Chapter 20

Reprogramming cortex

The consequences of cross-modal plasticity during development

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Introduction

How are the organization and function of sensory cortex and thalamic nuclei derived, and are the underlying determining factors conserved across sensory modalities? Specifically, are the organization and function of a brain region primarily influenced by intrinsic factors expressed within the area (i.e. molecular gradients, patterns of gene expression) or extrinsic factors that originate outside the region (i.e. sensory experience)? This is a fundamental issue in understanding the development of sensory pathways, and is difficult to address using traditional experimental methods. However cross-modal experiments provide insight by redirecting the inputs of one sensory modality to a different modality, thereby allowing the role of intrinsic and extrinsic factors to be distinguished. These 'rewiring' experiments also reveal how input activity modifies cortical organization as well as the limitations imposed on this plasticity by the underlying cortical substrate. In this chapter we will discuss how reprogramming the brain, by inducing visual inputs to innervate the auditory pathway, can reveal the relative influence of intrinsic and extrinsic factors in determining the function and organization of sensory cortex and thalamic nuclei. We will describe its effect on retinal innervation, its physiological and behavioral consequences and its potential influence on cortical circuitry.

Cortical development

The model for studying sensory system development is the visual system and much work has explored the influence of intrinsic and extrinsic factors on cortical development. Studies of the formation of cortical layers and the arealization of cortex suggest a critical role for intrinsic factors such as differential expression of gene families and molecular gradients in the developing cortical plate, before the arrival of axons from the thalamus (Sur and Leamey 2001). However, extrinsic factors, such as the amount and pattern of electrical activity in input pathways, also contribute to cortical development. The existence of retinal waves of spontaneous activity suggests that electrical activity generated within the developing brain may be sufficient for the establishment of thalamo-cortical connections (Meister *et al.* 1991; Wong *et al.* 1993). This theory is supported by the presence of ocular dominance columns before eye opening (Rakic 1976; Crowley and Katz 2000; Crair *et al.* 2001).

Visual experience, which influences the amount and pattern of electrical activity in pathways to the cortex, also appears to be critical for the maintenance and refinement of cortical connections. The visual cortex displays remarkable plasticity during development, and is profoundly influenced by visual experience. Specifically, depriving one eye of vision during a critical period of development, when visual experience has a maximal effect on cortical structure, induces robust changes in the anatomy and physiology of visual cortex (Wiesel and Hubel 1965; Hubel *et al.* 1977; LeVay *et al.* 1980). Altering the spatial correlation between the two eyes, but not the overall level of activity, by artificially inducing strabismus causes ocular dominance columns to become exclusively monocular and modifies intracortical connections (Lowel and Singer 1992). However, binocular deprivation produces remarkably little change in ocular dominance columns, indicating that the balance of activity rather than the absolute level of activity is critical for the formation of intracortical connections during the critical period (Crowley and Katz 1999). Cortical plasticity is also influenced by limiting the overall light exposure of the animal, such that rearing animals in the dark prolongs the critical period. After the critical period, visual experience has a minimal effect on cortical organization and function. Although these experiments demonstrate the importance of input activity in developmental plasticity, they cannot separate the relative contributions of intrinsic and extrinsic factors in determining the organization and function of a cortical area.

Rewiring and retinal innervation in the thalamus

In contrast to traditional visual deprivation experiments, 'rewiring' experiments allow the role of patterned visual activity in specifying the function and organization of a cortical area or thalamic nuclei to be separated from the influence of intrinsic factors. In addition, rewiring experiments may also expose the limitations imposed on this cross-modal plasticity by the underlying substrate, in this case primary auditory cortex (A1) or the medial geniculate nucleus (MGN). In these experiments visual input is redirected to the auditory pathway by inducing retinal ganglion cell axons to innervate the MGN through surgical removal of its normal inputs at birth (see Figure 20.1). This creates an alternative target for retinal axons and allows functional connections to form in the auditory thalamus, conveying visual information through existing thalamocortical connections to A1. Such re-routing has been done in mice (Lyckman *et al.* 2001), ferrets (Sur *et al.* 1988, 1990, 1992, 1993; Sharma *et al.* 2000), and hamsters (Schneider 1973; Kalil and Schneider 1975; Frost 1982; Frost and Metin 1985).

Rewiring experiments that examine the patterning of retinal innervation in the lateral geniculate nucleus (LGN) and the rewired MGN of the thalamus suggest that the same intrinsic molecular gradient facilitates patterning in both nuclei. In the normal mammalian visual pathway, retinal input is organized retinotopically in the LGN. In addition, inputs from each eye are segregated into discrete eye specific zones, or layers. Visual inputs into the rewired MGN also show discrete eye-specific segregation. Intraocular injections of red and green choleratoxin subunit B (CTB) into the right and left eye of adult rewired mice demonstrate that retinal input from each eye shows little overlap in the MGN (Figure 20.2A and B). Similar results were obtained in rewired ferrets. This suggests that intrinsic factors unique to the LGN do not determine the pattern of eye-specific projections, as they develop similarly in visual and auditory targets. However, genetic expression patterns in the developing brain demonstrate that certain molecular cues are not unique to individual sensory pathways. In a remarkable demonstration of efficiency, the brain uses the same molecular cues in patterning different modalities. The ephrin family of molecules is one such cue. The ephrins and their respective Eph receptors are expressed in multiple gradients throughout the developing thalamus, including the LGN, MGN, and ventrobasal

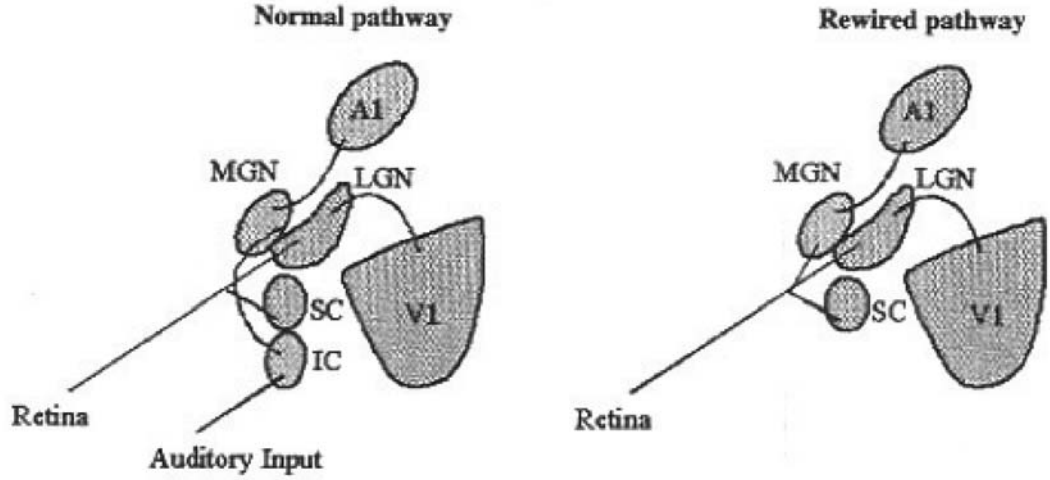

Figure 20.1 Schematics of the principal visual and auditory pathways in normal *(left)* and rewired animals *(right)*. A1: primary auditory cortex; IC: inferior colliculus; LGN: lateral geniculate nucleus; MGN: medial geniculate nucleus; SC: superior colliculus; V1: primary visual cortex.

nucleus (VB). Repulsive interactions mediated by the ephrins and their receptors ensure the establishment of the somatotopic map in VB, as well as the retinotopic map in the LGN. Ipsilateral retinal axons, which show high Eph A3 receptor expression, target areas of low ephrin expression in the LGN. This same pattern is seen the rewired MGN. In ephrin knockout mice, this eye-specific patterning is disrupted similarly in the LGN and rewired MGN. In both nuclei, ipsilateral axons show weaker regional preference in the knockout mice. Thus the ephrins appear to shape rewired retinal projections in the same way that they influence normal LGN patterning (Figure 20.2C). Therefore, ephrin expression in the MGN and throughout the auditory pathway may impose constraints on cross-modal plasticity and the extent to which connections along the auditory pathway are shaped by visual input. After the critical period, visual experience has a minimal effect on cortical organization and function (but see Sawtell *et al.* 2003).

Physiological consequences of rewiring

Visual activity, which has a very different spatial and temporal pattern than auditory activity, leads to visual responses in 'rewired' A1 that resemble responses in primary visual cortex (V1) (Sur *et al.* 1988; Roe *et al.* 1990, 1992; Sharma *et al.* 2000). For instance, experiments using extracellular electrophysiology and optical imaging of intrinsic signals find neurons in rewired A1 develop visual response features such as orientation selectivity (Roe *et al.* 1992; Sharma *et al.* 2000). Neurons in rewired A1 also develop direction-selectivity (Roe *et al.* 1992; Sharma *et al.* 2000) and an orderly retinotopic map (Roe *et al.* 1990). Thus individual neurons within A1 are selective for different attributes of a visual stimulus such as a direction of stimulus motion, a particular line orientation or a retinotopic location (size and receptive field location in visual space) of the stimulus. Each neuron has a slightly different preference for these features compared to its neighbors, such that a coherent stimulus feature map should develop in the cortex. Optical imaging of intrinsic signals reveals that a systematic map of orientation information does develop in rewired A1, and that it is similar to the orientation map found in V1 (Sharma *et al.* 2000). The optical imaging experiment examines changes in reflectance from exposed ferret visual cortex, illuminated with long-wavelength light, during binocular visual stimulation with full field square wave gratings (see Figure 20.3A). This optical signal is acquired with an imaging system (Optical Imaging) and analyzed using in-house programs. Rewired A1 also contains

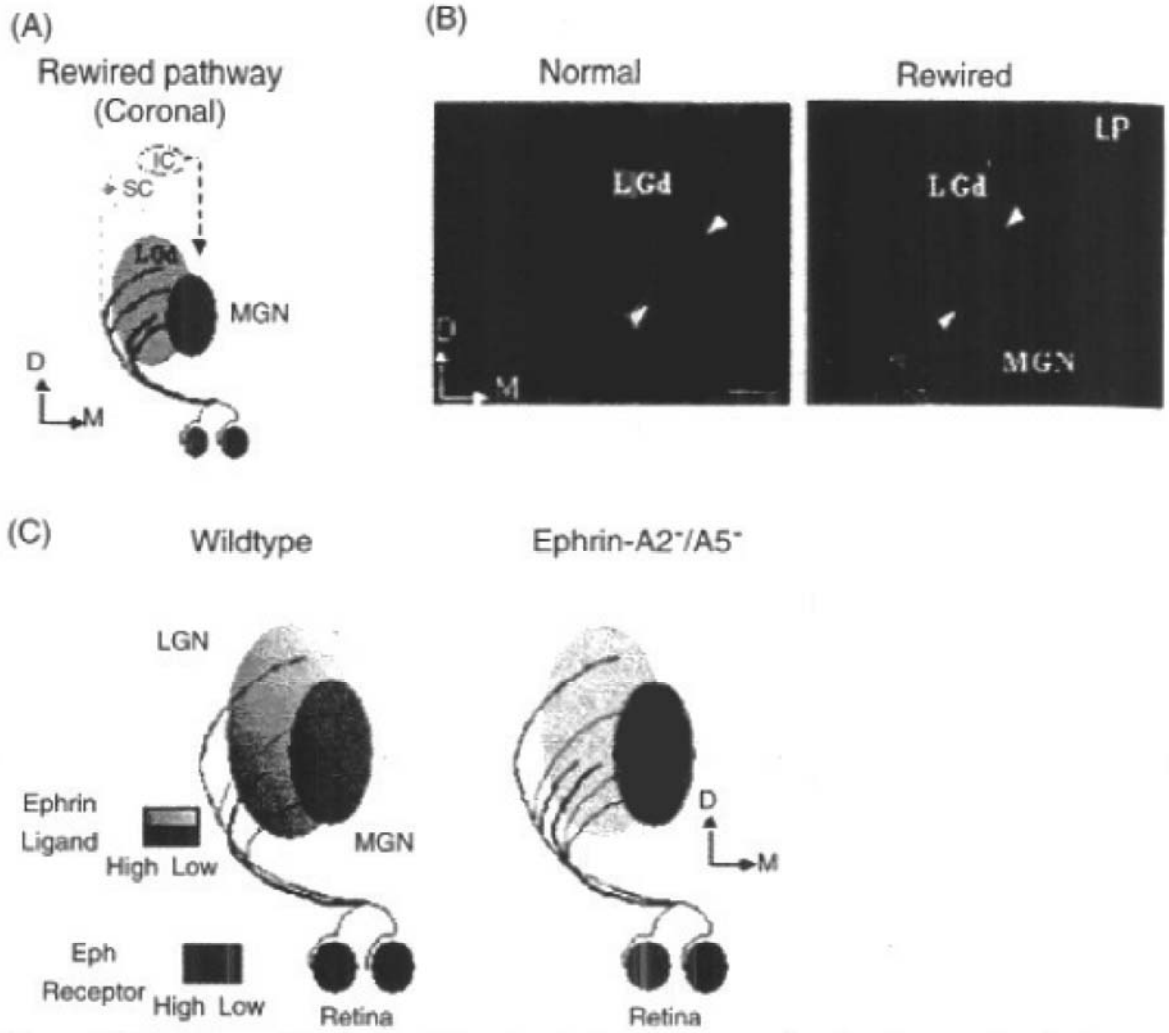

Figure 20.2 (A) Schematic of rewired visual projections in a coronal section. In normal animals, retinal axons innervate the lateral geniculate nucleus (LGN) (orange) and superior colliculus (SC) (dotted orange). Auditory input reaches the medial geniculate nucleus (MGN) (blue) from the inferior colliculus (IC) (dotted blue). In 'rewired' animals, SC and IC lesions deafferent the MGN and induce retinal axons to innervate the MGN. D: dorsal; M: medial. (B) Representative 50 um coronal sections in a normal (left) and a rewired (right) mouse. In the rewired mouse, the retinal axons overshoot the medial boundary of the LGN and project into the MGN. Enhanced retinal projections into the lateral posterior nucleus (LP) are also seen in rewired mice. Retinal axons are labeled with alexafluor conjugated CTB. Contralateral projections are labeled red and ipsilateral projections are labeled green. White arrowheads mark the LGN/MGN boundary. Scale bar = 0.1 mm. (C) Schematic representation of visual projections in wild-type and ephrin knockout mice. Contralateral projections are labeled in red. Ipsilateral projections are labeled in green. In wild-type rewired mice, ipsilateral axons show high EphA3 receptor expression and avoid high ephrin regions in the lateral geniculate nucleus (LGN) and medial geniculate nucleus (MGN). In ephrin knockout mice, ipsilateral axons still show high EphA3 receptor expression but target broader regions of the LGN and MGN. Ipsilateral axons spread ventrally in both the LGN and MGN of ephrin knockout mice. As a result, there is a greater representation of the ipsilateral eye, and a total increase in rewired projections, in the MGN of ephrin knockout mice. See colour plate section for a colour version of this figure.

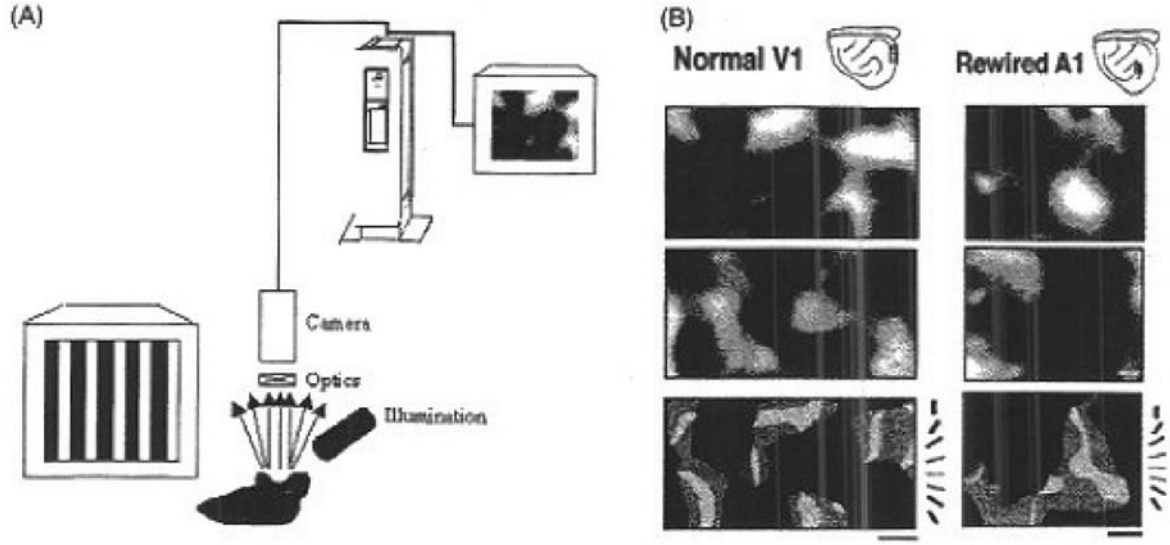

Figure 20.3 (A) Schematic representation of the experimental setup for optical imaging of intrinsic signals. Binocularly presented visual stimuli consisting of full field square wave gratings were presented at four or eight different orientations drifting in two opposite directions. The exposed cortex of the ferret was illuminated and the changes in reflected light were captured by a camera with and without visual stimulation. The surface blood vessel pattern was visualized with green light and optical imaging data was acquired during stimuli presentation under illumination with long wavelength red light. This optical signal was acquired with an imaging system (Optical Imaging) and analyzed using in-house programs. The pixels with significant changes in reflectance appear black, correlate with the underlying electrophysiological changes, and are displayed on an additional monitor during the experiment. (B) Orientation maps in normal visual cortex and rewired auditory cortex demonstrate the role of input activity in cortical development. Left: lateral view of normal primary visual cortex (V1) in the ferret brain. The upper two panels show activity maps in normal V1 using optical imaging of intrinsic signals in response to vertical and horizontal grating stimuli, respectively. Dark regions denote areas of high activity. The bottom map is a composite map of all orientations tested. The color key to the right of the panel shows the orientations represented. Right: lateral view of rewired primary auditory cortex (A1) in the ferret brain. The upper two panels represent the single orientation activity maps generated in rewired A1 under the same conditions as the left panels. The bottom map is a composite map of all orientations tested. Scale bars, 0.5 mm (modified from Sur and Leamey, *Nat. Rev. Neurosci.*, 2001, and from references therein).

iso-orientation domains similar to V1, where the neurons all respond to the same preferred orientation, which are organized around pinwheel centers (Figure 20.3B).

Visual inputs directed to rewired A1 also shape its local and long-range connections such that they resemble connections in V1 (Sharma *et al.* 2000), suggesting that patterned input activity can have a profound influence on the structure and organization of A1. Rewired A1 neurons form connections between domains with the same orientation preference, just like V1 neurons. In addition, the patchy connections seen in V1, which are often elongated along the orientation axis of the injection site, are also observed in rewired A1 (Gao and Pallas 1999; Sharma *et al.* 2000). In contrast, normal A1 connections tend to be band-like and extend along the iso-frequency axis of the cortical sound frequency map. Although the organization of visual information and connectivity of rewired A1 is similar to V1, there are several notable differences. For instance, the orientation domains in rewired A1 are larger and less orderly than in V1. In addition, horizontal connections in rewired A1 are less orderly than in V1, and the spatial acuity of the rewired auditory pathway is lower than the normal visual pathway (von Melchner *et al.* 2000). This is probably a result of the fact that retinal W cells form the primary source of inputs to the MGN (Roe *et al.* 1993). These differences may also

reflect underlying structural constraints imposed by A1 that cannot be modified by experience (i.e. the structure of A1 cortical layers). Even though receptive fields and orientation modules in rewired A1 are larger than in visual cortex, these rewiring experiments provide powerful evidence that patterned visual activity influences the functional role and organization of a cortical area. That is, input activity plays an instructive role in the establishment of cortical connections.

Behavioral consequences of rewiring

In addition to having a profound influence on cortical organization and physiology, rewiring experiments also suggest that visual input directed to the auditory pathway can influence behavior. A study of rewired ferrets suggests that patterned visual inputs can influence behavior (von Melchner *et al.* 2000). Unilateral rewired ferrets were trained to discriminate between light and sound (Figure 20.4A). Sound stimuli were presented and the ferrets received a juice reward at an 'auditory' reward spout for correctly identifying the stimulus as auditory. Similarly, light stimuli were presented in the normal visual field, and ferrets received a juice reward for correctly identifying the stimulus as visual at a different visual reward spout (Figure 20.4B). After training the ferrets were tested with light stimuli presented in the rewired visual field. The ferrets responded overwhelmingly at the visual reward spout, which is not surprising given that the rewired hemisphere receives both the normal visual projections to visual cortex and the rewired projection from the retina to the MGN to auditory cortex. The normal visual projection from LGN/LP to the rewired hemisphere was then ablated, and after a period of recovery the ferrets were re-tested with visual stimuli presented to the rewired visual field. The ferrets still responded overwhelmingly at the visual reward spout, indicating that the intact projection from the retina to the MGN to auditory cortex is capable of mediating the response to the visual stimulus. Finally the auditory cortex was ablated, and the ferrets were again re-tested after a period of recovery. The ferrets now responded at chance levels at the visual reward spout, indicating that the animals were no longer able to identify the visual stimulus, presumably because they were blind in the rewired visual field. Thus, the rewired projection from the retina through the MGN to auditory cortex is able to mediate visual behavior and this visual input influences the behavioral function of the auditory cortex.

Rewired visual projections in mice also influence affective behavior mediated by subcortical pathways, such as conditioned fear (Newton *et al.* 2002). In fear conditioning experiments a discrete auditory cue is paired with a mild foot shock which quickly induces conditioned fear after as few as one tone-shock pairing (Fendt and Fanselow 1999; LeDoux 2000). In contrast, a discrete visual cue is less effective, requiring many more light-shock pairings to elicit a defensive response to the light alone (Heldt *et al.* 2000). Dense direct connections from the MGN to the lateral nucleus of the amygdala (Figure 20.5A) are thought to be crucial for auditory cued conditioned fear responses (Rogan and LeDoux 1995; Doron and LeDoux 1999). An indirect thalamo-cortical-amygdala pathway from the MGN via auditory cortex to perirhinal cortex also conveys information to the amygdala (Namura *et al.*1997; LeDoux 2000). However, lesions of the auditory cortex do not affect the magnitude or duration of freezing responses after fear conditioning (LeDoux *et al.* 1984). In addition, single unit recordings suggest that this cortical pathway shows slower learning-induced changes than the direct thalamo-amygdala pathway, and hence is unlikely to be the principal auditory cued conditioned fear pathway (Quirk *et al.* 1995, 1997). In contrast to the direct auditory pathway from the MGN to the amygdala, visual inputs primarily reach the amygdala through indirect pathways (Doron and LeDoux 1999; Shi and Davis 2001). Visually cued conditioned fear is thought to be mediated by projections from the LGN to V1/V2 to visual association area TE2/perirhinal cortex (Pr) to the amygdala, or by projections from LP to V2/TE2/Pr to the amygdala (see Figure 20.5A) (Shi and Davis 2001).

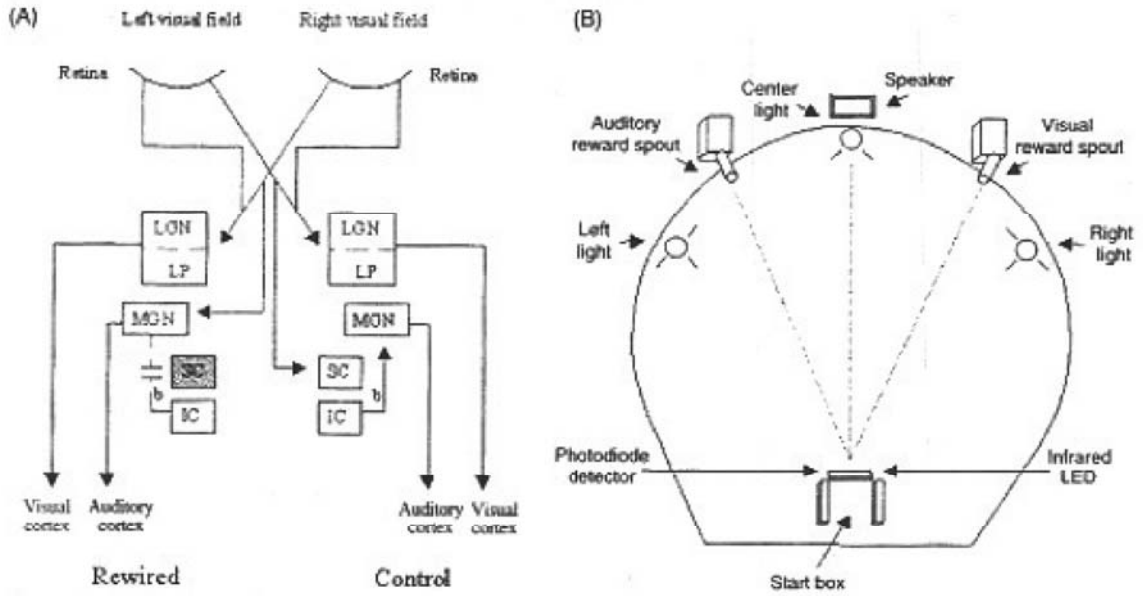

Figure 20.4 The behavioral role of retinal projections routed to the auditory pathway. (A) Pathway from the retina to the visual thalamus, including the lateral geniculate nucleus (LGN) and the lateral posterior nucleus (LP), and to the superior colliculus (SC) in the control hemisphere (right); and to the LGN/LP and medial geniculate nucleus (MGN) in the rewired hemisphere (left). The SC and adjacent brachium (b) of the inferior colliculus (IC) were ablated neonatally in the left hemisphere. Visual projections in each hemisphere represent the contralateral visual field. (B) Apparatus. Dashed lines denote the borders of the left and right monocular fields and the direction of central gaze. Animals were rewarded at the right spout after a light in the left monocular field, and at the left spout after a sound from a central speaker. Subsequently, their responses to light in the center of the right monocular field were tested. Animals initiated trials by standing in the start box with their muzzle between the infrared LED and a photodiode detector (Modified from von Melchner, Pallas and Sur, Nature, 2000).

Adult sham lesion and rewired mice underwent three sessions of fear conditioning with either a visual or an auditory cue (three cue-shock pairings per session), and behavioral testing after each session. The cued testing behavior of the different groups after one fear conditioning session are depicted in Figure 20.5B. Consistent with previous studies, after one session of fear conditioning, light-conditioned sham lesion mice did not freeze significantly more during the cue presentation compared to the habituation period (Figure 20.5B). Light-conditioned rewired mice, however, froze significantly more during the cue presentation after only one session of fear conditioning ($^{**}P < 0.01$, paired t-test), as did tone conditioned sham lesion and rewired mice ($^{***}P < 0.001$, paired t-test). After three sessions of fear conditioning, sham lesion mice also showed greater freezing during the cue presentation. These findings indicate that the behavioral function of a target (in this case, the amygdala) is influenced by its inputs, and that it can draw upon intrinsic properties of the target. Thus existing pathways can convey novel information to central structures, and this information is capable of mediating behavior.

Potential consequences for cortical processing and circuitry

There is some evidence that cortical areas have an inherent bias for the processing of subtypes of information. For instance visual and auditory cortex tend to be the most precise at processing spatial and temporal information respectively (Welch *et al.* 1986; Kitagawa and Ichihara 2002).

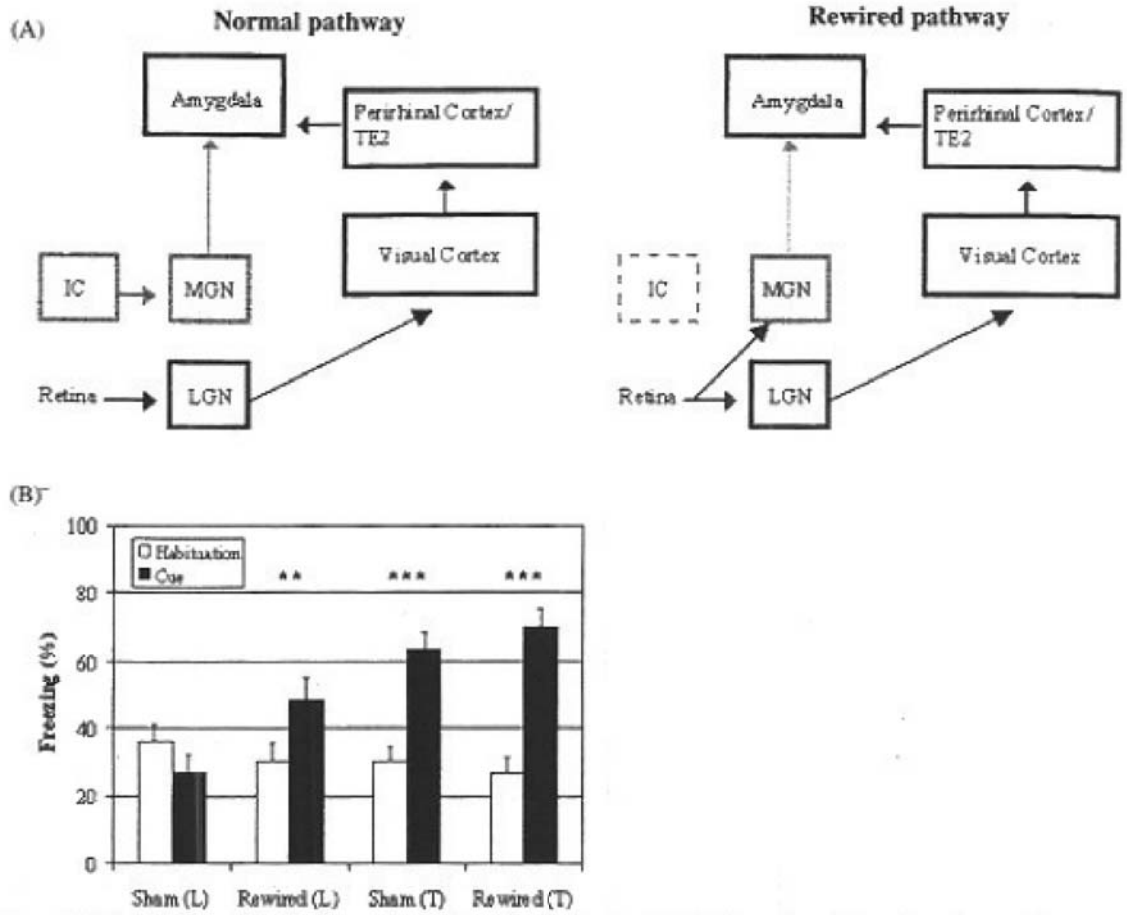

Figure 20.5 (A) Simplified schematic of the principal visual (black) and auditory (gray) cued fear conditioning pathways in normal (left) and rewired mice (right). The IC (shown as a dotted box) was lesioned bilaterally in neonatal mice to induce retinal projections to the MGN. IC: inferior colliculus; LGN: lateral geniculate nucleus; MGN: medial geniculate nucleus. (B) The mean freezing per group during the habituation (white bar) and cue presentation (black bar) periods of the cued testing session after one session of fear conditioning, with error bars denoting the standard error of the mean (significant paired t-tests, ** $P < 0.01$, *** $P < 0.001$).

This is apparent during normal cortical processing when sensory information from two modalities are in conflict, producing sensory illusions. For instance, the 'ventriloquism effect' involves a discrepancy between the spatial location of an auditory and a visual stimulus, resulting in the perceived location of the event originating from the spatial location of the visual stimulus (Howard and Templeton 1966). Similarly a spatial localization task where the visual stimulus is in conflict with proprioceptive information, known as 'visual capture' results in the perceived location being determined by the visual information (Hay *et al.* 1965). Although visual signals dominate these spatial tasks, the perceived temporal characteristics of visual signals can be modulated by conflicting auditory information. For instance, when a single flash is presented coincident with an auditory beep, a second auditory beep produces an illusory second flash (Shams *et al.* 2002). The perceived duration and flicker rate (Gebhard and Mowbray 1959; Shipley 1964) of a visual stimulus can also be influenced by conflicting auditory signals.

Given the intimate relationship between structure and function in the nervous system it is possible that such inherent processing biases may be evident in functional plasticity in the cortex. For instance, visual function elicited in rewired A1 may be influenced by the temporal processing properties intrinsic to neurons or networks of the auditory cortex. Thus it might be interesting to

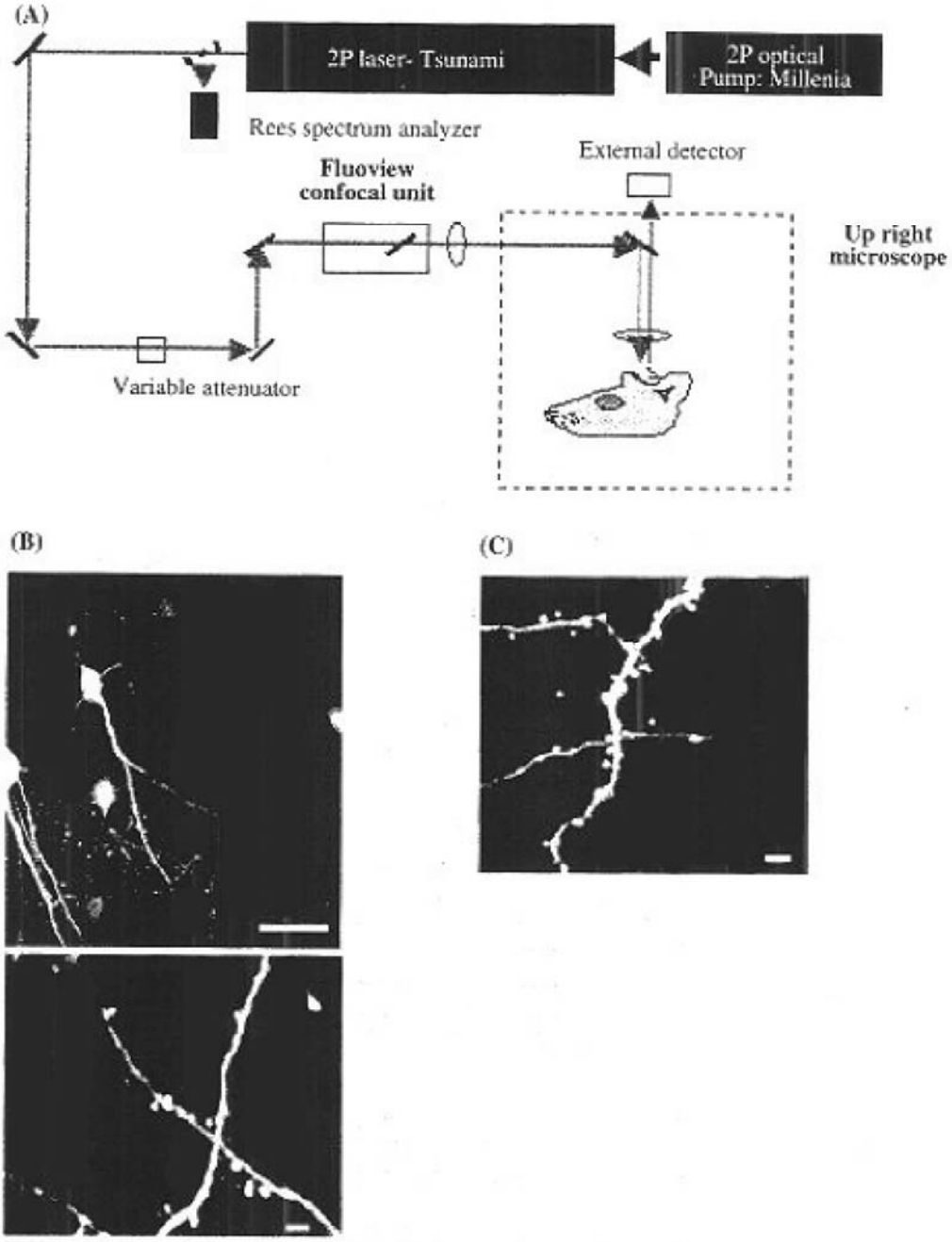

Figure 20.6 (A) Schematic representation of the experimental setup for *in vivo* two-photon laser scanning microscopy. A two system laser provides high intensity pulsed infrared light used for excitation. The excitation beam (red) is directed through mirrors into a modified Olympus confocal unit used for scanning. The beam is then scanned through an upright microscope and a high NA objective lens into the sample. Fluorescence emission is collected though the objective lens and detected by an external photomultiplier tube located on top of the microscope. (B) V1 neurons imaged *in vivo* using two-photon microscopy. The top panel shows layer 2/3 neurons and their dendrites, scale bar = 50 um; bottom panel shows spines imaged *in vivo*, scale bar = 5 um. (C) A1 spines imaged *in vivo* using two-photon microscopy, scale bar = 5 um.

look for structural correlates of these processing biases by studying structural plasticity at the synaptic level in different cortical modalities. Functional plasticity leads to alterations in synaptic properties and, on a slower timescale, to changes in synaptic morphology. In order to understand the interplay between structural plasticity and sensory input, one must be able to study synaptic

structure in the presence of sensory stimulation in the intact brain. Two-photon microscopy is a relatively noninvasive novel technique that allows deep tissue imaging (see Figure 20.6A) (Denk *et al.* 1990). Using this technique, it has recently been possible to study the structural dynamics of dendritic spines, which are the post-synaptic sites of excitatory synapses (Figure 20.6B and C). Studies in somatosensory and visual cortices have shown that spine dynamics are sensitive to sensory experience (Lendvai *et al.* 2000; Majewska and Sur 2003; Oray *et al.* 2003). Additionally, basal rates of dendritic spine rearrangements have been shown to vary between cortical modalities. Spines are more dynamic in auditory and somatosensory cortices and less so in visual cortex, suggesting that structural plasticity may be shaped by sensory input or factors inherent to the cortical area (Majewska *et al.* 2006). Using *in vivo* two-photon imaging in the auditory cortex of rewired animals could lead to important insights into the relationship between synaptic plasticity, cortical processing, and the influence of intrinsic and extrinsic factors on the structure of a cortical area. Despite the limitations of rewiring experiments, this line of research demonstrates that the developing brain has an extraordinary capacity to reprogram itself and adapt to its inputs.

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