3.07 Developmental Studies on Rewiring the Brain: What They Tell Us about Brain Evolution

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Glossary

arealization	A process by which neuroectoderm that will give rise to the cerebral cortex is partitioned into anatomically and functionally distinct areas.
cerebral cortex	A telencephalic structure where learning, memory, reasoning, and sensory perception occur.
lateral geniculate nucleus (LGN)	A subdivision of the thalamus that normally processes and relays visual information.
medial geniculate nucleus (MGN)	A subdivision of the thalamus that normally processes and relays auditory information.
thalamus	A diencephalic structure that processes and relays information from the senses to the cortex.
transcription factor	A molecule that regulates the transcription of other genes.

3.07.1 Introduction

Understanding neural development can inform us about how a brain structure evolves. By examining the development of a cortical region, one can elucidate the role that molecular cues and afferent inputs play in determining the evolution of a cortical structure, its function, and associated behaviors. Cross-modal experiments provide insight through a gain-of-function approach, whereby inputs of one sensory system are redirected to a different sensory modality. This allows the role of intrinsic and extrinsic factors to be distinguished and their relative contribution to cortical structure, function, and behavior to be determined. Here we will discuss how molecular cues in early development may influence the evolution of a cortical structure, as well as how rewiring visual inputs to innervate the auditory pathway provides insight into the role of patterned electrical activity as a key extrinsic factor determining the ultimate organization and function of a structure (see A History of Ideas in Evolutionary Neuroscience, Relevance of Understanding Brain Evolution).

3.07.2 Early Development and the Evolution of Cortical Structure: Molecular Influences on Cortical Arealization

The mammalian cerebral cortex develops as a continuous sheet of cells that is divided into anatomically and functionally distinct areas during the course of development (see The Development and Evolutionary Expansion of the Cerebral Cortex in Primates). This results in a pattern of cortical areas that is generally consistent among individuals within a species but varies between species, especially with respect to size and areal position (Krubitzer and Kahn, 2003). Influence over the pattern of these areas can potentially come from two sources: extrinsic sensory input, which reaches the cortex in an area-specific manner, and intrinsic molecular cues, which are encoded in the genome and expressed during development. Identifying the contributions of each of these is essential for understanding the mechanisms underlying the formation and diversification of the cerebral cortex. The first indication of arealization in the developing cortex is regional gene expression (Rubenstein *et al.*, 1999). Two studies have used mice in which thalamocortical axons fail to reach the cortex to examine the effect of blocked sensory input on early arealization

(see The Role of Transient, Exuberant Axonal Structures in the Evolution of Cerebral Cortex). Interestingly, in these mice (*Gbx2*$^{-/-}$ or *Mash1*$^{-/-}$), the initial expression of regionally expressed cortical genes appears normal (Miyashita-Lin *et al.*, 1999; Nakagawa *et al.*, 1999). This indicates that patterned gene expression occurs independent of extrinsic factors and argues that cortical pattern formation may be investigated using a logic similar to that used to study pattern formation in other embryonic tissues.

Identifying interactions among networks of transcriptional factors and signaling pathways has been critical in understanding the basic mechanisms of embryonic patterning (Wolpert, 2002). While a variety of transcription factors have been implicated in cortical arealization (O'Leary and Nakagawa, 2002; Sur and Rubenstein, 2005), one of the most heavily studied is Emx2. This molecule is expressed in a gradient across the caudal cortex, and a loss of Emx2 function results in an expansion of the rostral cortical markers at the expense of markers for the caudal cortex (Bishop *et al.*, 2000). Constitutive overexpression of Emx2 in mouse cortical precursors using *nestin cis*-regulatory elements is capable of altering both the size and position of primary sensory areas, and this change is complementary to that seen when Emx2 function is reduced (Hamasaki *et al.*, 2004). Intercellular signaling also appears to be involved in arealization, with the most well-studied pathway being the Fgf receptor (Fgfr) pathway. Fgf8, which is a secreted ligand in this pathway, is expressed in a high-rostral, low-caudal gradient across the mouse cortex during development. One study has shown that Fgf8 is capable of changing the location and patterning of mouse cortical areas when ectopically expressed early in embryogenesis (Fukuchi-Shimogori and Grove, 2001). Furthermore, mice homozygous for a hypomorphic Fgf8 allele show rostral shifts in the expression of arealization marker genes (Garel *et al.*, 2003), and projections that originate in the caudal cortex project ectopically into the rostral cortex (Huffman *et al.*, 2004). Fgf8 and Emx2 appear to interact with one another during cortical development (Fukuchi-Shimogori and Grove, 2003; Garel *et al.*, 2003; Hamasaki *et al.*, 2004), although the nature of this interaction awaits clarification.

Thinking about cortical arealization as a network of molecular interactions can help us understand how changes in cortical properties may have arisen in evolution. Subtle mutations at the genomic level may result in alterations in molecular interactions that can lead to profound phenotypic changes when amplified over the course of development. This, in turn, provides a mechanism for bringing about gross phenotypic change in evolution (reviewed in Pires-daSilva and Sommer, 2003). It is possible to imagine, for example, that a mutation causing a subtle change in expression level or binding affinity in a patterning molecule such as Fgf8 may result in a significant change in cortical arealization, which would then be subject to evolutionary selective pressure. This can also help us understand how the wiring of sensory input into the cortex may change during evolution. In addition to mediating early arealization, intrinsic factors also function in establishing thalamic input into the cortex (Lopez-Bendito and Molnar, 2003). For example, loss of function of the transcription factors Pax6 and Emx2 disrupts normal thalamocortical pathway development (Bishop *et al.*, 2000; Hevner *et al.* 2002; Jones *et al.*, 2002), and the Ephrin signaling pathway also appears to be involved in targeting thalamic projections into the cortex (Gao *et al.*, 1998; Vanderhaeghen *et al.*, 2000). Thus, molecules involved in establishing thalamocortical connections may act as substrates for evolutionary changes in cortical wiring.

3.07.3 Development of Structural Organization: Sensory Influences on Cortical Organization and Connectivity

Although early patterned gene expression in the cortex appears to occur independent of extrinsic factors such as the amount and pattern of electrical activity in input pathways, these can exert a substantial influence at both early and late stages of development and provide insight into the evolution of a cortical structure. For instance, while ocular dominance columns are present before eye opening (Rakic, 1976; Crowley and Katz, 2000; Crair *et al.*, 2001), the existence of retinal waves of spontaneous activity suggests that electrical activity generated within the developing brain may also contribute to the early establishment of central visual connections (Meister *et al.*, 1991; Wong *et al.* 1993).

Subsequently, visual experience plays a vital role in shaping the organization and connections of visual cortex. A balance of activity between the eyes appears to be essential for normal cortical development during the critical period, when visual experience has its maximal effect, with disruptions

to the amount or the pattern of electrical activity in only one eye having the greatest impact on cortical structure. For instance, monocular deprivation during the critical period induces robust changes in the anatomy and physiology of visual cortex (Wiesel and Hubel, 1965; Hubel *et al.*, 1977; LeVay *et al.*, 1980). In contrast, binocular deprivation during the critical period has little influence on 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). Even though these loss-of-function experiments suggest that input activity has a profound influence on the organization of the cortex, they cannot distinguish between the contributions made by the overall amount of activity and the specific pattern of activity in inducing these cortical changes.

Artificially induced strabismus, which alters the spatial correlation between the two eyes but not the overall level of activity, causes ocular dominance columns within primary visual cortex to become exclusively monocularly driven (Lowel and Singer, 1992). More generally, gain-of-function paradigms, such as the one used in rewiring experiments, allow separation of the relative influence of patterned visual activity from that of the amount of activity or of intrinsic factors in specifying the function and organization of a cortical area. In these experiments, visual input is redirected to the auditory pathway by inducing retinal ganglion cell axons to innervate the medial geniculate nucleus (MGN) through surgical removal of its normal inputs at birth (see Figure 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 primary auditory cortex (A1). Such rerouting has been done in mice (Lyckman *et al.*, 2001), ferrets (Sur *et al.*, 1988; Roe *et al.*, 1990, 1992, 1993; Sharma *et al.*, 2000), and hamsters (Schneider, 1973; Kalil and Schneider, 1975; Frost, 1982; Frost and Metin, 1985).

Retinal axons do not enter the MGN during normal development or in adulthood, but do so when the MGN is deafferented during an early developmental window. Molecular characterization of the denervated MGN indicates that removal of normal inputs upregulates molecules that promote sprouting in other systems, presumably attracting axons of the optic tract to branch and innervate the nucleus (Ellsworth, 2004). Remarkably however, once retinal axons enter the MGN, they pattern themselves in a manner similar to that in their major thalamic target, the lateral geniculate nucleus (LGN; see Figure 2a). Indeed, experiments examining the patterning of

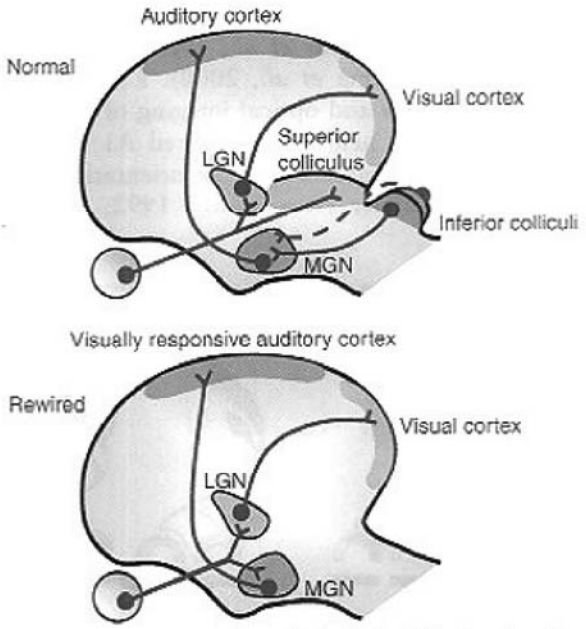

Figure 1 Schematics of the principal visual (blue) and auditory (red) pathways in normal (upper panel) and rewired animals (lower panel). LGN, lateral geniculate nucleus; MGN, medial geniculate nucleus. Modified from Sur, M., and Rubenstein, J. R. 2005. Patterning and plasticity of the cerebral cortex. *Science* 310, 805–810.

retinal innervation in the LGN and the rewired MGN suggest that the same intrinsic molecules facilitate pattern formation in both nuclei. In the normal mammalian visual pathway, retinal input is organized retinotopically in the LGN and is segregated into discrete eye-specific regions. A similar eye-specific segregation occurs in the rewired MGN (Ellsworth *et al.*, 2005), with input from the right and left eye showing little overlap (Figure 2b). There appears to be conservation of patterning molecules across sensory modalities, with molecules such as the ephrins and their respective Eph receptors expressed in multiple gradients throughout the developing thalamus, including the LGN, MGN, and ventrobasal (VB) nucleus. In addition, in ephrin knockout mice, this eye-specific patterning is disrupted similarly in the LGN and rewired MGN (Figure 2a; Ellsworth *et al.*, 2005). Thus, the ephrins appear to shape rewired retinal projections in the same way they influence normal LGN patterning. Therefore, ephrin expression in the MGN and throughout the auditory pathway may provide a scaffold as well as impose target-derived constraints on the extent to which connections along the auditory pathway are shaped by visual input.

Nevertheless, 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). Extracellular electrophysiology and optical imaging of intrinsic signals find that neurons in rewired A1 develop visual response features such as orientation and direction selectivity (Roe *et al.*, 1992; Sharma *et al.*, 2000) as well as an orderly retinotopic map (Roe *et al.*, 1990). That is, rewired A1 neurons 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 develops in rewired A1, similar to the one found in V1. Optical imaging experiments reveal that a systematic map of orientation information develops in rewired A1, which is similar to the orientation map found in V1 (Sharma *et al.*, 2000). This orientation map in rewired A1 contains iso-orientation domains, where the neurons all respond to the same preferred orientation, organized around pinwheel centers (Figure 3).

In addition to influencing the organization of visual response feature maps, the visual inputs directed to rewired A1 also shape its local and long-range

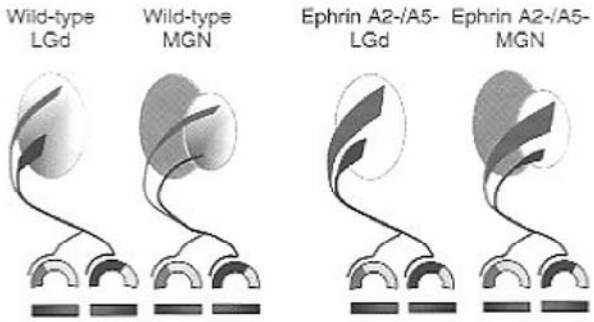

Figure 2 Target-mediated cues influence normal and novel retinal projections. a, Schematic representation of Eph–ephrin interactions in the retina and retinal targets in wild-type and ephrin knockout mice. Contralateral projections are labeled in red; ipsilateral projections are labeled in green. Ephrin expression is represented by the blue gradient within the target nuclei, while Eph receptor expression is depicted by the blue gradient under each retina. Left, in wild-type mice, ipsilateral axons arise from the temporal retina and express high levels of EphA receptor. As a result, these axons target regions of the dorsal lateral geniculate nucleus (LGd) with low ephrin-A expression. A similar ephrin gradient is also apparent in the MGN. As a result of these parallel ephrin gradients, eye-specific projections are similar in the LGN and rewired MGN: in rewired wild-type mice, ipsilateral retino-MGN projections target regions of the MGN with low ephrin expression. Right, in ephrin-A knockout mice, ipsilateral axons still show high EphA-receptor expression but target broader regions of the LGN and MGN. Ipsilateral axons spread ventrally in both the LGN and rewired MGN of ephrin knockout mice. b, Representative coronal sections in a normal (left) and a rewired (right) mouse. In the rewired mouse, the retinal axons overshoot the medial boundary of the LGd and project into the MGN. Enhanced retinal projections into the lateral posterior (LP) nucleus 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 LGd/MGN boundary. Scale bar: 0.1 mm. Modified from Ellsworth, C. A., Lyckman, A. W., Feldheim, D. A., Flanagan, J. G., and Sur, M. 2005. Ephrin-A2 and -A5 influence patterning of normal and novel retinal projections to the thalamus: Conserved mapping mechanisms in visual and auditory thalamic targets. *J. Comp. Neurol.* 488, 140–151.

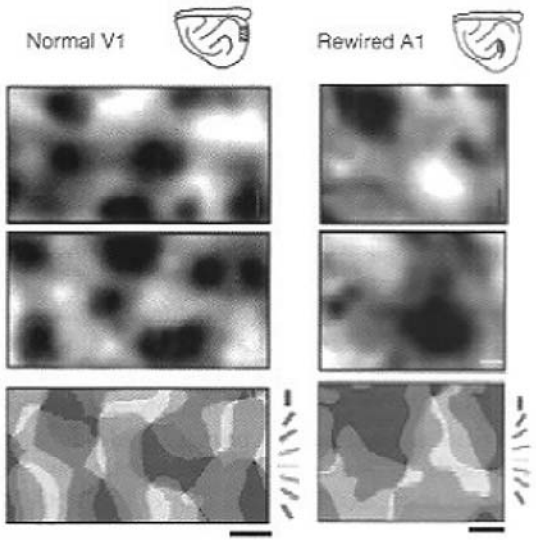

Figure 3 Orientation maps in normal visual cortex and rewired auditory cortex demonstrate the role of input activity in cortical development. Left, lateral view of normal primary visual cortex (V1) in the ferret brain. The upper two panels show activity maps in normal V1 using optical imaging of intrinsic 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. The color key to the right of the panel shows the orientations represented. Scale bars: 0.5 mm. Modified from Sharma, J., Angelucci, A., and Sur, M. 2000. Induction of visual orientation modules in auditory cortex. *Nature* 404, 841–847.

connections such that they resemble connections in V1 (Sharma *et al.*, 2000). Rewired A1 neurons form connections between domains with the same orientation preference, just like V1 neurons. 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). This differs significantly from the band-like connections that extend along the isofrequency axis in normal A1. At the same time, despite the similarities in the organization of visual information and connectivity of rewired A1 and V1, there are several notable differences. Rewired A1 orientation domains are larger and less orderly, as are horizontal connections relative to V1. In addition, the receptive fields in rewired A1 are larger (Roe *et al.* 1992) and spatial acuity of the rewired auditory pathway is lower than the normal visual pathway (von Melchner *et al.*, 2000). This may result from the large contribution of retinal W cell inputs to the rewired MGN (Roe *et al.* 1993). These differences may also reflect underlying structural constraints imposed by A1 that cannot be modified by experience (e.g., certain patterns of connections within and between the A1 cortical layers). Even though receptive fields and orientation domains in rewired A1 are larger than in visual cortex, these rewiring experiments provide powerful evidence that patterned visual activity plays an instructive role in the establishment of cortical connections by modifying the function and organization of a cortical area.

3.07.4 Specification of Cortical Areas: The Relationship between Inputs, Outputs, and Function

In addition to having a profound influence on cortical organization and physiology, rewired visual inputs can influence behavior. A study of unilaterally rewired ferrets suggests that patterned visual inputs influence behavior and drive the outputs of A1 (von Melchner *et al.*, 2000). Unilaterally rewired ferrets were trained to discriminate between light and sound (Figures 4a and 4b). After training, the ferrets were tested with a light presented in the rewired visual field. The normal and rewired ferrets primarily responded at the visual reward spout, an expected result given that the rewired hemisphere receives visual information through both the normal visual inputs to visual cortex and the rewired projection from the retina to the MGN to auditory cortex (Figures 4c and 4d). The normal visual projection from LGN/lateral posterior (LP) nucleus to the rewired hemisphere was then ablated, and after a period of recovery the ferrets were retested with a light presented to the rewired visual field. The rewired ferrets still responded primarily 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 (Figure 4c). The normal ferrets, however, responded at chance levels at the visual reward spout when retested after ablation of the LGN/LP and superior colliculus (SC) (Figure 4d). Finally the auditory cortex was ablated, and the rewired ferrets were again retested after a period of recovery. The rewired 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 (Figure 4c). 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.

In addition, rewired visual projections in mice influence learned behavior mediated by subcortical pathways, such as conditioned fear (Newton *et al.*, 2004). In fear-conditioning experiments, a discrete auditory cue is paired with a mild foot shock, which induces rapid 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 5a) are thought to be crucial for auditory cued conditioned fear responses (Rogan and LeDoux, 1995; Doron and LeDoux, 1999; see also LeDoux *et al.*, 1984; LeDoux, 2000; Namura *et al.*, 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 5a; Shi and Davis, 2001).

A study of adult sham lesion and rewired mice suggests that the rewired visual input to the MGN mediates the acceleration of visually cued fear conditioning (Newton *et al.*, 2004). Under these circumstances, the rewired visual inputs to the MGN are able to elicit the output fear response normally associated with an auditory stimulus. In these experiments, adult sham lesion and rewired

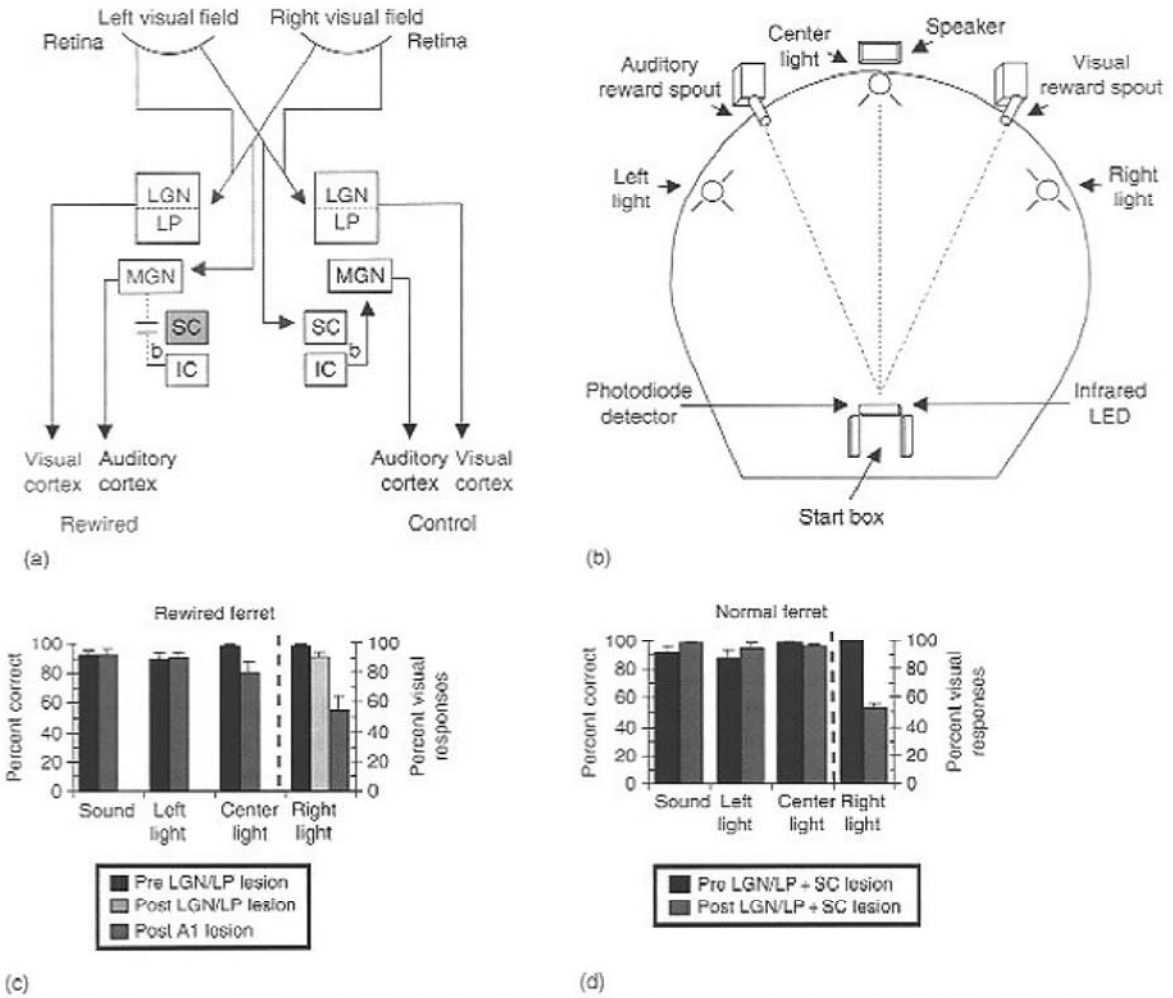

Figure 4 Retinal projections routed to the auditory pathway mediate visual behavior in rewired ferrets. a, Pathway from the retina to the visual thalamus, including the LGN and the lateral posterior (LP) nucleus, and to the superior colliculus (SC) in the control hemisphere (right); and to the LGN/LP and 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, Experimental apparatus and the design of the behavioral experiment. 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 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. c, Response of a rewired ferret to sound and light stimuli under three separate conditions: after training with sound and light stimuli, but before the ablation of the visual LGN/LP pathway (red bars); after the LGN/LP lesion (yellow bar; only the response to the right light is shown); and after the A1 lesion in the rewired hemisphere (green bars). Response bars (mean + s.d.) depict the performance in the final 10–19 days in the pre-LGN/LP lesion condition, and in the first 10–18 days in the post-LGN/LP and post-A1 lesion conditions. d, Response of a normal ferret to sound and light stimuli under two separate conditions: after training with sound and light stimuli, but before the ablation of the LGN/LP and SC pathways (red bars) and after (green bars). Response bars depict performance in the final 9 days in the pre-LGN/LP + SC lesion condition, and in the first 12 days in the post-LGN/LP + SC condition. Modified from von Melchner, L., Pallas, S. L., and Sur, M. 2000. Visual behaviour mediated by retinal projections directed to the auditory pathway. *Nature* 404, 871–876.

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 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 5b). Light-conditioned rewired mice, however, froze significantly more during the cue presentation after only one session of fear conditioning, as did tone-conditioned sham lesion and rewired mice.

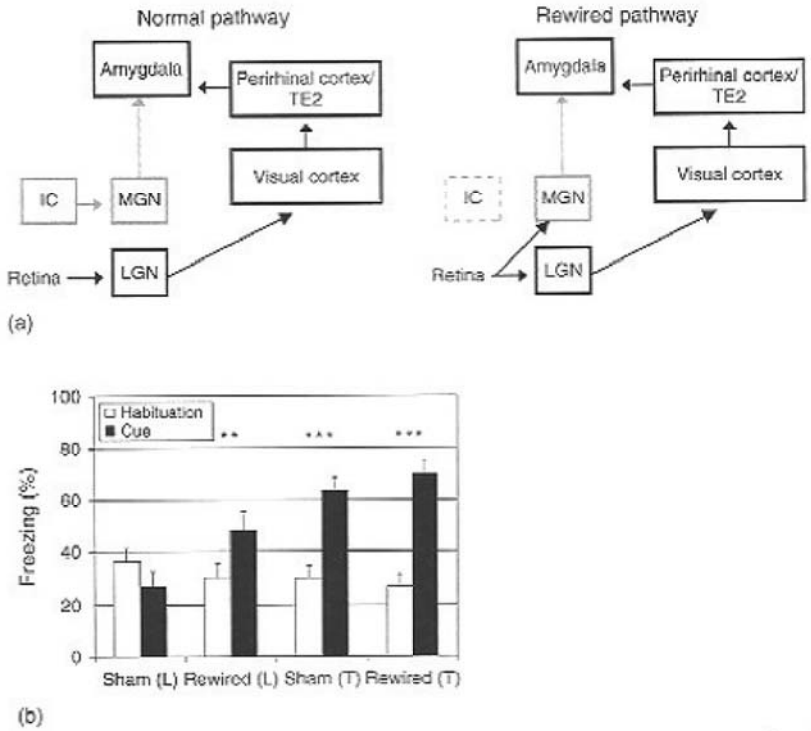

Figure 5 Retinal projections to the auditory pathway mediate visually cued learning in rewired mice. a, Simplified schematic of the principal visual (black) and auditory (gray) cued fear conditioning pathways in normal (left) and rewired mice (right). The IC (shown as a dotted box) was lesioned bilaterally 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, ** $p < 0.01$, *** $p < 0.001$). Modified from Newton, J. R., Ellsworth, C., Miyakawa, T., Tonegawa, S., and Sur, M. 2004. Acceleration of visually cued conditioned fear through the auditory pathway. *Nat. Neurosci.* 7, 968–973.

These findings indicate that the behavioral function of a target (in this case, the amygdala) is influenced by its inputs, and that it can activate the output response associated with the target. Thus, existing pathways can convey novel information to central structures, and this information is capable of mediating behavior.

3.07.5 Rewiring Experiments and Brain Evolution

Despite the limitations of rewiring experiments, this line of research demonstrates that the developing brain has an extraordinary capacity to reorganize itself and adapt to its inputs. Furthermore, the influence of molecular cues in early development on cortical arealization and the impact of rewired visual inputs on the organization and the connectivity of subsequent auditory structures provide insight into the evolution of a cortical area. In essence, these gain-of-function experiments provide information on certain principles by which novel connections might become functional and even adaptive, setting the stage for evolutionary change. During evolution, targets may express novel molecular cues as a result of mutations, and these, in combination with existing molecular cues, may form new structural patterns and functional connections. The electrical drive provided by these novel inputs can be utilized by target structures to form network connections that enable these structures or their downstream targets to process the novel information. Certain downstream pathways driven by the novel input may confer substantial adaptive advantage, as exemplified by rapid visually cued fear conditioning in rewired mice caused by novel retinal inputs to the MGN and subsequent utilization of the projection from the MGN to the lateral amygdala.

More generally, the studies discussed in this article suggest that there is a dynamic interplay between intrinsic and extrinsic factors throughout the evolution of a cortical region. Both factors play a critical role in determining the overall structure and function of a cortical area, but tend to exert their greatest influence at different times and in complementary ways during development.

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