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Review

Vision and Cortical Map Development

Leonard E. White[1,2,*] and David Fitzpatrick[1]
[1]Department of Neurobiology
[2]Department of Community and Family Medicine, Doctor of Physical Therapy Division
Duke University Medical Center, Durham, NC 27710, USA
*Correspondence: len.white@duke.edu
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Functional maps arise in developing visual cortex as response selectivities become organized into columnar patterns of population activity. Recent studies of developing orientation and direction maps indicate that both are sensitive to visual experience, but not to the same degree or duration. Direction maps have a greater dependence on early vision, while orientation maps remain sensitive to experience for a longer period of cortical maturation. There is also a darker side to experience: abnormal vision through closed lids produces severe impairments in neuronal selectivity, rendering these maps nearly undetectable. Thus, the rules that govern their formation and the construction of the underlying neural circuits are modulated—for better or worse—by early vision. Direction maps, and possibly maps of other properties that are dependent upon precise conjunctions of spatial and temporal signals, are most susceptible to the potential benefits and maladaptive consequences of early sensory experience.

The information necessary to represent visual scenes resides in the spatial and temporal properties of a distributed pattern of neural activity in the primary visual cortex (V1). This activity arises from the aggregate responses of individual neurons that are differentially tuned to features of visual stimuli, such as their position in visual space and the energy engendered by their orientation, spatial frequency, and direction of motion. For carnivores and primates, neurons with similar preferences are clustered into radial columns, which are arrayed in a systematic fashion across the cortical surface. This arrangement of response preferences in V1 into so-called functional maps was first recognized nearly 50 years ago in the seminal work of D.H. Hubel and T.N. Wiesel, who probed the organization of visual cortex with microelectrodes and neuroanatomical tracers (see Hubel and Wiesel, 2005). In the last two decades, it has become possible to use optical means for measuring signals (either intrinsic or exogenous) that indirectly reflect underlying neuronal selectivities and preferences and thereby characterize the spatial layout of functional maps across the accessible reaches of the visual cortex (usually the representation of central visual space in V1 and/or V2 of model carnivore and primate species) (Blasdel and Salama, 1986; Bonhoeffer and Grinvald, 1996).

Based largely on the results of such imaging studies of population activity in V1, numerous functional maps have been proposed to account for the spatial organization of coherent population activity in V1 (Bonhoeffer and Grinvald, 1991; Shmuel and Grinvald, 1996; Issa et al., 2000; Blasdel and Campbell, 2001; Bosking et al., 2002; see also Swindale, 2000). We find it useful to categorize these functional maps into one of two groups: (1) maps that recapitulate the topological (near-neighbor) relations established in the lateral geniculate nucleus; and (2) maps that represent functional properties that emerge from geniculocortical interactions and intracortical processing. In the first category are the retinotopic (visuotopic) map and the ocular-dominance map, both of which are established in layer 4—the principal thalamic recipient layer—and organized to accommodate the two sets of monocular inputs that arise from the principal layers of the lateral geniculate nucleus. Maps in the second category do not simply reflect the neuronal properties and spatial patterns of organization that are established in antecedent levels of the visual pathway. The best example in this category is the map of orientation preference, a columnar map of a neuronal response property that is elaborated with a high degree of selectivity in the visual cortex, but not in the lateral geniculate nucleus (Hubel and Wiesel, 1962, 1968; Swindale et al., 1987; Bonhoeffer and Grinvald, 1991). Orientation-preference maps in V1 of carnivores and primates are characterized by numerous iterations of pinwheel motifs and linear zones that represent orientation preference in a smooth and continuous fashion across the surface of V1, save for point discontinuities at pinwheel centers (Bonhoeffer and Grinvald, 1991; Bosking et al., 1997; Blasdel, 1992; Rao et al., 1997). We and others have argued that this functional map should best be considered a map of orientation in space-time, i.e., a map of spatiotemporal energy, rather than a map of contour orientation per se (Mante and Carandini, 2005; Basole et al., 2003, 2006). Another member of this second category is the map of direction preference, which is present in V1 in carnivores and in middle temporal visual areas in primates (Albright, 1984; Malonek et al., 1994; Shmuel and Grinvald, 1996; Weliky et al., 1996; Swindale et al., 2003; Diogo et al., 2003; Xu et al., 2004). The map of direction preference is nested geometrically within the map of orientation preference, such that each iso-orientation domain is subdivided into a pair of smaller domains that represent opposite directions of stimulus motion (Shmuel and Grinvald, 1996; Weliky et al., 1996; Kisvárday et al., 2001).

While the functional significance of cortical maps continues to be a subject of debate (see, e.g., Swindale, 2000; Chklovskii and Koulakov, 2004; Horton and Adams, 2005), they have served as useful models for exploring the mechanisms responsible for the development of neuronal response properties in V1 and the neural circuits from which they arise. These mechanisms can be divided into two basic classes: (1) molecular recognition mechanisms that rely on gradients of diffusible ligands and cell-surface receptors to specify map topology and (2) activity-dependent mechanisms that rely on correlated patterns of pre- and postsynaptic activity to guide map formation. The latter can be further refined according to the source of the neural activity patterns: activity that arises endogenously within the developing retino-geniculo-cortical network and—at later times in development—activity that is driven by visual experience. Undoubtedly, a finely tuned orchestration of all of these mechanisms is essential for the proper establishment and subsequent maturation of functional cortical maps. This is best exemplified by the development of the map of visual space in the tectum, where the mechanisms are best understood (for reviews, see Goodhill and Xu, 2005; Lemke and Reber, 2005; O'Leary and McLaughlin, 2005). The initial formation of this map depends on molecular gradients that insure the guidance of axons to the topologically appropriate portions of the map; similar molecular mechanisms are likely to operate in V1 (Cang et al., 2005). But such mechanisms provide only course instruction of map topology; at later stages in development, patterns of retinal activity are required to achieve the finely tuned precision that is characteristic of the mature map.

The precise role of molecular recognition mechanisms in the formation of other cortical maps remains unclear (Crowley and Katz, 2002; Huberman et al., 2006); but a similar sequence—an initial stage that specifies the basic structure of the map, followed by a subsequent stage of map refinement—is generally thought to account for the development of all cortical maps. Furthermore, because the maps of visual space and ocular dominance are fully evident before birth in primates and before the postnatal separation of the eyelids in carnivores, the formative stages of these maps occur in the absence of patterned visual experience. Sensory experience does alter the structure of these maps when input from the two eyes is rendered unbalanced, as has been shown repeatedly for the map of ocular dominance and more recently for the retinotopic map (Smith and Trachtenberg, 2007), but this is after their initial formation and early progression toward functional maturity (for recent reviews of critical period plasticity, see Knudsen, 2004; Hensch, 2005; Sengpiel, 2005; Taha and Stryker, 2005). Similarly, the experience-dependent plasticity of orientation maps, which is evident when the visual experience of juvenile animals is restricted to a narrow range of stimulus orientations, is thought to reflect the plastic potential of the map that persists for some time after its formation (Sengpiel et al., 1999; Tanaka et al., 2006).

Our purpose here is to review recent evidence suggesting that visual experience plays a more substantial role in the earlier, formative stages of orientation and direction preference map development than would have been predicted based on studies of topological maps. We will focus on the natural history of visual cortical development in the ferret, a species that has become widely used for studies of visual system development and the organization of functional maps in visual cortex, and we will discuss lessons learned from studies that have sought to manipulate the impact of vision on the formation and maturation of orientation and direction maps. A survey of recent work in this field will show that visual experience may have a profoundly beneficial or detrimental influence over the formation of these maps in the developing visual cortex. Recognition of this conclusion should impact our understanding of cortical development and the rules that govern the construction of functional maps. Understanding these rules is essential for guiding interventional efforts aimed at mitigating the central impact of abnormal experience filtered through malformed or diseased sensory organs and promoting the benefits of optimal sensory-evoked patterns of neural activity in developing cortical networks.

An Explosive Phase of Circuit Construction in Supragranular V1 Ensues following the Onset of Patterned Visual Experience

The distinction of two phases of map development has served as a useful means of recognizing an early, experience-independent establishment phase and a subsequent refinement phase during which experience acts to shape map properties. This framework implies that most of the information that is required for map construction—establishing the basic layout of the map and determining which regions will express a particular preference—is innate and that sensory experience plays only a modest role in elaborating a program that has been largely determined by experience-independent mechanisms.

It is worth keeping in mind, however, that at the time when light activation of the retina first becomes effective in driving visual cortical activity, the density of cortical synapses in V1 is only a fraction of that found in maturity, and that the vast majority of cortical synapses are added during a phase of development when visual experience impacts the spatial and temporal patterns of neural activity in V1. Indeed, the onset of visual experience—at birth in primates and eye opening in carnivores—coincides with an explosive increase in the density of cortical synapses in all cortical layers, including the supragranular layers from which emergent maps in V1 are detected. In rhesus monkey V1, for example, this phase of rapid synaptogenesis ensues late in the third trimester before birth and continues exponentially over the first two postnatal months

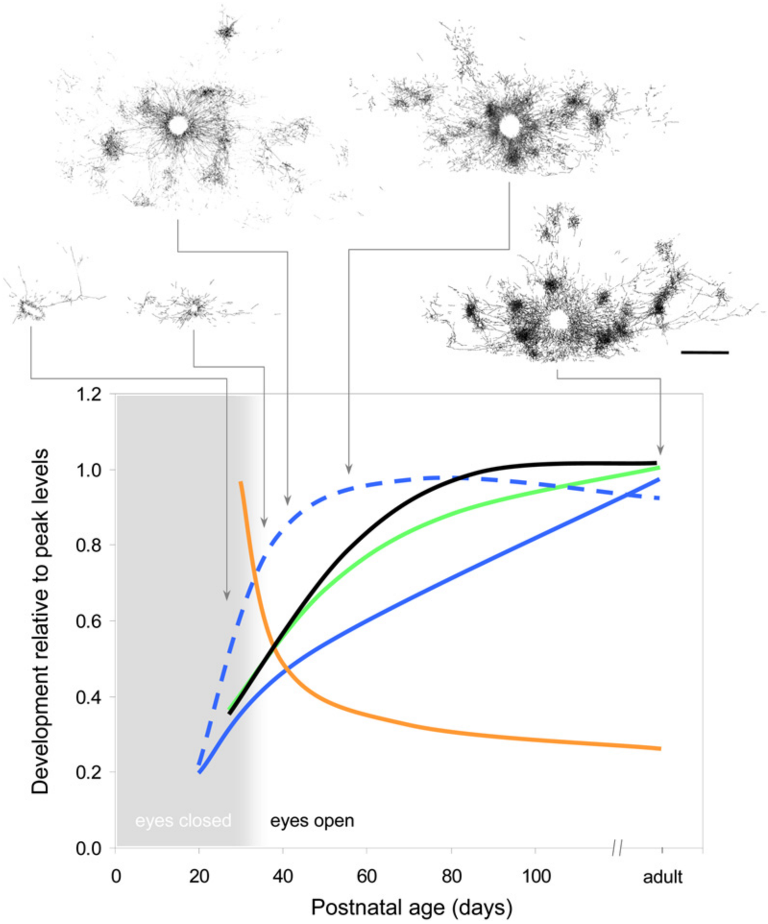

Figure 1. Summary of Changes that Ensue following Eye Opening in Ferret Visual Cortex and Lateral Geniculate Nucleus

Black curve represents average volumetric synaptic density in cortical layer 2/3 (from Erisir and Harris, 2003). This marked increase in synaptogenesis in supragranular layers is accompanied by an outgrowth of long-range horizontal connections, which accelerates after eye opening. The axonal reconstructions above were traced from tangential sections containing small clusters of neurons (located in vacant space) and their supragranular axons labeled with biocytin (White et al., 2001; see also Durack and Katz, 1996; Ruthazer and Stryker, 1996); arrows indicate age of animals (scale bar = 1 mm). The maturation of NMDA-receptor currents in visual cortex follows a similar developmental trajectory, as exemplified by the increasing expression of the NR2A subunit (green line) (after Erisir and Harris, 2003; see also Roberts and Ramoa, 1999). Likewise, the expression of parvalbumin immunoreactivity (solid blue line) and calbindin immunoreactive (dashed blue line) in cortical inhibitory neurons also increases (after Gao et al., 2000). Finally, the response latency of neurons in the lateral geniculate nucleus decreases (orange line), suggesting a coordination of maturation in the thalamus and cortex (after Tavazoie and Reid, 2000). Curves are representations of functions fit to published values normalized to each parameter's peak value in this phase of cortical maturation.

before achieving a stable density of synaptic profiles in neuropil by the third month that persists until adolescence (Bourgeois and Rakic, 1993). In carnivores, which open their eyelids some time after birth (after the first postnatal week in cat and after the fourth week in ferret), a similar phenomenon has been documented: the density of synapses in V1 increases rapidly in the month that follows the onset of patterned visual experience (Cragg, 1975; Erisir and Harris, 2003).

This explosive increase in V1 synaptogenesis is accompanied by a comparable increase in the outgrowth of intrinsic axonal projections in V1. Thus, the long-range horizontal connections in layer 2/3 that are known to establish connections among cortical columns with similar response properties (Gilbert and Wiesel, 1989; Malach et al., 1993; Bosking et al., 1997) are elaborated and achieve their mature distributions over this same period of postnatal development (Callaway and Katz, 1990, 1992; Luhmann et al., 1990; Lübke and Albus, 1992; Burkhalter et al., 1993; Durack and Katz, 1996; Galuske and Singer, 1996; Ruthazer and Stryker, 1996). For example, at about the time of eye opening in ferret visual cortex, horizontal connections are modest, with considerably less spatial extent of coverage across the cortical surface and a lower degree of clustering than are ultimately achieved in maturity (Durack and Katz, 1996; Ruthazer and Stryker, 1996). Adult-like distributions of intrinsic connections are achieved at about the same time in postnatal development that the rate of synaptogenesis begins to decline and synaptic densities in layer 2/3 of V1 reach a stable level. Figure 1 illustrates this point by showing representative reconstructions of horizontal connections in layer 2/3 from developing ferret visual cortex, labeled with extracellular injections of an anterograde axonal tracer (White et al., 2001), plotted together with a schematic representation of synaptic density (black curve) also obtained from layer 2/3 of ferret V1 (Erisir and Harris, 2003). Although studies of developing horizontal connections in V1 have often emphasized regressive phenomenon, such as collateral pruning and selective synapse elimination as important means of achieving functional maturity, the sculpting of intrinsic cortical connectivity occurs in a larger context of net circuit construction (Purves et al., 1996).

The Map of Orientation Preference Strengthens during This Constructive Phase of Cortical Maturation

Taken together, these neuroanatomical observations indicate that the construction of neural circuits in

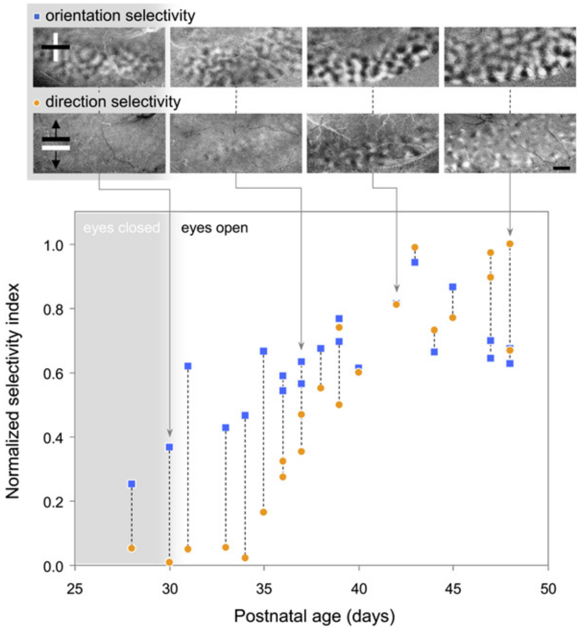

Figure 2. Development of Orientation and Direction Maps in Ferret Visual Cortex Assessed by Means of Intrinsic Signal Optical Imaging (after Li et al., 2006)

Graph plots normalized orientation (blue squares) and direction (orange circles) selectivity indices obtained from the same animals (dashed vertical lines); representative difference images for four animals are shown above (arrows indicate age; scale bar = 1 mm). Note the maturation of orientation maps after eye opening and the relative time-lag in the development of direction maps, which become detectable after about 1 week of visual experience.

supragranular layers of V1 is largely accomplished during a period of time in which these circuits are responsive to patterned visual experience. Furthermore, as shown in Figure 2, this phase of rapid circuit construction ensues just as the first detectable mapping signals reveal the presence of a map of orientation preference in V1. Thus, maps of orientation are recognizable—although often not homogenous in columnar structure or signal strength—at the time of eye opening in ferret kits (Chapman et al., 1996; White et al., 2001; Coppola and White, 2004). Thereafter, columnar structure becomes more uniform across the cortical map and the strength of the mapping signals increases substantially before achieving functional maturity approximately three weeks after eye opening (see Figure 2, blue squares; see also Chapman et al., 1996; White et al., 2001; Li et al., 2006). This process, as documented with intrinsic signal optical imaging techniques, parallels (with a several day lag) the maturation of neuronal orientation selectivity assessed electrophysiologically (Chapman and Stryker, 1993; Chapman et al., 1996; see also Gödecke et al., 1997). The period of postnatal cortical maturation that is characterized by the rapid construction of neural circuits in supragranular layers of V1, therefore, coincides with the phase of emergent map development when neuronal selectivities sharpen, map structures become more robust, and the mature configuration of the map is achieved (cf. Figures 1 and 2). In contrast to the early experience-independent formation of visual space and ocular-dominance maps, orientation maps arise during a time when visual experience has the potential to supervise the progression and outcome of circuit construction.

Interestingly, this trajectory of orientation map development over the first two months of postnatal life (in carnivores) accords remarkably well with a broad spectrum of molecular changes that impacts the balance of excitation and inhibition in neural circuits of the visual cortex (see Figure 1). During this same period of cortical maturation, there is a marked increase in the expression of NMDA receptors in layer 2/3 of V1 (Trepel et al., 1998; Smith and Thompson, 1999; Chen et al., 2000); especially striking is the coincident upregulation of NR2A subunits, which imparts a maturational change in the kinetics of the currents that flow through activated NMDA receptor channels (Roberts and Ramoa, 1999; Chen et al., 2000; Erisir and Harris, 2003). Similarly, the development of GABAergic inhibitory neurons in visual cortex (Guo et al., 1997; Gao et al., 2000) and a shift in the composition of the subunits that constitute GABA-A receptors ensues in this same period of cortical maturation, with a resulting sharpening of the kinetics of the shunting currents gated by GABA (Hendrickson et al., 1994; Gingrich et al., 1995; Chen et al., 2001; see also Murphy et al., 2005). The time course over which inhibitory circuits in V1 mature (especially circuits involving parvalbumin-containing basket neurons) extends well beyond the age at which stable expression of orientation selectivity and the map of orientation preference is achieved (Guo et al., 1997; Gao et al., 2000; Chen et al., 2001), providing support for the view that changes in the strength of inhibition and the overall balance of excitation and inhibition are key factors in modulating the susceptibility of topological maps (namely, the map of ocular dominance) to experience-dependent plasticity in later critical periods (for review, see Hensch, 2005; Murphy et al., 2005). However, the possibility that these developmental changes in glutamate and GABA receptors may also play an important role in the maturation of emergent maps in V1 during the so-called "precritical period"—prior to the time when visual experience is thought to exert its greatest influence (Katz and Crowley, 2002; Ruthazer, 2005; Feller and Scanziani, 2005)—should not be overlooked. Indeed, in ferret visual cortex at least, the maturation of NMDA receptors appears to coincide as well or better to the maturation of the map of orientation preference in V1 as it does to the onset, peak, or termination of the critical period for ocular-dominance plasticity (Issa et al., 1999; Erisir and Harris, 2003; Liao et al., 2004; see also Fagiolini et al., 2003). These phenotypic changes that accompany cortical maturation have yet to be causally linked definitively to the development of any specific receptive field property of neurons in V1; nevertheless, it seems likely that the aggregate effect of these and other as yet undefined changes serve to consolidate the structure and function of the cortical circuits from which computational properties like orientation and direction selectivity emerge.

The Development of the Map of Direction Preference Lags behind the Formation of the Map of Orientation Preference

Clearly, a diverse collection of cellular, molecular, and neurophysiological properties undergo rapid maturational changes during the time when the map of orientation preference achieves adult levels of definition and expression. However, not all functional properties of the visual cortex march in step with the progression of cortical maturation exemplified by the development of the map of orientation preference. In particular, the establishment and subsequent maturation of the map of direction preference appears to be out of step, at least for the first 1–2 weeks following the onset of patterned visual experience (Li et al., 2006).

To investigate the formation and maturation of the cortical maps of orientation and direction preference, we used intrinsic signal optical imaging and electrophysiological methods to document the early emergence of these maps in juvenile ferret visual cortex. Previous electrophysiological studies report the existence of direction selective units in newborn macaques and very young kittens (Hubel and Wiesel, 1963; Wiesel and Hubel, 1974; Hatta et al., 1998); however, the prevalence of sharply tuned neurons in visually naive animals is low (Blakemore and Van Sluyters, 1975; Imbert and Buisseret, 1975), and it was not known whether these neurons are organized into a map of direction preference at the onset of visual experience when orientation maps are first detectable. Our initial goal, therefore, was to determine whether or not direction columns are detectable and spatially organized near the time of eye opening, as are orientation and ocular-dominance columns (Chapman et al., 1996; Ruthazer et al., 1999; White et al., 2001). The image panels and graph in Figure 2 depict the normal development of the maps of direction and orientation preference across the first two months of life. In the youngest ferrets, direction-selective cortical responses were barely detectable with intrinsic signal imaging and, when differential responses to opposite directions of motion were observed, they were at best only crudely organized into columnar patterns. More uniform, adult-like columnar patterns of direction selective responses were not observed until about 1 week after eye opening, well after the establishment of uniform maps of orientation preference (see Li et al., 2006). Orientation selectivity was seen at or even before eye opening, as already noted, and increased during the next 2–3 weeks, achieving a plateau by 7–8 weeks. Direction selectivity signals, on the other hand, did not differ significantly from nonstimulated background signals until about 5 days after eye opening (see Figure 2, orange circles). Once direction selectivity signals became detectable reliably, they rapidly increased in strength such that mature levels of direction and orientation selectivity were achieved at approximately the same time. Mathematical functions fit to the measurements of direction and orientation selectivity in juvenile ferrets were distinct (see Li et al., 2006), indicating that the time lag in the expression and maturation of direction selectivity cannot be explained by a downward scaling of the same developmental program that accounts for the maturation of orientation selectivity.

This sequence of emergent map development provides an explanation for why continuity in the mapping of orientation preference (full-cycle representation with point singularities) takes precedence over continuity in the direction map (half-cycle representation with linear fractures) (Weliky et al., 1996; Shmuel and Grinvald, 1996). It also accounts for the nested geometrical relation between the maps of direction and orientation preference (Weliky et al., 1996; Shmuel and Grinvald, 1996; Kisvárday et al., 2001; Swindale et al., 2003). Neurons that respond to the same axis of motion are first organized into ocular-dominance and orientation columns that subsequently differentiate into paired subregions that prefer opposite directions of motion. This delayed differentiation of direction-selective domains also challenges the general notion that functional maps are established early via the operation of experience-independent mechanisms of cortical development. It leaves open the possibility that the establishment of direction selectivity and the formation of the columnar map of direction preference only after the onset of patterned visual experience might not be simply coincidental. To directly test this possibility, we also investigated the formation of the maps of orientation and direction preference in juvenile ferrets that were completely deprived of visual experience.

Visual Experience Influences Map Formation during This Early Constructive Phase of Cortical Development

Studies of the development of the map of orientation preference provided the first clue that experience played an important role in cortical maturation in a early (precritical) phase of postnatal development, prior to the time when ocular-dominance maps are most susceptible to alterations in binocular vision (White et al., 2001). Thus, the strengthening of the map of orientation preference that occurs after eye opening in ferrets reared with the benefit of normal day-night cycles does not occur in dark-reared animals (Figure 3). These results suggest that experience plays an important role in the addition of cortical synapses and the maturation of synaptic mechanisms that are required to achieve full map strength. Moreover, it is not just the quantity of activity induced by experience that drives map strengthening. Vision through closed lids, which arguably should result in a greater amount of cortical activity than what is present in animals reared in absolute darkness, has a more devastating impact on orientation selectivity and columnar map structure, virtually abolishing the map of orientation preference (White et al., 2001; see Figure 3, right column). The closed eyelids of lid-sutured animals do not completely prevent light

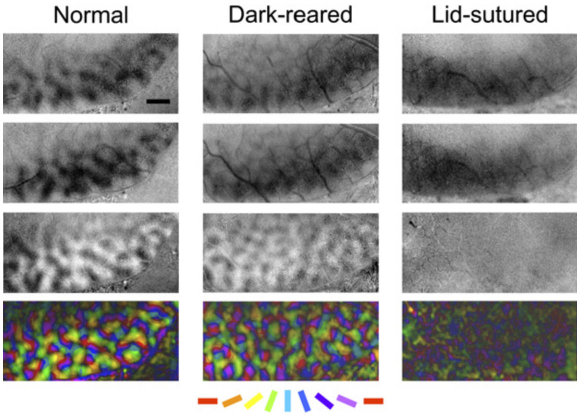

Figure 3. Representative Maps of Orientation Preference from Age-Matched, Juvenile Normal, Dark-Reared, and Binocularly Lid-Sutured Ferrets (after White et al., 2001)
The upper two rows show single-condition images (stimulated condition minus blank image) evoked by horizontal (first row) and vertical (second row) grating stimuli; the third row shows difference images generated by subtracting horizontal and vertical single-condition images (scale bar = 1 mm). The bottom row shows polar-magnitude maps generated by vector summation, where color represents orientation preference (legend below middle column) and brightness represents the magnitude of selectivity. Note the presence of well-formed but attenuated orientation maps in dark-reared ferrets (effects quantified in Figure 4). In contrast, very little columnar structure was evident in lid-sutured ferrets, making maps of orientation preference nearly undetectable in this group. Thus, the impact of abnormal visual experience engendered by lid-suture was far more devastating for the development of the map of orientation preference than was the absence of visual experience.

activation of retinal ganglion cells; rather, they severely reduce patterned visual experience by passing only very low spatial and temporal frequencies without eliminating all luminance contrast (Crawford and Marc, 1976; Loop and Sherman, 1977; Sherman and Spear, 1982). Taken together, then, these results in normal and lid-sutured ferrets suggest that the pattern of visually-evoked neural activity, not just its presence, is crucial for guiding the ongoing construction of the neural circuits that instantiate the mature map of orientation preference.

The development of the map of direction preference makes an even more compelling case for the role of experience in this constructive phase of cortical maturation. Studies of direction selectivity in dark-reared ferrets indicate that the normal lag in the formation and maturation of the map of direction preference until after the onset of patterned visual experience is not merely coincidental (Li et al., 2006). Animals that were deprived of vision by dark rearing during the first 2 weeks after eye opening failed to develop maps of direction preference, even though maps of orientation preference (and ocular dominance) were well established in these same ferrets (Figure 4). Remarkably, this was also true of animals that were provided normal day-night cycles following deprivation during this early 2 week period. Such animals showed complete restoration of all known bandwidths of selectivity and preferences that define functional maturity in visual cortical networks, despite the persistence of severe impairments in cortical direction selectivity. These last findings argue that early dark rearing did not simply delay the normal progression of visual cortical development, as the effect of dark rearing on critical period plasticity is usually interpreted (Cynader and Mitchell, 1980; Mower et al., 1981; Hensch, 2005). Rather, these results suggest that dark rearing deprives the developing visual system of an important source of spatial, temporal, and/or luminance cues that are required for the formation of directionally selective circuits in cortical networks.

Mechanisms that Mediate Experience Dependency in Map Construction

These developmental observations show that direction selectivity has an obligatory requirement for normal visual experience during a remarkably brief period of cortical maturation following eye opening, a unique experience dependency that distinguishes direction selectivity from other mapped properties of the visual cortex, including orientation selectivity, spatial frequency, ocular dominance, and visuotopy (Yu et al., 2005; Farley et al., 2007), all of which are present and well organized in ferrets raised in the complete absence of visual experience (White et al., 2001; Li et al., 2006; see also Daw et al., 1978). What accounts for this unique visual dependency and why is it played out in such an early window of map development that is often termed "precritical" precisely for its supposed insensitivity to the impact of sensory experience (Katz and Crowley, 2002; Ruthazer, 2005; Feller and Scanziani, 2005)? Perhaps the answers to these questions lie in the nature of the computations that must be performed by directionally selective circuits in visual cortex.

Direction selectivity is distinct from other neuronal response properties of the visual cortex in that it relies on detecting the temporal order of stimulus presentation. At the first stage of cortical processing, geniculocortical and intracortical inputs to direction selective simple cells are arranged in a fashion that instantiates a spatial gradient of timing signals: response latencies progressively decrease for sequential positions along the preferred direction, which produces a net summation of excitatory inputs for this direction of motion that is absent for motion in the opposite direction (Adelson and Bergen, 1985; Reid et al., 1991; Livingstone, 1998; Saul and Feidler, 2002; Priebe and Ferster, 2005). Activity-dependent mechanisms of development, such as spike-timing-dependent plasticity, could bring about the selective convergence of inputs whose receptive field locations and response latencies establish the appropriate space-time gradient (i.e., near spatiotemporal quadrature; see Peterson et al., 2004) if the proper inputs are coactive in a narrow time window prior to a neuron's spike (Buchs and Senn, 2002; Wenisch et al., 2005). The relationship between the time interval and the magnitude of the relevant synaptic change is a very sensitive function of the time window, with no changes observed if the presynaptic activity and

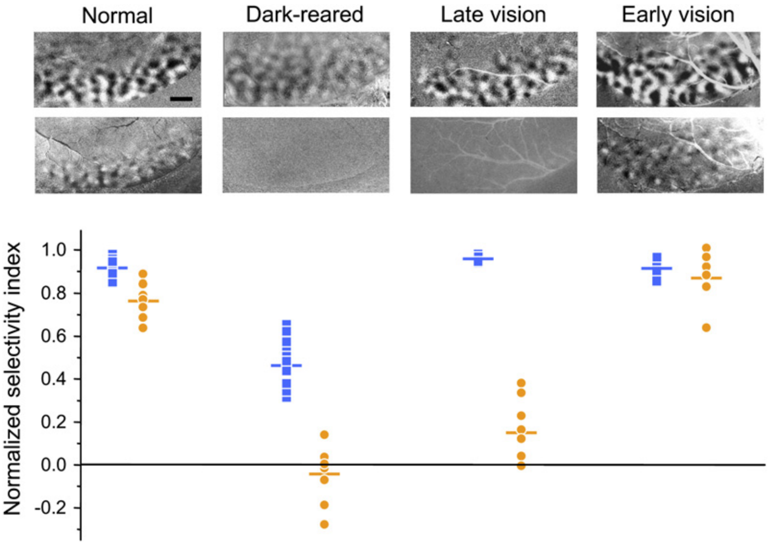

Figure 4. Early Vision Is Necessary for the Development of Direction Selectivity in Ferret Visual Cortex (after Li et al., 2006)

Upper panels: difference images of orientation selectivity (upper row) generated by subtracting horizontal and vertical single-condition images and difference images of direction selectivity (bottom row) for the same animals generated by subtracting responses to upward- and downward-moving grating stimuli (scale bar = 1 mm). The attenuation of orientation selectivity induced by dark-rearing can be normalized by provision of 2–3 weeks of normal visual experience beginning a few days after eye opening (early vision) or about 3 weeks after eye opening (late vision). In contrast, the formation of the map of direction preference is uniquely dependent on early vision. Unlike orientation columns, direction columns are only detected in ferrets that were provided with vision in the first 2–3 weeks after eye opening (normal and early-vision groups). Lower graph: quantification of orientation and direction selectivity indices from the four groups of experimental animals (blue squares, orientation selectivity index; orange circles, direction selectivity index; horizontal lines, median values).

postsynaptic activity are separated by 100 ms or longer (Song et al., 2000; Bi and Poo, 1998). Although such stringent temporal conditions for this instructive signal might be met by endogenous patterns of neural activity (Wenisch et al., 2005), the absence of direction maps in dark-reared ferrets indicate that such activity is insufficient to support the emergence of direction selectivity. Rather, the findings discussed above suggest that the space-time correlations in neural activity engendered by moving stimuli are crucial for the construction of direction-selective responses. Spike-timing-dependent plasticity may thus provide a framework for understanding why coordinated activity in neural circuits, such as ongoing activity in visual cortex modulated by normal patterns of sensory experience (Fiser et al., 2004), evidently leads to a strengthening of neural connections and an enhancement of physiological function. Conversely, noisy or otherwise uncoordinated patterns of neural activity, such as sensory signals filtered through injured or diseased sensory organs and—quite possibly—immature patterns of neural activity that are generated endogenously prior to the onset of patterned visual experience (Chiu and Weliky, 2001), may weaken (or fail to strengthen) synaptic connections producing dysfunctional neural circuits.

But why should the neural circuits responsible for direction selectivity be sensitive to this constructive influence of experience in such an early and brief phase of development immediately after eye opening? Not only are neural circuits in the visual cortex undergoing massive growth and phenotypic maturation during this time, but—in ferrets at least—more subtle changes in the organization of connections between retinal ganglion cells and the lateral geniculate nucleus are also unfolding, as are shifts in the response latencies of geniculate neurons. In normal ferrets at about the time of eye opening, geniculate receptive fields show spatial complexities indicative of exuberant retinogeniculate convergence and a broad range of temporal cues, with a preponderance of long latency responses (see Figure 1, orange curve; Tavazoie and Reid, 2000). Although the anisotropic spatial structure of these immature receptive fields could promote the establishment of orientation selectivity in layer 4 simple cells, as originally proposed (Tavazoie and Reid, 2000; see also Ringach, 2007), the combination of spatial complexity and broad timing may be incompatible with the coincident establishment of cortical direction selectivity. In the ensuing 2 weeks, however, geniculate receptive fields become single-Gaussian in shape, and the distribution of response timing narrows with a shorter modal latency (Tavazoie and Reid, 2000). Since the map of direction preference emerges over the same course of time (see Figure 2), it is possible that these subcortical events may provide an essential antecedent condition for the expression of direction selectivity at the level of cortical circuits in V1. Consistent with this possibility, studies of geniculate receptive fields in dark-reared ferrets show severe spatial and temporal disturbances characterized by abnormal convergence of multiple inputs from both ON- and OFF-center retinal ganglion cells (Ackerman et al., 2002). This suggests that the spatial and temporal refinement of neuronal receptive fields in the lateral geniculate nucleus is dependent upon early visual experience and that the persistence of aberrant patterns of retinogeniculate convergence interferes with the establishment of the map of direction preference in dark-reared animals.

The need to coordinate the maturation of neural circuits in the thalamus and cortex could explain why the effects of experience on direction selectivity occur so early in cortical maturation. Evidently, the instruction necessary for the development of direction selectivity must ensue when geniculate neurons are relatively immature, so that their subsequent maturation, especially with respect to the temporal cues derived from their response latencies, may be optimized to meet the space-time requirements of postsynaptic cortical targets. Retrograde signals could be generated at the cortical level by visually evoked patterns of neural activity that influence the refinement of geniculate receptive fields and sharpen the timing of information flow through the thalamic relay. Studies of hippocampal cultures (Fitzsimonds et al., 1997) and the developing retinotectal system (Du and Poo, 2005) suggest molecular mechanisms that could mediate such retrograde synaptic modification in neural systems, and it is conceivable that similar mechanisms operate in the mammalian visual pathway to supply the stringent demands of response selectivity in the visual cortex. If so, the instructive influence of visual experience for the development of direction selectivity would be expected to wane once the spatiotemporal properties of geniculate neurons have been appropriately consolidated. The formation of the cortical map of direction preference illustrates the complexities of coordinating the refinement of both local cortical circuits and antecedent neural circuits, and the key role of visual experience for provision of essential spatiotemporal cues that orchestrate this process.

Conclusions and Future Directions

Much effort is currently devoted to teasing apart the intricate molecular mechanisms that are responsible for establishing the basic layout of topological maps in visual cortex and subcortical visual centers. The results of such efforts have led to the now conventional view that functional maps are established early in development under the governance of molecular recognition mechanisms that are subject to activity-dependent modulation as nascent neural circuits become operational (Huberman et al., 2006). Patterns of neural activity driven by sensory experience were considered necessary only in later stages of map maintenance when previously established map structures are sustained and fine-tuned according to the demands imposed by the functional ecology of the organism interacting with its environment. However, this framework for understanding functional maps in visual cortex is difficult to reconcile with the explosive phase of circuit construction that ensues after the onset of sensory experience and several important characteristics of orientation- and direction-map development. A somewhat different view of cortical maturation and the role of sensory experience is needed to more fully account for the development of emergent maps in visual cortex.

Rather than serving only as a means of maintaining prior map structure, studies of developing orientation and direction maps in normal and visual-deprived ferrets indicate that experience can exert a profound influence over the formation and maturation of these cortical maps, which normally proceeds during a phase of rapid circuit construction in visual cortex. Moreover, the impact of experience can be either beneficial or deleterious: normal patterns of visual experience can interact synergistically with endogenous programs of development to promote the full maturation of columnar structure in the visual cortex, or—if patterns of activity are rendered abnormal, as in the case of binocular lid-suture—this synergy may be abrogated and early columnar structures nearly lost. However, not all functional maps are equally sensitive to the impact of experience: orientation (and ocular-dominance) columns form in the absence of vision, but not direction columns. The formation and maturation of the map of direction preference in ferret visual cortex requires normal visual experience in a remarkably brief period of time (perhaps less than 2 weeks) beginning at about the time of natural eye opening. This period of sensitivity concludes just as the critical period for ocular-dominance plasticity is nearing its peak (Issa et al., 1999; Liao et al., 2004). Obviously, lessons learned from studies of ocular dominance plasticity, as instructive as they may be for understanding competition-based rules of synaptic plasticity, may not apply to other categories of columnar structures and functional maps in visual cortex.

It will be especially interesting to determine whether the rules that govern the construction of the map of direction preference will prove to be paradigmatic for understanding the formation of functional properties in other cortical areas and subcortical structures that are similarly dependent upon the precise conjunction of spatial and temporal cues, including maps of auditory space (Knudsen et al., 1987; Cohen and Knudsen, 1999), dynamic spatial maps in the parahippocampal gyrus (Hafting et al., 2005; Leutgeb et al., 2005), and maps of movement intention in premotor cortex (Rizzolatti and Craighero, 2004; Graziano, 2006). Furthermore, a more complete description of these rules will shed light on why selective deficits in human motion perception are prevalent in developmental disorders and global motion perception is especially vulnerable to the disruption of visual experience in early infancy (Spencer et al., 2000; Talcott et al., 2000; Lewis and Maurer, 2005; MacKay et al., 2005).

Despite significant progress in describing the phenomenology pertaining to the construction of emergent maps in visual cortex, numerous questions have yet to be fully addressed. Perhaps chief among them is the lingering question of whether the role of visual experience in emergent map construction is merely ‘‘inductive’’ (providing general signals for the growth and differentiation of neural circuits) or whether it is also ‘‘instructive’’ (providing specific spatial and temporal signals that define the architecture and functional properties of developing neural circuits). The map of direction preference in ferret visual cortex and its obligatory requirement for early experience presents an excellent opportunity to address this important question; preliminary findings are pointing toward an instructive role of early experience (Y. Li et al., 2006, Soc. Neurosci., abstracts #619.6; S. Van Hooser et al., 2007, Soc. Neurosci., abstracts #346.8). Another shortcoming of the current evidence is that it is derived largely from studies of population activity using optical-imaging techniques; what is lacking is a picture of the early emergence of orientation and direction selectivity in populations of individual neurons in developing visual cortex. Earlier single-unit studies are largely consistent with current imaging data (Blakemore and Van Sluyters, 1975; Imbert and Buisseret, 1975; Chapman and Stryker, 1993; Hatta et al., 1998), but these studies necessarily sample the responses of one or a small number of neurons at a time with a bias toward the largest and most responsive units. Recently, in vivo two-photon imaging of somatic calcium signals has been applied to the study of map structure in visual cortex, demonstrating a surprising degree of precision in the arrangement of neuronal preferences within functional columns (Stosiek et al., 2003; Ohki et al., 2005, 2006). Application of this technology to studies of map formation should provide provisional answers to numerous questions, such as: are there early neuronal ‘‘pioneers’’ whose preferences and selectivities establish the basic columnar architecture of cortical maps prior to the maturation of neighboring neurons and before the onset of visual experience; and can structured visual experience alter neuronal preferences (reverse in the case of direction preference) as columnar structures are expressed in map development? Finally, a series of additional questions pertain to the cellular, synaptic, and molecular mechanisms that must transduce visually driven neural activity into patterns of gene expression, protein modification, synaptic plasticity, and directed axonal growth and synaptogenesis. With the advent of a wide variety of molecular probes that may be introduced into developing cortical systems in vivo and the ability to track neuronal preferences and selectivity with two-photon imaging of functional signals, it is now becoming possible to explore the full spectrum of neurobiological mechanisms of map formation at the level of populations of identified neurons sampled from columnar structures within functional maps. Such experimental possibilities herald an exciting era of discovery that promises to provide new insight into the early events that are responsible for the development of emergent maps in sensory cortex and the mechanisms by which experience shapes the ongoing construction of cortical circuits.

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