstem and thalamic somatosensory nuclei to primary somatosensory cortex, as well as growth of new connections in subcortical and cortical areas (Florence et al. 1998; Jones and Pons 1998; Jain et al. 2000). When the face is stimulated, its expanded cortical representation within the former hand and arm representation is activated in addition to the extant face area. Activation of the former hand/arm cortex is considered to underlie the phantom percept, but the percept is a maladaptive one: sensory stimulation of one body region, the face, is associated with a wrong region of the body, a missing limb.

Why does the brain signal a wrong percept even though the primary somatosensory cortex has been remapped? One possibility is that the body image resides in some higher, fixed, cortical locus, and even though the primary somatosensory cortex is remapped, this later area continues to interpret activation from the face as arising from the limb. However, this possibility is unlikely. The remapping of primary somatosensory cortex ensures that later cortical areas would also be remapped, for they are all driven by the postcentral cortex and from the new face input. Furthermore, compared to primary somatosensory cortex, the capacity for plasticity is likely to be even more pronounced in the later areas. Interestingly, there is one pathway that likely remains unchanged even after deafferentation – this is the descending pathway from somatosensory cortex to the spinal cord. These projections from the hand/arm region are likely to continue targeting the appropriate spinal cord segments, even though the cortex is now receiving input from the face via subcortical or intracortical projections. The implication of this is that a percept is due not only to the sensory input but also to the outflow, and the two have to be consistent in order to interpret an input as arising from a part of the body or from a modality. On this view, the phantom limb percept arises by a combination of sensory stimulation from the face (which activates remapped cortex) but an output referral to the spinal segments that still relate to the missing limb.

In rewired ferrets, then, it is important that not only the inputs to auditory cortex be visual but also that the output projections of auditory cortex be consistent with the input, that is, be able to mediate visual responses. One possibility is that the outflow of the auditory cortex should now target existing visual structures. But our data to date indicate this is unlikely: the inputs to primary auditory cortex in rewired ferrets arise from essentially the same cortical areas that provide input to auditory cortex in normal ferrets (Pallas et al. 1993), and it is likely that the connections are reciprocal. Furthermore, rewired auditory cortex projects downstream to

auditory thalamic nuclei and not to visual thalamic nuclei. More likely is the fact that due to deafferentation of the MGN, auditory input is absent in ascending pathways in the rewired hemisphere, so that all of the "auditory" structures have been simply turned visual. This complete "take-over" of pathways and networks is in fact essential for respecifying the perceptual role of the auditory cortex as visual.

Similarly, it is reasonable to propose that in congenitally deprived humans, there exists a consistent set of pathways to and from cortex that allow the cortex to process information from a new modality. In normal, undeprived, humans, we propose that the recruitment of cortical areas of one modality for tasks of another that preserve a modality-specific percept would involve some specific rules: the activation should not involve the output cells of the area, and preserve the output specificity of the input modality.

Conclusions

Cross-modal plasticity provides a important way by which natural stimuli, rather than deprivation paradigms, can be used to examine a central issue in brain development: to what extent is the connectivity and function of a cortical area influenced by its inputs during development? Routing retinal inputs to the MGN causes the auditory cortex to be driven by spatial and temporal patterns of electrical activity due to vision, without altering the thalamocortical pathways from the MGN to auditory cortex. Several features of auditory cortex are subsequently altered, including thalamocortical connections and intracortical networks that map visual space and process visual orientation selectivity. The perceptual role of auditory cortex is also altered, so that rewired ferrets interpret activation of the auditory cortex by visual stimuli as vision. Thus, the nature of input activity has a profound role in the construction of cortical networks that process the input. In normal development, such sculpting provides a means

of self-organization of cortical processing networks. The behavioral findings underscore the importance of output as well as input projections in perception, and indicate that the role in behavior of an area of the cortex arises from a consistent set of inputs, processing networks, and outputs.

Acknowledgements

I thank Christine Waite for her help with preparing this review. The research described here was supported by grants from the NIH and the March of Dimes.

References

Angelucci, A., F. Clasca, E. Bricolo, K. S. Cramer, and M. Sur, 1997. Experimentally induced retinal projections to the ferret auditory thalamus: development of clustered eye-specific patterns in a novel target, J. Neurosci., 17:2040-2055.

Angelucci, A., F. Clasca, and M. Sur, 1998. Brainstem inputs to the ferret medial geniculate nucleus and the effect of early deafferentation on novel retinal projections to the auditory thalamus, J. Comp. Neurol., 400:417-439.

Angelucci, A., J. Sharma, and M. Sur, 2000. The modifiability of neocortical connections and function during development, in The Mutable Brain, (J. H. Kaas, ed.), Amsterdam: Harwood Academic Publishers, pp. 351-392.

Antonini, A., and M. P. Stryker, 1993. Rapid remodeling of axonal arbors in the visual cortex, Science, 260:1819-1821.

Bavelier, D., and H. J. Neville, 2002. Cross-modal plasticity: where and how?, Nat. Rev. Neurosci., 3:443-452.

Bonhoeffer, T., and A. Grinvald, 1991. Iso-orientation domains in cat visual cortex are arranged in pinwheel-like patterns, Nature, 353:429-431.

Callaway, E. M., and L. C. Katz, 1990. Emergence and refinement of clustered horizontal connections in cat striate cortex, J. Neurosci., 10:1134-1153.

Callaway, E. M., and L. C. Katz, 1991. Effects of binocular deprivation on the development of clustered horizontal connections in cat striate cortex, Proc. Natl. Acad. Sci. USA, 88:745-749.

Chapman, B., and M. P. Stryker, 1993. Development of orientation selectivity in ferret visual cortex and effects of deprivation, J. Neurosci., 13:5251-5262.

Chapman, B., M. P. Stryker, and T. Bonhoeffer, 1996. Development of orientation preference maps in ferret primary visual cortex, J. Neurosci., 16:6443-6453.

Clasca, F., A. Angelucci, and M. Sur, 1995. Layer-specific programs of development in neocortical projection neurons, Proc. Natl. Acad. Sci. USA, 92:11145-11149.

Constantine-Paton, M., and M. I. Law, 1978. Eye-specific termination bands in tecta of three-eyed frogs, Science, 202:639-641.

Crair, M. C., D. C. Gillespie, and M. P. Stryker, 1998. The role of visual experience in the development of columns in cat visual cortex, Science, 279:566-570.

Crair, M. C., J. C. Horton, A. Antonini, and M. P. Stryker, 2001. Emergence of ocular dominance columns in cat visual cortex by 2 weeks of age, J. Comp. Neurol., 430:235-249.

Crowley, J. C., and L. C. Katz, 1999. Development of ocular dominance columns in the absence of retinal input, Nat. Neurosci., 2:1125-1130.

Crowley, J. C., and L. C. Katz, 2000. Early development of ocular dominance columns, Science, 290:1321-1324.

Ellsworth, C. A., A. W. Lyckman, and M. Sur, 2002. Ephrin-a mediates eye-specific patterning of retinogeniculate projections in rewired mice, Soc. Neurosci. Abs., 28:820.823.

Ellsworth, C. A., A. W. Lyckman, and M. Sur, 2001. Eye-specific patterning of retinogeniculate terminations in the medial geniculate nucleus of rewired mice, Soc. Neurosci. Abs., 27:27.13.

Feldheim, D. A., Y. I. Kim, A. D. Bergemann, J. Frisen, M. Barbacid, and J. G. Flanagan, 2000. Genetic analysis of ephrin-A2 and ephrin-A5 shows their requirement in multiple aspects of retinocollicular mapping, Neuron, 25:563-574.

Ferster, D., and K. D. Miller, 2000. Neural mechanisms of orientation selectivity in the visual cortex, Annu. Rev. Neurosci., 23:441-471.

Finney, E. M., I. Fine, and K. R. Dobkins, 2001. Visual stimuli activate auditory cortex in the deaf, Nat. Neurosci., 4:1171-1173.

Florence, S. L., H. B. Taub, and J. H. Kaas, 1998. Large-scale sprouting of cortical connections after peripheral injury in adult macaque monkeys, Science, 282:1062-1063.

Fregnac, Y., and M. Imbert, 1984. Development of neuronal selectivity in primary visual cortex of cat, Physiol. Rev., 64:325-434.

Frost, D. O., 1982. Anomalous visual connections to somatosensory and auditory systems following brain lesions in early life, Brain Res., 255:627-635.

Frost, D. O., D. Boire, G. Gingras, and M. Ptito, 2000. Surgically created neural pathways mediate visual pattern discrimination, Proc. Natl. Acad. Sci. USA, 97:11068-11073.

Galli, L., and L. Maffei, 1988. Spontaneous impulse activity of rat retinal ganglion cells in prenatal life, Science, 242:90-91.

Gao, W., and S.L. Pallas, 1999. Cross-modal reorganization of horizontal connectivity in auditory cortex without altering thalamocortical projections, J. Neurosci., 19:7940-7950.

Gilbert, C. D., and T. N. Wiesel, 1989. Columnar specificity of intrinsic horizontal and corticocortical connections in cat visual cortex, J. Neurosci., 9:2432-2442.

Godecke, I., and T. Bonhoeffer, 1996. Development of identical orientation maps for two eyes without common visual experience, Nature, 379:251-254.

Hata, Y., and M.P. Stryker, 1994. Control of thalamocortical afferent rearrangement by postsynaptic activity in developing visual cortex, Science, 265:1732-1735.

Herrmann, K., A. Antonini, and C. J. Shatz, 1994. Ultrastructural evidence for synaptic interactions between thalamocortical axons and subplate neurons, Eur. J. Neurosci., 6:1729-1742.

Hubel, D. H., and T. N. Wiesel, 1965. Binocular interaction in striate cortex of kittens reared with artificial squint, J. Neurophysiol., 28:1041-1059.

Hubel, D. H., and T. N. Wiesel, 1968. Receptive fields and functional architecture of monkey striate cortex, J. Physiol., 195:215-243.

Jain, N., S. L. Florence, H. X. Qi, and J. H. Kaas, 2000. Growth of new brainstem connections in adult monkeys with massive sensory loss, Proc. Natl. Acad. Sci. USA, 97:5546-5550.

Johnson, J. K., and V. A. Casagrande, 1993. Prenatal development of axon outgrowth and connectivity in the ferret visual system, Vis. Neurosci., 10:117-130.

Jones, E. G., and T. P. Pons, 1998. Thalamic and brainstem contributions to large-scale plasticity of primate somatosensory cortex, Science, 282:1121-1125.

Katz, L. C., and J. C. Crowley, 2002. Development of cortical circuits: lessons from ocular dominance columns, Nat. Rev. Neurosci., 3:34-42.

Katz, L. C., and C. J. Shatz, 1996. Synaptic activity and the construction of cortical circuits, Science, 274:1133-1138.

Kim, D. S., and T. Bonhoeffer, 1994. Reverse occlusion leads to a precise restoration of orientation preference maps in visual cortex, Nature, 370:370-372.

Kujala, T., K. Alho, M. Huotilainen, R. J. Ilmoniemi, A. Lehtokoski, A. Leinonen, T. Rinne, O. Salonen, J. Sinkkonen, C. G. Standertskjold-Nordenstam, and R. Naatanen, 1997. Electrophysiological evidence for cross-modal plasticity in humans with early- and late-onset blindness, Psychophysiology, 34:213-216.

Lowel, S., and W. Singer, 1992. Selection of intrinsic horizontal connections in the visual cortex by correlated neuronal activity, Science, 255:209-212.

Lyckman, A. W., S. Jhaveri, D. A. Feldheim, P. Vanderhaeghen, J. G. Flanagan, and M. Sur, 2001. Enhanced plasticity of retinothalamic projections in an ephrin-A2/A5 double mutant, J. Neurosci., 21:7684-7690.

Meister, M., R. O. Wong, D. A. Baylor, and C. J. Shatz, 1991. Synchronous bursts of action potentials in ganglion cells of the developing mammalian retina, Science, 252:939-943.

Merzenich, M. M., R. J. Nelson, M. P. Stryker, M. S. Cynader, A. Schoppmann, and J. M. Zook, 1984. Somatosensory cortical map changes following digit amputation in adult monkeys, J. Comp. Neurol., 224:591-605.

Miller, K. D., J. B. Keller, and M. P. Stryker, 1989. Ocular dominance column development: analysis and simulation, Science, 245:605-615.

Neville, H. J., A. Schmidt, and M. Kutas, 1983. Altered visual-evoked potentials in congenitally deaf adults, Brain Res., 266:127-132.

Pallas, S. L., A. W. Roe, and M. Sur, 1990. Visual projections induced into the auditory pathway of ferrets. I. Novel inputs to primary auditory cortex (AI) from the LP/pulvinar complex and the topography of the MGN-AI projection, J. Comp. Neurol., 298:50-68.

Pallas, S. L., and M. Sur, 1993. Visual projections induced into the auditory pathway of ferrets: II. Corticocortical connections of primary auditory cortex, J. Comp. Neurol., 337:317-333.

Pallas, S. L., J. Hahm, and M. Sur, 1994a. Morphology of retinal axons induced to arborize in a novel target, the medial geniculate nucleus. I. Comparison with arbors in normal targets, J. Comp. Neurol., 349:343-362.

Pallas, S. L., and M. Sur, 1994b. Morphology of retinal axon arbors induced to arborize in a novel target, the medial geniculate nucleus. II. Comparison with axons from the inferior colliculus, J. Comp. Neurol., 349:363-376.

Pons, T. P., P. E. Garraghty, A. K. Ommaya, J. H. Kaas, E. Taub, and M. Mishkin, 1991. Massive cortical reorganization after sensory deafferentation in adult macaques, Science, 252:1857-1860.

Ramachandran, V. S., and D. Rogers-Ramachandran, 2000. Phantom limbs and neural plasticity, Arch. Neurol., 57:317-320.

Read, H. L., J. A. Winer, and C. E. Shreiner, 2001. Modular organization of intrinsic connections associated with spectral tuning in cat auditory cortex, Proc. Natl. Acad. Sci USA, 98:8042-8047.

Reiter, H. O., and M. P. Stryker, 1988. Neural plasticity without postsynaptic action potentials: less-active inputs become dominant when kitten visual cortical cells are pharmacologically inhibited, Proc. Natl. Acad. Sci. USA, 85:3623-3627.

Roe, A. W., P. E. Garraghty, M. Esguerra, and M. Sur, 1993. Experimentally induced visual projections to the auditory thalamus in ferrets: evidence for a W cell pathway, J. Comp. Neurol., 334:263-280.

Roe, A. W., S. L. Pallas, J. O. Hahm, and M. Sur, 1990. A map of visual space induced in primary auditory cortex, Science, 250:818-820.

Roe, A. W., J. -O. Hahm, and M. Sur, 1991. Experimentally induced establishment of visual topography in auditory thalamus, Soc. Neurosci. Abs., 17:898.

Roe, A. W., S. L. Pallas, Y. H. Kwon, and M. Sur, 1992. Visual projections routed to the auditory pathway in ferrets: receptive fields of visual neurons in primary auditory cortex, J. Neurosci., 12:3651-3664.

Ruthazer, E. S., and M. P. Stryker, 1996. The role of activity in the development of long-range horizontal connections in area 17 of the ferret, J. Neurosci., 16:7253-7269.

Sadato, N., A. Pascual-Leone, J. Grafman, V. Ibanez, M. P. Deiber, G. Dold, and M. Hallett, 1996. Activation of the primary visual cortex by Braille reading in blind subjects, Nature, 380:526-528.

Schneider, G. E., 1973. Early lesions of superior colliculus: factors affecting the formation of abnormal retinal projections, Brain Behav. Evol., 8:73-109.

Sharma, J., A. Angelucci, and M. Sur, 2000. Induction of visual orientation modules in auditory cortex, Nature, 404:841-847.

Shatz, C. J., S. Lindstrom, and T. N. Wiesel, 1977. The distribution of afferents representing the right and left eyes in the cat's visual cortex, Brain Res., 131:103-116.

Shatz, C. J., and M. P. Stryker, 1978. Ocular dominance in layer IV of the cat's visual cortex and the effects of monocular deprivation, J. Physiol. (Lond.), 281:267-283.

Sherman, S. M., and P. D. Spear, 1982. Organization of visual pathways in normal and visually deprived cats, Physiol. Rev., 62:738-855.

Somers, D. C., S. B. Nelson, and M. Sur, 1995. An emergent model of orientation selectivity in cat visual cortical simple cells, J. Neurosci., 15:5448-5465.

Somers, D. C., V. Dragoi, and M. Sur, 2001. Orientation selectivity and its modulation by local and long-range connections in visual cortex, in Cerebral Cortex: The Cat Primary Visual Cortex, (A. Peters and B. Payne, eds.), San Diego, Academic Press, pp. 471-520.

Stellwagen, D., and C. J. Shatz, 2002. An instructive role for retinal waves in the development of retinogeniculate connectivity, Neuron, 3:357-367.

Sur, M., P. E. Garraghty, and A. W. Roe, 1988. Experimentally induced visual projections into auditory thalamus and cortex, Science, 242:1437-1441.

Sur, M., S. L. Pallas, and A. W. Roe, 1990. Cross-modal plasticity in cortical development: differentiation and specification of sensory neocortex, Trends. Neurosci., 13:227-233.

Sur, M., A. Angelucci, and J. Sharma, 1999. Rewiring cortex: the role of patterned activity in development and plasticity of neocortical circuits, J. Neurobiol., 41:33-43.

Sur, M., and C. A. Leamey, 2001. Development and plasticity of cortical areas and networks, Nat. Rev. Neurosci., 2:251-262.

Swindale, N. V., D. Shoham, A. Grinvald, T. Bonhoeffer, and M. Hubener, 2000. Visual cortex maps are optimized for uniform coverage, Nat. Neurosci., 3:822-826.

Van Sluyters, R. C., and F. B. Levitt, 1980. Experimental strabismus in the kitten, J. Neurophysiol., 43:686-699.

Vitek, D. J., J. D. Schall, and A. G. Leventhal, 1985. Morphology, central projections, and dendritic field orientation of retinal ganglion cells in the ferret, J. Comp. Neurol., 241:1-11.

Von Melchner, L., S. L. Pallas, and M. Sur, 2000. Visual behaviour mediated by retinal projections directed to the auditory pathway, Nature, 404:871-876.

Weeks, R., B. Horwitz, A. Aziz-Sultan, B. Tian, C. M. Wessinger, L. G. Cohen, M. Hallett, and J. P. Rauschecker, 2000. A positron emission tomographic study of auditory localization in the congenitally blind, J. Neurosci., 20:2664-2672.

Weliky, M., W. H. Bosking, and D. Fitzpatrick, 1996. A systematic map of direction preference in primary visual cortex, Nature, 379:725-728.

Weliky, M., and L. C. Katz, 1997. Disruption of orientation tuning in visual cortex by artificially correlated neuronal activity, Nature, 386:680-685.

Weliky, M. and L. C. Katz, 1999. Correlational structure of spontaneous neuronal activity in the developing lateral geniculate nucleus in vivo, Science, 285:599-604.

White, L. E., D. M. Coppola, and D. Fitzpatrick, 2001. The contribution of sensory experience to the maturation of orientation selectivity in ferret visual cortex, Nature, 411:1049-1052.

Wiesel, T. N., and D. H. Hubel, 1965. Comparison of the effects of unilateral and bilateral eye closure on cortical unit responses in kittens, J. Neurophysiol., 28:1029-1040.

Wiesel, T. N., and D.H. Hubel, 1974. Ordered arrangement of orientation columns in monkeys lacking visual experience, J. Comp. Neurol., 158:307-318.

Figure Legends

Figure 1. Visual and auditory pathways in normal animals, and the visual pathway to auditory cortex in rewired animals. **a.** In normal ferrets, the major projections of the retina are to the lateral geniculate nucleus (LGN) and to the superior colliculus; the LGN in turn projects to primary visual cortex and other cortical fields. The auditory pathway starts with the cochlea, and consists of projections from the inferior colliculi in the two hemispheres to each medial geniculate nucleus (MGN), which projects to the primary auditory cortex and other cortical fields. **b.** Deafferenting the MGN in neonatal ferrets by removing ascending auditory projections causes retinal fibers to innervate the MGN. The MGN still projects to the auditory cortex, but now relays visual information. Thus, the thalamocortical projections are anatomically the same in rewired animals as in normal animals, but in rewired animals are driven by a very different spatiotemporal pattern of activity. This has a profound effect on the development of networks in auditory cortex, and on its function. Adapted from Sur and Leamey (2001).

Figure 2. Orientation selectivity of cells in V1 of normal ferrets and in A1 of rewired ferrets, and a comparison with cells in the MGN of rewired ferrets. **a.** Histogram of the orientation selectivity index of cells in V1 and rewired A1 demonstrates that cells are similarly tuned in the two areas. Orientation index = [Response at the preferred orientation – Response at the orthogonal orientation] / [Response at the preferred orientation + Response at the orthogonal orientation]. Adapted from Roe et al. (1992). **b.** Histogram of the orientation index for MGN cells shows that the cells are unselective or at most weakly selective for orientation. Thus, orientation selectivity arises in A1 of rewired ferrets, as it does in V1 of normal ferrets. Adapted from Roe et al. (1993).

Figure 3. The orientation map in normal V1 and in rewired A1. **a.** Optical imaging of an expanse of V1 (crosshatched on line drawing of ferret brain at top) shows domains of cortex (black blobs in middle images) that respond to vertically oriented gratings (upper image), and other domains that respond to horizontally oriented gratings (lower image). From a number of such images obtained in response to a stimulus of a single orientation, a composite orientation map is obtained by vector averaging the response at each pixel (bottom). Here, the angle of the average orientation vector is represented by the key at right. **b.** Similar optical imaging data from an expanse of A1 in a rewired ferret (crosshatched on line drawing at top), including images in response to vertical or horizontal gratings (middle) and a composite orientation map (bottom). Though the orientation map in rewired A1 has larger domains with variable spacing, an important similarity between the composite maps in rewired A1 and normal V1 is the presence of pinwheels around which cells preferring different orientations are systematically represented. Scale bars below upper images, 0.5 mm. Adapted from Sharma et al. (2000).

Figure 4. Horizontal connections in cortex, and the effect of rewiring. **a.** In V1 of a normal ferret, an injection of cholera toxin B (at site marked by star) retrogradely labels cells that project to the injection site. The cortex was sectioned parallel to the pia, and the density of horizontally projecting cells in layer 3 is depicted by the key in the middle. Horizontal connections of cells in the superficial layers of V1 are patchy and link cells with similar orientation preference. **b.** In A1 of a normal ferret, horizontal connections spread along the iso-frequency axis of cortex. **c.** In A1 of a rewired ferret, horizontal connections are patchy, and resemble connections in V1. **d.** A power spectrum analysis of the spatial pattern of horizontal connections reveals the extent of periodicity of the connections – the more the power outside the central DC peak, the more periodic the connection pattern. Horizontal connections are highly periodic in V1, and are

significantly more periodic in rewired A1 compared to normal A1 (star denotes $p<0.05$ comparing rewired and normal A1). Scale bars, 0.5 mm. Adapted from Sharma et al. (2000).

Figure 5. The behavioral consequence of routing retinal projections to the auditory thalamus and of visual activation of auditory cortex. **a.** Visual pathways in the normal hemisphere (right) and in the rewired hemisphere (left). The projection from the inferior colliculus (IC) to the medial geniculate nucleus (MGN) courses through the brachium (b) of the IC. In the rewired hemisphere, this projection was sectioned and the superior colliculus (SC) was ablated. Ferrets were trained to respond at one reward spout when visual stimuli were presented in the left visual field (which is seen by the right, normal, hemisphere) and at a different reward spout when auditory stimuli were presented. After training was complete, ferrets were tested with visual stimuli presented in the center or in the right visual field, and responses noted. **b.** Ferrets learned to associate one reward spout with sound and another with light presented in the left visual field. When light was subsequently presented in the center or right visual field, they responded at the visual reward spout, indicating that the stimulus was seen (eg., dark bar in rightmost column). In the second phase of testing, the visual thalamus (LGN/LP) in the rewired hemisphere was lesioned, leaving the retina-MGN-A1 projection as the only pathway conveying visual information in the rewired hemisphere. Animals still responded at the visual reward spout to light in the right visual field (open bar in rightmost column). In the third phase of testing, A1 was lesioned. Now animals responded at chance levels to light in the right field (grey bar in rightmost column), indicating that they were blind in the right field. Importantly, in the second phase, a visual stimulus in the right field was seen even when only the retina-MGN-A1 projection was intact and the key visual structures in the thalamus and midbrain were lesioned. Furthermore, visual percepts were blocked in these animals after ablation of A1 in the third phase (and not any

visual area). Thus, the rewired projection is capable of mediating visual behavior. See text for details. Adapted from von Melchner et al. (2000).

Figure 1

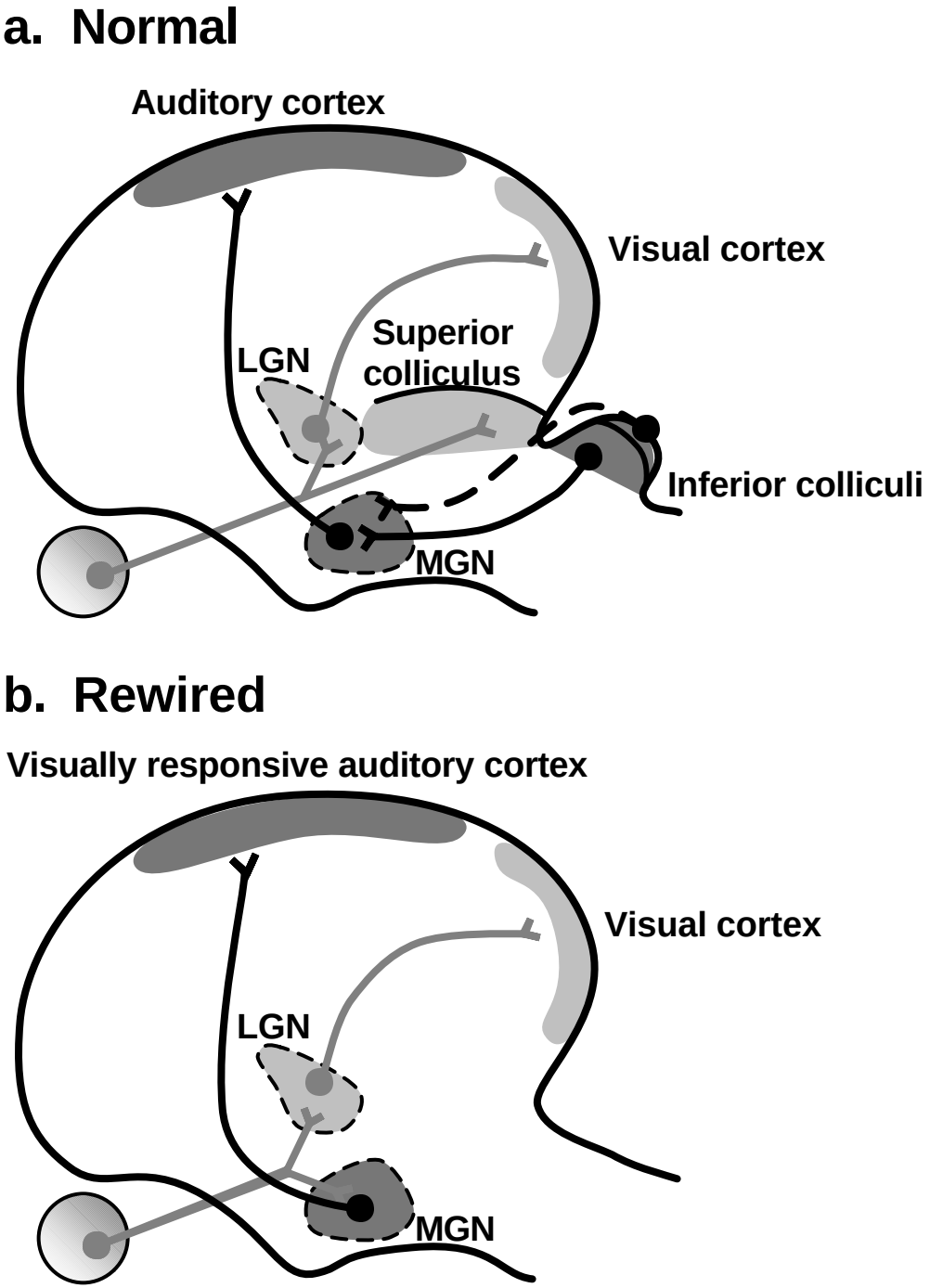

a. Normal
Auditory cortex
Visual cortex
Superior colliculus
LGN
Inferior colliculi
MGN
b. Rewired
Visually responsive auditory cortex
Visual cortex
LGN
MGN

Figure 2

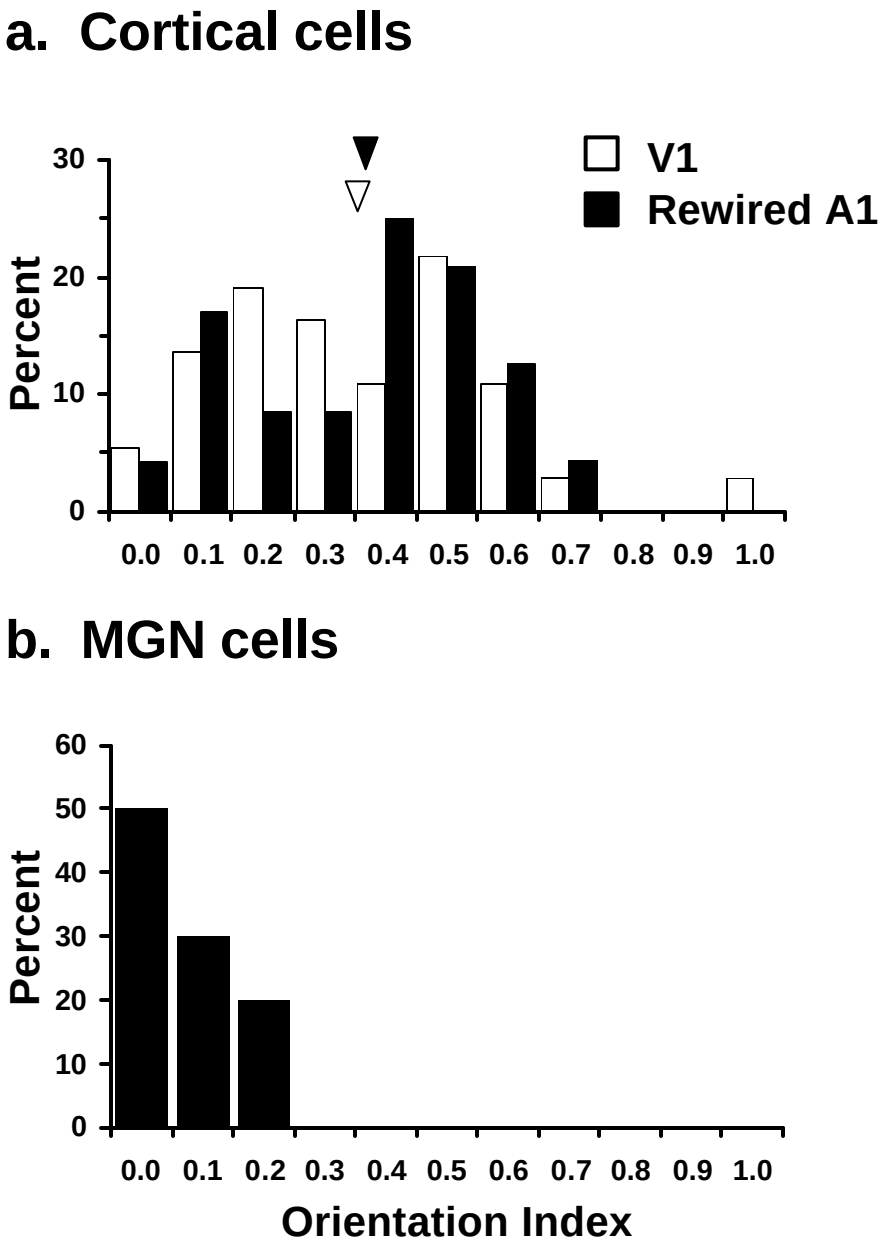

a. Cortical cells
V1
Rewired A1
Percent
30
20
10
0
0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0
b. MGN cells
Percent
60
50
40
30
20
10
0
0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0
Orientation Index

Figure 3

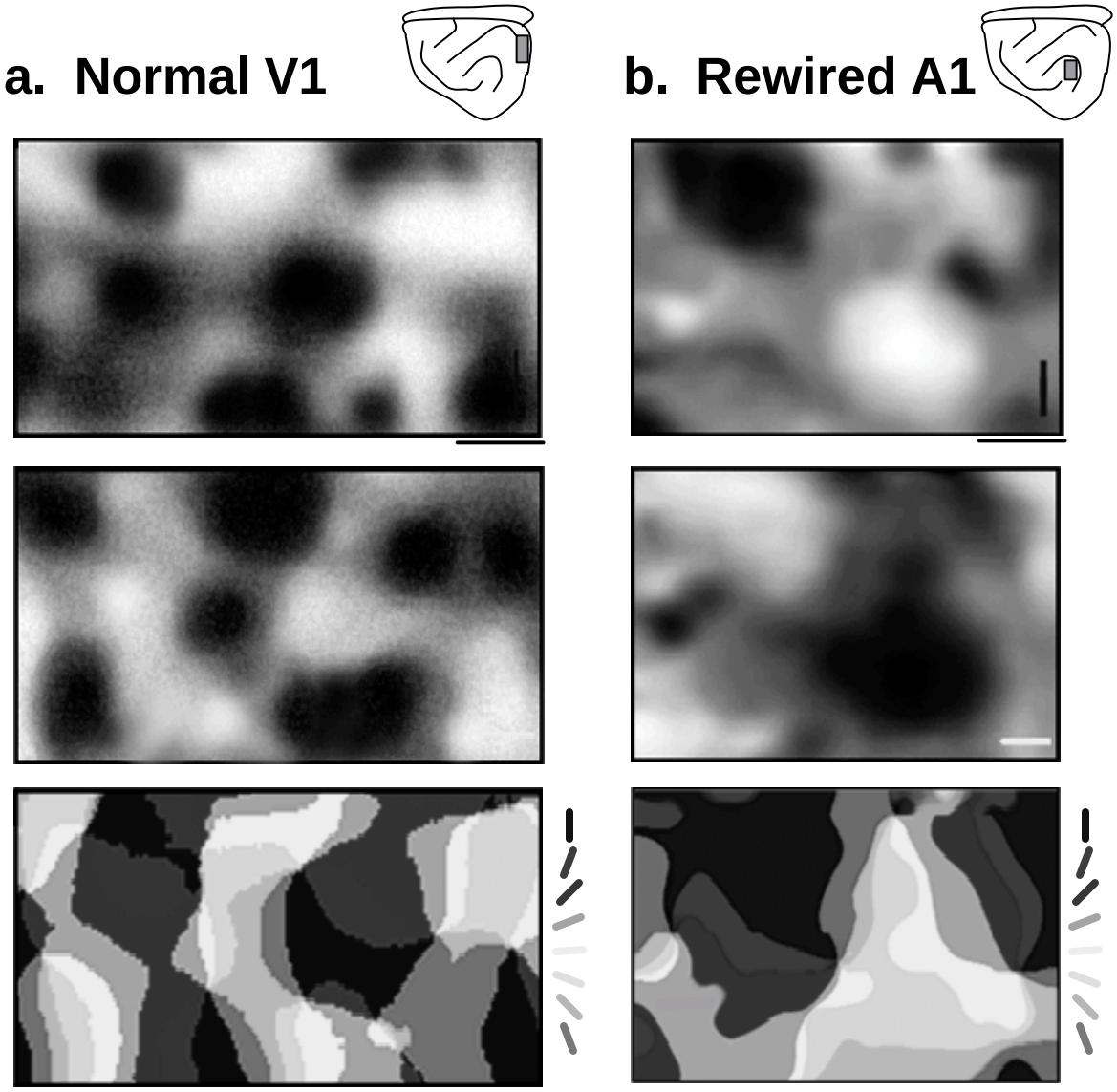


Figure 4

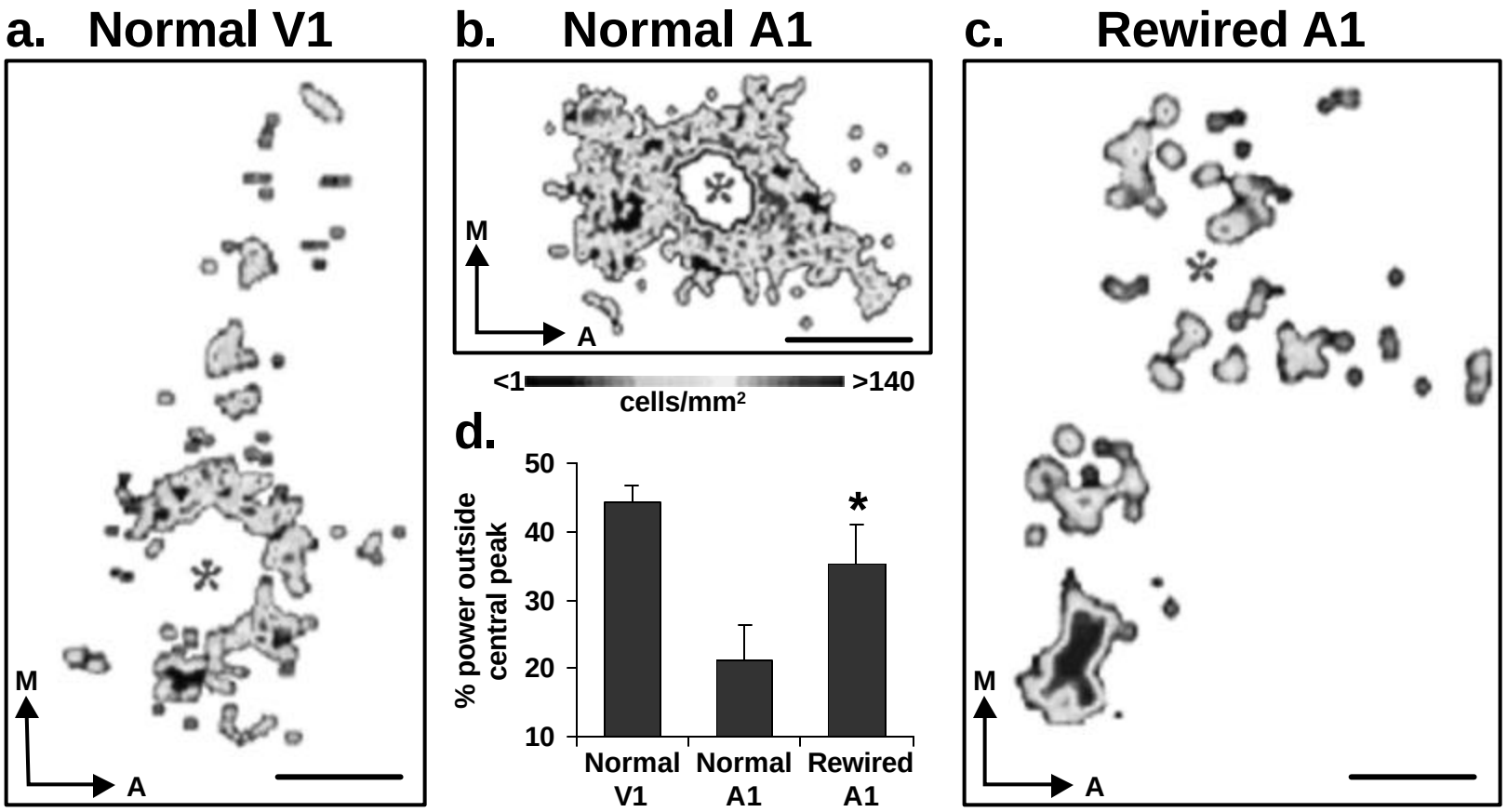
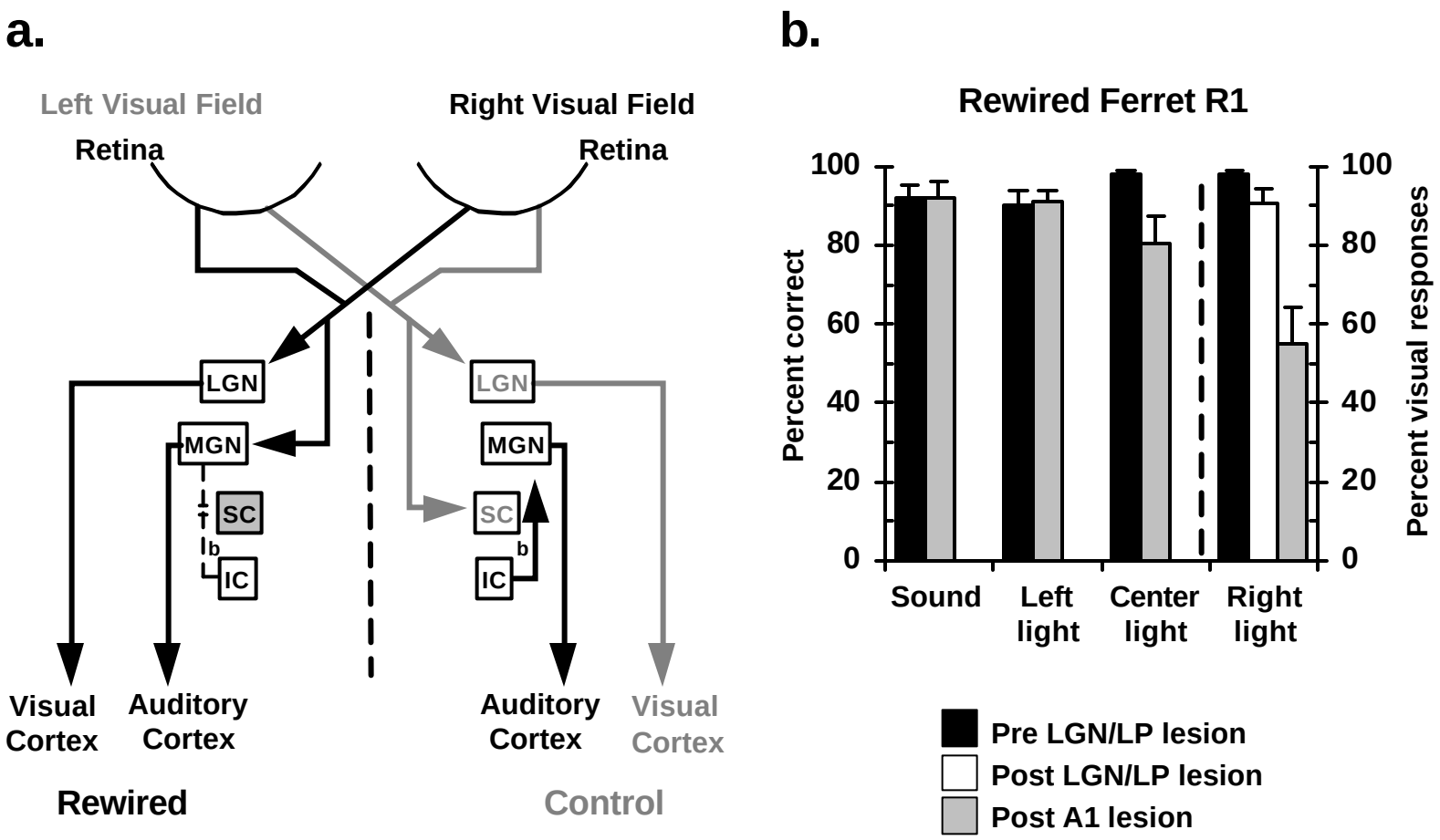

a. Normal V1
b. Normal A1
c. Rewired A1
M
A
<1
>140
cells/mm²
d.
% power outside central peak
50
40
30
20
10
Normal V1
Normal A1
Rewired A1
*

Figure 5


a.
Left Visual Field
Right Visual Field
Retina
Retina
LGN
LGN
MGN
MGN
SC
SC
b
b
IC
IC
Visual Cortex
Auditory Cortex
Auditory Cortex
Visual Cortex
Rewired
Control
b.
Rewired Ferret R1
Percent correct
Percent visual responses
100
80
60
40
20
0
Sound
Left light
Center light
Right light
Pre LGN/LP lesion
Post LGN/LP lesion
Post A1 lesion