

Adult Visual Cortical Plasticity

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The visual cortex has the capacity for experience-dependent change, or cortical plasticity, that is retained throughout life. Plasticity is invoked for encoding information during perceptual learning, by internally representing the regularities of the visual environment, which is useful for facilitating intermediate-level vision—contour integration and surface segmentation. The same mechanisms have adaptive value for functional recovery after CNS damage, such as that associated with stroke or neurodegenerative disease. A common feature to plasticity in primary visual cortex (V1) is an association field that links contour elements across the visual field. The circuitry underlying the association field includes a plexus of long-range horizontal connections formed by cortical pyramidal cells. These connections undergo rapid and exuberant sprouting and pruning in response to removal of sensory input, which can account for the topographic reorganization following retinal lesions. Similar alterations in cortical circuitry may be involved in perceptual learning, and the changes observed in V1 may be representative of how learned information is encoded throughout the cerebral cortex.

Introduction

After the discovery of a critical period early in postnatal life, one might have expected that all properties of visual cortical neurons would be fixed in adulthood. Torsten Wiesel and David Hubel established that the balance of input from the two eyes, and the thalamocortical arbors, can be altered by eye closure only during the first few months after birth (Hubel and Wiesel, 1970; Hubel et al., 1977; Wiesel and Hubel, 1963). This led to the expectation that the critical period window on cortical plasticity would establish the limits on the alteration of all cortical connections, yet experience-dependent changes in perception require the visual cortex to be capable of encoding new information throughout life. The forms of visual cortical plasticity range from declarative memory, encoding information about places, faces, and events, to a form of implicit memory known as perceptual learning. Perceptual learning refers to the improvement in ability to detect or discriminate visual stimuli that results from repeated practice. Since both declarative and implicit learning can take place at any age, the underlying mechanisms of cortical plasticity must also be free from the time constraints of the critical period. It is important to keep in mind that the critical period applies to specific cortical areas, functional properties and neural connections, such as ocular dominance and thalamocortical connections in primary visual cortex (V1). Where, then, does one find the mechanisms of adult cortical plasticity that mediate declarative and implicit memory? It is reasonable to assume that declarative memories reside in higher levels of the visual cortical hierarchy, including the medial temporal lobe and inferotemporal cortex. Perceptual learning, on the other hand, involves changes at many locations in the visual pathway, including V1. In this review we will discuss large experience dependent changes in receptive field (RF) properties, cortical topography, and cortical circuitry that occur in adult V1.

A key element to the role V1 plays in perceptual learning is the circuitry that enables V1 neurons to integrate information over larger parts of the visual field, and to have selectivity for more complex visual stimulus configurations, than what was shown in the initial studies of V1 RFs. The higher order properties are conferred in part by a plexus of connections, formed by cortical pyramidal cells, which extend for long distances parallel to the cortical surface (Gilbert and Wiesel, 1979, 1983a, 1983b, 1989; Rockland and Lund, 1982; Stettler et al., 2006). These long-range horizontal connections enable neurons to integrate information over large parts of the visual field and give neurons selectivity for stimulus context. If one uses more complex stimuli consisting of multiple line segments, one sees that neural responses to a stimulus placed in the RF are modified by the global context within which the local feature is shown (for reviews see Albright and Stoner, 2002; Allman et al., 1985; Gilbert, 1998). The contextual influences that modulate a neuron's response by stimuli "outside" the RF led to the distinction between the "classical" and "nonclassical" RFs. But it has long been known that influences flanking the RF, whether facilitatory or inhibitory, can modulate neural responses. Perhaps the more relevant distinction is between the area within which a simple stimulus, such as a single oriented lined segment, can induce a neuron to fire, and the area over which the components of a complex stimulus can influence a neuron's response. Neurons are as dependent on the global characteristics of image components extending far outside their core RFs as they are on the attributes of local features within the RF center. This contextual modulation plays a role in contour integration and saliency and can account for the specificity in perceptual learning, whereby alterations in contextual interactions confer specificity for the configuration of the discriminated stimuli (Crist et al., 2001).

The contextual interactions in V1 are consonant with the Gestalt rules of perceptual grouping (Wertheimer, 1923). These

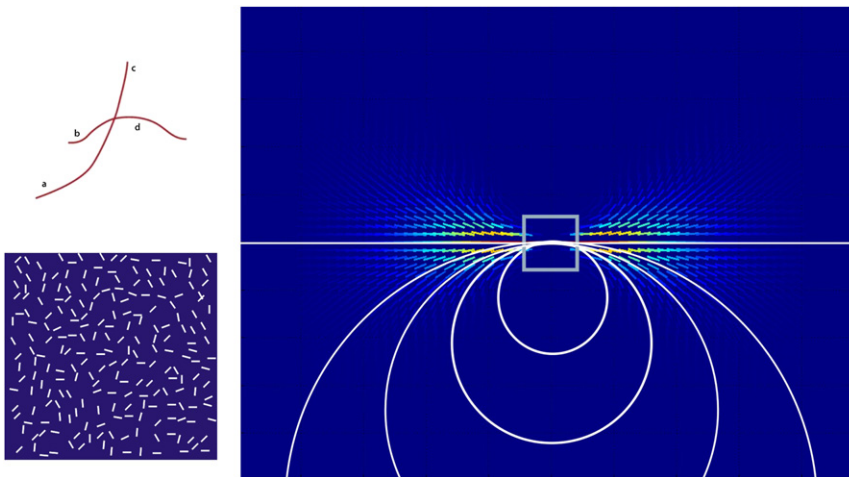


Figure 1. The Gestalt Rule of Good Continuation and the Association Field

In complex scenes observers tend to perceptually link or group line segments that lie along smooth contours. Upper left, observers perceptually link line segments a and c and perceptually segregate those having a large change in orientation, such as line segments a and d (from Wertheimer, 1923). This reflects a geometry of collinear and cocircular interactions, known as the association field, represented in the right panel. The gray square in the center of the right panel represents the RF measured with a single oriented line segment, but the association field, as represented by the colored oriented line segments flanking the RF, mediates collinear and cocircular facilitatory interactions between multiple line segments lying along smooth contours, enabling neurons to be influenced by the properties of contours extending well outside their RFs. The colors of the line segments indicate the strength of the association field interactions at

different positions, red being the strongest, light blue the weakest. Bottom left, the association field contributes to contour integration and contour saliency, where smooth contours tend to pop out from a complex background (adapted from Field et al., 1993).

rules, including proximity, similarity, and good continuation, allow one to link the components of extended contours in complex visual environments (Figure 1). Though linking contour elements in natural scenes might seem to present a hopelessly large number of possible solutions, our visual system simplifies the problem greatly by taking into account the statistical properties of scene contours, which follow principles of collinearity and cocircularity (Geisler et al., 2001; Sigman et al., 2001). The framework underlying these interactions, in natural scene structure, in perceptual grouping and at the level of cortical RFs, is known as the association field (Field et al., 1993). We perceptually group those contour elements that lie along smooth contours (good continuation) and these contours are salient—they tend to pop-out in complex visual environments. V1 RFs reflect this property. The property of orientation selectivity, first shown by Hubel and Wiesel, is a local attribute, seen in the response of neurons to a simple stimulus such as a single, oriented line segment. It has a corresponding property in intermediate level vision, that of contour integration. Even in V1, neurons' responses show selectivity for the properties of extended contours with complex geometries. Neurons' responses are greatly facilitated by collinear interactions, where a line placed outside the RF, which by itself will elicit no response, can facilitate a neuron's response several-fold when placed in conjunction with a collinear line segment within the RF (Figure 2; Kapadia et al., 1995, 2000). Blocking the continuity between line segments by a perpendicular line will eliminate the facilitation, but moving the perpendicular line segment into a different depth plane than the two collinear line segments, which restores their perceived continuity, recovers the facilitatory interaction of the collinear lines on neurons' responses (Bakin et al., 2000).

The properties of natural scene contours, the perceptual strategies by which we link contour elements, and the contextual interactions seen in V1 RFs are represented by the intrinsic circuitry of V1. An important feature of V1 connections is the plexus of long-range horizontal connections, which enable

neurons to integrate inputs from an area of cortex representing an area of visual field that is much larger than their classical RFs. The extent and orientation dependence of long-range horizontal connections match the properties of salient contours and the geometry of natural scene contours (Figure 3; Gilbert and Wiesel, 1989; Stettler et al., 2002; Li and Gilbert, 2002). By the same token, the visual system contains an internal representation of these principles, as observed in psychophysical studies of contour saliency (Field et al., 1993; Li and Gilbert, 2002), in facilitatory contextual influences on neuronal responses in V1 (Kapadia et al., 2000; Li et al., 2006; McManus et al., 2011) and in the long-range horizontal connections (Gilbert and Wiesel, 1989; Stettler et al., 2002). Together, these findings support the idea that the association field is represented in V1, and that the circuitry underlying lateral interactions in V1 mediates the linkage of scene elements into global contours.

The horizontal connections play a role in experience-dependent plasticity. Such plasticity is invoked in the normal process of perceptual learning and in recovery of function following CNS damage, such as that associated with stroke or neurodegenerative disease.

Plasticity following Lesions

Even in adult animals, the adult visual cortex is capable of undergoing experience-dependent change. A valuable model for studying the mechanism of cortical plasticity at the levels of RF properties, changes in circuitry and molecular mechanism involve the reorganization of cortical topography following retinal lesions (Calford et al., 2000; Chino et al., 1992; Eysel et al., 1999; Giannikopoulos and Eysel, 2006; Gilbert et al., 1990; Gilbert and Wiesel, 1992; Heinen and Skavenski, 1991; Kaas et al., 1990; Schmid et al., 1996). Focal binocular lesions initially silence the corresponding retinotopic region (the lesion projection zone, LPZ) in V1. During recovery following the lesions, neurons within the LPZ regain responsiveness to visual input from intact retinal regions surrounding the lesion area (Figure 4). Cortical reorganization following removal of a part of the sensory input has been

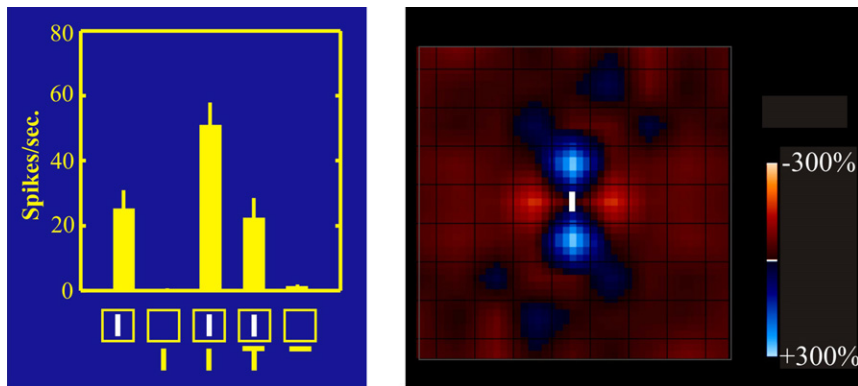


Figure 2. Contextual Influences Modifying Neuronal Responses

Left, a simple stimulus, such as a single oriented line segment, will elicit a response at one location, but by itself will produce no response at an adjoining location. This defines the boundaries of the RF. But if one line is placed within the RF and a second line at the adjoining location, the response of the neuron can be multiplied several-fold. This interaction reflects the sensitivity of neurons for the continuity of contours extending for long distances outside the RF, and interrupting this continuity by introducing a cross-bar between the collinear lines blocks the contour related facilitation (Kapadia et al., 1995). Consequently, the response properties are highly nonlinear—one cannot predict the response to a complex stimulus consisting of multiple components from the

response to the individual components. Right, the interaction between contour elements can be represented as a two-dimensional map of facilitatory (blue) and inhibitory (red) influences relative to the response of a neuron to a line segment centered in the RF (white bar) (Kapadia et al., 2000). These interactions constitute the representation of the association field in V1.

observed in nearly all sensory modalities. Reorganization of V1 retinotopic map has been documented with fMRI in patients with macular degeneration (Baker et al., 2005) and in stroke patients with partially damaged input fibers to V1 (Dilks et al., 2007). The phenomenon of reorganization has been questioned by one study involving fMRI (Smirnakis et al., 2005), but fMRI reflects cortical inputs, including the subthreshold activation mediated by horizontal connections, rather than cortical outputs, as reflected in spiking activity, and therefore cannot be used to define the boundary of the LPZ (see Calford et al., 2005 for a discussion of evidence of the distinction between fMRI and electrophysiological techniques for documenting cortical reorganization). Even so, for subjects with macular degeneration, fMRI shows activation in the presumed LPZ when they perform a visual discrimination task, as opposed to passive viewing (Masuda et al., 2008). This may reflect an interaction between recurrent pathways to V1 and the horizontal intrinsic connections, where it has been proposed that the effectiveness of intrinsic cortical circuits is gated by top-down influences (Gilbert and Sigman, 2007). But other fMRI studies strongly support the phenomenon of reorganization in patients with macular degeneration, even in the absence of active discrimination tasks, with clear activation in the LPZ of V1 (Baker et al., 2005). Reorganization has also been documented in stroke patients with partially damaged input fibers to V1 (Dilks et al., 2007). Whether the activation of the LPZ requires a top-down contribution, the reorganization nonetheless involves plasticity of circuits within V1, which is the first stage where extensive topographic reorganization of the LPZ is observed. As described below, the reorganization in cortical topography is mediated by the long-range horizontal connections. In normal cortex, these connections play a modulatory role, and allow for the propagation of information across the visual map—in V1 for the purpose of contour integration. Following retinal lesions, these connections become strengthened, enabling neurons in cortical regions surrounding the LPZ to drive activity within the LPZ to spiking levels, thereby accounting for the shifting RFs of LPZ neurons to the locations outside the retinal lesion. Notably, the extent of the horizontal connections, roughly 8 mm in V1, accounts for the extent of recovery of activity within the LPZ.

Cortical reorganization may have adaptive value in mediating functional recovery following CNS lesions. Psychophysical experiments done in patients with macular degeneration show enhanced perceptual fill-in through parts of the visual field affected by the lesion (Zur and Ullman, 2003). By strengthening the association field, which under normal circumstances mediates contour integration and saliency, visual cortical reorganization can promote perceptual fill-in across gaps in contours created by retinal scotomata. If a neuron shifts its RF along its association field from the lesioned part of the retina to the surrounding intact retina, it may still represent a “line label” for the original RF position, so that by being activated by contours crossing the retinal scotoma it will signal the presence of the contour at the lesioned retinal locations, in addition to the surrounding areas. Computational modeling of cortical reorganization demonstrates how cortical reorganization can mediate perceptual fill-in through a retina with the large areas of geographic atrophy and local salt-and-pepper photoreceptor loss occurring during macular degeneration (McManus et al., 2008). The model is supported by the finding that, after reorganization, neurons retain an orientation preference similar to what they had before reorganization (Das and Gilbert, 1995).

Because the extent of recovery of visual driven activity in the LPZ approximates the extent of the long-range horizontal connections, approximately 8 mm, these seem to be ideal candidates for the source of visual input into the LPZ. The changes in horizontal connections, originally documented by postmortem analysis of their density in the LPZ compared with normal cortex (Darian-Smith and Gilbert, 1994) has more recently been observed in vivo with the use of two-photon imaging (Yamahachi et al., 2009). This technique allows one to image neuronal processes lying hundreds of microns below the cortical surface. It provides high-resolution images in vivo, enabling one to discern individual axonal boutons and dendritic spines and to follow the same cellular features over repeated imaging sessions spanning weeks to months. The initial studies on dendritic and axonal dynamics in various sensory systems showed a remarkable amount of turnover in dendritic spines and axonal boutons (Chklovskii et al., 2004; De Paola et al., 2006; Majewska et al., 2006; Stettler et al., 2006; Trachtenberg et al., 2002). Though

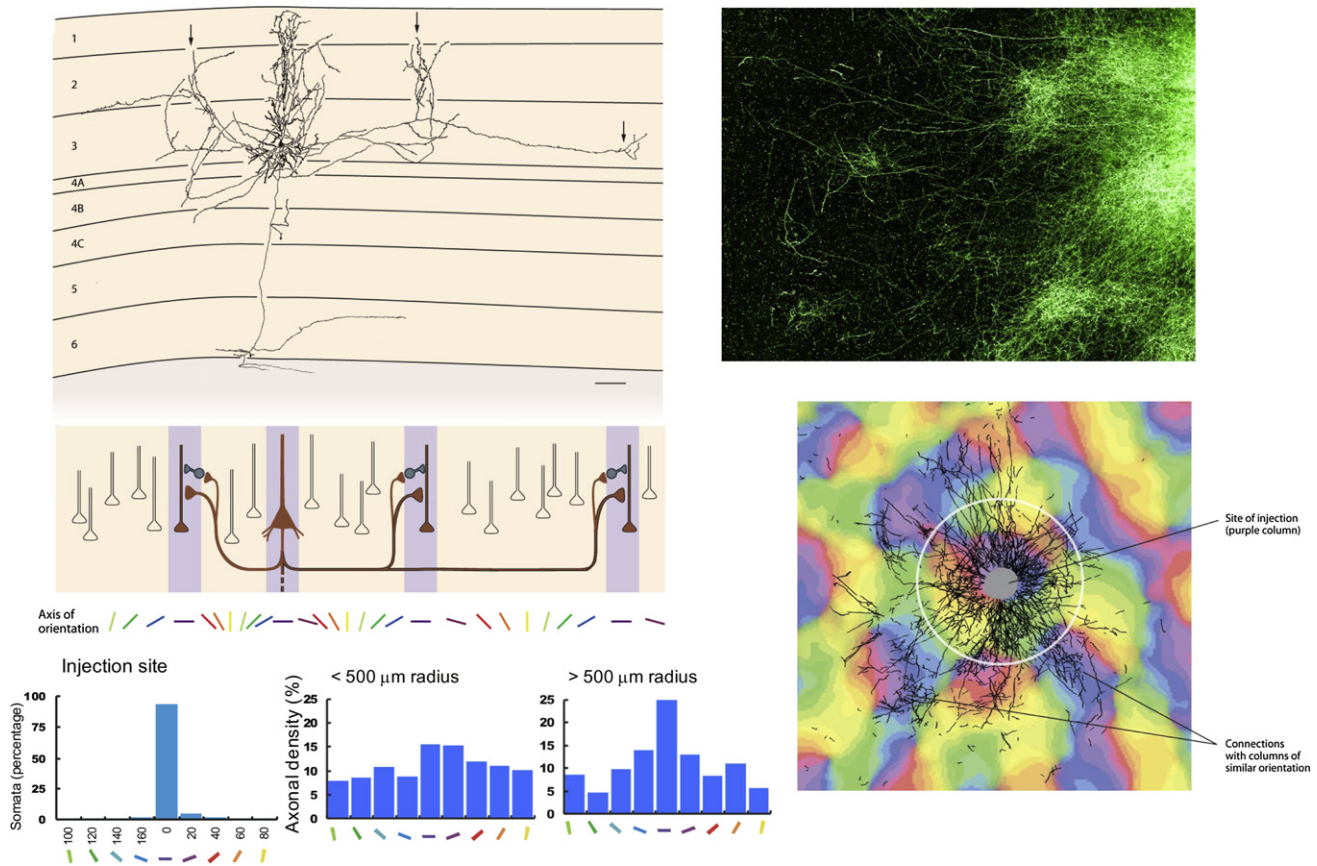


Figure 3. Relationship between Long-Range Horizontal Connections and Cortical Functional Architecture

An individual superficial layer cortical pyramidal cell (top left) forms long range connections that extend many millimeters parallel to the cortical surface, enabling their neuronal targets to integrate information over an area of cortex representing an area of visual field much larger than their classical RFs. Labeling these connections with an adenovirus carrying the eGFP gene allows one to image the axons of a population of labeled cells with a confocal microscope (top right, surface view of labeled horizontal connections in V1). Combining this labeling technique with intrinsic signal optical imaging enables one to establish the relationship between the axon collateral clusters formed by the horizontal connections and the columnar functional architecture (bottom right), where short range connections contact a wide range of orientation columns but long range connections link columns of similar orientation preference (indicated by the histograms at bottom left) (from Gilbert, 2012; McGuire et al., 1991; Stettler et al., 2002).

there has been some debate as to the amount of spine turnover and the proportion of stable spines (Grutzendler et al., 2002; Zuo et al., 2005), *in vivo* imaging has revealed a degree of dynamics of neuronal structure hitherto inaccessible by classical post-mortem anatomical techniques. A constitutive process of dendritic remodeling is seen among inhibitory neurons (Chen et al., 2011) as well as excitatory neurons. Against this background of synaptic turnover, manipulation of sensory experience, such as retinal lesions, induces a substantial increase in the extent of axonal changes.

As seen in Figure 5, within hours of making a retinal lesion, the horizontal axons in V1 undergo rapid and exuberant sprouting. At the same time there is pruning of older connections, and there is continuing turnover of axonal arbors for a number of weeks. Over time, the density of the connections from nondeprived cortex to the LPZ increases (Darlan-Smith and Gilbert, 1994; Yamahachi et al., 2009). This change provides a mechanism for the propagation of visually driven activity into the LPZ and the reorganization of cortical topography. The sprouting

occurs within the clusters of collaterals of the horizontal axon plexus, but because the cells of origin can be far from the cellular targets of the sprouting axons, the extent of reorganization can be quite large. Cortical reorganization is accompanied not only by sprouting but also by pruning of the horizontal connections, with a continuing cycle of axon addition and removal in response to the injury. This program of exuberant outgrowth and pruning is a recapitulation of the pattern of formation of connections seen early in development. Retinal lesions also produce an upregulation in the rate of turnover of dendritic spines (Figure 12; Keck et al., 2008). Many studies have focused on dendritic spines as the morphological correlates of cortical plasticity. Turnover of dendritic spines is subject to alterations in experience, with an upregulation in the rate of turnover, relative to baseline, following retinal lesions and also during learning (see below). Presynaptic changes, including sprouting and pruning of axon collaterals and turnover of axonal boutons, have been even more dramatic. Changes akin to those observed in the network of horizontal connections in visual

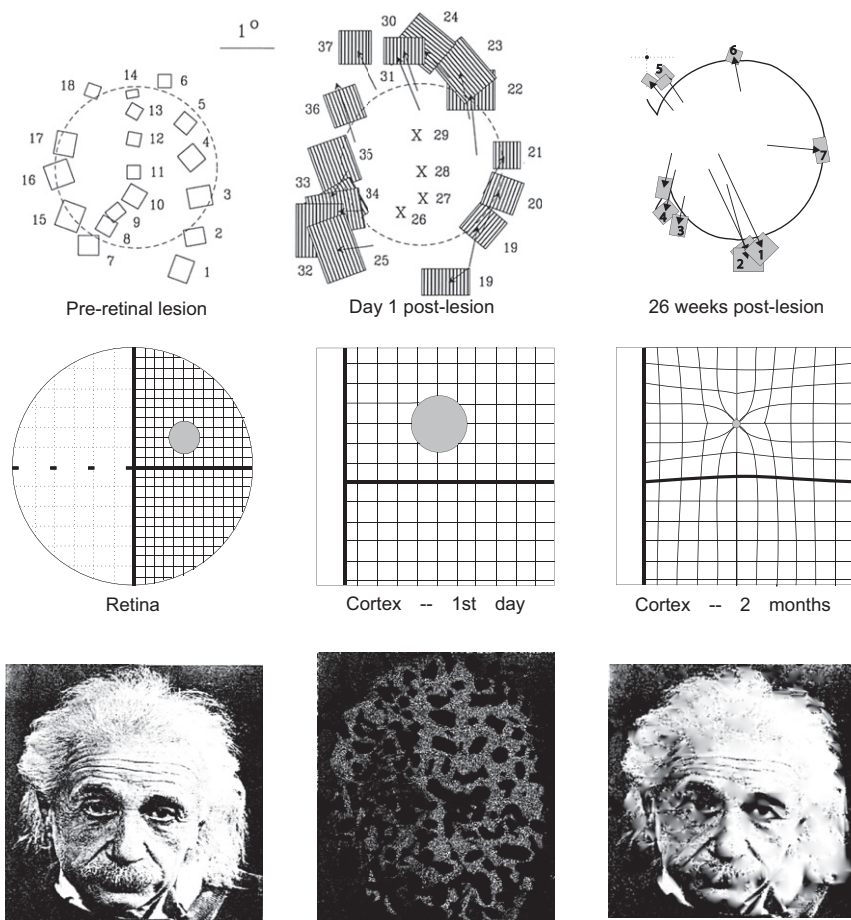


Figure 4. Changes in RFs and Topography following Retinal Lesions and Model of Perceptual Fill-In

Top row, a series of electrode penetrations in superficial layers of V1 shows topographic arrangement of RFs in the mapped cortical area. Binocular retinal lesions (dashed line) in this part of the visual field makes neurons in the center of the cortical lesion projection zone (LPZ) unresponsive to visual stimuli (sites denoted by X's). However, even on the same day of making lesions, neurons with RFs just inside the LPZ boundary have shifted their RFs to positions outside the retinal scotoma (cross-hatched RFs, middle). (Recordings made before and after placing lesions were located at the same cortical sites. The arrows start at the original RF position before the lesion and point toward the new RF position, for that cortical position, at the time of recording). Over the subsequent weeks (top right) the entire LPZ regains visually driven activity, with larger shifts in RF position (Darian-Smith and Gilbert, 1995). Middle row, the shifting RFs can be schematically represented as a remapping of cortical topography, with the initial LPZ shrinking the representation of the lesioned part of the retina and expanding the representation of the retinal loci surrounding the retinal scotoma. Bottom row, modeling the perceptual consequences of topographic remapping. The model assumes that each neuron is a labeled line for a given position and orientation, but by shifting its RF is activated by stimuli outside the retinal scotoma, thereby mediating perceptual fill-in at positions within the scotoma. Viewing an image, left, through a retina with areas of geographic atrophy and a salt and pepper loss of photoreceptors in between (which is meant to simulate visual field losses in adult macular degeneration), middle, it is difficult to identify the viewed object. But if one allows RFs to shift along the association field, maintaining their original orientation (Das and Gilbert, 1995),

the image can be effectively filled in (right). Though locally distorted, the simulated process of fill-in mediated by cortical topographic reorganization allows the image to be readily identified (from Darian-Smith and Gilbert, 1995; Gilbert and Wiesel, 1992; McManus et al., 2008).

cortex accompany reorganization in other sensory systems, including the somatosensory system (Marik et al., 2010), with sprouting from nondeprived cortex to the LPZ. In addition to changes of excitatory connections, inhibitory connections also show substantial remodeling. This is particularly pronounced for the inhibitory neurons located within the LPZ. These neurons were labeled by expressing eYFP under the control of the promoter for GAD65, the enzyme responsible for synthesis of the inhibitory transmitter GABA. The axons of the inhibitory neurons within the LPZ grow into the nondeprived regions surrounding the LPZ, the source of the excitatory axons which are sprouting into the LPZ (S.A. Marik, H. Yamahachi, and C.D.G., 2010, Soc. Neurosci., abstract). Inhibitory neurons also show dendritic changes (Keck et al., 2011). The reciprocal pattern of sprouting of excitatory and inhibitory axons may serve to maintain a balance of excitatory/inhibitory input to the reorganized cortex. Such balance is a general rule that governs cortical circuits, keeping neuronal activity within normal bounds (Froemke et al., 2007; Ozeki et al., 2009; and see review by Priebe and Ferster, 2012). The changes in axonal morphology occur quite rapidly, beginning on the same day as the making of the lesion, which can account for the initial

shifts and expansion of RFs of neurons lying just within the LPZ boundary.

The remapping of cortical topography following retinal lesions opens the possibility that experience can affect the functional properties of neurons in early sensory areas and that it can do so throughout life. Thus one must make the distinction between properties and connections that are mutable only during the critical period early in postnatal life (such as ocular dominance and thalamocortical connections) and other aspects of cortical function and other cortical circuits that can undergo change into adulthood (such as cortical topography and horizontal connections). The nature of the experience dependent changes suggests that preexisting circuits that are used for the normal integrative properties of visual cortex can become modified to promote adaptive functional changes for recovery after CNS lesions. Strengthening the association field, which is used for contour integration in normal visual processing, enables perceptual fill-in across retinal lesions. The findings on plasticity of primary visual cortex following retinal lesions raise the possibility that normal visual experience can induce plastic changes there as well, perhaps by recruiting the same cortical circuits. The phenomenon of topographic remapping following retinal lesions

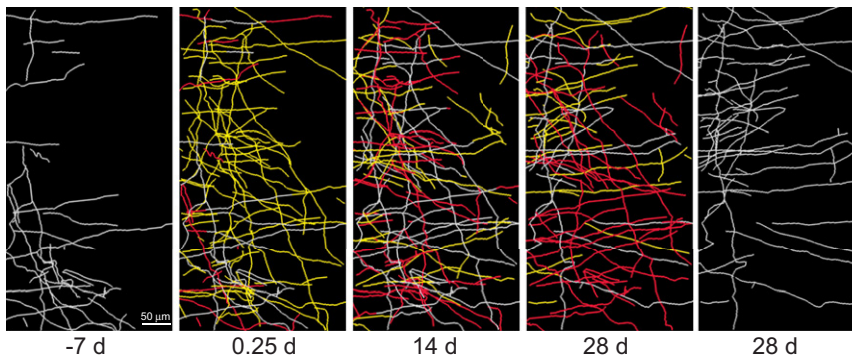


Figure 5. Axonal Sprouting and Pruning in V1 of Monkey MA Induced by Focal Binocular Lesions

Axonal tracing of two-photon microscope Z stacks acquired through a depth of 200 μm in the LPZ. Gray, axon segments that remained unchanged compared to the previous time point; yellow, segments that were added relative to the previous time point; red, segments eliminated after the previous time point. The last panel shows the axons present at the end of the sequence of imaging sessions (from Yamahachi et al., 2009).

has provided a tractable model for the study of the circuitry underlying cortical plasticity, including both excitatory horizontal connections and inhibitory connections, and has revealed the rapidity with which changes in these connections can be induced. These results provide motivation for determining whether similar mechanisms are involved in normal visual experience. We now turn to consider a prominent feature of experience dependent change in the visual system, perceptual learning. Here, we propose that the same mechanisms involved in recovery after CNS lesions are involved in the functional and structure changes associated with learning.

Cortical Changes Associated with Perceptual Learning

Performance on various visual discrimination or detection tasks can be substantially improved with repetitive practice, as is seen in a decrease of threshold for discrimination of the trained stimulus attributes such as orientation, or an increase in efficiency for detection of familiar shapes embedded in distracters (for review see Sagi, 2011). Helmholtz described perceptual learning as “the judgment of the senses may be modified by experience and by training derived under various circumstances, and may be adapted to the new conditions. Thus, persons may learn in some measure to utilize details of the sensation which otherwise would escape notice and not contribute to obtaining any idea of the object” (Helmholtz, 1866).

Perceptual learning, like other forms of nondeclarative memory (including habits and motor skill learning) is characterized by its automaticity and, unlike declarative memory, it is independent of the medial temporal lobe (Squire, 2004). Amnesic patients show normal patterns of perceptual learning (Fahle and Daum, 2002). A hallmark of perceptual learning is its specificity. As stated by Thorndike’s law of identical elements, the transfer of any learning from one task to another cannot happen unless the two tasks share identical elements (Thorndike and Woodworth, 1901a, 1901b, 1901c). When applied to perceptual learning, identical elements encompass not only identical stimulus components but also the specific task performed on the stimulus. Training at one visual field location and learning in a task involving discriminating lines of a particular orientation does not transfer to other locations or other orientations (for review see Sagi, 2011). Moreover, learning is specific for stimulus context or for the configuration of the stimulus. As shown in Figure 6, training on a three-line bisection task can lead to a marked reduction in the threshold, but it does not affect perfor-

mance on a vernier discrimination task, where the stimulus target is in the same visual field location and has the same orientation, and the tasks involve similar attributes (target position) but the context (parallel lines versus collinear lines) is different (Crist et al., 1997). Because of the selectivity of early visual cortical neurons for simple stimulus attributes, and because their RFs are restricted to a small visual field area, the specificities of perceptual learning have been attributed to functional changes in early visual cortical areas.

Numerous studies have found cortical changes associated with perceptual learning, but the changes have manifested themselves in very different ways. Some have observed changes in cortical magnification, the amount of cortical territory representing a unit of the sensory input, which can be described as “cortical recruitment.” Animals trained on a tactile vibration frequency discrimination task have a larger representation of the trained digit in primary somatosensory cortex, and animals trained on an auditory frequency discrimination task have a larger representation of the trained frequency in primary auditory cortex (Recanzone et al., 1992a, 1992b, 1993). It is plausible that the larger cortical area and larger numbers of neurons that are activated by the stimulus increases the signal-to-noise involved in discriminating the stimulus, a phenomenon referred to as probability summation. But it has been observed that performance does not always correlate with the size of the cortical area (Brown et al., 2004; Recanzone et al., 1992a; Talwar and Gerstein, 2001). The overrepresentation of a particular frequency can reduce the amount of Fisher information around the frequency peak and result in poorer rather than improved performance at that frequency (Han et al., 2007). Interestingly, cortical expansion occurring in the initial phase of training can reverse over time, even though the behavioral effects of training are retained (Yotsumoto et al., 2008). The initial expansion, however, can be a step during the encoding of learned information, and it can facilitate subsequent learning (Reed et al., 2011). In training on pitch discrimination, over representation of the familiar frequencies due to cortical recruitment in A1 can be detrimental to discrimination of the trained frequencies (Han et al., 2007). Related to the idea of cortical recruitment, fMRI studies have given somewhat conflicting results on changes associated with perceptual learning. Cortical recruitment would lead to an increase in BOLD activation with learning. In visual perceptual learning, an fMRI study reported that practicing a motion detection task caused a significant enlargement

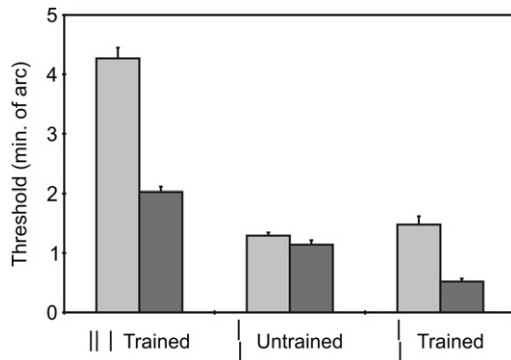


Figure 6. Specificity of Perceptual Learning

Left, training on a three-line bisection task, where the observer has to determine whether the central line among three parallel lines is closer to the one on the left or right, leads to a decrease in the task threshold. The threshold in this task is the offset from the central position of the middle bar that is required to reliably see to which side the line is closer. The light gray bars indicate the thresholds before training and the dark gray bars the thresholds after training on the three-line bisection task for the left and middle pair. Consistent with the specificity of perceptual learning, practice on this task does not transfer to a vernier discrimination task involving the same target line with a different context, a collinear line (middle). Specific training on the vernier task leads to substantial improvement in the threshold on that task (right, gray bar indicates threshold before and black bar after training on vernier task) (from Crist et al., 1997).

of the cortical territory representing the trained stimulus in area MT (Vaina et al., 1998). On the other hand, sharpening of tuning, and the associated activation of fewer neurons having greater sensitivity to changes in the trained attribute (as has been seen with training on orientation discrimination; Schoups et al., 2001; Teich and Qian, 2003), could lead to a decrease in activation. Training on a contrast discrimination task leads to reduced activation in Brodmann's areas 18 and 19, as well as areas associated with attentional control (Mukai et al., 2007) and training on orientation discrimination also reduces activation in visual cortical areas (Schiltz et al., 1999). Another study found an increase in BOLD activation in the initial period of training, which then decreased to previous levels despite the maintenance of learned performance (Yotsumoto et al., 2008). Studies on perceptual learning in the visual system do not always show map expansion, but rather show more specific changes in the tuning characteristics of visual cortical neurons (Crist et al., 2001). Cortical recruitment would seem to conflict with the requirement of specificity of perceptual learning, where presumably any task involving the expanded cortical representation should show improvement. As shown in Figure 6, for example, training on three-line bisection does not transfer to vernier discrimination, even though both involve the same cortical area. Subsequent training on vernier discrimination can then produce marked improvement specifically on that task. Moreover, expansion in one part of a sensory map would require shrinkage in the representation of other parts of the map and a consequent decrement in performance in the untrained area. Yet one can obtain substantial improvement in training at one visual field position without "robbing" performance from the adjacent positions. An alternative means of increasing the amount of information carried by an ensemble of neurons

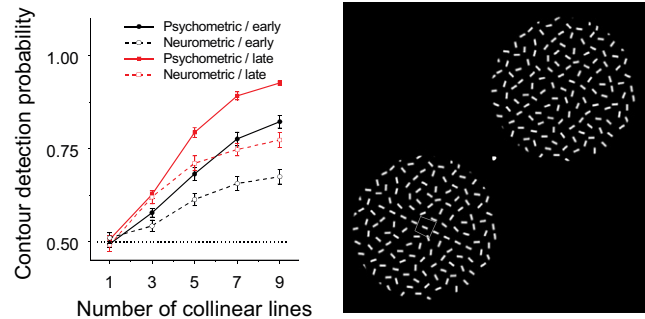


Figure 7. Perceptual Learning and Changes in V1 Associated with a Contour Detection Task

A patch of randomly oriented lines is presented in each of the two visual hemifields on either side of a fixation spot. Embedded in one patch is a linear contour consisting of a series of collinear line segments. The monkey is trained to make a saccade in the direction of the patch containing the embedded contour. In half the trials the contour lies over the RF recorded from a neuron in the superficial layers of V1. The perceptual saliency of the contour is measured as a function of the number of collinear line segments, with longer lines being more salient. In the initial period of training (first week), the monkey's performance is shown in the psychometric curve (black dashed line) and the contour-related facilitation in neuronal responses is shown in the neurometric curve (black solid line). Perceptual learning in the task is reflected in the change observed in the second week of training, with a shift up in both the psychometric (red dashed line) and neurometric (red solid line) curves. The effect is that the animal can reliably detect contours composed of fewer line segments, and there is a stronger contour related facilitation at the neuronal level (Li et al., 2008).

engaged in a task, rather than increasing the number of neurons involved, is to change the noise correlations within the ensemble, such that neurons fire more independently and therefore improve the signal-to-noise in the network. While such changes were observed in area MSTd in animals trained on a heading direction task, these changes, when analyzed for neurons with different functional relationships, did not increase the amount of information in the network (Gu et al., 2011). The way in which perceptual learning is represented in the cortex may be dependent on the nature of the discrimination task. It is important, for example, to distinguish between learning on lower order properties, such as those associated with inputs to the cortex (somatosensory vibration or acoustic frequency), feedforward properties such as orientation tuning, and the higher-order properties that are dependent on context, such as three-line bisection, vernier discrimination, or contour detection and shape discrimination. The cortical changes associated with contextually dependent perceptual learning have to account for its specificity. In fact, the way learning is represented in these tasks is to influence contextual interactions that are relevant to that task. This is exemplified by changes in contour integration accompanying learning in a contour detection task (Figure 7; Li et al., 2008) and changes in modulation of responses by changing the distance between parallel lines in a three-line bisection task (Crist et al., 2001; Li et al., 2004). By enhancing the modulation in neuronal tuning to stimulus components that are relevant to the task, learning increases the task relevant information conveyed by neurons.

As subjects learn a task, there is a change in the functional properties of neurons encoding the information involved in the

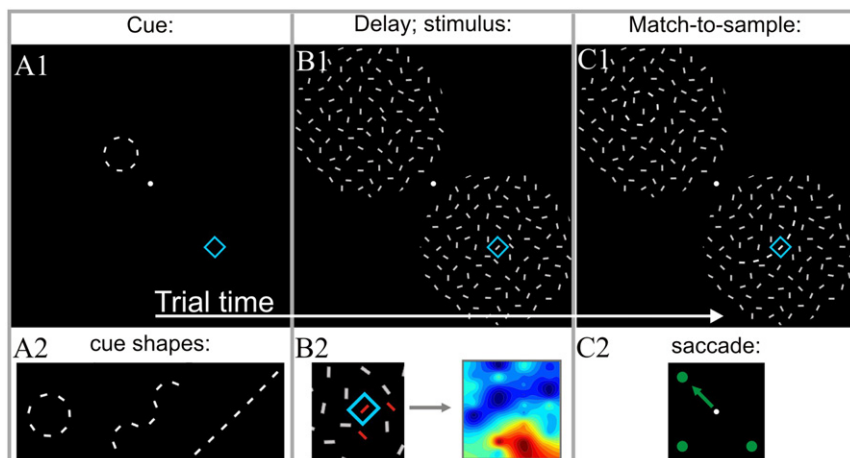


Figure 8. Shape Selectivity of Neurons in V1 of Monkeys Trained on a Shape Discrimination Task

Animals were trained to identify the shape of a contour embedded in a complex background after being given a shape cue. A1 and A2, the cue was presented in isolation (A1), and after a delay period in which stimuli of various geometries were presented (B1), the animal was shown the cue and a false target, each embedded in a complex background on opposite hemifields (C1). The task involved making a saccade toward the hemifield containing the cued target (C2). Over successive trials, during the delay period between presentation of the cue and the target (B1 and B2), a computer algorithm searched for the shape that elicited the maximum response from the cell by placing line segments with various positions and orientations in the RF surround, gradually building up the optimum three-line, five-line, and seven-line contours. Several shapes were used as cues: a circle, line, and wave (A2). The response to

different shapes are represented as heat maps (B2), with the color indicating the strength of response in the shape space, and the axes representing the position and orientation of the line segments at the ends of the contour (from McManus et al., 2011).

task. Remarkably, one can see this occur even in V1. As shown in Figure 7, the ability to detect a contour composed of collinear line segments embedded in a complex background improves with practice. Longer contours made of a larger number of line segments are easier to detect than those made of fewer line segments, and the number of segments required to reliably detect the contour decreases with practice. One can see from the black dashed psychometric curve the increase in detectability as a function of the number of line elements. This represents the animals' performance early in the period of training, during the first week. This curve steepens with practice (red dashed curve), showing the improvement in performance as a result of perceptual learning in the task. If one measures the contour related responses in V1, there is a corresponding steepening of the neurometric curve that tells how well an ideal observer can detect the embedded contours of different lengths simply based on neuronal responses.

Perceptual learning can enable neurons to carry information that is required to perform complex visual discrimination tasks, not only for contour detection, as described above, but for discriminating the shapes of contours embedded in complex scenes. For animals trained in a task requiring discriminating a circle, a straight line or a wave shape, neurons take on selectivity for related shapes (Figures 8 and 9). This illustrates that neurons in V1 can be selective for more complex stimulus geometries than short oriented line segments, and that their responses are as dependent on the global characteristics of contours extending outside their classical RFs as they are on the features within the RF center. Furthermore, each neuron's shape selectivity depends on the shape the animal is currently looking for, reflecting the importance of top-down influences on the functional properties of these neurons. The same neurons change their shape selectivities according to the cued shape the monkey is looking for, and shape expectation induces a global shift in the set of shape selectivities of the population of superficial layer V1 neurons. One can think of the properties developed as a result of learning this task in terms of the association field: the anatomical circuitry (Figure 3) allows a wide range

of potential shape selectivities, which represent the full extent of the association field. At any given time only a subset of these connections are effective, and only a portion of the association field expressed, depending on the shape that the animal is expecting.

Perceptual learning may also change which cortical areas represent the trained stimulus. In visual search tasks the ability of a stimulus to pop-out from an array of distracters depends on familiarity with the stimulus (Wang et al., 1994). One can follow the development of this pop-out quality during the period of training. Subjects learn to identify the target one location at a time, as if the target is being represented at multiple locations within a retinotopically organized area (Figure 10; Sigman et al., 2005). Consistent with this idea, cortical activation measured with fMRI shows a shift in activation, from lateral occipital cortex, when the array contains untrained stimuli, to early visual cortex (V1/V2), when the array contains the trained stimulus. The training is useful for enabling subjects to identify shapes rapidly and in parallel with other shapes. Engaging early visual cortex in the task allows such parallel processing of shape features. This finding suggests that extensive training can shift the cortical representation of the learned shape from higher to lower visual areas for more efficient and less effortful processing. This idea is supported by the evidence that extensive training on a perceptual task significantly reduces activity in the frontoparietal attentional network (Mukai et al., 2007; Pollmann and Maertens, 2005; Sigman et al., 2005). As a consequence, the automatic and pop-out quality of visual search targets differing in attributes associated with early, retinotopically mapped areas (Treisman, 1998; Treisman and Gelade, 1980) can be extended to more complex objects as a result of training. Training can alter the engagement of a cortical area in a task, as seen with animals trained on a disparity discrimination task, where inactivation of area MT affects performance before, but not after, training (Chowdhury and DeAngelis, 2008). Depending on the amount of experience one has with a given feature, and the task in which that feature is involved, the cortical area representing the feature can change. One can imagine that the ability to process, in

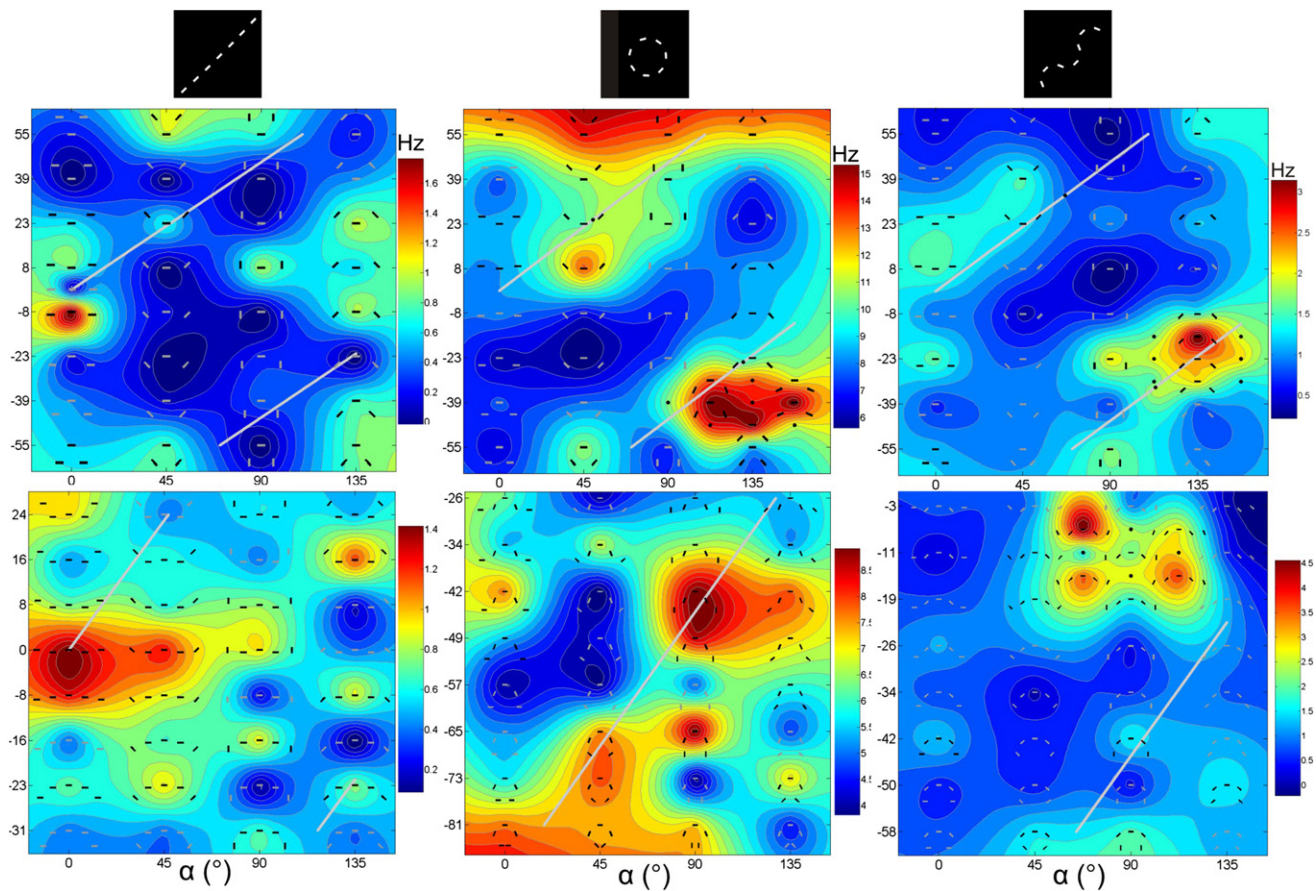


Figure 9. Influence of Learning and of Shape Expectation on V1 Shape Selectivity

The examples shown illustrate heat maps of the stimulus-response profiles of three typical neurons, with dark red indicating the strongest neuronal responses to certain contour shapes measured in a delayed match-to-sample experiment (Figure 8). As the algorithm searches for the neuron's optimal stimulus, it zeroes in on a particular portion of the shape space. The axes in the plots define a battery of geometric shapes of contours tested during the delay period (Figure 8); some shapes are illustrated as cartoons superimposed on the 2D map at corresponding points), with the top row graphs showing the best three-line contours and the bottom row the best five-line contours. The x axis (α) represents the angle of orientation of the outermost flanking bar, and the y axis (β) represents the position of the flanking bar relative to the bar centered in the RF. When the cue was a straight line (left pair), the optimum contour had a collinear profile, when the cue was a circle the neuron showed selectivity for cocircular line segments (middle pair), and when the cue was a wave shape (right pair), the optimum contour showed a reversal in curvature mirroring the wave-like profile of the cue (from McManus et al., 2011).

parallel, multiple alphanumeric characters when one learns to read would benefit from the representation of these characters in early visual cortex, and activation of V1/V2 during word identification supports this idea (Szwed et al., 2011).

Taken together, the above experiments show the effect of perceptual learning on the representation of shapes within V1. The engagement of lateral interactions in perceptual learning on contour detection and integration, as well as in perceptual tasks such as 3-line bisection and vernier discrimination, can account for its specificity. Changes in lateral connections during perceptual learning harkens back to the changes observed following retinal lesions, leading to the suggestion that both classes of experience dependent change recruit common mechanisms. Learning can modulate the influence of subsets of connections to a neuron, those carrying information about stimulus components that are relevant to the task, leaving the representation of untrained stimulus characteristics unaffected. But it is important also to emphasize that the RF properties

acquired through learning are only present when the animals is performing the trained task. As a consequence the process of learning may involve a heterosynaptic interaction between feedback connections to V1 and intrinsic connections within V1. Learning on the task would require establishing a mapping between the two sets of inputs, such that the appropriate set of lateral connections are gated when the feedback information is signaling a particular task.

Changes in neuronal function associated with perceptual learning have been found in a number of cortical areas. The experiments described above show how information about contour shape and saliency may be represented in area V1, and how learning on contour detection and discrimination tasks may involve changes in the functional characteristics of V1 neurons. Other experiments on learning orientation discrimination or on perceptual tasks such as three-line bisection and vernier discrimination (De Weerd et al., 2012; Ghose et al., 2002; Li et al., 2004; Schoups et al., 2001; Shibata et al., 2011;

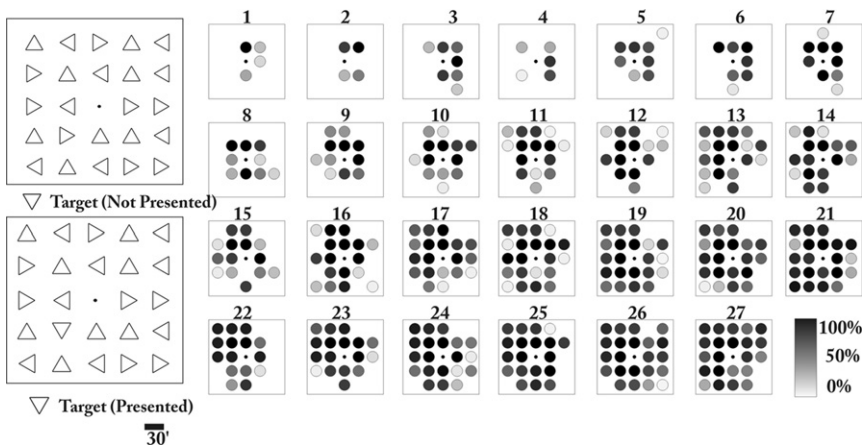


Figure 10. Learning on a Visual Search Task
Subjects were required to find a target, the downward pointing triangle, which was presented at random positions from trial to trial in a 5 × 5 field of triangles of different orientations (left). Initial performance was at chance levels, but after practice the target popped out from the distracters and was reliably detected. The improvement in performance did not occur simultaneously at all stimulus positions but instead occurred at one location at a time until subjects were able to detect the target at all positions in the array (right series from 1 to 27, with each circle representing a position in the array and the blackness of the circle indicating the performance level at that position). This suggested that the cortical representation of the target occurred at multiple locations within a retinotopically organized area (from Sigman et al., 2005).

Teich and Qian, 2003), also have demonstrated the involvement of V1. Similar to contour integration, training on detection of a difference in texture between center and surround stimuli significantly increases fMRI signals in early visual areas (Schwartz et al., 2002). Training on detection of an isolated target near contrast threshold can also selectively boost activity in early visual cortex (Furmanski et al., 2004). But these results should not be taken to indicate that V1 is the exclusive area involved. Learning on orientation discrimination has also implicated area V4 (Raiguel et al., 2006; Yang and Maunsell, 2004). Training monkeys to identify natural scene images that are degraded by adding noise specifically enhances V4 neuronal responses to those familiar and degraded pictures (Rainer et al., 2004). While training on discrimination of a simple stimulus can sharpen neuronal selectivity in early visual areas, learning to discriminate among complex objects was found to enhance object selectivity of neurons in the inferior temporal cortex (area IT) (Freedman et al., 2006; Kobatake et al., 1998; Logothetis et al., 1995). Learning to associate pairs of objects leads to similar patterns of activity among neuronal ensembles in IT after animals learn to associate the objects (Messinger et al., 2001; Sakai and Miyashita, 1991). Learning is represented in areas whose function is relevant to the trained attribute. For example, learning to discriminate small differences in direction of movement has resulted in functional changes in area MT, an area dominated by neurons selective for direction of movement (Vaina et al., 1998; Zohary et al., 1994). Contrary to this finding, other studies have suggested that perceptual learning involves changes not in areas representing the stimulus but in the read out of the sensory representation and the subsequent perceptual decision (Law and Gold, 2008). This is supported by an fMRI study that showed a correlation between learning on an orientation discrimination and activation in anterior cingulate cortex, but no such correlation with V1 activation (Kahnt et al., 2011). Psychophysical experiments on discrimination of orientation in a noisy background suggests changes in weighting of existing filters rather than changes in sensory tuning (Doshier and Lu, 1998), though electrophysiological studies have demonstrated tuning changes in V1 and V4 (Ghose et al., 2002; Schoups et al., 2001; Teich and Qian, 2003). The difference in these studies' conclusions may be due to stimulus and task design.

Moreover, as discussed above, the changes in orientation tuning seen with single unit studies might not lead to a general change in activation that would be picked up with the BOLD signal. Changes in early electroencephalographic components with learning support the idea that changes within early visual cortical areas, rather than feedback from higher order areas, mediate the improved performance (Bao et al., 2010). Supporting evidence for perceptual learning related changes comes from studies implicating functional changes in sensory areas V1 and V4 in learning on various visual discrimination tasks, rather than “readout” areas receiving unchanging sensory signals (Adab and Vogels, 2011; Crist et al., 2001; Ghose et al., 2002; Li et al., 2004, 2006, 2008; Raiguel et al., 2006; Schoups et al., 2001). The involvement of V1 in perceptual learning is also supported by the disruption of consolidation of learning by posttraining transcranial magnetic stimulation of V1 (De Weerd et al., 2012). Primary sensory cortex has been implicated in perceptual learning in other modalities, including somatosensory cortex after training in tactile vibration frequency discrimination and auditory cortex after training in pitch discrimination (Recanzone et al., 1992a, 1992b, 1993). A dichotomy of learning mechanisms has also been proposed (Adini et al., 2004): training under certain circumstances mainly enhances processing of sensory information in the visual cortex, which is less transferable between different stimuli; while training in other conditions mainly improves higher-order, cognitive functions such as decision making, which can be generalized to some untrained stimuli. When considering the unsettled issue on the exact cortical locus of the learning-induced changes, it is useful to take into account the fact that visual perception, as well as perceptual learning, is mediated by a chain of processes distributed across many cortical areas, including the visual cortex devoted to sensory processing, the frontal-parietal cortex responsible for attentional control, and the executive neural network involved in perceptual decisions. Learning can influence which areas are engaged in a task (Chowdhury and DeAngelis, 2008; Sigman et al., 2005). After training monkeys in an oddball detection task, increased neuronal responsiveness in V1 was observed in association with the animals' familiarity with the target (Lee et al., 2002). Learning to search for a geometric shape within distracters causes a concomitant decrease in

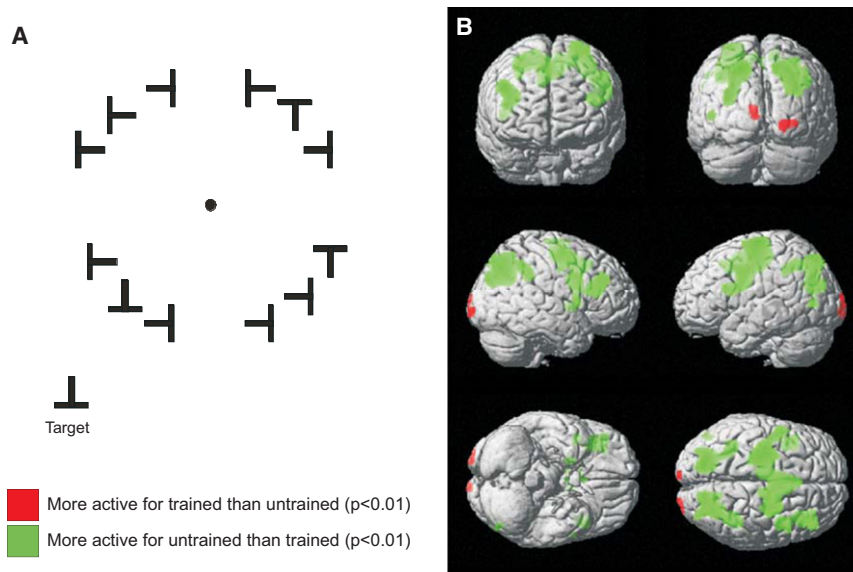


Figure 11. Effect of Learning on a Visual Search Task on Patterns of Cortical Activation Elicited by Trained versus Untrained Stimuli

Shift of stimulus representation to early visual cortex after training human subjects in a visual search task.

(A) The stimulus contained a number of Ts that were rotated by multiples of 90 degrees and distributed in the four quadrants of the visual field. The upside down T was the target. The task was to report the quadrant within which the target T appeared.

(B) Differential activation between the trained and untrained conditions. The first row shows the front and back views of the brain; the second row, the left and right hemispheres; the third row, the ventral and dorsal (bottom and top) views. The untrained condition was more active (shown in green) than the trained condition over an extended network that mainly involved the parietal and frontal cortices and lateral occipital cortices. The trained condition was more active (shown in red) than the untrained condition in the middle occipital cortex, corresponding to early visual areas in retinotopic cortex including V1 (from Sigman et al., 2005).

fMRI signals in higher visual areas responsible for shape processing (Figure 11; Sigman et al., 2005).

Learning can therefore involve plasticity of representations in any area of the cerebral cortex, including primary sensory areas. The functional specialization of each area determines the extent to which plasticity in that area mediates the process of learning, but also representation of learned information can shift between areas as performance becomes more automatic. Though learning can involve encoding very different kinds of information according to the task involved, there may be a similarity in the circuit mechanisms involved in all forms of learning. According to this idea, each area has its own association field, linking elements of a sensory or motor space via the horizontal connections, and different tasks involve recurrent signals that permit the expression of components of the association field that are required for performing the task.

Given the functional changes associated with perceptual learning and the ubiquity with which cortical areas represent learned information, there is increasing interest in the changes

in cortical circuits that are responsible for encoding learned information. With the advent of two-photon microscopy, it is now possible to image the dynamics of axons and dendrites in the living brain for extended periods of time, both during development and in the adult (De Paola et al., 2006; Hofer et al., 2009; Majewska et al., 2006; Niell et al., 2004; Portera-Cailliau et al., 2005; Ruthazer et al., 2006; Stettler et al., 2006). Training animals on a motor task—learning to change gait on an accelerated rotarod—leads to an increase in the turnover of spines of layer 5 pyramidal neurons. The extent of spine remodeling correlates with behavioral improvement after learning, supporting the idea that such structural plasticity underlies memory formation (Figure 12; Yang et al., 2009). These studies have shown that cortical circuits are very dynamic. Much attention has been directed toward the effect of experience on dendritic spines, with the suggestion that they may be the seat of the “engram” (Hübener and Bonhoeffer, 2010). But an alternative idea would suggest the learning entails changes throughout a cortical network, with information being distributed over multiple nodes.

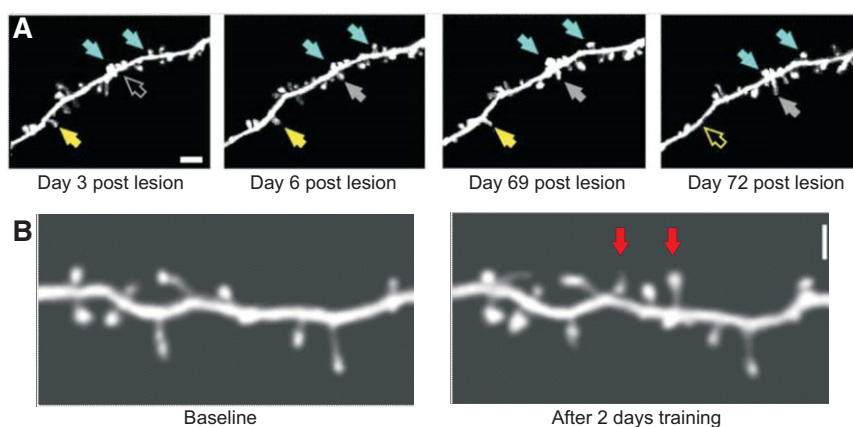


Figure 12. Experience-Dependent Changes in the Turnover of Dendritic Spines

(A) Retinal lesions cause an increase in spine turnover in the LPZ of mouse visual cortex. The blue arrows indicate stable spines, filled and open yellow arrows indicate disappearing spines, and open and filled gray arrows indicate newly appearing spines (Keck et al., 2008).

(B) Similar changes have been observed in mice during motor skill learning, with the appearance of newly formed spines (red arrows) in motor cortex that correlates with the improvement in performance (from Yang et al., 2009).

To this end, it is helpful to analyze changes occurring in many cell types, in axons as well as dendrites, and to determine how many and which inputs are affected. The long-range horizontal connections, which have been implicated in reorganization of cortical topography following lesions, present a likely substrate for the morphological changes associated with perceptual learning. By influencing subsets of horizontal inputs to cortical neurons one can achieve the context specificity seen in perceptual learning. Many observations on perceptual learning involve improvement in V1 are related to the higher order, integrative properties of V1 neurons, those based on contextual interactions, including contour integration, three-line bisection, vernier discrimination or shape discrimination (Polat and Sagi, 1994; Crist et al., 2001; Li et al., 2004, 2008; McManus et al., 2011). But inhibitory connections are likely to be involved as well—there is evidence that plasticity itself requires a shifting balance of excitatory and inhibitory connections. In auditory cortex, plasticity is associated with an initial period of disinhibition followed by a balancing of inhibition and excitation that leads to shifting tuning (Froemke et al., 2007). Inhibitory neurons show experience-dependent change, both in their dendrites (Chen et al., 2011) and their axons (S.A. Marik, H. Yamahachi, and C.D.G., 2010, Soc. Neurosci., abstract). Interareal connections can be affected by learning as well. Changes in the degree of divergence of connections from area TE to area 36 of perirhinal cortex is seen in monkeys trained on a visual pair association task (Yoshida et al., 2003). Feedback connections may also require change, if one considers the need for top-down influences to gate intrinsic cortical connections. This might be reflected in a shift of feedback connections on their target dendrites. Finding morphological correlates of learning is challenging—the governing belief concerning the synaptic basis of learning involves LTP and LTD, changing the weight of existing synapses. But recent high resolution in vivo imaging has shown that cortical circuits are capable of undergoing rapid and exuberant changes, including both sprouting and pruning, in multiple cell types. This has led to a changing view of the degree to which cortical circuits can change, even in the adult.

Future studies are likely to shed light on the mechanism underlying the specificity of perceptual learning. One can imagine that changes in specific neuronal inputs could account for the context specificity of perceptual learning. Training on a three-line bisection task, for example, does not affect performance on vernier discrimination, and this specificity could be achieved by affecting a subset of horizontal connections, those coming from the visuotopic locations involved in the task. Moreover, studying circuit changes at the level of morphology can help establish the direct involvement of an area in the observed improvements in task performance. As one gets a fuller characterization of the panoply of circuit changes associated with learning, we will be able to understand how information is encoded at the level of cortical circuits.

Summary

The adult visual cortex is capable of undergoing experience dependent change, adapting to the regularities of the environment. This leads to perceptual learning after repeated practice on discrimination tasks and to recovery of function after retinal

lesions. The functional changes have been observed in V1, though learning can involve plasticity in any cortical area. Further studies will illuminate the sequence of shifting function along the visual hierarchy. Experiments with retinal lesions have demonstrated the capacity of cortical circuits to undergo rapid and exuberant sprouting and pruning. An open question is whether circuits respond in a similar way under normal conditions of perceptual learning—are there alterations in synaptic weights in an otherwise quiescent axonal plexus, or does encoding new information require changes in axon collateral structure? The dynamic nature of the expression of task relevant information suggests an interaction between recurrent pathways carrying information about perceptual task and intrinsic circuits carrying information about stimulus context, enabling neurons to select different inputs to perform different tasks. Determining how this interaction occurs requires studying the biophysics of neural integration in the intact cortex and in behaving animals. The functional recovery following CNS lesions and the encoding of information during perceptual learning may invoke the same underlying mechanism, the association field mediated by long-range horizontal connections. While the association field in V1 mediates contour integration, it may be a general mechanism for experience dependent plasticity and adaptive processing in all cortical areas, which may utilize the same circuit mechanisms but link features that are specific for each area. Given the involvement of V1 in learning dependent changes and the detailed knowledge of its circuitry, functional architecture and RF properties, it is an ideal model system for the study of how learned information is encoded in cortical networks.

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