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CORTICAL PLASTICITY: From Synapses to Maps

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ABSTRACT

It has been clear for almost two decades that cortical representations in adult animals are not fixed entities, but rather, are dynamic and are continuously modified by experience. The cortex can preferentially allocate area to represent the particular peripheral input sources that are proportionally most used. Alterations in cortical representations appear to underlie learning tasks dependent on the use of the behaviorally important peripheral inputs that they represent. The rules governing this cortical representational plasticity following manipulations of inputs, including learning, are increasingly well understood.

In parallel with developments in the field of cortical map plasticity, studies of synaptic plasticity have characterized specific elementary forms of plasticity, including associative long-term potentiation and long-term depression of excitatory postsynaptic potentials. Investigators have made many important strides toward understanding the molecular underpinnings of these fundamental plasticity processes and toward defining the learning rules that govern their induction. The fields of cortical synaptic plasticity and cortical map plasticity have been implicitly linked by the hypothesis that synaptic plasticity underlies cortical map reorganization. Recent experimental and theoretical work has provided increasingly stronger support for this hypothesis. The goal of the current paper is to review the fields of both synaptic and cortical map plasticity with an emphasis on the work that attempts to unite both fields. A second objective is to highlight the gaps in our understanding of synaptic and cellular mechanisms underlying cortical representational plasticity.

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INTRODUCTION

In contrast to the predominant general view that applied two decades ago, it is currently accepted that cortical maps are dynamic constructs that are remodeled in detail by behaviorally important experiences throughout life. A wide variety of neuronal response reconstruction (mapping) studies in different modalities conducted in a variety of mammalian species, including humans, have shown that the cortex reorganizes its effective local connections and responses following peripheral or central alterations of inputs and in response to behavior. This capacity for reorganization at least partly accounts for certain forms of perceptual and motor learning. Currently, considerable research is aimed toward understanding the neuronal bases of this cortical reorganization and, particularly, toward establishing a causal relationship between synaptic plasticity phenomenology and representational or topographic map plasticity phenomenology. Proving that synaptic plasticity is necessary and sufficient for lesion- and experience-driven dynamic cortical representational remodeling is a challenging task. Indeed, establishing a causal relationship between forms of synaptic plasticity such as hippocampal long-term potentiation (LTP) and learning has proven to be very difficult. Establishing a causal relationship between cortical synaptic plasticity and cortical map reorganization may be more amenable to experimental analysis. In any event, it should be a valuable step toward establishing a more general understanding of the relationship between synaptic plasticity and perceptual, cognitive, and motor skill learning. The goal of this review is to briefly summarize the literature on both synaptic plasticity and topographic map plasticity, and some of the relationships that link these two levels of analysis.

To simplify the task, the focus in this review is directed toward studies conducted in adult primary sensory cortical areas. Many relevant developmental studies of cortical plasticity and many studies of cortical plasticity conducted in other cortical and subcortical zones are not encompassed in this limited treatment. Other general reviews are suggested below in the appropriate sections.

CORTICAL CIRCUITRY AND ORGANIZATION

The difficult task of understanding the neural mechanisms underlying cortical map plasticity and reorganization is compounded by the fact that we do not yet understand exactly how the cortex processes information. What are the roles of recurrent feedback? What are the respective contributions of the different cortical layers in information processing? How important and what are the specific roles of inhibition? What is the functional role of fast and slow synaptic transmission, of paired-pulse depression and facilitation? Although there is no

general theory of how the cortex operates, there are some general principles of cortical architecture and processing. These should be taken into consideration when interpreting studies of synaptic and cortical map plasticity and are briefly described below.

Flow of Information Through the Neocortex

Primary auditory, visual, and somatosensory cortices share common anatomical structures and local circuit architectures. Sensory cortex is generally divided into six layers: L-I–VI (Brodmann 1909). Sensory information reaches the cortex from the thalamus via the thalamocortical axons arising from the appropriate thalamic nuclei. The thalamocortical axons terminate primarily in L-IV and also, to a lesser extent, in L-VI and lower L-III (Hubel & Wiesel 1972, LeVay & Gilbert 1976, Landry & Deschenes 1981, Garraghty & Sur 1990). Accordingly, L-IV cells generally exhibit the shortest latency to sensory stimuli (Armstrong-James et al 1992, Welker et al 1993). Numerous papers have examined cortical architecture and information flow through the cortex in detail (for reviews, see Mountcastle 1979, White 1989, Abeles 1991, Van Essen et al 1992). However, a clear picture of inter- and intralaminar circuitry, or the transformations that take place within them, has not yet emerged. It has been suggested, based on anatomical, latency, and pharmacological data, that the principal vertical flow of information through the cortical layers may be L-IV $\rightarrow$ L-II/III $\rightarrow$ L-V $\rightarrow$ L-VI (Bolz et al 1989, Douglas et al 1989, Schwark & Jones 1989) or L-IV $\rightarrow$ L-II/III/V $\rightarrow$ L-VI (Armstrong-James et al 1992). However, at best this reflects a preferential flow, since many other interlaminar connections are present, including a robust L-VI $\rightarrow$ L-IV projection. Output to other cortical and subcortical areas occurs primarily via pyramidal cells in L-V and L-VI. L-V pyramidal cells project both to other cortical areas and to subcortical areas.

If there is a preferred flow of information vertically through the cortex, one would expect to find different response characteristics in different cortical layers, since each stage of cortical processing is presumably contributing to the processing of information and thus transforming the neuronal response characteristics in some manner. Indeed, in general, receptive fields tend to be larger and responses tend to be more complex outside of L-IV. Experiments in rat and monkey somatosensory cortex indicate that the smallest receptive fields are found in L-IV, while supragranular layers exhibit larger receptive fields than those observed in L-IV, and infragranular layers exhibit the largest receptive fields (Simons 1978, Chapin 1986, Armstrong-James & Fox 1987) or sizes equivalent to those in the supragranular layers (Sur et al 1985). Laminar analysis in cat visual cortex indicates similar patterns. Gilbert (1977) reported that the smallest receptive fields were in L-IV, intermediate size fields were in

L-III, and the largest receptive fields were in the infragranular layers. Other interlaminar differences include the observation that the degree of orientation tuning is also sharper in the supra- and infragranular layers (Chapman & Stryker 1993) and that the proportion of simple cells in the visual cortex is highest in L-IV, whereas complex cells are found mostly in supra- and infragranular layers (Hubel & Wiesel 1968, Gilbert 1977). Together these data support the notion that at each level of cortical processing, the neurons are sampling from a larger input space, receiving convergent information from the previous level, diverging out to the next level, and in the process, forming larger and more complexly integrated and combinatorial receptive fields.

In addition to the vertical flow of information, there is substantial horizontal interconnectivity, which integrates information from neighboring regions and from specific, more distant cortical zones (Lorente de Nó 1938). Excitatory horizontal projections arise mainly from L-II/III and L-V pyramidal cells and project preferentially to supra- and infragranular layers (e.g. Schwark & Jones 1989, White 1989, Abeles 1991, Tanifuji et al 1994). For any given layer, it is not clear what percentage of synapses originate from within the same cortical column, from more distant cortical regions, or from other cortical fields. However, even in L-IV, only 15–20% of the synapses are of thalamic origin (LeVay & Gilbert 1976, Benshalom & White 1986); most synapses seem to originate from intra- and interlaminar neurons. Horizontal connectivity may be of particular relevance in cortical map reorganization, since it appears that areas that develop novel receptive fields and other emergent response properties after peripheral input manipulations may rely in large part on connections from neighboring cortical sectors (see below).

CORTICAL PLASTICITY

A common feature of sensory cortical areas primarily devoted to touch, vision, and hearing is that they all represent their respective sensory epithelial surfaces in a topographic manner. In the somatosensory cortex, maps of the skin surface are somatotopic; that is, neighboring cortical regions respond to neighboring skin sites. Similarly, the auditory and visual cortex are organized according to tonotopic and retinotopic coordinates, respectively. A decade and a half of research has shown that these maps are not static in adults, but in fact undergo plastic changes in response to both peripheral manipulations and behaviorally important experience throughout life. Within certain limits, the cortex can allocate cortical area in a use-dependent manner.

The current working model regarding the neural mechanisms underlying cortical representational remodeling is that it is a result of synaptic plasticity, primarily LTP of excitatory synapses following a Hebbian learning rule.

Hebbian plasticity and Hebbian-based learning rules have guided much of the work in both the field of cortical synaptic plasticity and cortical representational reorganization. At the synaptic level, Hebbian plasticity refers to increases in synaptic strength between neurons that fire together (Hebb 1949). At a higher level of neuronal organization, Hebbian-based learning rules relate to the detection of temporally correlated inputs. In the case of topographic representations of sensory epithelia, peripheral inputs that fire in close temporal proximity are more likely to represent neighboring points on the peripheral sensory sheets. In terms of the excitatory intracortical connections in cortical networks, Hebbian learning should drive neurons engaged by behaviorally important stimuli to respond to them in a more temporally coherent manner. Thus, detection of temporally correlated inputs provides a mechanism for the formation of topographic maps and for cortical cell assemblies that specifically represent learned stimuli (for reviews, see Merzenich 1987; Merzenich et al 1990a,b; Merzenich & Sameshima 1993; Merzenich & deCharms 1996).

For the purpose of this review, we consider three levels of analysis at which cortical plasticity has been studied.

1. Synaptic plasticity, which is studied by addressing changes in synaptic parameters such as excitatory postsynaptic potential (EPSP) amplitudes and onset dynamics recorded in response to a given stimulation protocol. These studies are generally conducted in slice preparations.

2. Cellular conditioning, which studies the direct induction of plastic changes at an intermediate level by documenting changes in the selective responses of single neurons in vivo as a result of short-term (minutes or tens of minutes) conditioning protocols.

3. Representational plasticity, in which changes in distributed responses are reconstructed following enduring changes of inputs, e.g. induced by peripheral dennervation or other input manipulations, by central lesions, or by repetitive behavioral training. Most of these experiments have been performed a few hours to many months after an external manipulation, or after days to weeks of intensive behavioral training.

Synaptic Plasticity

A fundamental notion in neuroscience is that a change in the synaptic efficacy between two neurons is a substrate for learning and memory. Of particular interest to the current review is associative, or Hebbian, synaptic plasticity. This form of synaptic plasticity is thought to underlie the experience-dependent changes in receptive fields described below and is used in virtually all computational models of cortical plasticity. Here, we focus primarily on cortical

synaptic plasticity. In a few cases in which cortical data is lacking, the available hippocampal data are introduced. For more comprehensive reviews of synaptic and activity-dependent plasticity in cortex as well as in other areas and systems, see Byrne (1987), Brown et al (1990), Teyler et al (1990), Madison et al (1991), Tsumoto (1992), Bear & Kirkwood (1993), Bliss & Collingridge (1993), Linden & Connor (1995), Bear & Abraham (1996), and Katz & Shatz (1996).

LTP OF EPSPs One of the first examples of associative, or Hebbian, plasticity was described in hippocampal CA1 neurons. When presynaptic input from CA3 axons was paired with postsynaptic depolarization, the amplitude of the EPSPs was enhanced. This enhancement was long-lasting and is referred to as LTP (Kelso et al 1986, Malinow & Miller 1986, Sastry et al 1986, Wigström et al 1986). This form of associative plasticity is of particular interest because it is an instantiation of Hebb's postulate—essentially, that simultaneous pre- and postsynaptic activity results in the strengthening of the synaptic connection. For neurons to implement Hebb's rule, they must possess a coincidence detector that records the co-concurrence of pre- and postsynaptic (or very rapidly successive) activity. A particular subtype of the glutamate receptor, the NMDA receptor, fulfills this role. In the presence of Glu and postsynaptic depolarization, the NMDA receptors permit the influx of Ca^{2+}, which is a critical early step in the induction of LTP.

Studies on neocortical LTP have proven to be more complex than those of hippocampal LTP. Unlike the hippocampus, cell types and afferent pathways are not well segregated or well classified. This makes it more difficult to interpret extracellular field recordings, to reliably record from the same cell type, and to elicit monosynaptic EPSPs from a well-defined input pathway. Nevertheless, neocortical LTP is a well-established phenomenon that appears to be similar to that observed in the hippocampus and that can be induced in both cortical slices and in vivo.

One of the first demonstrations of associative synaptic plasticity in neocortex was with intracellular recordings from cat motor cortex in vivo (Baranyi & Fehér 1981). Baranyi & Fehér (1981) paired synaptic input from the ventrolateral nucleus of the thalamus with stimulation of a second pathway or intracellular depolarization. The facilitation was, however, often short lasting, accompanied by changes in input resistance and observed in less than 50% of sampled neurons. In vivo plasticity studies in the motor cortex were subsequently elaborated by Asanuma and colleagues (e.g. Iriki et al 1989, 1991) and by Woody and colleagues (e.g. Baranyi et al 1991, Aou et al 1992).

However, as with hippocampal studies, slice preparations have proven to be a more practical system in which to study synaptic plasticity. Figure 1 shows an

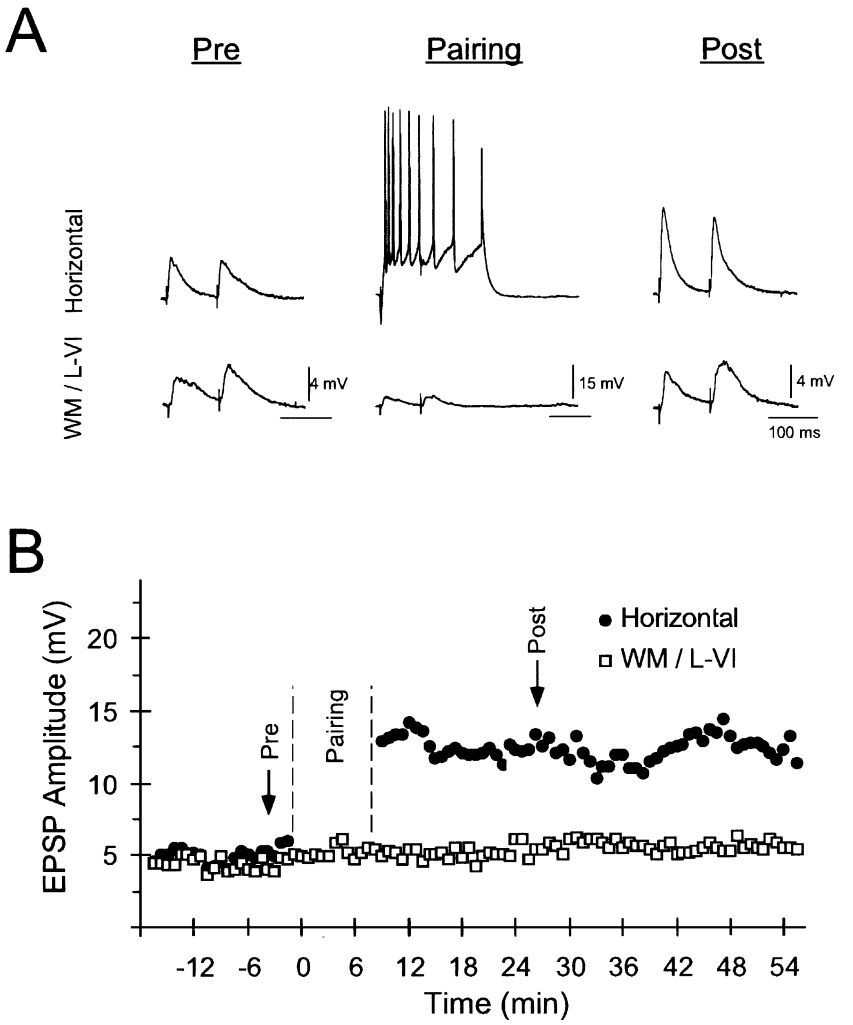

Figure 1 Associative long-term potentiation (LTP) in rat auditory cortex. (*A*) Intracellular recordings from a L-II/III pyramidal neuron while stimulating horizontal (L-II/III) and vertical (WM/L-VI) pathways. Traces show the postsynaptic response to paired-pulse stimulation (100-ms interpulse interval) before, during, and after the induction of associative LTP. LTP was induced by pairing stimulation of the horizontal pathway with a 250 ms, 1 nA depolarizing postsynaptic pulse. Both pathways were stimulated every 15 s during testing and training. (*B*) Time course of the amplitude of the first excitatory postsynaptic potential (EPSP) of both pathways. Pairing of the horizontal pathway produced a long-lasting potentiation without changing the EPSP amplitude of the white matter (WM)/L-VI pathway. Slices were from a rat of 5 weeks of age.

example of associative LTP from a slice preparation from rat auditory cortex. Recordings show EPSPs from two independent pathways elicited in a L-II/III pyramidal cell. One stimulating electrode was placed vertically at the border of L-VI and the white matter (WM); a second electrode was placed horizontally in L-II/III. As is often the case for this LTP preparation, the L-VI/WM projection produced a clear compound EPSP, which was a mixture of mono- and polysynaptic inputs. Associative LTP was induced with a spaced pairing protocol (Gustafsson et al 1987, Buonomano & Merzenich 1996) in which a single pulse was paired with a 250-ms depolarizing pulse at the same rate as testing (every 15 s). After roughly 7 min of pairing, there was an increase of approximately 150% in the EPSP amplitude of the paired pathway (horizontal) but not in that of the unpaired pathways. Associative LTP could also be induced in the same manner in the L-VI/WM pathway.

When discussing cortical LTP, it is important to consider the induction protocols used. Three protocols have been used to induce LTP: (*a*) tetanus, often a 100-Hz, 1-s stimulus applied to the afferent pathway; (*b*) theta-burst stimulation (TBS), in which 10 brief bursts at 5 bursts/s are applied, with each burst consisting of 4 pulses at 100 Hz, again delivered to the afferent pathway; and (*c*) through pairing, in which intracellular depolarization of the postsynaptic cell is paired with low-frequency afferent stimulation. This last protocol can either be massed (e.g. in which 60 pulses at 1 Hz may be paired with a 60-s depolarizing pulse) or spaced (Figure 1) [e.g. in which multiple short depolarizing pulses may be paired with presynaptic stimulation delivered at the same rate as are test pulses (often 0.1 Hz)]. These protocols are likely to differ significantly in their physiological relevance (see section on Cellular Mechanisms and Models of Cortical Map Plasticity).

Given the heterogeneity of cortical cell types, it is also important to consider which cell and layers are being recorded from and which layers are being stimulated. Many studies have relied on stimulation of the underlying WM and recording from pyramidal cells in L-II/III and L-V. These studies have shown that both tetanus-induced (for a review, see Tsumoto 1992, Bear & Kirkwood 1993) and pairing-induced LTP (Bindman et al 1988, Frégnac et al 1994) can be produced in these layers. However, these protocols often exhibited success rates below 50%. Blocking GABAergic inhibition, removing Mg^{2+}, or using slices from immature animals all seem to increase the probability of inducing LTP (see Tsumoto 1992, Bear & Kirkwood 1993). The general hypothesis is that manipulations that decrease inhibition or increase the NMDA current result in more robust LTP. Bear and colleagues (Kirkwood et al 1993, Kirkwood & Bear 1994) have shown that LTP is more reliably induced by recording field potentials or intracellularly in L-II/III by stimulating in L-IV. Using TBS, they were able to induce LTP with a success rate of over 80%. They went on to

show that cortical LTP exhibits many of the properties seen in hippocampal LTP, including (*a*) associativity, i.e. plasticity can be induced by pairing synaptic input with intracellular depolarization; (*b*) dependence on NMDA receptors; and (*c*) input-specificity, i.e. independent inputs to a postsynaptic neuron could be independently potentiated.

Associative plasticity (Hebbian plasticity) has been demonstrated using pairing protocols in a variety of different areas and cortical lamina, including auditory cortex (Figure 1) (DV Bounomano, unpublished findings), somatosensory (Crair & Malenka 1995, Markram & Tsodyks 1996), and visual cortex (Kirkwood & Bear 1994, Frégnac et al 1994). At the same time, there has been significant variation of the success rate for inducing LTP in sampled neurons depending on age and the sites of stimulation and recording. Crair & Malenka (1995) argued that age-dependent variability may be the result of a critical period. Using a pairing protocol, they induced LTP in the thalamo-cortical synapses of the mouse barrel cortex. They recorded a dramatic decrease in the percentage of cells that exhibited LTP in mice older than 7 days of age.

LONG-TERM DEPRESSION OF EPSPs In discussing long-term depression (LTD) of excitatory synapses, it is important to distinguish between different types of LTD. Homosynaptic LTD refers to synaptic depression, in which synaptic activity is necessary and sufficient to induce synaptic depression. Heterosynaptic LTD is a passive form of depression; activating a second pathway produces a depression of an inactive pathway(s). Associative LTD can be defined as (*a*) instances in which both pre- and postsynaptic events are necessary, specifically, when LTD is induced when presynaptic and postsynaptic activity follow a specific temporal patterning, or (*b*) instances when one pathway is activated in conjunction with a specific degree of depolarization/hyperpolarization of the postsynaptic cell. Note that these definitions are not absolute and can overlap.

The first protocol widely accepted as producing homosynaptic LTD was described in the hippocampus (Dudek & Bear 1992, Mulkey & Malenka 1992). Subsequently Kirkwood et al (1993) showed that the same low-frequency stimulation protocol (900 pulses at 1 Hz) induced LTD of the L-IV $\rightarrow$ L-II/III connections of visual cortex. In both the hippocampus and cortex, this form of homosynaptic LTD is dependent on NMDA receptors and is input specific. This low-frequency protocol did not induce LTD in the WM/L-VI $\rightarrow$ L-IV connections in adult animals, although it could produce LTD in these connections in slices from juvenile animals when inhibitory postsynaptic potentials (IPSPs) were blocked (Dudek & Friedlander 1996).

Heterosynaptic LTD has been reported in the CA1 region of the hippocampus (Lynch et al 1977, Pockett et al 1990, Cummings et al 1996, Scanziani et al 1996), in CA3 (Bradler & Barrionuevo 1990), and in the neocortex (Hirsch et al

1992, Volgushev et al 1994). Heterosynaptic LTD induction protocols generally consist of tetanization of one pathway while observing LTD in another inactive pathway, or of producing strong postsynaptic depolarization through intracellular current injections. One of the first demonstrations of heterosynaptic LTD was in vivo in the perforant path-to-dentate gyrus projection (Levy & Steward 1979, Abraham & Goddard 1983). In that preparation, tetanization of the ipsilateral perforant path produced a reliable and long-lasting depression of the input from the contralateral perforant pathway. Scanziani et al (1996) have recently shown in CA1 neurons in vitro that tetanic stimulation of one pathway (resulting in LTP) produces LTD in a second pathway.

An example of associative LTD has been reported by Artola & Singer (1990) in rat visual cortex slices. They used tetanic stimulation of a test pathway while pharmacologically manipulating the degree of postsynaptic depolarization. Specifically, tetanic stimulation in the presence of 0.1–0.2 μM bicuculline produced LTD of the WM $\rightarrow$ L-II/III or L-II $\rightarrow$ L-II/III pathway. In the presence of 0.3 μM bicuculline, the same stimulus elicited LTP. Low levels of bicuculline should leave inhibitory inputs partially intact, resulting in relatively little postsynaptic depolarization. Higher concentrations of bicuculline should result in a higher level of postsynaptic depolarization. Thus, the authors proposed that there was a modification threshold for the induction of LTD and LTP. Although LTD was not dependent upon NMDA receptors, it was proposed that LTD and LTP must rely on the influx of Ca^{2+}. If the Ca^{2+} influx is below a particular threshold, LTD occurs; if the threshold is exceeded, LTP occurs. Experiments with Ca^{2+}-chelators applied to visual cortex neurons support this notion (Kimura et al 1990). Note that we identified this form of depression as associative LTD because in vivo, it is the activity of other inputs that determines the level of postsynaptic depolarization and whether LTD or LTP is induced. Frégnac et al (1994) used an associative protocol to induce a depression of input to L-II/III pyramidal cells of guinea pig and cat visual cortex. By pairing low-frequency WM stimulation with hyperpolarization for 90 trials, they were able to induce synaptic depression in 40% of the cases. The depression generated was pathway specific but generally did not last more than 10–15 min.

A second form of associative LTD that has recently been reported relies on multiple presentations of pre- and postsynaptic activity, in which presynaptic activity always follows postsynaptic depolarization by a certain delay. Markram et al (1997) have shown in L-V pyramidal cells that if a presynaptic action potential (AP) precedes a postsynaptic AP by 10 ms, LTP ensues. By contrast, if the presynaptic AP follows the postsynaptic AP by 10 ms, LTD ensues (see also Debanne et al 1994).

Low-frequency stimulation protocols appear to be the most reliable way to induce LTD in the cortex, and therefore relatively less is known about

heterosynaptic and associative forms of depression in the cortex. At the same time, it seems likely that heterosynaptic and associative LTD are likely to be more relevant than the homosynaptic forms of LTD for generating cortical representational plasticity. The prevailing working hypothesis for both experimentalists and theoreticians is that the reorganization of cortical stimulus representations and maps relies on the depression of inputs from inactive afferents. Heterosynaptic LTD is seen as one mechanism that could achieve that depression (see below).

INHIBITORY PLASTICITY It is not the strength of EPSPs alone that determines whether or not a neuron will fire in response to an input. Rather, it is the balance of excitatory and inhibitory inputs. Twenty-five percent of all neocortical neurons are believed to be GABAergic (Hendry et al 1987, Beaulieu et al 1992, Ren et al 1992), and approximately 20% (Beaulieu et al 1992) of all synapses are GABAergic. In addition to depressing or blocking neuronal responses, inhibition may play an important role in shaping neuronal responses (e.g. Dykes et al 1984, Sillito 1984, Crook & Eysel 1992), particularly governing the temporal response properties of neurons (Buonomano & Merzenich 1995, Buonomano et al 1996). Further, inhibitory plasticity may play an important role in cortical map reorganization (Jacobs & Donoghue 1991, Jones 1993). Deafferentation of visual cortex (Hendry & Jones 1987) or somatosensory cortex (Welker et al 1989b, Garraghty et al 1991) produces a down-regulation of GABA markers, while chronic stimulation can produce an up-regulation (Welker et al 1989a). Thus, it is very important to understand (*a*) whether plasticity applies exclusively for the synapses between excitatory cells (Ex $\rightarrow$ Ex synapses) or whether it is also observed in inhibitory circuitry, that is, applies for the EPSPs from an excitatory cell onto an inhibitory cell (Ex $\rightarrow$ Inh synapses) and/or for the IPSPs between an inhibitory and an excitatory cell (Inh $\rightarrow$ Ex synapses); and (*b*) whether or not synaptic plasticity follows learning rules similar to or different from NMDA-mediated LTP.

Tetanus-induced plasticity of $GABA_A$-mediated fast IPSPs onto pyramidal neurons (Inh $\rightarrow$ Ex) has been examined in adult rat visual cortex (Komatsu & Iwakiri 1993, Komatsu 1994). IPSPs were recorded in L-V pyramidal cells and elicited by L-IV stimulation in the presence of both NMDA and AMPA receptor blockers. High-intensity tetanic stimulation (50 Hz, 1 s) produced a long-lasting increase of approximately 40% in the amplitude of the IPSP. As with LTP, the change was specific to the conditioned pathway. LTP of IPSPs was induced whether the postsynaptic cell was voltage clamped at -80 or $+30$ mV during conditioning, indicating that unlike associative EPSP plasticity, IPSP potentiation was independent of the membrane potential. Komatsu & Iwakiri (1993) also reported that LTD of IPSPs could be induced if tetanization

was applied without NMDA receptor blockade in the presence of bicuculline. Although these experiments show that, like excitatory plasticity, both increases and decreases in IPSP amplitude can be induced, both the rules governing the changes and whether plasticity can be induced with more physiological protocols remain to be determined.

Unfortunately very little is known regarding the plasticity of Ex → Inh synapses. To our knowledge, there have not been any studies of Ex → Inh plasticity in the cortex, although there have been a few reports of Ex → Inh plasticity in the hippocampus. McMahon & Kauer (1997) reported that the excitatory inputs onto local inhibitory neurons in CA1 undergo LTD in response to the same tetanic stimulation that induces LTP in pyramidal neurons. This form of LTD was not dependent on depolarization in the interneurons. Regarding the computational role of Ex → Inh plasticity, it is important to note that this form of plasticity may not exhibit pathway specificity. It has been suggested that the spines on which Ex → Ex synapses generally occur may play an important role in synapse specificity by establishing biochemical compartmentalization (Koch & Zador 1993). Since most Ex → Inh and Inh → Ex synapses do not terminate on dendritic spines, it may be that if synaptic plasticity occurs, it is not equivalently input specific. Indeed the LTD reported by McMahon & Kauer (1997) was not.

Cellular Conditioning

Cellular conditioning experiments are important intermediate approaches between synaptic plasticity and cortical map plasticity experiments. Most of these studies represent an in vivo test of Hebb's rule, in experiments designed to modify the selective response properties (often, the receptive fields) of single neurons by associating inputs across a narrow window of time or by directly manipulating the membrane potential in conjunction with the application of external stimuli.

For example, Frégnac et al (1988, 1992) used extracellular recordings from orientation-selective cells in V1 of kittens and cats and paired iontophoretically driven neuronal activity with presentation of bars of light of varying orientation. One orientation (S^+), generally the nonpreferred orientation of the cell, was paired with neuronal activity by passing a positive current through a KCl electrode. A second orientation (S^-), generally the preferred orientation, was paired with a decrease in neuronal firing by applying a negative current though the electrode. Frégnac and his coworkers (Frégnac et al 1988, 1992) showed that a significant percentage (32%) of sampled neurons exhibited a shift in orientation preference consistent with the training protocol, i.e. an increased response to S^+ and/or a decreased response to S^-. They also demonstrated that changes in receptive field properties were more easily induced in younger animals. Gruel

et al (1988) have reported similar changes in orientation selectivity after pairing bar presentations with iontophoretic applications of glutamate.

Related cellular conditioning experiments in the auditory cortex have been performed by Cruikshank & Weinberger (1996) and by Ahissar and colleagues (Ahissar et al 1992). Cruikshank & Weinberger (1996) used a protocol similar to that of Frégnac et al (1992). A tone close to the cell's best frequency was paired with a decrease in neuronal activity (S^-), while a tone further from the cells best frequency was paired with neuronal activity (S^+). In the Cruikshank & Weinberger study, 7 of 22 (32%) cells showed either an increase in S^+ and/or a decrease in S^-. However, the fact that only 2 of 7 cells exhibited both an increase in S^+ and a decrease S^-, in conjunction with the fact that there was a significant difference in the average magnitude of the responses to S^+ and S^- before training began, makes these results more difficult to interpret than those of Frégnac and colleagues. Single-unit extracellular studies by Ahissar et al (1992) were specifically designed to assess associative training-induced changes in the correlation strengths of functionally coupled neuronal pairs that were separated by several hundred microns across the cortex. One neuron of a pair functioned as a conditioned stimulus (CS) neuron, and the second functioned as a conditioned response (CR) neuron. The unconditioned stimulus (US) was an auditory stimulus capable of driving the CR neuron and guiding the monkey's performance on an auditory task. Activity in the CS neuron triggered the US and therefore activity in the CR neuron. Cross correlations before and after training revealed a short-lasting increase in the coupling between the CS and CR neuron. These results revealed apparently powerful plasticity changes in excitatory intracortical interneuronal connections obeying a Hebb rule.

Together, these more direct contemporary cellular conditioning experiments along with various preceding single-neuron plasticity experiments (for reviews, see Woody 1986, Weinberger 1995) support the relationship between Hebbian synaptic plasticity and changes in selective neuronal responses, including cortical receptive fields. Pairing an external stimulus (S^+) with postsynaptic activity should be equivalent to in vitro associative LTP experiments in which WM stimulation is paired with postsynaptic activity. The relationship with the decrease in activity (or strength of discharge correlations) for an S^- stimulus and LTD is less clear. A decrease in S^- is unlikely to be accounted for by low-frequency LTD. More likely, a form of associative or heterosynaptic LTD is in operation. As mentioned above, Frégnac et al (1994) were able to produce LTD by pairing synaptic inputs with hyperpolarization, which may be equivalent to their S^- protocol in which they inhibited APs by passing negative current through an extracellular electrode. On the other hand, Gruel et al (1988) only conditioned an S^+ stimulus but reported decreased responses to nonpresented stimuli. Thus, Frégnac et al's (1994) in vivo and in vitro results support an associative form of

LTD, while Gruel et al's (1988) findings would appear to implicate a form of heterosynaptic LTD. More quantitative data is needed to determine how robust these effects are and to define necessary conditions for inducing changes in specific cortical neuron responses.

In one final type of direct experimental protocol, plasticity was induced by intracortical microstimulation (ICMS) (Dinse et al 1993, Recanzone et al 1993, Spengler & Dinse 1994). In vivo experiments in sensory cortex of rats and monkeys revealed that low-intensity burst stimulation (13 pulses at 300 Hz every second for a few hours) generated marked changes in specific selective responses over a cortical zone several hundred microns across. As ICMS proceeded, the specific inputs that neurons responded to initially only at the stimulation site began to emerge for cells at progressively greater distances away from the stimulus site. Furthermore, over this same zone, the original inputs that were effective minutes or hours before in driving the same neurons were profoundly suppressed, apparently simultaneously with the development of their new excitatory receptive fields. The specific changes on the excitatory and inhibitory side of the neurons undergoing this representational change are still unknown. However, through the period of induction of change, cells may undergo a closely coordinated change in the excitatory-inhibitory balance (Recanzone et al 1993).

Cortical Representational Plasticity

Primary cortical sensory areas such as S1, A1, and V1 are organized topographically. It is now clear that representational topographies and, more generally, the distributed representations of applied sensory stimuli can be remodeled by inducing peripheral or central changes in input sources and schedules. However, although the effects of input disturbances or behavioral training are commonly recorded by distributed response–mapping experiments conducted in the cortex, it is not necessarily the case that the only site—or, indeed, the primary site—of plasticity is in the cortex. At the same time, the cortex is clearly a contributing site of plasticity (see section on Sites of Cortical Map Plasticity). For comprehensive reviews of cortical map reorganization in both developmental and adult studies, see Merzenich et al (1984, 1987, 1990a,b), Wall (1988), Kaas (1991), O'Leary et al (1994), Merzenich & Jenkins (1992), Gilbert (1992, 1996), Merzenich & Sameshima (1993), Weinberger (1995), and Merzenich & deCharms (1996).

SOMATOSENSORY CORTEX One early demonstration of adult cortical plasticity was in the primate somatosensory cortex. There are two topographic representations of the body surface within cytoarchitectonic areas 3b and 1 in adult monkeys (Merzenich et al 1978). Transecting the median nerve of a monkey

removes the normal input to both these areas from the glabrous (ventral) portion of digits D1–D3 (D1 is the thumb). Such a manipulation does not, however, result in a permanent large area of unresponsive cortex; it produces a dramatic reorganization of the somatotopic map (Merzenich et al 1983a,b). Immediately after transection, inputs from dorsal skin areas, the volar palm, and the bordering zones on D3 and D4 are unmasked in a limited sector of the cortex previously representing glabrous surfaces of D1–D3 innervated by the median nerve. This unmasking is thought to be the result of existing horizontal connections or thalamocortical inputs that were previously suppressed by inhibitory circuitry. Over the course of a few weeks, representations of the bordering glabrous skin surfaces progressively expand to occupy larger and larger portions of the former median nerve cortical representational zone (Figure 2). Over the same time period, the reorganized cortical zone develops a progressively more refined spatial representational resolution, topographic order, and response salience.

In a related series of experiments in monkeys, the cortical representations of the hand in area 3b were examined before and after the amputation of digit D3, or D2 and D3 (Merzenich et al 1984). Two to eight months after amputation, most of the cortex that originally responded only to the skin surfaces on the amputated digit(s) now responded to inputs from adjacent digits or the subjacent palm. In the cases of D2 and D3 amputation, a zone occupied by inputs from noncutaneous input sources (e.g. from deep receptors innervating the hands or muscles) generally remained, indicating that the major topographic changes for cutaneous afferent representations were limited to a cortical zone extending 500–700 μm on either side of the initial boundaries of the amputated digits. Although the cortical area representing the digits significantly expanded, representational changes were relatively local. Most of the changes applied to the representation of the intact, immediately adjacent digits. There was not a significant increase of the representation of more distant digits, for example, D5.

These experiments demonstrated that immediately after nerve transection, a large portion of the cortex was unresponsive but that over the course of a few weeks, this unresponsive area came to be excited by inputs from neighboring skin surfaces. Other similar examples of reorganization in adult somatosensory cortex in response to denervation or amputation have been reported in the raccoon (Rasmusson 1982, Kelahan & Doetsch 1984), flying fox (Calford & Tweedale 1988), cat (Kalaska & Pomeranz 1979), and rat (Wall & Cusick 1984).

One of the most dramatic examples of cortical reorganization was reported by Pons et al (1991). They mapped the cortex of monkeys that had undergone deafferentation of the dorsal roots (C2-T4) several years before, thereby depriving a cortical area of over 1 cm^2 of its normal input from the arm and hand. Their maps revealed that all of the deprived area had developed novel responses

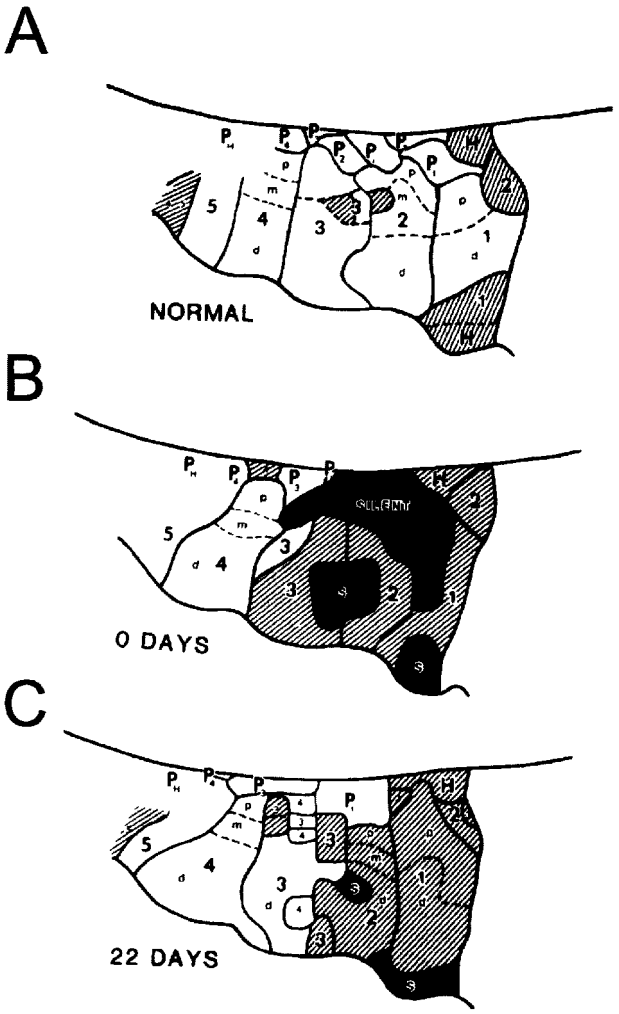

Figure 2 Progression of the reorganization of the cortical map in response to median nerve transection. Somatotopic representation of the hand in area 3b from a single monkey before (*A*), immediately after (*B*), and 22 days after (*C*) transection of the median nerve. Numbers 1–5 represent the digits; the letters p, m, and d represent the proximal, middle, and distal portion of each finger. *Hatched areas* represent the dorsal surface of the hand, and *black* represents silent areas. Transection of the median nerve deprives the cortex of input from the glabrous surface of digits D1–D2. Immediately after transection, much of the cortex remained silent, while some areas exhibited responses to the dorsal surface of D1–D3. A few weeks after transection, very little cortex remained unresponsive, and novel responses to D3 and the dorsal surface of D1–D3 emerged. [Modified from Merzenich et al (1983b).]

to neighboring skin areas, including the face and chin. Results in several mapping studies in humans indicate that large-scale remodeling can occur in human somatosensory and motor cortical areas in the weeks or months immediately following limb amputation (Fuhr et al 1992, Kew et al 1994, Yang et al 1994, Knecht et al 1995).

Hebbian plasticity is thought to play an important role in both cortical development and cortical reorganization in adult animals. Since Hebbian plasticity is based on the temporal correlations of inputs and since inputs from neighboring skin areas should in general be more correlated than nonadjacent areas, neighboring cortical areas should represent neighboring surface areas, thus establishing a topographic map (Merzenich 1987, Merzenich et al 1990a,b). A prediction that emerges is that if the correlation between neighboring skin surfaces can be artificially changed, modifications in the cortical maps should be observed. This hypothesis was initially tested by artificially changing the normal correlations between skin surfaces by surgically connecting the skin surface of two fingers (the formation of syndactyly) or by translocating patches of innervated skin across the hand. Several months after digit fusion, cortical mapping revealed that somatotopic boundaries between the fused digits had disappeared and that many cortical units had double digit receptive fields (Clark et al 1988, Allard et al 1991). An alternative form of this experiment was conducted in human subjects in which the representations of digital skin were mapped using magnetoencephalography (MEG) before and after the reversal of a congenital digital syndactyly (Mogilner et al 1993). Before their surgical separation, input sources from adjacent digits very strongly overlapped with one another. After digit separation, which could be expected to again dramatically alter the temporal structure of inputs delivered to the cortex, digital representations rapidly moved apart representationally in the cortex.

Similarly compelling results were obtained in experiments in which innervated skin islands were translocated across the hand (Clark et al 1986, Merzenich et al 1990a,b). In these experiments, new representations of these skin surfaces emerged at new locations in the cortex in a topographic location consistent with their new temporal neighborhood relationships, and therefore consistent with the hypothesis that Hebbian synapses underlie cortical map formation and alteration.

BARREL CORTEX The barrel cortex is the part of the somatosensory cortex in rodents that represents the mystacial pad, that is, the long facial vibrissa. Each vibrissa is represented in a roughly circular cortical area referred to as a barrel. The topographic arrangement of the barrels obeys the same arrangement as the vibrissae on the mystacial pad. The cells within the barrel respond preferentially to a principal whisker but can respond to a lesser degree to neighboring whiskers.

Given the clear topographic arrangement of the vibrissae, the ease of vibrissae manipulation and stimulation and the barrel system has proved to be useful in the study of cortical plasticity.

Developmental studies have shown that damage to the vibrissa follicle produces alterations in both barrel formation and projection of the thalamocortical afferents (Van der Loos & Woolsey 1973, Killackey et al 1976). Clipping all vibrissae but one of newborn rats does not result in anatomical changes in barrel morphology but does alter the receptive fields. Neurons from barrels corresponding to clipped vibrissae tend to respond to the spared vibrissa.

In adult rats it has been shown that whisker pairing, which involves clipping all vibrissae but two neighboring ones, produces plasticity of the cortical representation of the vibrissae (Diamond et al 1993, 1994). Recordings in the barrel cortex 30 days after clipping all whiskers but D1 and D2 showed that (*a*) The cells in barrels D1 and D2 continued to respond preferentially to their principal whisker (D1 and D2, respectively); however the response magnitude was increased. (*b*) Cells in D2 that had responded equally well to whisker D1 and D3 in control animals developed an asymmetric receptive field and responded better to the unclipped intact neighbor D1. (*c*) Responses of cells in barrel D2 to the clipped whiskers were reduced in comparison to those responses in D2 barrels from control animals. This last observation was important because it confirmed that in addition to the potentiation of the spared inputs, a depression of the lesioned inputs was occurring in parallel. This effect is difficult to study in experimental models involving permanent lesions to the sensory periphery.

VISUAL CORTEX Removal of the normal input to part of the adult primary visual cortex also results in map reorganization. Since many V1 neurons exhibit binocular receptive fields, it is necessary to lesion both retinas in order to deprive part of V1 of all its normal input. Kaas et al (1990) have lesioned a 5–10° area of the one retina and enucleated the second retina of adult cats to achieve this. Recordings made weeks after the lesions revealed that the area previously responsive to the lesioned area acquired new receptive fields corresponding to areas surrounding retina around the lesion. Chino et al (1992) reported that the changes to the lesioned eye required the removal of all normal retinal input, that is, both retinas had to be lesioned. By mapping V1 two months after producing a focal lesion in one retina, they showed that the topography was relatively unaltered: The cortical area corresponding to the retinal lesion did not respond to any stimuli to the lesioned eye but responded normally to the unlesioned eye. However, a few hours after enucleation of the unlesioned eye, the silenced area developed responses to retinal locations surrounding the focal lesion. By contrast, Schmid et al (1996) have reported that focal lesions in one eye will produce altered topographic maps in response to the lesioned map

while simultaneously exhibiting normal topographic maps to the normal eye. Schmid et al (1996) also reported that the novel responses were comparatively weaker and underwent rapid habituation, indicating that the novel responses were not equivalent to normal responses. These results also contrasted with those generated by Chino et al (1995) after bilateral lesion induction in which relatively normal orientation selectivity and response amplitude were reported to emerge in the zone formerly representing the lesioned retinal sector.

Striate cortex deprivation experiments have also been performed by using matched focal binocular retinal lesions (Heinen & Skavenski 1991, Gilbert & Wiesel 1992). Gilbert & Wiesel (1992) observed increases in receptive field size immediately after focal binocular lesions appeared for cortical cells with receptive fields near the edge of the retinal scotoma. After a few months, the silenced area responded to retinotopic loci representing the retinal zones that formerly surrounded the lesion. In a related series of experiments, Sugita (1996) reported that V1 neurons in monkeys can develop novel receptive fields to the ipsilateral hemifield after monkeys have worn reversing spectacles for several months. These studies suggest that neurons can acquire novel inputs not only from neighboring retinal areas but also from distant nonadjacent areas.

AUDITORY CORTEX Studies in the guinea pig auditory cortex have shown that after restricted monaural lesions of the cochlea there is a reorganization of the tonotopic map in response to the lesioned ear (Robertson & Irvine 1989). One month after an initial cochlear lesion, neurons in the deprived cortex responded to tone frequencies adjacent to the frequency range damaged by the lesion. The intensity thresholds of recorded responses in the reorganized zone were similar to those recorded in normal cortex. Rajan et al (1993) recorded that a similar reorganization occurred in the cat auditory cortex and that the tonotopic map to the nonlesioned ear remained unaffected. Bilateral lesions to the high-frequency (basal) cochlear sector in monkeys also produced an increased representation of frequencies neighboring those whose inputs were destroyed by the cochlear lesion (Schwaber et al 1993).

Together, these results have shown that in all three systems, when a given cortical area is deprived of its normal afferent inputs, it reorganizes so that the deprived area becomes responsive to sensory inputs formerly represented only within the cortical sectors surrounding those representing lesioned input sources.

Training-Dependent Cortical Map Plasticity

The examples of cortical map reorganization discussed so far were primarily produced by depriving the cortex of its normal inputs by lesioning limited sensory input sources. Here, we examine cases showing that changes in cortical

map organization also occur as a result of training animals on tasks that produce specific, differential patterns of activity in identified cortical sectors. These training-dependent experiments have established several correlations between changes in distributed representations of behaviorally important stimuli (cortical representational reorganization) and the progression of learning.

SOMATOSENSORY CORTEX As discussed above, elimination of a limited, defined set of normal inputs results in an expansion of the representation of still-intact inputs formerly represented in neighboring areas. As a consequence of that plasticity, the skin formerly represented only in the adjacent cortical zones becomes represented over a far larger territory, in finer topographic grain and detail. Skill-learning studies show that a relative increase in the activity of a limited subset of inputs that does not involve the deprivation of any of the cortex of its normal inputs can also result in representational expansion. For example, monkeys were trained on a task in which they were required to regulate the contact of one or two fingertips on a revolving, grooved disk, which resulted in heavy differential stimulation in a cognitively demanding behavioral task (Jenkins et al 1990). Maps of primary sensory area 3b before and after a few months of training revealed a several-fold increase in the cortical representation of the specific surfaces of the digit tips that were in contact with the disk during training. Interestingly, as in digital amputation experiments, the average receptive field size for inputs that were expanded in their representational territories were approximately correspondingly smaller. These results, derived in adult monkeys, demonstrated that the cortex can dynamically allocate area in a use-dependent manner to different differentially engaged inputs, apparently throughout life. Related reports have shown that similar natural stimulation of a skin surface results in an expansion of the cortical representation of that surface (Xerri et al 1994). In one study, the authors reported an almost twofold expansion of the cortical representation of nipple-bearing skin in lactating female rats compared with nonlactating female rats, as well as a concomitant decrease in the receptive field size. In a second study, they described a roughly twofold increase in the size of representation of digit tips that a monkey employed in a difficult small-object retrieval task, with a closely corresponding reduction in receptive field size.

In a related human study, Pascual-Leone & Torres (1993) analyzed differences in the hand representations of adults who had become proficient as Braille readers. Using magnetoencephalography (MEG), they showed that the scalp area over which potentials were recorded was significantly larger for the right index (reading) finger as compared with the left finger or as compared with the right finger of non-Braille readers. Representations of parts of the hand that were not employed in Braille reading were, in contrast, differentially smaller than in control hands. Similarly motivated experiments using MEG have shown

that the somatosensory representation of the digits of the left hand of string players is larger in comparison with fingers of their right hands or with the fingers of the left hands of control subjects (Elbert et al 1995).

In another important study of this class, Recanzone et al (1992a–d) trained monkeys to discriminate between successive vibratory stimuli that differed in frequency. In their studies, the hand position was constant, with all stimuli applied to a fixed location on the surface of a single digit. The population of neurons responding to the training stimuli or to stimulation of the constantly stimulated skin location enlarged several-fold in extent in both cortical areas 3b and 3a. In the latter field (Recanzone et al 1992c), that change represented a substitution of normally suppressed cutaneous inputs for the usually dominant muscle afferent inputs. In contrast to studies in which stimuli applied in behavior engaged the finger with significant trial-by-trial variability in stimulus location (e.g. Xerri et al 1994), or in which they moved across the skin (e.g. Jenkins et al 1990), in these monkeys receptive fields representing the trained skin enlarged several-fold. This was interpreted as a consequence of the fact that by Hebbian plasticity, any input into the cortex driven from the invariantly stimulated skin location would be integrated into a necessarily larger receptive field. In contrast, when stimuli move across the hand (as in Jenkins et al 1990) or are delivered to inconstant skin locations (as in Xerri et al 1994), each small sector of skin is an effective source of competitive input for the Hebbian network, and receptive fields therefore shrink in size as the zones of representation of the engaged skin surface grow in size. Interestingly, Recanzone et al (1992a–d) found that the improvement in frequency discrimination was apparently accounted for by a learning-induced change in the temporal coherence of the response in the engaged cortical population. The striking increase in distributed response correlation recorded in their study was strong evidence for the generation of plastic changes in intracortical connections between excitatory neurons.

In addition to the syndactyly and skin island transfer experiments described above (Clark et al 1988, Merzenich et al 1990a, Allard et al 1991, Merzenich & Jenkins 1992), the importance of temporal correlations has also been tested directly using a behavioral training protocol. Wang et al (1995) trained owl monkeys on a tactile task in which one bar (oriented perpendicularly to the fingers) simultaneously stimulated the distal segments of digits 2–4; that stimulation alternated with stimulation of a second bar that simultaneously stimulated the proximal phalanges of the same three digits. The monkey was required to attend to the alternating stimuli and to respond whenever two consecutive stimuli were applied to either the distal or proximal digit segments. For primates, including humans, the usual stimulation across fingers is substantially nonsimultaneous; by the operation of Hebbian plasticity mechanisms, the coincident input across the distal and proximal phalanges is expected to produce an abnormal interdigit

correlation pattern. Typical receptive fields for the normal hand representation of area 3b are confined to a single digit segment and very rarely include multiple digits. However, Wang et al (1995) found that the normal segregation between digit representations was broken down in trained animals. After training, approximately 40% percent of units representing the digits had developed receptive fields that had equally strong and equally short latency inputs from two or three digits (see Figure 3). Note that as in the Recanzone et al (1992a–d) study described above, the many-fold enlargement of receptive fields recorded in this study was an expected consequence of Hebbian plasticity, operating in a behavior in which incoming stimuli are from fixed skin locations. Note also that again, neurons all across the wide cortical zones engaged by these stimuli came to respond with virtually identical response latencies. This dramatic change in distributed response coherence was again consistent with a change in positive intracortical coupling of excitatory neurons all across the directly engaged cortical sector.

AUDITORY CORTEX Training-dependent changes in auditory map organization have been recorded in primary auditory cortex after training monkeys on a frequency discrimination task (Recanzone et al 1993a,b). Over a period of several weeks of behavioral training, the monkeys' ability to discriminate different frequencies significantly improved. Detailed mapping of the tonotopic representation of A1 revealed that the representation of the frequency band was several times larger in trained monkeys compared with that of control monkeys. Data from seven different monkeys revealed a significant correlation between behavioral performance and the cortical area representing the trained frequencies.

A second type of training-dependent cortical plasticity experiment has been conducted in several variations by Weinberger and colleagues (Weinberger et al 1993). Using a classical conditioning protocol, a tone of a given frequency (the CS+) was paired with an aversive electrical shock. Tuning curves recorded at the same sites of the auditory cortex before and after conditioning revealed a shift in the best frequencies in the direction of the frequency of the CS+; these shifts lasted up to a few weeks and could be reversed at any point by extinction training (see Diamond & Weinberger 1986, Bakin & Weinberger 1990, Weinberger et al 1993, Weinberger 1995).

RELATIONSHIP BETWEEN SYNAPTIC AND CORTICAL MAP PLASTICITY

As discussed above, numerous instances of synaptic and cortical map plasticity have been documented. Fewer experimental and theoretical studies have attempted to causally link synaptic plasticity and cortical map reorganization. In

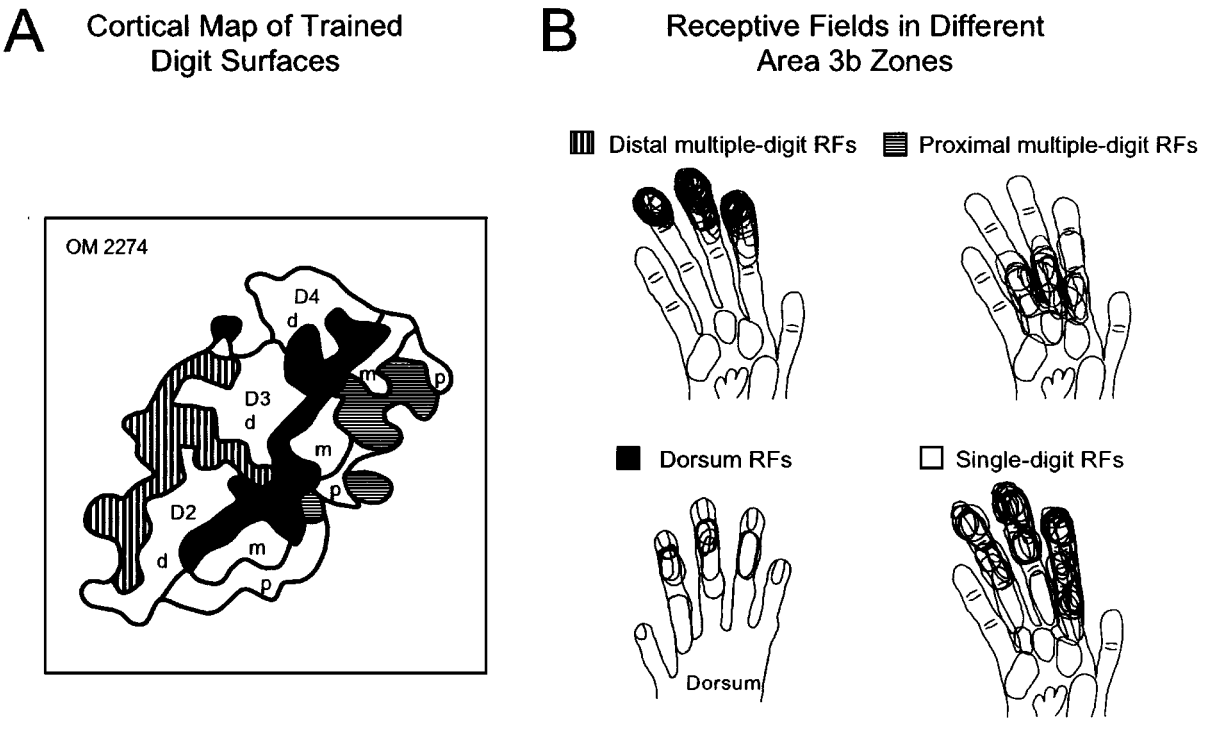

Figure 3 Training-dependent cortical map reorganization. Map and receptive fields of the hand representation of area 3b from a monkey that underwent behavioral training. Training involved extensive simultaneous stimulation across the proximal or distal portions of digits D2–D4. (*A*) The map shows that in contrast to normal maps, there was a significant portion of the map that exhibited multiple digit receptive fields, which were specific to either the proximal (*horizontal striping*) or distal (*vertical striping*) phalanges. (*B*) The receptive fields of the map shown in *A*, sorted according to the four observed classes: distal multiple-digit, proximal multiple-digit, dorsum, and single-digit receptive fields. [Modified from Wang et al (1995).]

considering its origin, it is important, first of all, to affirm that at least part of the plasticity underlying cortical map reorganization actually arises in the cortex. Second, it is important to determine whether or not synaptic plasticity, for example cortical LTP, is necessary and sufficient for cortical map reorganization. Establishing necessity and sufficiency is a difficult task. It is helpful to define a set of minimal criteria that must be satisfied in order to establish necessity and sufficiency. There have been several thoughtful attempts to define how we might determine the necessary, sufficient, and exclusive neural correlates of learning and memory (e.g. Rose 1981, Byrne 1987). Modified to address the relationship between cortical synaptic plasticity and cortical reorganization, reasonable criteria include:

1. Synaptic plasticity of the appropriate pathways should be observed in animals that are undergoing or have undergone cortical representational reorganization. A simple experiment that would address this criterion, for example, would be to demonstrate that slices from animals that have undergone representational plasticity exhibit potentiated synaptic connections of the appropriate thalamo-cortical or cortico-cortical pathways as compared with the different behaviorally nonengaged pathways from the same animals.

2. The same manipulations (e.g. pharmacological or genetic) that block synaptic plasticity should prevent cortical reorganization. Versions of these experiments have already been performed. However, to date, such experiments are still confounded by alternative interpretations of positive experimental results (see below).

3. Induction of synaptic plasticity in vivo should be sufficient to generate cortical reorganization measured by changes in cortical map topography. These are among the more difficult experiments to complete; however, two approaches can be envisioned. First, induction of LTP in vivo in certain pathways may result in measurable changes in cortical mapping. Second, genetic approaches may permit the induction of spatially and temporally localized LTP. Cortical mapping before and after this "genetic induction" protocol should result in the hypothesized changes in map topography.

4. The forms of synaptic plasticity and the learning rules that govern this plasticity should be sufficient to fully explain the experimental data. That is, computer simulations that solely incorporate known experimental forms of plasticity should be sufficient to generate models that account for the detailed phenomena of cortical representational reorganization. As we discuss below, it is clear that this criterion has also not yet been satisfied.

Sites of Cortical Map Plasticity

Although we have reviewed many studies demonstrating that manipulations of the normal sensory inputs in adult animals induce representational reorganization of cortical sensory representations, we have not addressed the question of where in the nervous system this cortically recorded change actually arises. However, it is not the goal of the current review to address this large and growing field in detail. Suffice it to say that virtually every level of the nervous system seems to exhibit plasticity under certain circumstances. Deafferentation has been reported to produce long-lasting topographic, receptive field, and anatomical changes in adult animals in the spinal cord (Basbaum & Wall 1976, Devor & Wall 1981, Lisney 1983, Wilson & Snow 1987; but see Brown et al 1984, Pubols 1984), dorsal columns (see Devor & Wall 1981, Welker et al 1992, Florence & Kaas 1995), and the thalamus (Eysel et al 1981, Land & Akhtar 1987, Garraghty & Kaas 1991).

While it is clear that the nervous system can undergo changes at subcortical levels, studies indicate that in many cases the primary site of plasticity appears to be within the cortex. One approach for determining whether the site of cortical map reorganization is cortical or subcortical has been to record both in the sensory thalamus and cortex. If reorganization is not observed in the thalamus, or observed to a limited extent, the sites of plasticity can only reside in the thalamocortical or intracortical projections. Wang et al (1995) showed that after they trained monkeys on a tactile task in which adjacent digits received simultaneous stimulation, many somatosensory cortical units developed multiple-digit receptive fields. In contrast, thalamic recordings did not reveal any multiple-digit receptive fields. Thus, the convergence of information from different fingers seemed to be occurring in the cortex. Related findings have been reported in the visual system. Gilbert & Wiesel (1992) showed that while binocular focal lesions of the retina produced atypical responses in the deprived cortical areas, areas of the lateral geniculate nucleus corresponding to the scotoma remained silent two months after lesioning. Furthermore, cellular conditioning experiments of cortical neurons (Gruel et al 1988, Frégnac et al 1992, Cruikshank & Weinberger 1996) clearly indicate that plasticity is occurring within the cortex.

Cortically based changes underlying novel cortical receptive fields could result from the strengthening or sprouting of thalamocortical axons and/or intracortical horizontal projections. It appears that novel receptive fields are largely, at least initially, the result of horizontal information flow mediated through cortico-cortical connections. Darian-Smith & Gilbert (1994) demonstrated that months after focal lesions to both retinae, collateral axons from cortical neurons surrounding the scotoma in the visual cortex have branched predominately into the deprived area as opposed to the normal area. In contrast,

labeling of thalamocortical axons showed that they did not extend into all of the reactivated cortex (Darian-Smith & Gilbert 1995). Further support of the importance of cortico-cortical plasticity was provided by whisker pairing (cutting all vibrissae but two) experiments in the barrel cortex. Diamond et al (1994) showed that 24 h after whisker pairing, the receptive fields of L-IV neurons remained unaltered, while the receptive fields of supra- and infragranular neurons exhibited double whisker receptive fields. Since L-IV neurons are the primary target of thalamocortical connections and the L-IV receptive fields remained unaltered, the authors suggested that cortico-cortical plasticity was responsible for the recorded changes in receptive fields. In a second series of related experiments, Armstrong-James and colleagues (1994) analyzed the latencies of neurons in the D2 barrels after pairing D1-D2 or D2-D3 for 3, 7, 10, or 30 days. They found that after 10 days or less of pairing, the latencies of the novel responses were consistent with a potentiation of the intracortical, specifically inter-barrel, excitatory circuitry. However, after 30 days of pairing, there was a significant increase in the emergence of latencies below 10 ms. The authors interpret this to mean that the early changes were due to cortico-cortical plasticity and that later changes were likely due to the potentiation of existing thalamocortical connections or the formation of novel ones. Finally, several studies have shown that learning-induced plasticity in the somatosensory cortex of monkeys is paralleled by progressive changes in distributed response coherence (e.g. Recanzone et al 1992d, 1993; Dinse et al 1993; Wang et al 1995) and in the creation of large populations of neurons with virtually identical selective response properties, interpreted as primarily arising from a change in intracortical connection strengths.

Together, these experiments indicate that plasticity occurring within the cortex itself is a very important, if not the primary, site of certain types of cortical reorganization. However, it is often difficult to rule out contributions of plasticity occurring elsewhere. Future research will have to determine the relative contributions of different sites of plasticity and the experimental conditions in which they take apply differentially. One possibility is that the first and primary site of reorganization is in the cortex and that with time, reorganization occurs in subcortical areas in a retrograde fashion.

NMDA- and CaM-Kinase–Dependent Cortical Map Plasticity

Associative LTP, both in the hippocampus and cortex, is dependent on NMDA receptors. In the hippocampus, activation of Ca^{2+}/calmodulin-dependent kinase (CaM-kinase) is a critical downstream step after influx of Ca^{2+} through the NMDA channels (Malenka et al 1989, Malinow et al 1989) and is likely to be critical in cortical LTP as well. If associative LTP is the primary neural mechanism underlying cortical reorganization, blocking NMDA receptors

or CaM-kinase activity should prevent cortical map reorganization. Recently, Garraghty & Muja (1996) examined cortical reorganization after median nerve transection in squirrel monkeys in the presence and absence of the NMDA antagonist CPP. CPP was administered systemically from the time of nerve transection to the time of cortical mapping (approximately 30 days). In agreement with the results of Merzenich et al (1983a,b), Garraghty & Muja (1996) found that in control animals, virtually all of the cortex was responsive. In contrast, in animals exposed to CPP, most of the deprived cortex remained unresponsive. However, the mapping was apparently done in the presence of CPP; thus, if new connections were NMDA-mediated, they may have been masked. Kano et al (1991) reported similar results in the reorganization of the cat somatosensory cortex after peripheral deafferentation. Developmental studies in both the visual cortex (Bear et al 1990) and barrel cortex (Schlaggar et al 1993) also have shown that NMDA receptors antagonists interfere with cortical map development and plasticity.

A potential problem in interpreting these experiments is distinguishing whether reorganization was blocked because NMDA receptors are involved in synaptic plasticity or because the experimental manipulation may have functionally inactivated the cortex. NMDA receptor blockade can significantly decrease cortical responsivity to visual stimuli in kittens (Fox et al 1989) and in superficial layers of adult cats (Fox et al 1989; Miller et al 1989a,b; see also Kano et al 1991). Thus, the effects of NMDA blockers on cortical reorganization could result from cells not being sufficiently active, rather than from a direct effect of blocking NMDA-mediated LTP.

Glaszewski et al (1996) have examined barrel cortex plasticity in adult knockout mice without the α-CaM-kinase II gene. As adults, these mice do not exhibit significant hippocampal or visual cortical LTP (Silva et al 1992, Kirkwood et al 1997) but do exhibit cortical LTP in 4- to 5-week-old animals (Kirkwood et al 1997). Cortical reorganization was examined by removing all vibrissae but D1 in control and experimental animals. In normal mice, 18 days after vibrissae removal, there was a general increase in response to whisker D1 in neighboring cortical barrels. By contrast, in the knockouts, there was not a significant expansion of the cortical representation of vibrissae D1. It would be important to determine whether slices from the barrel cortex from knockout mice that underwent vibrissa clipping exhibit thalamo-cortical or cortico-cortical LTP, to satisfy criterion 2, above.

Cellular Mechanisms and Models of Cortical Map Plasticity

MODELS OF CORTICAL PLASTICITY To establish whether cortical synaptic plasticity is sufficient to account for cortical reorganization, theoretical and computer simulations are useful. These methods can establish in principle whether the forms of plasticity and the learning rules described experimentally

to date are indeed sufficient to account for experimental results derived in cortical representational plasticity studies. Further, predictions can be made as to what other mechanisms may be needed to guide experimental research. Numerous conceptual and computational models of the development of cortical maps (e.g. von der Malsburg 1973; Bienenstock et al 1982; Miller et al 1989a,b; Clothiaux et al 1991) and of cortical map reorganization in adults (e.g. Pearson et al 1987, Grajski & Merzenich 1990, Benuková et al 1994, Sutton et al 1994) have been proposed. Although these models differ significantly from each other, they share common underlying principles. We consider models of cortical map reorganization in adults. In the models by Pearson et al (1987) and Grajski & Merzenich (1990), two fundamental mechanisms are invoked to account for the emergence of novel receptive fields in response to deafferentation: (*a*) a Hebbian learning rule in which the synapses between coactive neurons tend to be strengthened, coupled with a passive synaptic decay term, and (*b*) a competitive mechanism. In these models, the competitive mechanism takes the form of postsynaptic normalization: The total synaptic input to a cell is maintained constant; if some synapses are weakened (strengthened), all others will be increased (decreased) by a certain fraction. While Hebbian, i.e. associative, plasticity is often emphasized as the mechanism underlying cortical map formation and reorganization, cortical reorganization in response to deafferentation can essentially be simulated based solely on passive decay and postsynaptic normalization. Consider how these models account for the data from Merzenich et al (1983a,b). Assume that nerve transection deprives the cortex of all inputs from digits D1–D3. As a result of the passive decay, term synapses from the D1–D3 pathway will be weakened. As a result of the weakening of synapses from D1–D3, synapses from D4 will be strengthened as a result of postsynaptic normalization. Hebbian plasticity is critical for simulating reorganization based on training for many other features of cortical reorganization. Nevertheless, it is essential to examine the experimental data supporting postsynaptic normalization and passive synaptic decay (see below).

Benusková et al (1994) presented a model of cortical reorganization of the barrel cortex in response to whisker pairing. This model relies on a form of associative plasticity in which LTD occurs if presynaptic activity is paired with postsynaptic activity that is below a critical modification threshold; if postsynaptic activity is above that threshold, LTP occurs (Bienenstock et al 1982, Artola & Singer 1993). This learning rule is coupled with a sliding modification threshold, as proposed by Bienenstock et al (1982). The threshold is high in active cells and low in inactive cells and changes dynamically according to the history of activity of the cell. Benuková et al (1994) used this form of associative plasticity and the sliding modification threshold to simulate the increased responses to the paired whiskers and to account for the decreased responses that emerged

for the cut whiskers. Conceptually this model works as follows: Clipping all but two whiskers decreases the average activity of the cell and thus decreases the modification threshold. As a result, synapses from the spared whiskers will be strengthened, the average activity will increase, and the modification threshold should rise again. However, in Benuková et al's (1994) simulations, the modification threshold rises from the onset of the simulations. It is thus not clear how dependent the results are on the initial conditions of the model.

EXPERIMENTAL SUPPORT Regarding the biological support for the synaptic and cellular mechanisms invoked by these models, there are at least four mechanisms that should be addressed: (*a*) associative (Hebbian) LTP, (*b*) postsynaptic normalization, (*c*) associative LTD/LTP, or what we can refer to as threshold LTD/LTP, and (*d*) a sliding modification threshold.

Associative LTP As discussed above, there is considerable experimental evidence describing associative LTP (Hebbian plasticity) in the cortex. However, different protocols are used to induce LTP, and the pairing protocols that directly demonstrate the associative plasticity are critical from a computational perspective. It seems less likely that the high-frequency conditions equivalent to tetanic stimulation are likely to occur in vivo. Similarly, although TBS is likely to be more physiological because it uses a frequency of activity that occurs in vivo, it would seem to require theta stimulation of the sensory input fibers. Moreover, tetanus or TBS protocols are expected to activate larger populations of neurons, including parts of the circuit that are not being directly stimulated or recorded from. For example, Kirkwood & Bear (1994) have suggested an inhibitory gating hypothesis in which inhibitory circuitry in L-IV may filter out high-frequency activity and not permit sufficient depolarization of the L-II/III pyramidal cells. However, such a mechanism would seem to apply only to TBS or tetanus protocols and is unlikely to interfere with pairing-induced LTP in which the cell is artificially depolarized independent of inhibition. Indeed, an example of a dissociation between TBS and pairing-induced LTP was recently found in visual cortex of mice lacking the RIβ subunit of protein kinase A (T Hensch & MP Stryker, personal communication). Intracellular pairings in these mice were effective for inducing LTP in the L-IV to L-II/III pathway, while extracellular TBS was ineffective. Although there are differences in the ability of different protocols to induce LTP, there are few data suggesting that the mechanistic underpinnings of the LTP produced by these different protocols are any different. Thus, it is likely that tetanic and TBS protocols provide a useful, if perhaps unphysiological, way of effectively and rapidly inducing synaptic plasticity. Induction in which lower-frequency stimulation is paired with postsynaptic depolarization, however, is the type that ultimately provides the computational features required by neural network models.

In contrast to associative LTP, the functional importance of low-frequency LTD is unclear. Most of the models proposed to date, including those described above, do not have a specific role for this form of synaptic depression. Again, low-frequency LTD may tap into the same cellular mechanisms used in vivo to induce LTD but under physiological conditions may be controlled by a different learning rule.

Postsynaptic normalization Postsynaptic normalization is a critical component of many models. To date, there is little direct experimental evidence for such a mechanism. There are numerous reasons why postsynaptic normalization might be difficult to observe, not least of which is because it may require a time course longer than the life span of acute slice experiments. On the other hand, other cellular mechanisms could be functionally equivalent to postsynaptic normalization. One such mechanism is heterosynaptic LTD, in which postsynaptic activity in the absence of presynaptic activity results in LTD. The examples of heterosynaptic LTD in the cortex (Hirsch et al 1992, Volgushev et al 1994) do not appear to be robust. However, a form of heterosynaptic LTD in the hippocampus may ultimately prove to be relevant (Scanziani et al 1996). For example, if heterosynaptic LTD occurs primarily when other synapses are potentiated, and if the total LTP was equal to the total LTD, effective postsynaptic normalization would be occurring. At the same time, the converse scenario, by which a decrease in the strength of some synapses (e.g. due to passive decay) would produce an increase in the strength of inactive synapses, would also be necessary.

Associative LTD and LTP Another issue of importance concerns the existence of a postsynaptic threshold for the induction of LTD and LTP. There is some experimental evidence supporting forms of associative plasticity in which the level of postsynaptic depolarization controls whether LTD or LTP ensues (Artola & Singer 1990). However, these experiments have involved tetanic electrical stimulation (50 Hz for 2 s). It has also been proposed that experiments showing a transition from LTD to LTP that depends on the frequency of afferent stimulation provide further support for the notion that the level of postsynaptic depolarization determines whether LTD or LTP is induced (hippocampus: Dudek & Bear 1992; visual cortex: Kirkwood et al 1996). These experiments show that low-frequency stimulation (1 Hz) results in LTD, while high-frequency stimulation (100 Hz) results in LTP, and that there is a smooth transition between these values. These data do not directly support the notion of a postsynaptic modification threshold, however, because the frequencies of discharge of the presynaptic fibers is changing and because it is not clear how different stimulation frequencies will affect the postsynaptic potential and how those inputs are integrated over time. Nevertheless, we can argue that it

is the postsynaptic potential that controls the direction of synaptic plasticity: Low-frequency stimulation (1 Hz, 900 pulses) results in LTD, and it is safe to assume that the same afferent stimulation protocol will induce LTP if each pulse is paired with depolarization. Thus, it would be of interest to perform experiments in which low-frequency presynaptic stimulation is paired with a range of different current injection intensities in order to determine whether or not there is smooth transition between LTD and LTP. The related issue of whether there is a sliding threshold for LTD and LTP is of course difficult to address, since experimental data for a threshold remains inconclusive. However, in the case of low- and high-frequency stimulation, there is evidence that the frequency of the afferent stimulation at which there is a smooth transition between LTD and LTP does slide. Specifically the frequency of the transition between LTD and LTP was shifted to lower frequencies in slices from rats that were reared in the dark (Kirkwood et al 1996).

From a computational and mathematical perspective, different implementations and models of cortical plasticity share similar principles and in some instances are even mathematically equivalent. For example, Miller & MacKay (1994) showed that under some assumptions, postsynaptic normalization and a sliding postsynaptic threshold are equivalent. However, from a biological perspective, the exact mechanisms underlying plasticity are important and will ultimately generate distinct experimental predictions. Clearly we do not yet have a sufficient understanding of synaptic and cellular plasticity to fully account, even in theory, for the experimental data on cortical reorganization. Specifically what is lacking is an understanding of the cellular mechanisms and learning rules that govern synaptic competition, LTD, and passive synaptic decay.

CONCLUSIONS

Research over the past 15 years has established that cortical maps of adult animals are not constant, but dynamic. The cortex can preferentially allocate cortical area to represent the selected peripheral inputs. The increased cortical neuronal population and plasticity-induced changes in the coherence of responses that these larger cell assemblies generate is thought to be critical for certain forms of perceptual learning. Parallel advances in the field of synaptic plasticity have successfully characterized various forms of synaptic cortical plasticity that appear to contribute to cortical reorganization. However, we do not yet have a sufficient understanding of synaptic and cellular plasticity to fully account for the experimental data on cortical representational reorganization. Many issues—including the role of inhibitory plasticity, the site(s) of plasticity, interlaminar differences, and the specific rules that govern competition and LTD—remain to be addressed. Future research aimed at understanding

plasticity and the learning rules governing this plasticity will be critical to our understanding both the neural mechanisms of cortical reorganization and the very nature of cortical processing.

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