REWIRING CORTEX: FUNCTIONAL PLASTICITY OF THE AUDITORY CORTEX DURING DEVELOPMENT

Jessica R. Newton and Mriganka Sur
Department of Brain & Cognitive Sciences, Picower Center for Learning & Memory, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139 USA

1. INTRODUCTION

How does the primary auditory cortex (A1) derive its function? Is it primarily determined by intrinsic factors expressed within cortex (i.e. molecular gradients, patterns of gene expression) or extrinsic factors that originate outside cortex (i.e. sensory experience)? This is a pivotal issue for understanding the development and function of A1, yet one that is difficult to address using traditional experimental methods because these techniques are unable to separate out the relative contributions of intrinsic and extrinsic factors. However, cross-modal experiments where the inputs of one sensory modality are re-directed to a different modality, in effect "rewiring" the brain, are able to distinguish the two and provide insight. 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 review rewiring experiments in which visual inputs are induced to innervate the auditory pathway, and describe its physiological and behavioral consequences as well as the implications for normal cortical processing and human cross-modal plasticity.

2. INTRINSIC AND EXTRINSIC FACTORS IN CORTICAL DEVELOPMENT

Much work on the influence of intrinsic and extrinsic factors on cortical development has focused on the developing visual cortex. The formation of cortical layers and the arealization of cortex seem to be primarily influenced by 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 & Leamey, 2001). However extrinsic factors, such as the amount and pattern of electrical activity in input pathways, also contribute to cortical development. Electrical activity generated within the developing brain may be sufficient for the establishment of thalamo-cortical connections, as suggested by the existence of retinal waves of spontaneous activity (Meister et al., 1991; Wong et al., 1993) and the presence of ocular dominance columns before eye opening (Rakic, 1976; Crowley & Katz, 2000; Crair et al., 2001).

Visual experience, which influences the amount and pattern of electrical activity in pathways to the cortex, appears to be critical for the maintenance and refinement of cortical connections. Classic experiments by Hubel and Wiesel demonstrated that visual cortex displays remarkable plasticity during development, and is profoundly influenced by visual experience. In particular, 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 & Hubel, 1965; Hubel et al., 1977; LeVay et al., 1980). Similarly artificially induced strabismus, which alters spatial correlations between the two eyes but not the level of activity, causes ocular dominance columns to become exclusively monocular and modifies intracortical connections (Lowel & Singer, 1992). Depriving both eyes 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 & Katz, 1999). Limiting overall light exposure also impacts

cortical plasticity, 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.

3. REWIRING THE BRAIN: THE PHYSIOLOGICAL CONSEQUENCES

In contrast to visual deprivation, "rewiring" experiments allow the role of patterned visual activity in specifying the function and organization of a cortical area to be distinguished from the influence of intrinsic factors. The limitations imposed on this cross-modal plasticity by the underlying cortical substrate, in this case A1, are also exposed. In these experiments visual input is re-directed 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 Fig. 1). This creates an alternative target for retinal axons and allows functional connections to form in the auditory thalamus, conveying visual information through existing thalamo-cortical connections to A1. Such re-routing has been done in *mice* (Lyckman et al., 2001), *ferrets* (Sur et al., 1988; Roe et al., 1990; Roe et al., 1992; Roe et al., 1993; Sharma et al., 2000), and *hamsters* (Schneider, 1973; Kalil & Schneider, 1975; Frost, 1982; Frost & Metin, 1985).

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; Roe et al., 1992; Sharma et al., 2000). For instance, 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.,

Normal Pathway **Rewired Pathway**

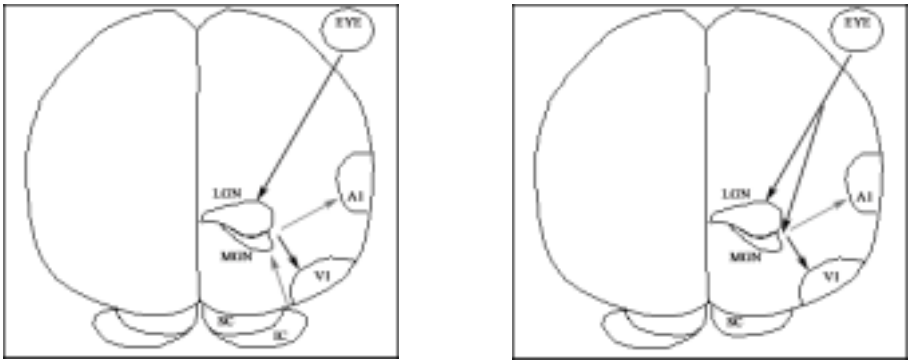

Figure 1. Schematics of the principal visual (black) and auditory (gray) pathways in normal animals *(left)* and rewired animals *(right)*. A1= primary auditory cortex, IC = inferior colliculus, LGN = lateral geniculate nucleus, MGN= medial geniculate nucleus, SC= superior colliculus, V1= primary visual cortex.

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). Rewired A1 also contains iso-orientation domains similar to V1, where the neurons all respond to the same preferred orientation, which are organized around pinwheel centers (see Fig. 2).

Orientation selectivity in V1 is believed to be generated in the cortex by a weak orientation selectivity bias conveyed by thalamic afferents, which is enhanced within the cortex by recurrent cortical connections (Somers et al., 1995). Although the development of orientation tuning does not require visual experience (Hubel & Wiesel, 1963; Crair et al., 1998), orientation selectivity can be altered by patterned visual experience during the critical period (Sengpiel et al., 1999). Thus it is interesting that 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). This suggests that

patterned input activity can have a profound influence on the structure and organization of the A1 cortical substrate.

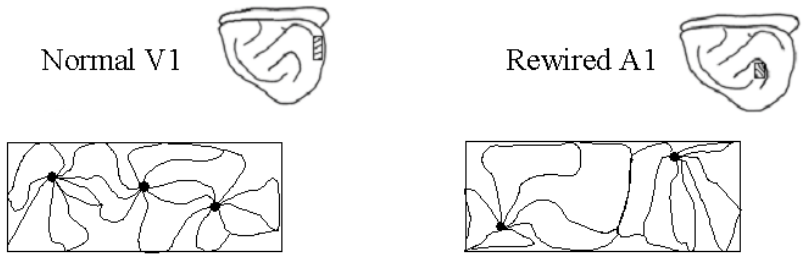

Figure 2. Schematics of the orientation maps in normal V1 (left) and rewired A1 (right). The black circles indicate the pinwheel centers, which are surrounded by iso-orientation domains where neurons all respond to the same preferred orientation.

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 & 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.

4. REWIRING THE BRAIN: THE BEHAVIORAL CONSEQUENCES

The impact of rewiring on behavioral function has also been explored. A study of rewired ferrets (von Melchner et al., 2000) suggests that in addition to specifying cortical function, patterned inputs can influence behavior. Unilateral rewired ferrets were trained to discriminate between light and sound. Sound stimuli were presented at several spatial locations, 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. 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 sub-cortical 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 & Fanselow, 1999; LeDoux, 2000). In contrast, a discrete visual cue is less effective,

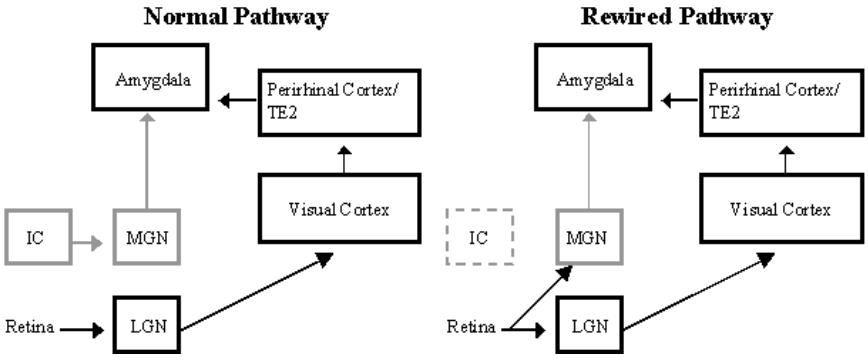

Figure 3. Simplified schematic of the principal visual (black) and auditory (gray) cued fear conditioning pathways in normal (*left*) and rewired mice (*right*). The IC (shown as a dotted box) was lesioned bilaterally in neonatal mice to induce retinal projections to the MGN. IC = inferior colliculus, LGN = lateral geniculate nucleus, MGN= medial geniculate nucleus.

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 (Fig. 3) are thought to be crucial for auditory cued conditioned fear responses (Rogan & LeDoux, 1995; Doron & LeDoux, 1999). An indirect thalamo-cortical-amygdala pathway from the MGN via auditory cortex to perirhinal cortex also conveys information to the amygdala (LeDoux, 2000; Namura et al., 1997). 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; Quirk 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 & LeDoux, 1999; Shi & 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 Fig.3; Shi & Davis, 2001).

Adult sham lesion and rewired mice underwent three sessions of fear conditioning with either a visual or an auditory cue (3 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 4. 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 (Fig. 4). Light conditioned rewired mice, however, froze significantly more during the cue presentation after only one session of fear conditioning (*$p<0.05$, paired t-test), as did tone conditioned sham lesion mice (***$p<0.01$, paired t-test). After three sessions of fear conditioning, sham lesion mice also showed greater freezing during the cue presentation.

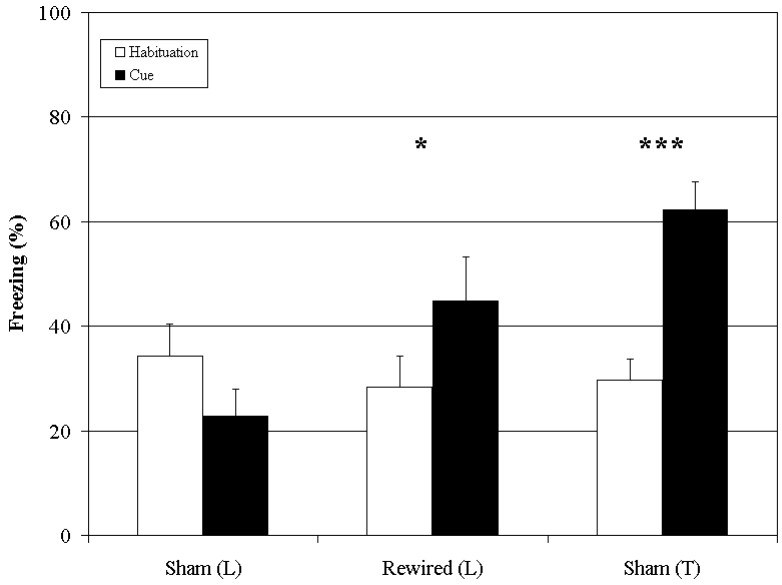

Figure 4. The mean freezing per group during the habituation (white bar) and cue presentation (black bar) periods of the cued testing session after one session of fear conditioning, with error bars denoting the standard error of the mean.

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. Existing pathways can convey novel information to central structures, and this information is

capable of mediating behavior. The use of a natural behavior such as conditioned fear, without the infliction of additional lesions, demonstrates unequivocally that central pathways derive function from their inputs.

5. HUMAN CROSS-MODAL PLASTICITY AND NORMAL CORTICAL PROCESSING

Human cross-modal plasticity experiments also provide evidence for cortical areas deriving function from their inputs. Studies of congenitally blind humans demonstrate that the visual cortex is activated during non-visual somatosensory tasks (Sadato et al., 1996; Kujala et al., 1997) as well as some auditory tasks (Weeks et al., 2000). Similarly, the auditory cortex in congenitally deaf individuals is involved in visual tasks (Neville et al., 1983; Finney et al., 2001; Bavelier & Neville, 2002; Finney et al., 2003).

There is some evidence that cortical areas have an inherent propensity 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 (Kitagawa & Ichihara, 2002; Welch et al., 1986). 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 & 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 & Mowbray, 1959; Shipley, 1964) of a visual stimulus can also be influenced by conflicting auditory signals.

Thus, inherent processing biases could impact 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. Such properties may be evident as more detailed experiments are carried out on structural, functional and behavioral dynamics of rewired auditory cortex. Regardless of limits, however, rewiring experiments demonstrate the extraordinary capacity of the auditory cortex for adapting to its inputs as it develops.

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