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- NOTES**
- 1 The volume of Area X at 25 days was measured by Burek *et al.* (1991) as 0.96mm³, not 0.096 mm³ as appears in their Table 1 (K.W. Nordeen, pers. com.).
- 2 This paper was written during the summer of 1998. Since then, several studies on songbirds have made progress towards disentangling developmental changes from learning-related plasticity (e.g., Leonardo, A. and Konishi, M. (1999) *Nature* **339**:466–470). With regard to parrots, Dr. Arla Hile has shown that male budgerigars reliably imitate the calls of their female mates, providing us with a convenient paradigm for vocal imitation in adult birds (Hile, A.G., Plummer, T.K., and Striedter, G.F. (in press) *Animal Behaviour*). Finally, our data on auditory responses in the vocal motor system of budgerigars have now been published (Plummer, T.K., and Striedter, G.F. (2000) *J. Neurobiol.*, **42**:79–94).

Modifiability of neocortical connections and function during development

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1. INTRODUCTION

In the adult mammalian cerebral cortex, specific and orderly connections to, from and within a cortical area underlie the generation of the functional response properties of single neurons, of more global patterns of neural activity and, ultimately, of specific neocortical functions. The developmental emergence of such precise circuitry relies on fine interactions between intrinsic/genetic and extrinsic/epigenetic mechanisms.

The early events in the development of neocortical circuits are thought to be guided by intrinsic cues (Goodman and Shatz, 1993). For example, the generation of cortical cells, their positioning within cortical layers, the initial outgrowth of axons, the recognition of appropriate targets, and the initial formation of axon arbors, all occur long before the onset of sensory experience and seem to be directed by molecular interactions (but see Herrmann and Shatz, 1995). Subsequent developmental events, such as the elaboration of more complex axon arbors and the rearrangement of connections, can occur before or after the onset of sensory experience, but, for at least some cortical circuits, appear to require neural activity. In the first part of this review we shall examine the role of sensory driven and spontaneously generated neural activity in shaping cortical circuitry and function. In the second part, we shall review more recent evidence supporting a specific role for the spatiotemporal patterning of neural activity in the development of cortical processing circuits.

2. ROLE OF VISUALLY DRIVEN AND SPONTANEOUS NEURAL ACTIVITY IN THE DEVELOPMENT AND PLASTICITY OF CORTICAL CIRCUITRY AND FUNCTION

Most of our current understanding of activity-dependent mechanisms of development and plasticity is based on classic studies of ocular dominance columns in the primary visual cortex (V1) of cats and primates. Other well-studied examples of cortical development are the generation of orientation selectivity, orientation maps, and the system of intrinsic long-range lateral connections within V1. In this section we review data on the development of these systems in carnivores and primates, and examine the specific roles of visual experience and spontaneous neural activity in guiding their emergence and maintenance.

2.1. Development and Plasticity of Thalamocortical Connections and Ocular Dominance Columns

2.1.1. Ocular dominance columns and bands

In carnivores and primates, layer 4 of the primary visual cortex (V1) is the main target of thalamic afferents from the lateral geniculate nucleus (LGN), although some geniculate input reaches layer 6 and 1 (Garey and Powell, 1971; Le Vay and Gilbert, 1976) and, in primates, also layers 2–3 (Livingstone and Hubel, 1982; Weber *et al.*, 1983; Itaya *et al.*, 1984). Within layer 4 of V1, afferents from the two eyes segregate into a series of alternating eye-specific stripes, the ocular dominance bands (Hubel and Wiesel, 1969; Le Vay and Gilbert, 1976; Shatz *et al.*, 1977; Anderson *et al.*, 1988), that represent the morphological correlate of physiologically identified ocular dominance columns (Hubel and Wiesel 1962, 1968). These functional columns span all cortical layers; within each column, most cells, with the exception of layer 4 cells, can be driven by stimulation of either eye, one eye being variably dominant over the other. Layer 4, instead, is an exception to the binocularity of V1 cortical cells, in that, by receiving direct input from the LGN, its cells are strictly monocular in primates, and largely so in cats.

Using autoradiographic techniques to visualize the transneuronal transport of tritiated tracers injected into one eye, it was established that the anatomical segregation of thalamocortical axons is absent early in development, and that it emerges progressively from an early immature pattern, whereby afferents subserving the two eyes are initially intermingled in layer 4. In the cat, ocular dominance segregation develops postnatally, beginning at about 3 weeks of age, after the time of natural eye opening, and ending at about 6 weeks (Le Vay *et al.*, 1978). In the ferret, another carnivore, segregation of geniculocortical afferents begins between postnatal day (P) 30 (the time of natural eye opening) and P37, and becomes adult-like around P63 (Ruthazer *et al.*, 1999). In monkeys, instead, ocular dominance bands begin to form prenatally, late in the third trimester of gestation, and thus prior to the onset of visual experience (Rakic, 1976, 1977). At birth, the bands are clearly segregated, showing an almost adult-like pattern (Des Rosiers *et al.*, 1978; Horton and Hocking, 1996a), and subsequently undergo a short period of postnatal refinement (Le Vay *et al.*, 1980; Horton and Hocking, 1996a). In kittens aged P19 to P39, individual thalamocortical axon arbors, labeled by injections of the *Phaseolus* lectin (PHA-L) into eye-specific LGN layers, ini-

tially form long, poorly ramified collateral branches homogeneously distributed in layer 4. Progressively, a fundamental remodeling of the axon arbor takes place which leads to the formation of discrete clusters of terminals: widely extended branches and inappropriately located collaterals are selectively eliminated, and significant growth and elaboration of terminal arborizations occurs within the clusters (Antonini and Stryker, 1993a).

Functionally, both in cats and monkeys, cells are initially binocular in layer 4 (Le Vay *et al.*, 1978, 1980), consistent with the initial intermingling of eye-specific thalamic afferents in this cortical layer. Data on the development of ocular dominance outside layer 4 are scarcer. In newborn monkeys, single cell recordings have revealed a distribution of ocular dominance similar to that of the adult (Wiesel and Hubel, 1974; Hubel *et al.*, 1977). More recently, optical recordings of intrinsic signals in postnatal macaques have confirmed the presence of a banded pattern of ocular dominance at 31/2 weeks of age, but the optical signals associated with ocular dominance are less pronounced than in adults, consistent with the incomplete segregation of LGN afferents in layer 4 at this stage of development (Blasdel *et al.*, 1995). In addition, the width of ocular dominance columns in these young monkeys is about 20% smaller than that in the adult. Electrophysiological recordings (Frégnac and Imbert, 1978; Le Vay *et al.*, 1978; Albus and Wolf, 1984) and, more recently, optical imaging of intrinsic signals (Crair *et al.*, 1998) in cat area V1, have shown that in young animals there is a marked bias of responses to the contralateral eye. Responses to the ipsilateral eye increase over time and become nearly identical to those through the contralateral eye at about 3 weeks of age (Crair *et al.*, 1998). Despite the overall dominance of the contralateral eye, optical maps obtained 2 weeks postnatally already show a banded pattern of alternating eye preference, even though the anatomical segregation of LGN afferents has not yet begun. These data suggest that the physiological ocular dominance columns get organized earlier than the anatomical columns in layer 4, possibly reflecting earlier maturation of the upper cortical layers, which might then guide, rather than follow, the segregation of thalamocortical axons.

Thus, whereas in carnivores development of ocular dominance patterns begins around or after the time of natural eye opening, in primates it begins prior to the onset of visual experience, suggesting that visual input is not necessary for ocular dominance columns to form.

2.1.2. Role of visual experience

The role of visual experience in the development of visual cortical connections and function has classically been studied by manipulating the amount of visually-driven activity by means of visual deprivation. Two types of visual deprivation have been employed: eye-lid suture, which disrupts form vision, but allows low levels of diffuse light to enter the eye, and dark rearing, which is a form of complete visual deprivation. It has long been known that abnormal visual experience can disrupt the normal development of connections and receptive field properties of visual cortical cells. Wiesel and Hubel (1963, 1965) first demonstrated the effects of monocular deprivation (MD) on the development of ocular dominance columns. If one eye is deprived of vision by suturing the eye-lid during a critical period of development, the physiological ocular dominance distribution of cells in V1 is drastically shifted: most cells become

monocularly driven by the non-deprived eye. These physiological effects of MD can be detected even after a brief, 2–3-day period of deprivation (Olson and Freeman, 1975, 1980; Movshon and Dursteller, 1977; Mioche and Singer, 1989). In cats, the critical period for the physiological effects of MD begins shortly after birth, peaks at 4–5 weeks of age and ends at about 4–6 months (Hubel and Wiesel, 1970; Olson and Freeman, 1980). In primates the critical period begins at or before birth, peaks during the first postnatal weeks and ends between 10 and 12 weeks of age (Le Vay *et al.*, 1980; Horton and Hocking, 1997).

The anatomical correlate of the physiological effects of MD is a dramatic shift of ocular dominance bands in layer 4 in favor of the non-deprived eye: the terminal patches of LGN axons subserving the open eye expand dramatically, whereas those arising from the deprived eye are reduced to very small patches (Hubel *et al.*, 1977; Shtatz and Stryker, 1978). In cats monocularly deprived before eye opening for 4 weeks, or even for a 4–7 day period at the peak of the critical period, deprived-eye single axon arbors are dramatically reduced in density and complexity compared to both non-deprived eye arbors and arbors in normal, age-matched animals (Antonini and Stryker, 1993b). Thus, MD does not simply arrest the axon's developmental growth, but induces a significant remodeling and elimination of axonal branches, both of which can occur extremely rapidly. Compared to short-term MD, long-term MD induces greater expansion and complexity of LGN arbors from the open eye, suggesting that the process of synapse and branch elimination is faster than the constructive process of branch formation (Antonini and Stryker, 1996).

These experimental results suggest that ocular dominance columns require normal visual experience to develop normally, that they can be structurally and functionally modified by early abnormal experience, and that the mechanism that normally drives their formation might be competition between LGN axons from the two eyes. However, these data do not provide any information on whether visual experience specifies structural and functional connections. Studies on the effects of binocular deprivation on visual cortical development have shed some light on this question.

Depriving kittens of binocular vision from birth does not alter the normal physiological ocular dominance distribution in V1 (Wiesel and Hubel, 1965; Frégnac and Imbert, 1978; Cynader and Mitchell, 1980; Mower *et al.*, 1981; Crair *et al.*, 1998), suggesting that visual experience does not specify functional development, and further supporting the hypothesis that competitive interactions between afferents from the two eyes are involved in the development of ocular dominance columns. However, other physiological and anatomical studies have broadened this interpretation. The two most frequently used paradigms of binocular deprivation – binocular lid-suture (BS) and dark rearing (DR) – have different functional effects on the development of cortical binocularity. Whereas in long-term dark reared cats the majority of V1 cortical neurons show binocular and non-specific receptive field properties (Imbert and Buisseret, 1975; Mower *et al.*, 1981; Cynader, 1983), in long-term binocularly sutured cats and monkeys there is a reduction in the number of binocular cells (Wiesel and Hubel, 1974; Blakemore and Van Sluyters, 1975; Kratz and Spear, 1976; Watkins *et al.*, 1978; Mower *et al.*, 1981), and a higher proportion of unresponsive or abnormally responsive V1 neurons (Wiesel and Hubel, 1965; Blakemore and Van Sluyters, 1975; Mower *et al.*, 1981). In addition, if BS is prolonged beyond 3 weeks of age, the

bias of responses through the contralateral eye, normally observed in young kittens, persists (Crair *et al.*, 1998). Whereas the effects of binocular closure on cortical binocularity might depend on uncorrelated visual stimulation of the two eyes by diffuse light through the sutured eye lids (see below for further discussion of this issue), these data suggest that the role of form vision is to maintain or refine, but again, not specify, functional connections, since total lack of visual experience does not prevent formation of functional ocular dominance columns.

Although DR does not prevent formation of physiological ocular dominance columns, injections of tritiated proline into one eye of dark reared or binocularly sutured cats have revealed reduced eye-specific segregation of thalamocortical afferents in layer 4 of area 17, but not area 18 (Swindale 1981, 1988; Mower *et al.*, 1985; Stryker and Harris, 1986). However, Le Vay *et al.* (1980) observed normal ocular dominance bands in a 7-week old monkey dark reared from the age of 3 days. This study is open to the criticism that a brief period of visual experience was allowed before the initiation of dark rearing. Experiments in dark reared cats have shown that brief exposure to light is enough to alter cortical plasticity (Mower *et al.*, 1983) and to induce ocular dominance band segregation (Swindale 1988; see also Horton and Hocking, 1996a for a discussion of this issue). A mismatch between functional and anatomical ocular dominance column development is observed in cats monocularly deprived after being reared in the dark beyond the normal critical period. In these animals there is a physiological (Cynader and Mitchell, 1980; Mower *et al.*, 1981), but not anatomical (Mower *et al.*, 1985; Swindale, 1988), shift in ocular dominance in favor of the open eye: geniculocortical axons in layer 4 of area 17 show a distribution similar to that seen in dark reared cats, and the majority of cells in layer 4 are binocular (Mower *et al.*, 1985), whereas outside layer 4 most cells are monocularly driven by the non-deprived eye. Further evidence that the critical period for plasticity in layer 4 might differ from that in other cortical layers comes from studies showing that MD initiated after 10–12 weeks of age in monkeys produces no anatomical changes in the size of ocular dominance bands in layer 4 (Le Vay *et al.*, 1980; Horton and Hocking, 1997), but still causes a physiological shift in eye dominance in the upper layers of the cortex (Le Vay *et al.*, 1980). These findings suggest plasticity of interlaminar connections, which lasts longer than that of thalamocortical axons. Furthermore, in cats, Daw *et al.* (1992) have provided physiological evidence that the duration of the critical period for MD varies with the cortical layer examined, ending between 5 and 8 weeks postnatally in layer 4, and declining more slowly for layers 2–3 and 5–6 between 6 weeks and 1 year of age.

A more complex picture emerges from this series of studies: 1) the development and plasticity of cortical binocularity and of the functional distribution of ocular dominance must reflect the development and plasticity of eye-specific segregation of geniculocortical axons in layer 4 of V1 as well as that of specific intracortical connections outside layer 4, possibly the interlaminar connections between layer 4 and the upper cortical layers; 2) the physiological critical period for the effects of MD is controlled by visual experience, since it is prolonged by DR, and likely reflects a prolonged plasticity of interlaminar connections; 3) the anatomical critical period for plasticity of the thalamocortical pathway is time-locked and independent of visual input, since it is not prolonged by DR; 4) since in binocularly deprived cats some

degree of segregation of LGN axons in layer 4 of V1 is present, and because in primates the initial stages of this segregation process occur prenatally, it follows that visual experience is not required to trigger the formation of ocular dominance bands but is required for segregation to proceed normally and achieve the normal adult pattern.

2.1.3. Role of spontaneous neural activity

A classic study by Stryker and Harris (1986) demonstrated that the emergence of ocular dominance bands is dependent on neural activity in the LGN afferents. Bilateral intravitreal injections of tetrodotoxin (TTX), a sodium channel blocker, for several postnatal weeks during the critical period, silence retinal activity: segregation of thalamocortical axons in layer 4 is prevented, and most cortical cells are driven by both eyes. Eye-specific patches within layer 4 do not form because geniculocortical axons, even though continue to grow and elaborate their terminal arborizations in the absence of retinal activity, fail to form clusters (Antonini and Stryker, 1993a). Thus, activity blockade does not prevent axonal growth and development, but rather seems to perturb the refinement of arbors into their normal adult pattern.

Neural activity is also required for physiological ocular dominance plasticity: blockade of pre- and postsynaptic cortical activity, by intracortical infusion of TTX during the critical period, prevents the physiological shift in ocular dominance induced by monocular deprivation (Reiter *et al.*, 1986).

Whereas neural activity required for ocular dominance plasticity and for the late developmental refinement of thalamocortical axons can be supplied by visual experience, we have seen that the initial segregation of ocular dominance stripes is not dependent on visual experience, yet it appears to require neuronal afferent activity. Similarly, segregation of retinogeniculate axons into eye-specific layers in the mammalian LGN occurs prior to eye opening (Linden *et al.*, 1981; Shatz, 1983), yet it is prevented by blockade of neural activity induced by intracranial infusion of TTX (Shatz and Stryker, 1988). Before the onset of visual experience, spontaneous activity in the visual pathway has been proposed to provide instructive cues for the eye-specific segregation of retinogeniculate and geniculocortical axons. Neural activity before the onset of vision, even before maturation of the photoreceptors, is present in the retina as rhythmic bursts of action potentials spontaneously generated by retinal ganglion cells (Galli and Maffei, 1988), and temporally correlated among neighboring cells (Maffei and Galli-Resta, 1990). These bursts consist of "waves" of excitation spreading across restricted retinal domains (Meister *et al.*, 1991; Wong *et al.*, 1995), which persist until just before the onset of visually driven activity (Wong *et al.*, 1993). Thus, the initial segregation of retinogeniculate and/or thalamocortical axons into eye-specific domains could be guided by spontaneous neural activity in the retina. In support of this hypothesis is recent evidence that in slices of retina and LGN, spontaneous retinal activity can drive cells in the LGN to fire periodic bursts of action potentials (Mooney *et al.*, 1996), and that, at least for the retinogeniculate pathway, monocular intraocular blockade of spontaneous retinal waves using cholinergic agents alters the eye-specific lamination in the LGN of P9 ferrets (Penn *et al.*, 1998). However, in a more recent study (Cook *et al.*, 1999), continuous retinal activity blockade with intraocular TTX during the first two postnatal weeks in ferrets delayed, but

did not prevent eye-specific segregation in the LGN. This study indicates that spontaneous activity in the retina, prior to visual experience, is not required to guide the segregation of retinogeniculate axons. To explain the apparent discrepancy between their result and that of Shatz and Stryker (1988), Cook *et al.* (1999) suggest that, whereas intraocular TTX release specifically blocks retinal activity, intracranial TTX infusion, used in the study by Shatz and Stryker (1988), is likely to block action potentials in relay and local circuit cells in the LGN, as well as in all thalamic afferents, thus interfering with multiple factors required for maturation of the LGN. Consistent with this study is a surprising recent report that binocular eye removal in P0 ferrets, prior to eye-specific segregation of retinogeniculate axons and before thalamic axons have reached cortical layer 4, still leads to segregation of ocular dominance-like stripes in V1 (Crowley and Katz, 1999; one interpretation of these results is that the cortical patches reflect the interdigitation of LGN and non-LGN inputs rather than inputs from putatively different LGN laminae). Thus, the initial establishment of ocular dominance bands appears to not require spontaneous retinal activity, yet retinal activity blockade by intraocular TTX does disrupt formation of ocular dominance columns (Stryker and Harris, 1986). This discrepancy can be explained by the observation that blockade of action potentials by TTX can cause non-specific sprouting of axon arbors within LGN and cortex (Sretavan *et al.*, 1988; Antonini and Stryker, 1993a; McAllister *et al.*, 1996), thus masking rather than disrupting normal developmental events.

Nevertheless, even without the retinae, it is still possible that spontaneous activity in the LGN and/or cortex drives the initial segregation of thalamocortical axons into ocular dominance bands. In support of this hypothesis, multielectrode recordings in the LGN of awake behaving ferrets aged P24–27 reveal spontaneous synchronous bursts of neuronal activity across all LGN layers (Weliky and Katz, 1999). The activity of neurons in different eye-specific layers is significantly correlated, but less so than activity of neurons lying within the same LGN layer. Activity correlations between the two eyes appear to be generated by cortical feedback to the LGN, whereas the specific spatiotemporal patterns of spontaneous LGN activity are induced by retinal afferents. In the absence of the eyes, spontaneous activity in the LGN shows a different temporal pattern, becomes more correlated across all LGN layers, and is sustained by cortical feedback. Thus in the absence of retinal inputs, activity in the thalamocortical loop may contain sufficient information to drive the formation of ocular dominance columns. An alternative interpretation of the results of Crowley and Katz (1999) is that the initial establishment of ocular dominance columns relies primarily on intrinsic activity-independent cues (op cit). Indeed, it is possible that both intrinsic and activity-dependent processes play a role but at successive times, with molecular cues setting up an initial coarse ocular dominance map and activity later doing "the fine sculpting work" (Hübener and Bonhoeffer, 1999).

Another series of studies have suggested that activity in the postsynaptic cell is also necessary to modify cortical structure and function. Intracortical infusion of muscimol, a GABA_A receptor agonist, reverses the effects of MD: most cells become monocularly driven by the deprived eye (Reiter and Stryker, 1988), and, in layer 4, the thalamocortical patches related to the deprived eye expand at the expense of those related to the non-deprived eye, which shrink (Hata and Stryker, 1994). Thus, identical manipulations of afferent activity can cause opposite anatomical and physiological

effects in the cortex, depending on whether the postsynaptic cells can respond or are inhibited.

Although postsynaptic activity plays an important role in ocular dominance plasticity, it is not known whether its blockade also prevents the segregation of LGN axons in layer 4 in addition to the development of physiological ocular dominance columns. Recent studies in a different system, the rat primary somatosensory cortex (S1), seem to suggest that this might indeed be the case. In rat S1, thalamocortical afferents and the postsynaptic cells that they contact are arranged in a characteristic somatotopic pattern (the "barrel" pattern) of parallel rows of clusters that mimic the peripheral arrangement of the facial vibrissae. Blockade of postsynaptic activity during the critical period, by intracortical infusion of glutamate receptor antagonists, disrupts the development of a normal barrel pattern both in the afferent axons as well as in the postsynaptic cells (Fox *et al.*, 1996). Curiously, however, TTX-induced blockade of cortical activity from birth does not seem to prevent either the normal barrel-like development of thalamocortical axons (Chiaia *et al.*, 1992, 1994a) or the thalamocortical reorganization normally associated with early peripheral lesions (Chiaia *et al.*, 1994a,b).

2.2. Development and Plasticity of Orientation Selectivity and Orientation Maps

Whereas the development of ocular dominance and the degree to which it can be modified by altering spontaneous or visually-driven activity has been well established, studies on the development and plasticity of another well-characterized visual cortical property, orientation selectivity, have been more controversial. Still, the data provide evidence for the role of neural activity in constructing and maintaining higher-order receptive field properties in cortex.

2.2.1. Orientation selectivity and maps

Neurons in the primary visual cortex of mammals display feature-specific responses. Among these features is the orientation of luminance gradients. Most V1 cells respond best to an edge of a specific orientation at a particular location in the visual field. Neurons preferring the same orientation are grouped together in columns and represented adjacent to columns of neurons preferring adjacent orientations (Hubel and Wiesel, 1962, 1963a, 1968). Thus, there is a systematic map of changing orientation preference across V1 (Blasdel and Salama, 1986; Bonhoeffer and Grinvald, 1991, 1993; Blasdel, 1992; Rao *et al.*, 1997).

Hubel and Wiesel first reported that in both cats and monkeys, orientation selectivity is already present in V1 shortly after birth, and qualitatively almost adult-like (Hubel and Wiesel, 1963b; Wiesel and Hubel, 1974). Later studies have disagreed with these initial reports on the degree to which orientation selectivity is adult-like in young kittens. Whereas Sherk and Stryker (1976) obtained data similar to that of Hubel and Wiesel, others found little or no orientation selectivity before the fourth postnatal week (Barlow and Pettigrew, 1971; Pettigrew, 1974), and still others reported that, around the end of the first postnatal week, at or before eye opening, about 25–30% of V1 cells are orientation-selective (Imbert and Buisseret, 1975; Blakemore and Van Sluysers, 1975; Buisseret and Imbert, 1976; Frégnac and Imbert, 1978; Albus and

Wolf, 1984). There is more general consensus that at 4 weeks of age in cats, the distribution of orientation selectivity is adult-like (Pettigrew, 1974; Blakemore and Van Sluysers, 1975).

These discrepancies can be attributed, at least in part, to the immaturity of the visual cortex in very young kittens, whose cells are poorly responsive to visual stimulation and habituate rapidly (Hubel and Wiesel, 1963b), making it difficult to characterize their receptive field properties (see also Chapman and Stryker, 1993, for a discussion of this point). Knowing the timing of emergence of orientation selectivity is crucial for studies addressing the role of visual experience in the specification of cortical receptive fields.

More recently, ferrets have been used to address this issue. Ferrets, whose visual system is very similar to that of cats (Law *et al.*, 1988), are born approximately 3 weeks earlier in development (Linden *et al.*, 1981). Visual cortex in the ferret is thus more accessible to early developmental studies and manipulations, and the animal is also a more stable physiological preparation at the time orientation selectivity develops. In ferret V1, visual responsivity can first be demonstrated by single cell extracellular recordings at P23. At this age, and up to P35, approximately 25% of V1 neurons in all cortical layers show orientation selectivity (Chapman and Stryker, 1993). Orientation selective responses gradually increase over the following two postnatal weeks, becoming adult-like first in layers 2–3, then in layer 6, while remaining poor in layer 4, as in adult ferrets. By P43–49 orientation selectivity has reached full maturation, being present in 75% of cells. Thus, in the ferret, orientation-specific responses first appear before the time of natural eye opening (P30–32), and then gradually mature after the onset of visual experience.

Chronic optical imaging of intrinsic signals, at different developmental ages in the same animal, has revealed that orientation maps first appear in the ferret between P31 and P36, i.e. around and soon after the time of natural eye opening, and acquire adult-like properties around P41–42. Early maps are low-contrast, show broad orientation tuning, and often, but not in all animals, are stronger for horizontal and vertical orientations (Chapman *et al.*, 1996; Chapman and Bonhoeffer, 1998). A remarkable characteristic of orientation maps is their stability over development: the earliest imaged orientation domains have the same size, shape and orientation preference as those in adult maps, but orientation tuning gets stronger with age. Thus, the time course of orientation map maturation parallels that of orientation selectivity in single cells, but lags slightly behind, possibly because optical imaging cannot reveal the early orientation-selective responses present in a minority of poorly responsive cells. Similar results have been obtained by optical imaging experiments in primary visual cortex of cats: orientation maps appear as early as P12 in V1 (Crair *et al.*, 1998), and P17 in area 18 (Gödecke *et al.*, 1997), i.e. just after eye opening, and show remarkable similarity to the adult maps, which appear around P30 (Gödecke *et al.*, 1997). The maps in young kittens are overall less selective for orientation than the adult maps, as in young ferrets. At least in kittens, the early maps from the ipsilateral eye are less selective than those from the contralateral eye. Orientation maps as well as single cell responses from the two eyes become equally selective around P21 (Crair *et al.*, 1998). Recent acute optical imaging studies in young postnatal monkeys have shown that orientation maps are already adult-like at the age of three and a half weeks (the

earliest age examined), and show many of the organizational features present in the adult maps (Blasdel *et al.*, 1995).

The stability of the orientation map layout over development is in marked contrast to the significant remodeling of thalamocortical and intrinsic V1 horizontal connections (see below) occurring over the same developmental period. This observation has led some to hypothesize that orientation preference might be a primary organizing feature of V1 development (Chapman *et al.*, 1996; Gödecke *et al.*, 1997; Crair *et al.*, 1997). However, the size, location and periodicity of orientation domains appear to remain stable over a time period when the cortical surface of area V1 is increasing (Purves and La Mantia, 1993). This suggests that new domains must be added as the cortex expands, and that orientation maps might not be as stable as they may seem during the course of development but rather must undergo some rearrangement (Blasdel *et al.*, 1995).

The presence of orientation-selective responses before eye opening in cats and ferrets, and of orientation maps around the time of natural eye opening in all species examined, suggests that visual experience is not required for the initial generation of orientation-selectivity in single cells, nor for the initial formation of orientation columns and maps. Spontaneous activity before the onset of vision could drive these initial developmental events. However, visual experience might be necessary for the later refinement of orientation selectivity and maps, since their maturation occurs after the onset of vision.

2.2. Role of visual experience

The role of visual experience in the development of orientation selectivity in single cells of cat primary visual cortex has been subject to dispute. Again, discrepancies could be explained by the immaturity and low responsivity of the kitten's visual cortex. The majority of visual deprivation studies in the cat have demonstrated an influence of sensory experience on the development of the tuning properties of single cells in V1. However, the severity of the effects of binocular deprivation appears to be a function of the length of deprivation. Short-term binocular deprivation has been reported to have no effects on the development of orientation selectivity (Sherk and Stryker, 1976; Braastad and Heggelund, 1985), but according to others, it reduces the number of orientation-selective cells to that seen in immature kittens (Pettigrew, 1974). Although discrepant, these and other studies suggest that at least some cortical neurons can develop normal orientation selectivity following short-term visual deprivation (see Frégnac and Imbert, 1984 for a review). There is more consensus that prolonged binocular deprivation leads to a progressive deterioration of specific receptive field properties (Frégnac and Imbert, 1978; Imbert and Buisseret, 1975; Mower *et al.*, 1981), and in the case of binocular closure, also to an increase in the number of unresponsive cells (Wiesel and Hubel, 1965; Watkins *et al.*, 1978; Mower *et al.*, 1981). Nevertheless, neurons remain organized in columns and at least broadly tuned for orientation (Blakemore and Van Sluyters, 1975; Buisseret and Imbert, 1976; Leventhal and Hirsch, 1977; Stryker *et al.*, 1978). Similarly, monocular deprivation dramatically reduces orientation-selective responses in cells driven by the deprived eye (Wiesel and Hubel, 1963; Imbert and Buisseret, 1975), but even after prolonged MD, at least layer 4 of V1, responses to the closed eye, although weaker, are present and some

are clearly orientation selective (Shatz and Stryker, 1978; Sherman and Spear, 1982; Mower *et al.*, 1985).

More recent single cell recording studies in the ferret have demonstrated that short-term binocular suture affects the development of orientation selectivity by impairing the maturation of orientation-selective responses in layers 2–3 and 6 (but not in layer 4): 50% of the cells in these layers develop normal orientation selectivity versus 25% in normal 4–5 week-old animals, and 75% in normal adults (Chapman and Stryker, 1993). Thus, in short-term binocularly deprived ferrets, orientation-selective responses are not abolished and can mature to some extent, but cannot reach full maturation.

A long series of controversial experiments begun in the 70's have attempted to investigate the role of visual experience on the organization and selectivity of visual cortical receptive fields. These studies have adopted more selective and less severe methods of deprivation, by rearing kittens in restricted visual environments. These data have been reviewed in detail elsewhere (Movshon and Kiorpes, 1990) and will be only briefly discussed here.

The initial reports on the effects of restricting pattern vision claimed a role for visual experience in specifying cortical orientation preference, by showing that the distribution of orientation preferences in V1 can be shifted towards the experienced orientation, and that orientations orthogonal to the experienced one do not develop (Blakemore and Cooper, 1970). These results could not be replicated by Stryker and Sherk (1975), who found that the same rearing paradigm as that of Blakemore and Cooper (1970) has no effect on cortical orientation preferences. The controversy was partly settled by a subsequent series of studies supporting the conclusion that orientation preference can be biased. These studies, however, also demonstrated that in V1 of kittens reared with exposure to restricted orientation patterns, many cells are unresponsive or abnormally responsive to visual stimulation (Hirsch and Spinelli, 1970; Stryker *et al.*, 1978), suggesting a passive loss of responses to the non-experienced orientations rather than an active modification of cells' orientation preferences towards the experienced orientation. Thus, these experiments support a permissive rather than instructive role for visual experience in the development of orientation selective responses. Whereas all the above studies used single-neuron recordings, which are subject to the problem of sampling bias, studies employing methods that allow experimenters to gather information from a large number of neurons, such as 2-deoxyglucose labeling (Rauschecker and Singer, 1981; Singer *et al.*, 1981) and more recently optical imaging of intrinsic signals (Sengpiel *et al.*, 1999), support an instructive role for visual experience in development of orientation selectivity. These studies found that cortical columns devoted to the experienced orientations expand relative to those subserving the non-experienced orientations – a result reminiscent of the effects of monocular deprivation on ocular dominance column development. Importantly, however, optical imaging reveals that over half of the visual cortex shows a preference for orientations never experienced by the animal, indicating again that visual experience is not the only determinant of cortical orientation selectivity (Sengpiel *et al.*, 1999).

Overall, these developmental, visual deprivation and selective-rearing studies together suggest that the early development of orientation selectivity is independent of visual experience, because it normally occurs prior to the onset of vision and is not affected by binocular or monocular deprivation. They also suggest that normal visual

perience is required for orientation preference and selectivity to achieve their normal adult distribution, because their maturation normally occurs after the onset of vision, is impaired by binocular deprivation, and is biased by selective manipulations of pattern vision. Early experience can instruct local modifications of orientation selectivity.

Whereas the tuning properties of single V1 neurons can be altered by visual experience during the critical period of development, the organization of receptive field properties into an orderly map of orientation preference does not seem to be affected by early manipulations of the visual environment. In cat area 18, short-term ocular suture does not alter the orderly arrangement of orientation columns revealed by optical recording of intrinsic signals (Gödecke *et al.*, 1997; Crair *et al.*, 1998), even though it impairs maturation of selectivity in single cells. The spacing of orientation domains, as well as the contrast (differential orientation-dependent values) of the orientation maps in kittens deprived of vision until P24, are comparable to those seen in age-matched normally reared kittens. However, if binocular suture is maintained beyond the third week of life, the selectivity of the orientation maps begins to deteriorate, so that by the seventh postnatal week maps are weak and poorly selective, and the maps from the ipsilateral eye never increase in selectivity to equal those from the contralateral eye (Crair *et al.*, 1998). These data suggest that, although visual experience is required for maintenance of orientation selectivity, the initial layout of orientation maps is determined by experience-independent mechanisms. This conclusion is further supported by a recent study by Kim and Bonhoeffer (1994). Using optical recording of intrinsic signals in cat area 18, these authors have shown that monocular lid suture for about one week at P33–40, after orientation maps have already formed, disrupts the map from the closed eye, and that reverse lid suture restores the map precisely in the initially deprived eye. These data indicate that visual experience does not alter the layout of maps, and suggest that a scaffold for the orientation map might be intrinsic to the cortex.

However, several considerations suggest caution in the interpretation of these results. First, it is worth noting that these data were obtained in cat area 18, and cannot be easily extended to area 17, from which most other developmental and plasticity data have been obtained. We have seen above that binocular deprivation reduces ocular dominance band segregation in cat area 17, but not in area 18 (Mower *et al.*, 1985; Malone, 1988). Thus, different mechanisms might operate in the development and plasticity of these two visual areas. Second, in the study by Kim and Bonhoeffer, both monocular and reverse suture were performed after orientation maps had formed. Single cell recordings (Shatz and Stryker, 1978; Kossut and Singer, 1991), anatomical (Antonini and Singer, 1993b, 1996), and more recently, optical imaging data (Crair *et al.*, 1997) have shown that, although weaker, anatomical and functional synaptic connections from the initially deprived eye persist in MD cats. These weakened connections might be sufficient to guide the establishment of new connections from the initially closed eye in a manner similar to the original map. However, Gödecke and Bonhoeffer (1996) have shown that matching orientation maps develop for the two eyes in cats raised under a reverse-suture paradigm from before the time of natural eye opening, so that the two eyes never had monocular visual experience. This result further suggests that the layout of maps is innately specified. As an alternative explanation to prespecification of map layout, it has been

argued that these data are also consistent with the hypothesis that the constraints imposed by the geometry of the cortical target region upon a simple self-organizing algorithm might be such that maps form and re-form in a consistent way (Wolf *et al.*, 1996). Crair *et al.* (1998) have recently demonstrated that orientation maps from the two eyes are already similar when maps can first be recorded in cat V1 (at P12), that maps become increasingly similar during the first 3 weeks of life, and that identical maps develop for the two eyes in animals deprived of pattern vision up to 3 weeks postnatally. These data support the conclusion that pattern vision is not required to establish the position and arrangement of orientation columns in V1. However, if binocular suture is prolonged beyond 3 weeks of age, the two eyes' maps become increasingly dissimilar, suggesting that visual experience is essential for maintaining matching maps from the two eyes (Crair *et al.*, 1998).

2.2.3. Role of spontaneous neural activity

Manipulations of visual experience do not disrupt the initial emergence of orientation selective responses in single V1 neurons, nor do they alter the layout of maps. Could spontaneous activity, before eye opening, instruct the formation of orientation selectivity and maps?

Blockade of cortical pre- and postsynaptic activity by continuous infusion of TTX for 25 days in area 17 of 21 day-old ferrets, just before orientation-selective responses can be detected in single cells and about ten days prior to the appearance of optical orientation maps, freezes orientation selectivity in an immature state. In TTX-treated animals the distribution of orientation selectivity resembles that in normal 4–5 week old ferrets, being present in only 25% of V1 cells (Chapman and Stryker, 1993). Thus, it appears that cortical neural activity is required to trigger maturation of orientation selectivity, but is not sufficient to drive its initial emergence. Since maturation of orientation selective responses from an initially immature state normally begins after the time of natural eye opening, visually-driven activity is likely to mediate this activity-dependent developmental event. Disruption of orientation selectivity by TTX is more severe than that caused by binocular lid suture (see above), suggesting that experience-independent activity can induce at least partial maturation of selective responses, but visual experience is required to bring development to completion. It is, however, conceivable that the early emergence of orientation selectivity could have been prevented had blockade of neural activity been initiated at earlier developmental ages.

2.3. Development and Plasticity of Intrinsic Long-range Horizontal Connections

A prominent characteristic of the neocortex of carnivores and primates is the existence of intralaminar long-range, lattice-like systems of horizontal connections, which appear to be present within all neocortical areas examined so far (Lund *et al.*, 1993). In primary visual cortex these intrinsic connections are prominent in layers 2–3 (Gilbert and Wiesel, 1983; Rockland and Lund, 1983; Rockland, 1985), arise primarily from excitatory pyramidal neurons (Gilbert and Wiesel, 1979; Rockland and Lund, 1983; Martin and Whitteridge, 1984), and form periodic patches of terminals which

repeat in the tangential domain for several millimeters from the cell body. These connections are reciprocal, and link preferentially cortical columns sharing a similar orientation preference (Ts'o *et al.*, 1986; Gilbert and Wiesel, 1989; Malach *et al.*, 1993; Veliky and Katz, 1994; Sharma *et al.*, 1995; Weliky *et al.*, 1995).

Although, the precise functional role of these cortical circuits remains to be determined, the link between horizontal connections and orientation columns has raised interesting questions about the relative timing of development of these two systems: the emergence and maturation of one system before the other might imply a primacy and guiding role of one in the development of the other.

3.1. Development of horizontal connections

The development of intrinsic horizontal connections in the primary visual cortex of cats has been examined in several studies. Although there is general consensus that the adult pattern of clustered connections emerges after the first week of life from an initially diffuse pattern, different studies disagree on the time course and degree of refinement of clusters after this initial stage.

Whereas Lübke and Albus (1992) have reported that intrinsic V1 connections in cats, labeled with the lipophilic carbocyanine dye Dil, refine rapidly, becoming patchy and adult-like by the end of the second postnatal week, all the other studies have observed a much slower and progressive maturation of these connections to the adult clustered pattern, passing through a crudely organized stage of development. According to the latter studies, crude clusters first emerge between P8–P12 (Callaway and Katz, 1990; Luhmann *et al.*, 1990; Galuske and Singer, 1996), i.e. at, or just before the time of natural eye opening, a time when only a few neurons have acquired orientation selectivity. Subsequently, up to the end of the fourth postnatal week (Callaway and Katz, 1990, 1991) or up to the eighth postnatal week (Luhmann *et al.*, 1990; Galuske and Singer, 1996), crude clusters are progressively refined to the adult-like pattern. There is some controversy over the process of cluster refinement. Single injections of WGA-HRP in different animals at different developmental ages reveal that number, spacing and tangential extent of clusters all increase steadily during the first three postnatal weeks, until the most distal clusters are up to 10 mm from the injection site; thereafter and up to the eighth postnatal week, the number and tangential extent of clusters progressively decline to adult levels (~ 3 mm from the injection site), with a consequent increase in cluster spacing (Luhmann *et al.*, 1990). Using more sensitive tracers and smaller injection sites, other studies have not confirmed an initial exuberance in the tangential extent, spacing and number of clusters, but rather have observed a progressive change in the size and sharpening of clusters. Callaway and Katz (1990), using small injections of two different retrograde tracers (latex microspheres with different fluorophores) in the same animal and location, at two different developmental ages, have shown that the number, location, periodicity and tangential extent of clusters are already adult-like at P12; thereafter and up to the end of the fourth postnatal week clusters become progressively smaller and sharper, and the number of retrogradely-labeled cells between clusters decreases via a process of selective elimination of collateral branches. Using the anterograde and retrograde diffusion of Dil from a single cortical locus at different ages, Galuske and Singer (1996) have shown that after the initial emergence of crude clusters around P12, subsequent devel-

opmental events involve a progressive tangential elongation of lateral connections, and the sharpening of clusters, both of which are completed around the end of the fourth postnatal week; over the following 3–4 weeks of life, patches become more uniform in size. Like Callaway and Katz, they also report that by P12 the periodicity of clusters (~1 mm) is already adult-like.

Despite these issues, likely due to methodological differences, it is clear that in the cat the time course of development of horizontal connections parallels that of orientation selectivity in single cells. Crude clusters appear around the time of natural eye opening, when orientation selective responses can first be recorded in 20–30% of V1 cells, and the progressive refinement of clusters occurs over the same time period of maturation of orientation selectivity and maps. The stability of cluster location and periodicity over development is also consistent with the observed stability in location, size and orientation preference of optically-imaged iso-orientation domains. Clusters however change in size over development, whereas iso-orientation domains do not. Again, expansion of the cortex over the course of development without changes in cluster spacing suggests that new clusters are added while existing ones shift their location (see also above).

Studies in the ferret have been more consistent in showing that the development of horizontal connections in this species follows a similar pattern as that in the cat. In ferrets however, crude clusters appear earlier relative to the time of eye opening, and get refined more rapidly, taking overall 1–2 weeks less than in the cat to reach maturation. Crude clusters are first detected around P27–28 in the ferret, before eye opening (P30–32), when only 25% of V1 cells show orientation selectivity, suggesting a role for spontaneous activity in initial cluster formation. Like in the cat, cluster refinement occurs after the onset of vision, concomitant with the maturation of orientation selectivity and maps, being completed around P41, and involves the selective elimination of misplaced long unbranched collaterals as well as the addition of new collateral branches within clusters (Durack and Katz, 1996; Ruthazer and Stryker, 1996). Importantly, some orientation-selective responses in ferret V1 appear as early as P23 (Chapman and Stryker, 1993; see above), a time when layer 2–3 cells have just completed their migration to the cortical plate, and only few long, unbranched and unclustered lateral connections have formed (Durack and Katz, 1996; Ruthazer and Stryker, 1996), but have not yet established functional synapses (Dalva and Katz, 1994; Nelson and Katz, 1995).

More recently, anatomical studies in the fetal monkey have shown that, as in cats and ferrets, the development of intrinsic V1 connections shows a transition from an initially continuous pattern to an adult-like patchy pattern. However, in primates these projections reach full maturation before birth (and thus entirely before the onset of vision), right around the time when LGN axons begin to segregate into ocular dominance bands in layer 4 (Coogan and Van Essen, 1996). The relationship between the emergence of orientation selectivity relative to the development of intrinsic horizontal connections has not been investigated in this species, but orientation selectivity as well as orientation maps are already well developed at birth (see above).

Thus, certainly in ferrets, and likely in cats and primates, the initial emergence of orientation selectivity in single neurons precedes that of crudely clustered horizontal connections. Theoretical and experimental studies on the mechanisms and circuitry

that might underlie the generation of orientation selectivity in adult visual cortex have suggested that poor orientation tuning in layer 4 of V1 might arise from the receptive field alignment of LGN inputs (Hubel and Wiesel, 1962; Chapman *et al.*, 1991; Forgotter and Koch, 1991; Reid and Alonso, 1995; Ferster *et al.*, 1996), and one among the various functions proposed for horizontal connections is the sharpening of orientation tuning (Eysel *et al.*, 1987; Eysel and Crook, 1990). In view of these studies, one possible scenario is that the initial emergence of poor orientation selectivity in V1 is generated by the afferent inputs, under the influence of retinal spontaneous activity (Miller 1992, 1994; Miyashita and Tanaka, 1992). The constancy of the earliest orientation preference maps, however, is in marked contrast to the dramatic remodeling of LGN afferent arbors taking place over the period when orientation selectivity and maps mature, presumably altering the geniculate inputs to a given orientation column. It is, thus, possible that the initial orientation selectivity is generated by mechanisms intrinsic to the cortex, and is not due to thalamocortical afferents. Whether the intrinsic cortical mechanisms involve neural activity or are activity-independent is not known, and could be tested by intracortical infusion of TTX in ferrets at earlier developmental ages than those examined by Chapman and Stryker (1993). However generated, this initial orientation selectivity might already be organized into functional columns, as suggested by previous electrophysiological studies (Blakemore and Vanuytters, 1975; Frégnac and Imbert, 1978; Albus and Wolf, 1984), and might guide the initial emergence of crude clusters in the horizontal connections; as crude clustered connections between iso-orientation columns begin to emerge, they might trigger an increase and sharpening of orientation tuning which, in turn, could induce further refinement of clusters. Data on the effects of cortical activity blockade upon development of horizontal connections and orientation selectivity are consistent with this hypothesis (see below).

3.2. Role of spontaneous and visually-guided neural activity

Similar to the development of thalamocortical connections, ocular dominance and orientation selectivity, the development of horizontal connections requires neural activity, both spontaneously generated and visually guided.

Binocular deprivation disrupts the late refinement of clusters by preventing the selective elimination of misplaced collaterals, but not the addition of new collaterals. Thus axonal growth and arborization is not prevented by visual deprivation, but selective growth is all away and Katz, 1991). The initial formation of crude clustering is, however, not disrupted by lack of visual experience and might be driven by spontaneous neural activity. Indeed, intracortical infusion of TTX in ferrets at P21, before the appearance of clustered connections, and before orientation-selective responses can be recorded from single cells, disrupts formation of early clustering (Ruthazer and Stryker, 1996). Thus, spontaneously generated neural activity is required for the early patterning of intrinsic connections, but once binocular enucleation at P21 in ferrets does not prevent cluster formation (Ruthazer and Stryker, 1996), it is spontaneous activity within the cortex or in the thalamocortical loop (Weliky and Katz, 1999), rather than in the retina, that guides the development of horizontal connections.

The effects of cortical activity blockade upon development of orientation selectivity and horizontal connections are consistent with a guiding role of orientation selectivity upon the development of these connections, as also suggested by developmental studies (see above). We have seen that infusion of TTX in ferret V1 at P21 prevents cluster formation, but not the initial emergence of orientation selectivity in single cells. If development of clustered horizontal connections were to guide that of orientation selectivity, then the early appearance of clusters should precede, or be concomitant to that of orientation selectivity, and disruption of clustered projections by TTX should prevent the emergence of early orientation selective responses. Because these predictions are not met by the available data, the hypothesis that the development of orientation selectivity reflects and is guided by that of intrinsic intralaminar connections does not appear to be tenable.

Whereas cortical activity blockade prevents the emergence of clustered long-range intrinsic V1 connections, similar manipulations of cortical activity seem to affect much less the patterning of intracortical connections in layer 4 of rat somatosensory cortex (Rhoades *et al.*, 1996). Several lines of evidence indicate that the development and plasticity of the barrel cortex of rodents differ in many aspects from those of the visual cortex of carnivores and primates, suggesting that different mechanisms might be involved in the development of these structures. The patchy pattern of thalamocortical projections in rat somatosensory cortex, unlike that in primary visual cortex of higher mammals, is present from its onset (Erzurumlu and Jhaveri, 1990; Schlaggar and O'Leary, 1994); both the thalamocortical and intrinsic horizontal connectivity patterns in barrel cortex are sensitive to disruption only very early in development (Rhoades *et al.*, 1997), and are not affected by intracortical infusion of TTX before their emergence (Chiaia *et al.*, 1992, 1994a; Rhoades *et al.*, 1996; but see Schlaggar *et al.*, 1993, and Fox *et al.*, 1996).

3. ROLE OF PATTERNED AFFERENT ACTIVITY IN THE DEVELOPMENT OF CORTICAL CIRCUITS AND FUNCTIONS

The overall view that has emerged so far is that the development of cortical function and circuitry is the result of a fine interplay between intrinsic/innate and experiential factors. The initial emergence of ocular dominance, orientation selectivity, and of their organization into columns and maps occurs independently of visual experience, but in most cases appears to require spontaneously generated neural activity in the thalamocortical loop or within the cortex itself, prior to the onset of vision. Experience becomes essential later in development, to maintain and refine the responsiveness of cortical neurons, their selectivity, as well as the segregation of functional properties and anatomical connections. Furthermore, early abnormal experience can modify cortical circuitry and function.

But, how does neural activity, either spontaneous or visually driven, influence ocular dominance segregation, clustering of horizontal connections and emergence of selective receptive field properties and functional maps?

The evidence that the developmental rearrangement of cortical connections requires both pre- and postsynaptic activity has led to the hypothesis that a Hebbian rule might govern this process, whereby synaptic connections get strengthened and stabilized

when pre- and postsynaptic neurons are coactive, and weakened or eliminated with lack of coincident activation (Hebb, 1949). Theoretical considerations have suggested that correlated neural activity among sets of afferents, by allowing synchronously active inputs to sum and thus succeed in driving the postsynaptic neuron, might be the mechanism driving the formation of orderly maps and patterned connections (Stent, 1973; von der Malsburg and Willshaw, 1976; Willshaw and von der Malsburg, 1976; Swindale, 1980; Bienenstock *et al.*, 1982; Schmidt, 1985; Miller *et al.*, 1989; Obermayer *et al.*, 1992; Goodhill, 1993). If neighboring cortical cells are further interconnected by local excitatory lateral connections, then inputs that fire together will be more likely to be stabilized on interconnected postsynaptic cells (Willshaw and von der Malsburg, 1976; Goodhill, 1993). According to these models, topographic maps would form because the spatiotemporal patterns of activity in the retina, whether spontaneously generated or visually driven, are such that the correlation in the activities of ganglion cells decreases with distance among cells (Mastrorade, 1983, 1989; Wong *et al.*, 1993). Ocular dominance columns would form because neural activity of cells within the same eye is more highly correlated than that between the two eyes. The formation of ocular dominance patterns would be a compromise between the two competing tendencies of cortical cells to form connections with afferents from neighboring cells in the same eye, and with afferents from corresponding retinal loci in the two eyes (Constantine-Paton, 1983; Goodhill and Löwel, 1995).

Although the experimental studies we have described so far provide incontrovertible evidence that neuronal activity plays a major role in the development of cortical connections and function, at present only a few studies have directly investigated a possible role for the spatiotemporal patterning, rather than the overall level, of activity. Three main experimental paradigms have been used to manipulate the temporal patterns of afferent neural activity: artificial strabismus, artificial stimulation of the optic nerves, and cross-modal plasticity.

3.1. Artificial Strabismus

Strabismus is a condition of misalignment of the two eyes' optical axes, whereby the images on the two retinæ cannot be brought into register. As a result, corresponding retinal loci in the two eyes are no longer correlated, but the total amount of activity that reaches the cortex via each eye is equal, and likely similar to that in normal animals. If artificial strabismus is induced in cats or monkeys by cutting the extraocular muscles of one eye, neurons in V1 become almost exclusively monocular (Hubel and Wiesel, 1965; Baker *et al.*, 1974; Crawford and Von Noorden, 1979, 1980; Van Sluyters and Levitt, 1980; Wiesel, 1982); anatomically, ocular dominance bands become more sharply delineated than in normal animals (Shatz *et al.*, 1977). In addition, it has recently been reported that the periodicity of ocular dominance bands, revealed by the transneuronal transport of intraocularly injected tritiated proline, or by [^{14}C]-2-deoxyglucose autoradiography, is increased in strabismic cats (Löwel, 1994) – a result predicted theoretically (Goodhill 1993; Goodhill and Löwel, 1995). Whereas the spacing of ocular dominance columns has generally been thought to be determined by factors intrinsic to the cortex, such as the width of the lateral connections or

the spread of afferent arbors (von der Malsburg and Willshaw, 1976; von der Malsburg, 1979; Swindale, 1980; Miller *et al.*, 1989), this is the first demonstration that not only ocular dominance column segregation but also the overall layout of the maps is influenced by visual experience, and more precisely, by the temporal patterning of neural activity (Goodhill and Löwel, 1995). A similar, but less pronounced increase in the spacing of ocular dominance bands has been observed in cats raised with alternating monocular exposure, a paradigm that also provides discordant input to the two eyes (Tieman and Tumosa, 1997). However, the observation that, at least in monkeys and humans, there is a high individual variability in the width, pattern and periodicity of ocular dominance bands (Horton *et al.*, 1990; Horton and Hocking 1996b) suggests caution in the interpretation of these results. In addition, recent studies have not confirmed an effect of strabismus on ocular dominance periodicity either in cats (Jones *et al.*, 1996) or monkeys (Murphy *et al.*, 1996). Similarly, the spatial periodicity of another V1 functional pattern, that of the cytochrome oxidase blobs, is also not altered in strabismic monkeys, and thus appears not to be determined by correlated activity in the two eyes (Murphy *et al.*, 1998).

In sum, the data from strabismic cats indicate that when the two eyes receive discordant inputs, cortical binocularity is disrupted, suggesting that the relative timing of activity in the two eyes is used at the cortical level to produce either eye-specific segregation (when the two eyes are activated asynchronously) or binocularity (when the eyes are activated synchronously).

Whereas correlated visual activity in corresponding retinal loci in the two eyes is required to maintain cortical binocularity, and possibly ocular dominance column periodicity (but see above), it does not seem to be necessary to establish the layout of orientation maps. Matching orientation maps develop when the two eyes have never had common visual experience (Gödecke and Bonhoeffer, 1996; see above), and orientation maps are continuous across ocular dominance columns in strabismic cats (Löwel *et al.*, 1994). These data also argue against a role for spontaneous retinal activity in setting up matching orientation maps for the two eyes, since this would require retinal waves to be synchronized between the two eyes. Again, it appears that the layout of orientation maps is intrinsic to the cortex, as might also be the initial emergence of orientation selectivity in single V1 cells. An explanation for the apparent contradiction between experience-dependent plasticity of orientation selectivity in single cells and experience-independent maturation of orientation maps has been proposed by Shouval *et al.* (2000). In their model, horizontal connections in V1 initially form an experience-independent scaffold that determines the orientation map layout and produces broadly tuned cells, and biases the development of orientation selectivity in single neurons. Plastic feedforward connections from the LGN can then provide the experience-dependent component of the orientation map that determines the sharpness of orientation tuning. This model can account for the result of Gödecke and Bonhoeffer (1996), but it does not take into account plasticity of horizontal connections, whose structure in the model is assumed to be rigid and adult-like from the start. Other models, instead, have shown that if the activity of LGN cells from the two eyes is correlated to some extent, but less than activity from the same eye (as demonstrated by Weliky and Katz, 1999), matching orientation maps can develop together with ocular dominance columns (Erwin and Miller, 1998).

In contrast to the formation of orientation maps, a correlation-based mechanism seems to drive the development of horizontal connections. Unlike in normal cats, where clusters of horizontal connections do not align with ocular dominance columns (Hubel and Wiesel, 1989), in strabismic cats the clusters fall in register with these columns: intrinsic long-range lateral connections come to link columns with similar ocular dominance (Löwel and Singer, 1992) and orientation preference (Schmidt *et al.*, 1997). These findings are consistent with the hypothesis that intrinsic horizontal connections are stabilized by correlations in the responses of interconnected neurons.

Artificial Stimulation of the Optic Nerves

Recent experimental evidence that the temporal patterns of activity within and between the two eyes are key factors regulating ocular dominance map development is provided by an experiment in which electric shocks were applied to both optic nerves in kittens, after bilateral blockade of retinal activity with TTX. When both optic nerves were stimulated asynchronously, cortical cells became predominantly monocular, as opposed to synchronous activation which disrupted formation of physiological ocular dominance columns (Stryker and Strickland, 1984). Similarly, synchronizing neural activity within and between the two eyes by stroboscopic illumination disrupts formation of eye-specific stripes in the dually innervated optic tectum of goldfish (Felleman and Schmidt, 1988), as well as the orderly arrangement of the retinotopic map in the ipsilateral eye and its alignment with the topographic map from the contralateral eye in the *Xenopus* frog optic tectum (Brickley *et al.*, 1998). Although these results show a clear role for afferent activity in ocular dominance column development, they might appear to be in conflict with the finding that early binocular enucleation does not prevent ocular dominance band formation (Crowley and Katz, 1999). However, the result by Crowley and Katz (1999) does not rule out a role for spatiotemporal patterns of activity in LGN afferents in generating ocular dominance columns. The result is, in fact, consistent with the observation that in the absence of retinal input, the thalamocortical loop contains degraded correlation-based cues for the regulation of geniculocortical afferents, but these cues are not completely eliminated and might be sufficient to guide the development of ocular dominance columns (Felleman and Katz, 1999).

A crucial role for the temporal patterning of activity, before and just after the time of unilateral eye opening, in the development of orientation and direction selectivity has been recently demonstrated by an experiment in which the normal patterns of spontaneous activity were perturbed during the emergence of the orientation map in the ferret (Weliky and Katz, 1997). Retinal ganglion cells in one optic nerve were synchronously activated by applying 30 Hz biphasic current bursts of 1.8 sec in duration, every 20 sec for 24 hours, from P18–20 until P41–43, although effective activation of optic nerve fibers began around P27–29. The other eye was enucleated at P15–17 to prevent binocular interactions. Natural eye opening was not prevented. Following this manipulation, only 17% of cells in V1 showed orientation and direction selectivity resembling the distribution of orientation selective responses in younger normal animals (Chapman and Stryker, 1993). However, the orientation maps in the stimulated

animals were unaltered compared to normal controls, showing iso-orientation domains of size, spacing and pattern similar to those in normal animals. Direction maps were similarly unaltered by this manipulation. These results suggest that patterned neural activity is not necessary to establish the initial layout of orientation and direction maps, but it is required for single cells to acquire their normal adult receptive field selectivity. However, orientation and direction selective responses were not entirely abolished by this manipulation, perhaps because effective stimulation of the optic nerve was initiated after some orientation selectivity had already emerged in the cortex – leaving open the question of whether the initial emergence of orientation selectivity is also independent of activity and determined by intrinsic factors. Because the distribution of selective responses in the cortex of the stimulated animals resembled that seen in normal immature ferrets, these results are consistent with both the aberrant activity patterns having altered the development of specific receptive fields, as well as having simply arrested their development in the initial immature state. Thus, these data do not provide incontrovertible evidence for an instructive role of patterned neural activity on the initial emergence of specific receptive field properties in visual cortex, because they are also consistent with activity simply playing a role in the refinement of orientation and direction selectivity.

Although these results are consistent with prespecification of the layout of orientation maps, other interpretations are possible. Synchronizing activity in one optic nerve might not have altered the layout of maps because the stimulation protocol was initiated late in development, or/and because it did not disrupt significantly the normal activity patterns. Effective stimulation of the optic nerve fibers was initiated around P27–29, before orientation maps can be detected in normal animals (Chapman *et al.*, 1996), but when some orientation selective responses are already present and might already be organized in a columnar fashion; in addition, spontaneous activity is present very early in development, and thalamic axons have already entered the cortex long before the initiation of the stimulation protocol. Thus, one cannot rule out the possibility that an initial map had already been established, but was perhaps too subtle to be detected by optical recordings. Furthermore, the aberrant activity patterns interfered with the normal patterns of spontaneous and, after eye opening, visual activity for only a small proportion of time (10%), leaving the normal patterns unperturbed 90% of the time. A more disruptive stimulation protocol might have disrupted the layout of maps (see also Goodhill, 1997). Of course, an alternative possibility is that maps are remarkably stable and prespecified by intrinsic factors, a hypothesis also advanced by other studies (see above: Chapman *et al.*, 1996; Kim and Bonhoeffer, 1994; Gödecke and Bonhoeffer, 1996; Crair *et al.*, 1998).

3.3. Cross-modal Plasticity

A different paradigm for investigating the role of patterned afferent activity in the development of cortical circuitry and function has been to experimentally redirect afferents carrying information about one sensory modality to central targets and pathways that normally process a different sensory modality. Such a paradigm allows one to investigate how a

sensory cortical area develops under the influence of afferent inputs whose temporal activity patterns are different from those carried by the normal inputs.

Following the pioneering studies of Schneider (1973), who first demonstrated that in the hamster, after specific neonatal lesions, retinal axons can be induced to innervate nearby inappropriate targets, cross-modal rewiring has been obtained in a number of different preparations and between different sensory modalities (Devor, 1975; Graziadei *et al.*, 1979; Frost, 1981, 1982; Asanuma and Stanfield, 1990). Sur *et al.* (1988) first induced retinal axons to innervate the auditory thalamus in the ferret, a carnivore with a highly developed visual pathway and which is born at a very early stage in development, so that cross-modal plasticity can be induced by neonatal (rather than *in utero*) surgery. At the same time, the cross-modal routing of retinal projections to the auditory pathway can be induced extremely early in development, unlike artificial strabismus or artificial optic nerve stimulation, allowing one to probe the role of patterned activity in the *establishment* (and not simply *maintenance*) of response features and cortical circuitry.

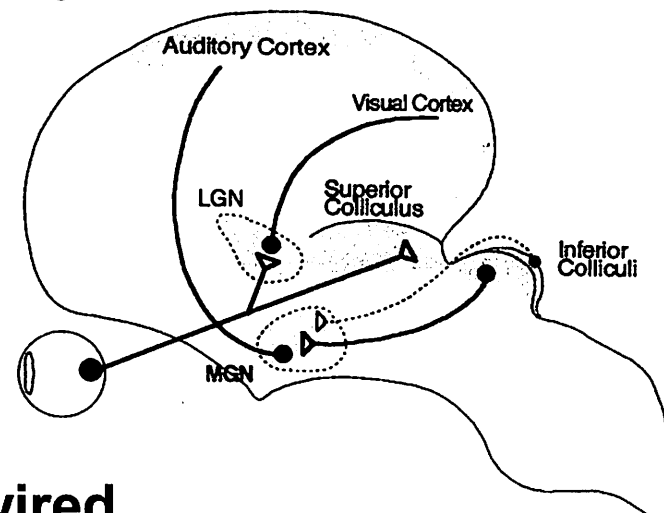
In ferrets, extensive neonatal deafferentation of the auditory thalamus, or medial geniculate nucleus (MGN), induces retinal axons to innervate the MGN (Angelucci *et al.*, 1998; Figure 1). The factors that induce retinal axons to invade a deafferented target are currently under study in our laboratory, and includes downregulation of repulsive molecules such as the ephrins (Lyckman *et al.*, 1999) as well as possible upregulation of attractant molecules or diffusible factors.

The novel retino-MGN projection arises from most, if not all, retinal ganglion cell types, including cells with small somata and fine axons (Roe *et al.*, 1993; Pallas *et al.*, 1994), typical of retinal W cells, but also cells with the largest axon caliber normally encountered in the optic tract, typical of Y cells (Angelucci *et al.*, 1998). Electrophysiological recordings indicate that the novel projection is functional, since cells in the MGN of adult "rewired" ferrets are visually responsive, as are cells in the MGN's main cortical target, the primary auditory cortex or A1 (Sur *et al.*, 1988). Importantly, visual input is relayed from the MGN to auditory cortex via thalamocortical projections that are unaltered anatomically (Fig.1B). Thus, whereas the physical identity of the MGN afferents to auditory cortex is unchanged in this preparation, the spatiotemporal patterns of neural activity reaching auditory cortex via these afferents are very different from normal.

3.3.1. Activity-dependent sorting of retinothalamic projections and thalamocortical synapses

Retinal projections to a novel target, the MGN, provide an ideal paradigm for examining the relative roles of afferents and targets in developmental pattern formation. In normal ferrets, retinal axons segregate into parallel eye-specific layers in the normal target, the lateral geniculate nucleus or LGN (Linden *et al.*, 1981). Moreover, axons from on-center and off-center retinal ganglion cells from each eye further segregate into on and off sublayers within each eye-specific layer (Roe *et al.*, 1989; Hahn *et al.*, 1999; Figure 2A). In contrast, within the ventral division of the normal MGN (MGv) the two cochleae are not represented separately – rather, afferents from the inferior colliculus (IC) form terminal clusters aligned within fibrodendritic lamellae, each lamella representing a narrow range of sound frequencies (Kudo and Niimi, 1980;

A.Normal



B.Rewired

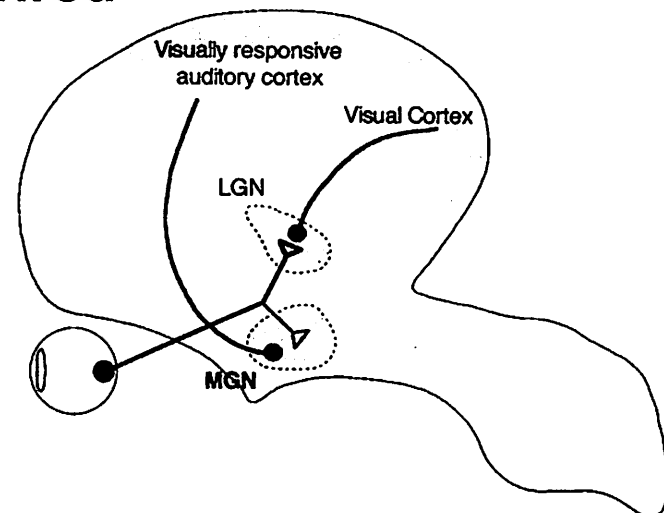
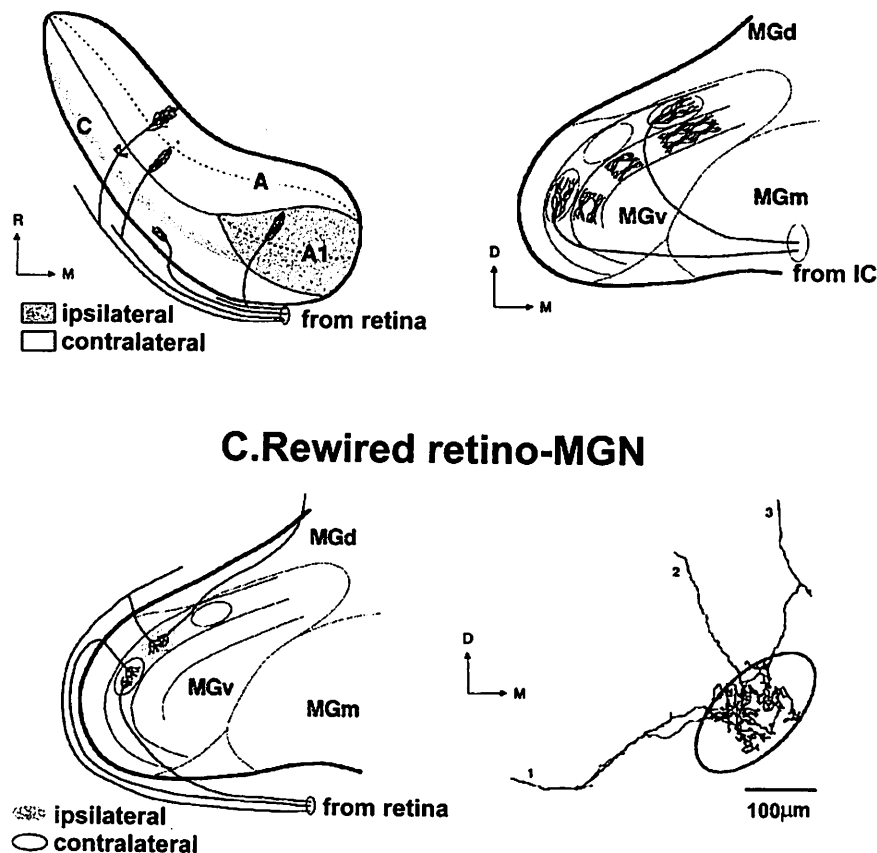


Figure 1 Brain lesions performed in neonatal ferrets to induce "rewiring" of retinal axons to the auditory thalamus. **A:** Visual (blue) and auditory (red) pathways in normal ferrets. The retina projects predominantly to the lateral geniculate nucleus (LGN) and superior colliculus. The LGN, in turn, projects to the primary visual cortex. The medial geniculate nucleus (MGN) receives most of its subcortical afferents from the ipsilateral inferior colliculus, although afferent projections also arise from the contralateral inferior colliculus (red dashed line) as well as from other ipsi- and contralateral brainstem nuclei (not shown). The MGN, in turn, projects to the primary auditory cortex. **B:** Visual (blue) and "rewired" (red) pathways in experimental ferrets. Ablation of the superior and inferior colliculi, together with transection of the brachium of the inferior colliculus, removes most of the subcortical inputs to the MGN, and induces retinal axons to innervate the deafferented MGN. The MGN still projects to the primary auditory cortex, as in normal ferrets, but in "rewired" ferrets it relays visual rather than auditory inputs. Note that the retina in "rewired" ferrets continues to project to the LGN, and the LGN to the visual cortex, as in normal animals. Anterior is to the left, dorsal to the top. Adapted from Angelucci *et al.* (1998).

A. Normal retino-LGN

B. Normal IC-to-MGN



C. Rewired retino-MGN

Figure 2 Terminal patterns of subcortical afferent inputs to the normal ferret LGN and MGN, and to the "rewired" ferret MGN. **A:** Schematic diagram of retino-LGN projections in normal ferrets. The LGN is shown in the horizontal plane. A, A1, C: eye-specific LGN layers. Dashed lines within the A layers delineate the border between the ON and OFF sublayers. Three main types of retinogeniculate axons are schematically depicted: X axons project to the A layers, Y axons to layers A and C, and W axons to the C layers only. **B:** Schematic diagram of the projections from the inferior colliculus (IC) to the ventral division of the MGN (MGv). The MGN is shown in the coronal plane. Afferents from the IC form terminal clusters (ovals) that align within dorsoventrally oriented fibrodendritic lamellae (shown in a lateral lamina). The lamellar pattern in MGv is due to the ordered alignment of its relay neurons, as schematically shown in the medial lamina. **C:** Left. Schematic diagram of retinal projections to the MGv in "rewired" ferrets. Retinal axons form adjacent but non-overlapping eye-specific terminal clusters (ovals) that align along the lamellae (see text). Right. Partial reconstruction of one retinal terminal cluster in the "rewired" MGv. This cluster, as many others in rewired MGN, is formed by the convergence of terminal arbors from several axons. Here we reconstructed only 3 of these axons. MGd, MGm: dorsal and medial division, respectively, of the MGN; D: dorsal; M: medial; R: rostral. Adapted from Angelucci *et al.* (1997).

Winer, 1992; Figure 2B). In the MGN of rewired ferrets, similar to the normal retino-LGN projection, retinal afferents segregate into eye-specific clusters. Eye-specific segregation in the MGN occurs over the first 3 postnatal weeks as a progressive refinement of initially diffuse and overlapped projections from the two eyes. In contrast, similar to the normal IC-to-MGN projection, retinal terminal clusters align within the MGv fibrodendritic lamellae, and the size, shape and orientation of clusters match those of the specific MGv relay cell dendrites (Angelucci *et al.*, 1997; Figure 2C). These data suggest that segregation of retinal axons into eye-specific domains is driven by the specific temporal patterns of spontaneous retinal activity, whereas the size and general layout of the eye-specific domains is determined by the cellular configuration of the target.

Physiologically, MGN in rewired ferrets, like LGN in normal ferrets, contains an orderly retinotopic map (Roe *et al.*, 1991), due to focal terminal arbors of retinal ganglion cell axons within the nucleus (Pallas *et al.*, 1994). Receptive fields of visually-responsive cells within the MGN are monocular and unoriented (Roe *et al.*, 1993), similar to their retinal ganglion cell input.

In rewired A1, the map of visual space, the generation of orientation- and direction-selective responses, and the map of orientation-selective cells, all provide clues to the interaction between afferent activity and the target in shaping cortical circuits. A role for the specific spatiotemporal patterns of afferent activity in the generation of topographic maps is supported by the finding of an orderly two-dimensional retinotopic map in A1 of rewired ferrets (Roe *et al.*, 1990; Figure 3). Such a map is not predicted by the anatomical patterns of MGN-to-A1 projections in rewired ferrets. In normal ferrets, the two-dimensional map of space in V1 is brought about by the orderly progression of receptive fields of cells within this cortical area. Spatially restricted feedforward projections from the LGN are thought to generate receptive fields of V1 cells and to connect, in a point-to-point manner, retinotopic locations in the LGN to corresponding sites in V1 (Figure 4A). By contrast, A1 in normal ferrets contains a topographic representation of a one-dimensional sensory surface (the cochlea), with one axis (the mediolateral) representing an orderly progression of sound frequencies (the tonotopic axis), and the orthogonal axis re-representing the same sound frequency (the isofrequency axis). Anatomically, projections from MGN to A1 are highly divergent and convergent along the isofrequency axis (Andersen *et al.*, 1980; Angelucci *et al.*, 1993; Figure 4B). Such MGN-to-A1 projection patterns are not altered in rewired ferrets, for thalamocortical axons are still highly divergent along the isofrequency axis (Pallas *et al.*, 1990; Angelucci, 1996; Figure 4C). The generation of a two-dimensional topographic map in rewired A1, despite highly convergent and divergent thalamocortical projections, suggests that a correlation-based mechanism operates intracortically to select and strengthen a specific subset of synapses from a broader set available anatomically.

3.3.2. Orientation selectivity and orientation maps in rewired cortex

Most response features of single cells in rewired A1 closely resemble those normally seen in V1, suggesting that similar mechanisms operate in the generation of receptive field properties in the two cortices. In our early work (Sur *et al.*, 1988), responses of neurons in rewired A1 were characterized qualitatively: every cell responded to elec-

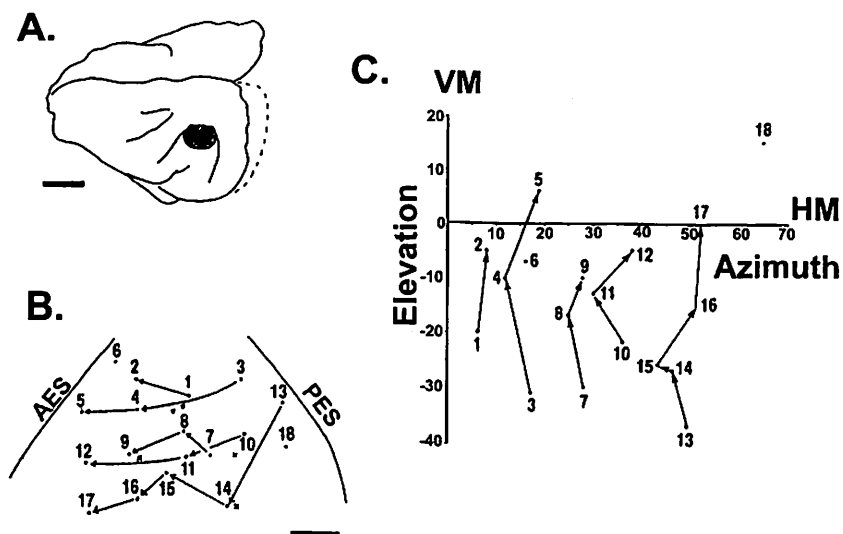


Figure 3 Two-dimensional map of the visual field within primary auditory cortex of a "rewired" ferret. **A:** Diagram of the dorsolateral view of the ferret brain. The *stippled* area indicates the region of A1 that was mapped by extracellular single-unit recordings. The *dashed line* indicates the extent of lesion of area V1 performed at birth in this animal as part of an earlier protocol to induce retinal projections to the MGN. This lesion was not made in a later protocol (see Figure 1 and Angelucci *et al.*, 1998). Scale bar: 5 mm. Anterior is to the left dorsal to the top. **B:** Recording sites within "rewired" A1. X: sites at which visual responses could not be mapped. Anterior is to the left, medial to the top. AES, PES: anterior and posterior ectosylvian sulcus, respectively. Scale bar: 1 mm. **C:** Progression of receptive field centers corresponding to rows of recording sites shown in B. HM: horizontal meridian; VM: vertical meridian. Adapted from Roe *et al.* (1990).

trical stimulation of the optic chiasm and hence received input from retinal axons via the auditory thalamus; two-thirds of these cells were visually driven as judged by audible responses to hand-held stimuli. In a subsequent study (Roe *et al.*, 1992), visual responses in rewired A1 were compared with responses in normal V1: nearly all V1 cells and A1 cells responded to electrical stimulation of the optic chiasm; two-thirds of V1 cells and a somewhat smaller proportion of A1 cells were judged responsive to hand-held stimuli; visual cells in rewired A1 had orientation tuning, direction tuning and velocity tuning indices that were quantitatively indistinguishable from V1 cells. The procedure we now use for routing retinal projections to the auditory thalamus (Angelucci *et al.*, 1998) involves a more complete deafferentation of the MGN, and causes more extensive retinal innervation of the nucleus along with input from a wide range of retinal fiber types. We find that visual responses in rewired A1 are similar to those in V1 in terms of peak and mean firing rates, with no statistical difference between them (Sharma *et al.*, 2000). Furthermore, stimulus-specific modulation of responses, as measured by the orientation and direction selectivity index, is similar in the two regions. Figure 5 shows polar orientation tuning plots of representative cells from similar percentile ranges recorded in normal ferret V1 and rewired A1; furthermore, the cumulative distributions of the orientation selectivity index of cells in the

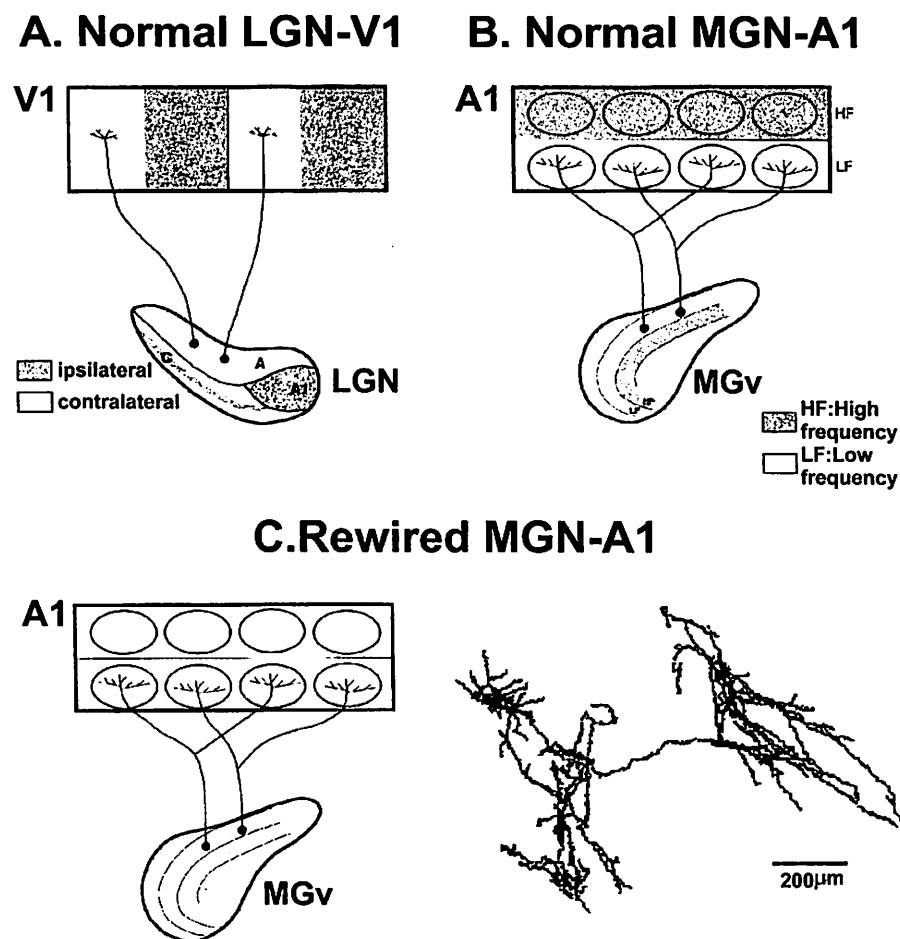


Figure 4 Thalamocortical projection patterns in the visual and auditory pathways of normal ferrets and in the "rewired" pathway of experimental ferrets. **A:** Schematic diagram of the projections from the normal ferret LGN to area V1. Thalamic axons arising from eye-specific LGN layers terminate into the corresponding ocular dominance column in layer 4 of V1. These axons form spatially restricted terminations in V1 and connect corresponding retinotopic locations in LGN and V1. A, A1, C: eye-specific LGN layers. **B:** Schematic diagram of the projections from the normal ferret MGv to area A1. Thalamic axons arising from a small locus in MGv (see Figure 2B) form several terminal patches (ovals) that align along anteroposteriorly oriented slabs in A1. The orientation of these slabs parallels that of the isofrequency contours reported in physiological mapping studies. Isofrequency contours at more medial (top) A1 locations represent progressively higher sound frequencies. Thalamicocortical axons connect slabs of similar frequency tuning in MGN and A1. **C: Left.** Schematic diagram of the projections from the MGN to A1 in "rewired" ferrets. The thalamocortical projection pattern in these animals appears similar to that seen in the normal auditory pathway (B), showing the same degree of divergence. **Right.** Serial section computer reconstruction of a PHA-L immunostained axonal arbor in area A1 of a "rewired" ferret. The axons are seen from a surface view after a 90° angle rotation along the anteroposterior axis of A1; medial is to the top, anterior to the left.

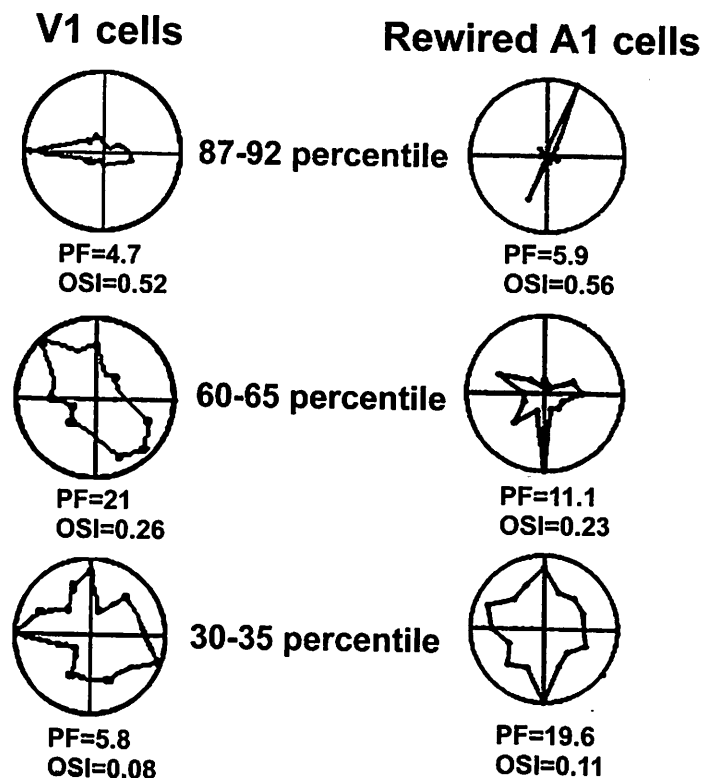
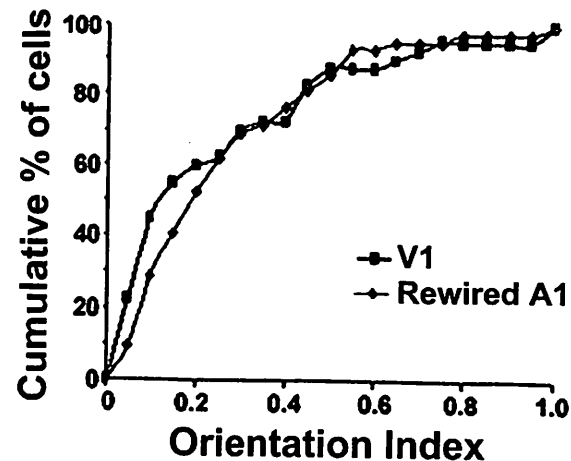


Figure 5 Comparison of single cell responses in normal ferret area V1 and in "rewired" ferret area A1. **Top:** Cumulative distribution of the orientation selectivity index of cells recorded in normal ferret V1 and in "rewired" ferret A1. The orientation selectivity index (OSI) was calculated as the second Fourier transform of spike responses, and scaled from 0 to 1. The orientation selectivity index of cells is very similar in V1 and "rewired" A1. **Bottom:** Polar plots of representative cells recorded in V1 (left) and in "rewired" A1 (right). PF: peak firing rate at the preferred orientation.

two cortices are indistinguishable. The direction selectivity of cells in rewired A1 and V1 are also very similar (Sharma *et al.*, 2000). Similar qualitative results have been obtained in somatosensory cortex of hamsters raised with experimentally-induced retinal projections to the somatosensory thalamus (Frost and Métin, 1985; Métin and Frost, 1989).

The finding that orientation- and direction-selectivity develop in auditory cortex under the influence of visual input strongly supports an instructive role for patterned afferent activity in the emergence of these functional receptive field properties. In addition, this is the first demonstration that the *initial establishment* of orientation selective responses in cortex is dependent on neural activity. In these experiments, visual activity is routed to auditory cortex at a much earlier stage of cortical development than in any previous study, i.e. at a time when thalamocortical axons have not yet invaded the cortical plate (Sur *et al.*, 1999). An alternative hypothesis to afferent-driven specification of cortical receptive field properties is that there might be basic processing modules in all sensory cortices that generate similar transformations on their inputs, regardless of modality. According to this view, direction- or orientation-selectivity would not be induced by specific patterns of afferent activity, but rather would constitute intrinsic and ubiquitous cortical properties (Sur *et al.*, 1990). However, the map of visual space created within rewired A1 (described above), and the map of orientation-selective cells in rewired A1 (described below) argue against this possibility.

Optical imaging of intrinsic signals in A1 of rewired ferrets reveals that orientation tuned neurons are organized into an orientation map (Sharma *et al.*, 2000; Figure 6). Similar to the map in V1, the map in rewired A1 shows a systematic distribution of orientation domains around singularities in a pinwheel-like fashion (Figure 6A,B). In addition, the strength of orientation tuning of pixels across the imaged regions is nearly identical in the two cortices (Figure 6C), resembling the orientation tuning of single cells. However, there are two differences between the orientation maps in rewired A1 and those in V1: orientation domains within V1 are smaller in size and they show a highly regular, spatially periodic organization (Rao *et al.*, 1997), while the domains in rewired A1 are larger (Figure 6D) and are organized much less periodically than in V1 (Figure 6E). Sharp orientation tuning (Figures 5, 6C) coupled with a less orderly map (Figure 6A,E) in rewired A1, indicate that these two cortical features can develop independently of each other. A result complementary to this is provided by artificial stimulation of the optic nerve in ferrets, which leads to poor orientation tuning in single cells, but a "normal" orientation map (Weliky and Katz, 1997).

We examined the possibility that differences in the layout of the orientation maps in V1 and rewired A1 reflect differences in the underlying organization of long-range horizontal connections in these two cortices (Sharma *et al.*, 2000; Figure 7). Focal injections of the anatomical tracer cholera toxin B in the superficial layers of ferret V1 result in a spatially periodic and anisotropic distribution of patches of retrogradely labeled cells, with the cells distributed mediolaterally along an axis parallel to the V1/V2 border (Figure 7A). In contrast, retrogradely labeled cells in normal A1 show a more band-like organization, little spatial periodicity and an anisotropic distribution along the isofrequency (anteroposterior) axis (Figure 7B). Horizontal connections in rewired A1 show features that are intermediate between V1 and normal A1. As in V1,

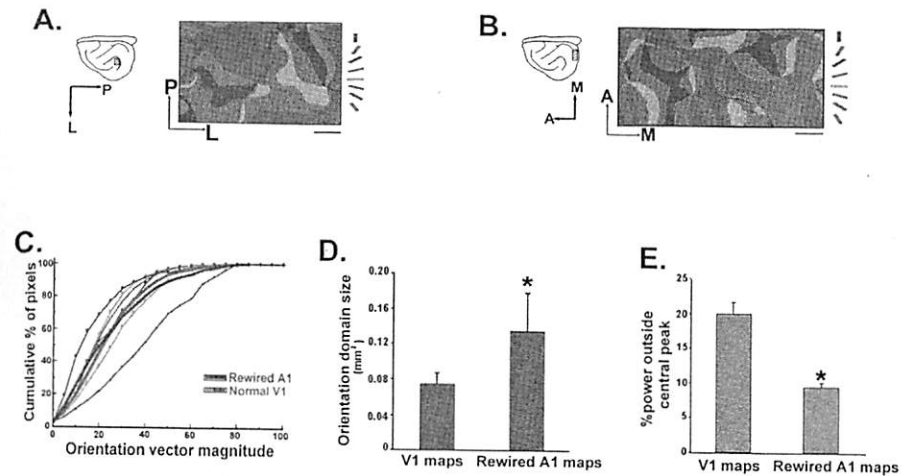


Figure 6 Comparison of orientation maps in normal ferret V1 and in "rewired" ferret A1. **A:** Orientation map in "rewired" A1. **Left.** Lateral view of the ferret brain showing *crosshatched* the location of the imaged region. **Right.** Composite map of the angle of orientation preference obtained by computing a vector average at each pixel of the responses to stimuli of eight different orientations. The orientation map shows a few singularities around which the different orientation domains are arrayed. The number of singularities is lower and the orientation domains are larger than in the V1 map (compare with B). **Color bar:** key used for representing different orientations; L: lateral; P: posterior. Scale bar: 0.5 mm. **B:** Orientation map in normal V1. **Left.** As in (A). **Right.** Angle map obtained in similar fashion as the map shown in (A). Single orientation domains are organized in a quasi-periodic fashion, and different domains are arranged in pinwheel-like fashion around singularities. A: anterior; M: medial. Scale bar: 0.5 mm. **C:** Cumulative distributions of the magnitude of the orientation vector of pixels in V1 (blue; $n = 3$) and "rewired" A1 (red; $n = 4$) maps. Light thin traces indicate individual cases, thick traces indicate means. The orientation vector magnitudes represent the strength of orientation tuning in cortex and were calculated by vector averaging at each pixel the signal values to eight different orientations. **D:** Size of orientation domains in V1 and "rewired" A1. The domains in "rewired" A1 are significantly larger than in V1. **E:** Histogram comparing the % power at non-zero spatial frequencies in V1 and "rewired" A1 maps. The periodicity of the orientation maps was quantified by computing a 2-dimensional autocorrelation function of individual single orientation maps, followed by computation of the power spectrum by Fourier transform of the autocorrelation. An aperiodic map would show a peak at zero spatial frequency in the power spectrum (corresponding to the mean power in the autocorrelation) and low, broadly distributed, power at other spatial frequencies. The map in "rewired" A1 is organized less periodically than the V1 map, for it shows less power at non-zero spatial frequencies. Adapted from Sharma *et al.* (2000).

retrogradely labeled cells in rewired A1 form patches that are distributed anisotropically along the mediolateral axis (i.e. orthogonal to the anisotropy axis of connections in normal A1; Figure 7C). However, in rewired A1, the patches are less tightly clustered and are larger in size than in V1 – but are smaller than patches in normal A1. Furthermore, the spatial distribution of patches is less periodic than in V1, but more so than in normal A1 (Figure 7D). Thus, horizontal connections within rewired cortex are altered by visual input, but in a manner that is constrained by intrinsic features of the auditory cortex.

Together, these data indicate that the development of orientation tuning in single cells is dependent on afferent activity, and is separable from the organization of these

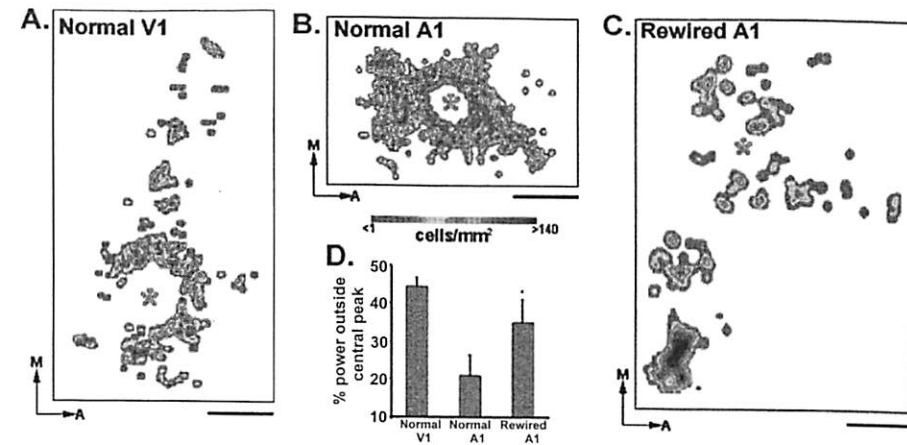


Figure 7 Patterns of horizontal connections in the upper layers of normal ferret V1 and A1 and of "rewired" ferret A1. **A-C:** Composite anatomical maps showing the cell density distributions in the 3 different cortices. **Color bar underneath B:** cell density ranging from <1 cell/mm² to >140 cells/mm², and applies to A and C. **Asterisks** indicate injection site centers. A: anterior; M: medial. Scale bars: 500 μ m. **D:** Histogram comparing the % power at non-zero spatial frequencies in anatomical maps of horizontal connections in V1, normal A1 and "rewired" A1. The periodicity of the connections was quantified as described in figure legend 6E. The power at non-zero spatial frequencies is significantly higher in "rewired" A1 compared to normal A1, indicating more periodic horizontal connection in the former. Adapted from Sharma *et al.* (2000).

cells into an orientation map. These data are also consistent with the observation that in certain adult mammalian species such as the rat, cells in primary visual cortex are well tuned for orientation but are not organized in a columnar fashion, nor into an orderly map (Girman *et al.*, 1999). The orientation map in V1 might arise by the clustering of horizontal connections which preferentially come to link domains of similar orientation preference (Bosking *et al.*, 1997). Consistent with this hypothesis, long-range intrinsic connections are not present in rat primary visual cortex (Tyler *et al.*, 1998). In cats, even with late manipulations of activity, horizontal connections are seen to be not a static feature of cortex – rather, they can be subtly altered by manipulations of afferent activity (Callaway and Katz, 1991; Löwel and Singer, 1992; Schmidt *et al.*, 1997). Our experiments with very early routing of visual activity to auditory cortex in ferrets show categorically that the pattern of thalamocortical activity can significantly shape horizontal connections and create an orientation map.

3.3.3. Visual behavior mediated by the rewired pathway

Rewired ferrets also provide a unique opportunity for examining a fundamental question about the perceptual modality of a cortical area: Is the behavioral role of a cortical region set by intrinsic determinants or by the pattern of afferent activity during development? If the perceptual modality of a cortical area were determined intrinsically and independent of afferents, then visual activation of the rewired projection to auditory cortex would be perceived by ferrets as an auditory stimulus. Conversely, if

the modality were determined by afferent activity, visual inputs would be perceived as visual.

Recent experiments demonstrate that rewired ferrets interpret visual stimuli that activate the rewired projection as visual rather than as auditory (von Melchner *et al.*, 2000). In these experiments, we routed retinal projections to the MGN in one (the left) hemisphere, leaving the right hemisphere unrewired. Animals were trained to associate sound stimuli with one juice reward spout and light presented in the left visual field (i.e., to their right, normal hemisphere) with a different reward spout. Subsequently, the LGN and associated thalamus in the left hemisphere were ablated and animals were presented light in the right visual field (i.e., to their rewired projection in the left hemisphere). The ferrets interpreted the stimulus as visual, or at least as more visual-like than auditory-like, for they consistently went to the visual reward spout. In a final phase of the experiment, A1 was ablated and the animals re-tested. They were found to be functionally blind in the right visual field. Several kinds of control experiments indicate that the animals did indeed perceive the light stimulus as visual. In a separate experiment, we examined the grating acuity of the rewired projection and found that it was only one-third or so of the normal visual pathway. One possible reason is that the fibers that innervate the MGN arise significantly from V retinal ganglion cells, which have large dendritic arbors and poor acuity. Alternatively, the cortical circuits that enable sharp acuity may not have developed in the rewired A1.

These experiments demonstrate that the perceptual modality of a cortical area can be instructed to a significant extent by the pattern of input activity during development. We routed retinal projections to the MGN at birth in ferrets, thus altering activity in thalamocortical fibers without altering the connections themselves. Even such a relatively subtle manipulation profoundly alters the perceptual role of cortex, so that the rewired cortex mediates visual behavior. One possible means by which this happens is that new connections develop between the rewired A1 and subcortical brain regions that mediate a visual response. Alternatively, it is possible that all auditory cortex in the rewired hemisphere is turned "visual", including downstream pathways and structures, with the concomitant respecification of their perceptual identity.

4. CONCLUSIONS

Experiments in ferrets with visual projections directed to the auditory pathway pointedly and uniquely address whether or not the *pattern of activity* has an *instructive role* in the *establishment* of cortical networks. Previous experiments on the influence of activity on cortical development have: (a) involved reductions in activity (by lid suture or activity blockade) and hence cannot address the issue of instruction by patterned activity; (b) used manipulations that start late in development, after properties such as orientation selectivity are already in place, and hence address at best the role of activity in the maintenance of networks rather than their establishment. Thus, one of the prevailing dogmas in the field is that there is an intrinsic scaffold of horizontal connections in visual cortex that is not shaped by activity. By providing a novel pattern of activity (driven by vision) to a cortex with a very different intrinsic connectivity at an extremely early stage in development, we are able to demonstrate that patterned activ-

ity significantly and instructively changes horizontal connections to create a visual orientation map in the auditory cortex. This is the first demonstration of such a change in horizontal architecture and the creation of a cortical map that relies on this architecture. Furthermore, activation of the auditory cortex by visual stimuli is interpreted as vision, demonstrating the profound instructive effect of patterned activity on the perceptual modality of a cortical area. At the same time, some features of the horizontal connections in rewired cortex are retained as similar to normal A1, and some features of visual behavior (i.e., grating acuity) are lower than in V1. Thus, there are limits on cortical plasticity, that are evident even with the extremely early manipulations that route retinal projections to the auditory pathway.

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