5 Models of Synaptic Plasticity and Cellular Analogs of Learning in the Developing and Adult Vertebrate Visual Cortex

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INTRODUCTION

This overview chapter focuses on the learning capacities of cells in the primary visual cortex of developing and adult mammals. The first section provides a general introduction. The second section provides an overview of cellular plasticity, where we also justify the choice of mammalian visual cortex as an experimental model to study activity-dependent processes. We then present three approaches, following a principle advocated by Braitenberg (1985), that understanding of a complex process can best be gained by synthesis from putative elementary mechanisms, rather than by a top-down analysis. When applied to the study of learning in neocortical neurons, this approach requires explicit a priori formulation of hypothetical building blocks at a cellular or subcellular level, and eventually, comparison of predictions with the observed biological phenomena at a more global and functional level.

The first approach corresponds to the modeler’s point of view. For example, can we think of plausible mechanisms acting locally but uniformly across a fixed network, which will induce functional self-organization? An overview of “algorithms” of synaptic plasticity is presented, which simulates how a pattern of complete connectivity (e.g., where every unit is presumed to be anatomically

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connected to every other unit) can be transformed into a patchy pattern (e.g., where only a subset of connections exist), as could be the case in visual cortex (Callaway & Katz, 1990). All these algorithms are variations on the same basic rule: They suppose that coactivity controls the gain of transmission of synapses. By coactivity we mean temporal correlation between pre- and postsynaptic activities, or between activities in different afferent fibers converging on the same target cell. We describe a specific algorithm, the “covariance hypothesis,” which has been used in modeling synaptic plasticity in cerebellum (Sejnowski, 1977a, 1977b). It has also been shown to adequately simulate the functional reorganization of visual cortex in response to manipulation of visual input during a critical period of postnatal development (Bienenstock, Cooper, & Munro, 1982).

A second or empirical approach, based on electrophysiological recordings in vivo, is described in the next section. Here we demonstrate the biological “implementation” of the covariance algorithm. In order to justify the experimental paradigms developed to test specific predictions from the theoretical scheme, we review evidence suggesting that the absence of extraretinal modulatory action freezes cortical plasticity in the anesthetized and paralyzed preparation. We describe recently developed electrophysiological procedures that have enabled us to overcome this problem. These techniques have allowed us to develop a variety of in vivo cellular analogs of visual cortical plasticity. Four paradigms in which locally imposed patterns of activity in the cortex of anesthetized and paralyzed kittens induced relatively long-lasting functional changes while recording individual neocortical neurons. These paradigms have in common external control, by the experimenter (“the teacher”), of the temporal contingency between specific characteristics of the visual message and imposed levels of postsynaptic activity of the recorded cell. We propose that these paradigms provide analogs of visual cortical plasticity because: (a) the imposed local control of activity reproduces specific patterns of neuronal discharge induced by rearing procedures which have been shown to affect visual cortical organization in the normally behaving animal, and (b) most functional modifications produced acutely (and under artificial exogenous constraints) are similar to those seen during the functional epigenesis of the developing kitten when subjected to these rearing conditions. At the end of this section, the results obtained during our electrophysiological recordings will be compared with the prediction of the covariance hypothesis.

The final section of this chapter summarizes a third approach, based on in vitro attempts to evaluate activity-dependent cortical changes in terms of synaptic plasticity. We briefly outline possible biophysical mechanisms which could explain how dynamic changes in the coactivity levels increase or decrease the efficacy of transmission of neocortical synapses.
CONCEPTS OF CELLULAR PLASTICITY

Cellular Plasticity and Behavioral Learning

Plasticity can be defined at the cellular level as the intrinsic capacity of a neuron to change its reactive properties as a function of past activity (Konorski, 1948; Tsukahara, 1981; Changeux & Konishi, 1987; Weinberger & Diamond, 1987). Considering the remarkable level of specificity of the cortical analyzer described in the adult vertebrate, the search for sensory plasticity in neocortical neurons might appear paradoxical. Indeed, in primary visual cortex, neuronal networks have been characterized functionally and neuroanatomically, in which cells are grouped in columns and form assemblies that are roughly spatially periodic in the laminar plane according to their stimulus specificity (review in Hubel, 1988). In primary and most associative areas, the characterization of trigger features of visually driven neurons is classically made using perceptual terms, and a common anthropomorphic view is to consider the activity of these neurons as corresponding to specific perceptions (e.g., “our grandmother is driving a yellow volkswagen car”); for a more quantified approach, see Newsome, Britten, & Movshon, 1989. However, in spite of the recordings of units with highly specialized stimulus requirements (Gross, Rocha-Miranda, & Bender, 1972; but compare with Rolls, 1987), it cannot be excluded that trigger requirements in nonprimary visual areas correspond to the recall of permanent “traces” following the repeated association of different attributes of visual stimuli (Miyashita, 1988; Miyashita & Chang, 1988).

In several studies using invertebrate preparations, substantial advances have been made in relating neuronal changes to various modifications of behavior or perceptual performances. For instance, in the marine slug *Hermissenda*, intracellular studies by Alkon and collaborators (review Alkon, 1988) demonstrated that artificial pairing of depolarizing current with the photic stimulation of a single photoreceptor (type B cell) is sufficient to induce a predictable behavioral change (such as foot contraction in response to light instead of the normal phototaxic behavior), indicative of the establishment of a conditioned response (such as produced by classical conditioning). In a large number of invertebrate preparations, cellular plasticity has been equated with behavioral learning, and neuronal changes are interpreted as correlates of overt behavior (Farley & Alkon, 1985; Carew & Sahley, 1986; Byrne, 1987). Sensory neurons have been identified, whose activity appears to encode the conditioned stimulus, and pools of motoneurons involved in the conditioned reflex are known precisely. In *Aplysia californica*, specific circuitry has been tested, involving to a large extent the presence of cells that facilitate transmission of the unconditioned stimulus, although the exact nature of their transmitter (peptidergic or
serotonergic) is still a matter of debate. Remarkably, the timing of events at the
neuronal circuit level appears to be identical to the timing of the events required
in the behavioral procedure to produce conditioning of the reflex.

Such parallels between neuronal function and behavioral outcome have been
more difficult to demonstrate in the mammalian brain (e.g., Woody, 1982b;
Thompson, 1986). In the study of the cellular bases of classical conditioning in
adult mammals, experimental evidence for functional changes which would
reflect the precise timing of events responsible for the development of the
conditioned reflex is still limited in scope. This raises the possibility that, in
contrast with what is observed in invertebrates, part of the interstimulus timing
specificity is lost at an intermediate stage of integration in the vertebrate brain.
The distributed nature of the transmission of information at the neocortical level
might, in this case, explain the relative failure of most experimenters to establish
causal links between cellular learning and expressed changes in behavior. In
visual cortex, rearing procedures, which dramatically affect the representation
of orientation preference in the young animal, do not relate in a systematic way
to similar changes in the global perception of corresponding orientations
(Hirsch, 1972; Blasdel, Mitchell, Muir, & Pettigrew, 1977; Hirsch, Tieman,
Tieman, & Tumosa, 1987).

In the present chapter we describe a series of studies in which modifications
in the response properties of visual cortical neurons in both kitten and adult cat
were produced in vivo during the course of electrophysiological recording
sessions. These plastic changes in receptive-field properties were brought about
by pairing specific visual stimuli with iontophoretic-induced alterations in the
cells’ discharge rates and were attributable to the timing relations between the
exteroceptive and intracerebral (iontophoretic) stimuli. We argue that these
modifications may serve as a fruitful analog for the neuronal plasticity
underlying some forms of perceptual learning, and may help bridge a gap in our
understanding of mechanisms of neocortical developmental plasticity, on the one
hand, and of adult learning and memory, on the other hand.

Activity Dependence in the Developing Cat Visual Pathway

Cellular plasticity will be considered in this chapter as the expression of activity-
dependent processes during development and learning. But this does not mean—
to paraphrase a controversial title in the experimental literature—that visual
cortical plasticity is just the mirror of experience (Spinelli & Jensen, 1979). The
same elementary mechanisms could be used during spontaneous functioning to
reach a stable state of final selectivity. By analogy with the proposed “epigenetic
landscape” of Waddington (1968), activity might be only influencing the
dynamic path (during development or learning) followed by the state of the
network. Valleys in the landscape (i.e., regions of minimum energy) where the
system will eventually stabilize, could indeed correspond to fixed configurations
of connectivity, entirely determined by intrinsic factors of the network.
In the developing cat before eye opening, visual pathways receive a tonic influence from spontaneously active elements in the retina (dark discharge). This level of maintained activity is filtered along the retino-geniculo-cortical pathway, and it is not surprising that it is in such central structures (e.g., visual cortex), where the level of spontaneous activity is low, that sensitivity to visual experience has been revealed.

Theories of Visual Cortical Plasticity

Classically, the role of evoked activity in relation to the functional development of visual neurons is thought to result in three types of processes (Prestige & Willshaw, 1975): the first one was set forth by Hubel and Wiesel, proponents of the “functional verification” hypothesis (Hubel & Wiesel, 1963). Visual activity is assumed to validate synaptic connections which are already hardwired before the onset of visual experience. This scheme would apply principally to the pioneering contacts forming the basic Anlage of the extrinsic geniculo-cortical connectivity, since only 3% of the final number of synapses are present at birth. It does not account for the postnatal development of the intracortical neuropil, which occurs much later, mainly at the turn of the 3rd postnatal week (Cragg, 1972).

The remarkable correspondence between the timetable of cortical synaptogenesis and the beginning of the critical period favors, however, an alternative empiricist view, advocated by Pettigrew and coworkers in the 1970s (Pettigrew, 1974; Pettigrew, Olson, & Barlow, 1973; Pettigrew & Garey, 1974), and according to which oriented growth processes would be under the control of visual activity from eye opening: after an initial “tabula rasa,” visual experience would determine the final connectivity. A compromise to this artificial nature/nurture dichotomy was offered by the theory of selective stabilization developed by Changeux, Courrege, and Danchin (1973; Changeux & Danchin, 1976; see also the selectionist hypothesis in Finkel & Edelman, 1987). A redundant envelope of connections (established during an early phase of development governed by genetic constraints) would be reduced and stabilized through activity-dependent processes. In terms of synaptic contacts and receptors, this latter hypothesis implies that if certain connections are stabilized, others disappear. This led Changeux to the provocative statement that “learning is to lose synapses” (Changeux, 1979). Although these three classes of activity-dependent processes are often opposed to each other, it is probable that they could occur simultaneously or even serially during the first months of postnatal life.

Critical postnatal dates. The retina becomes functional in kittens at around 3 to 5 days of postnatal age. Spontaneously active cells have been recorded in visual cortex as early as 5 to 8 days after birth (Buisseret & Imbert, 1976; Albus & Wolf, 1984), but geniculate afferents are usually thought to be active before the
target cells (Huttenlocher, 1967). Eye opening in kitten occurs at around 7 days of age (Blakemore & Cummings, 1975). However the period of sensitivity to visual experience—the so-called critical period (Hubel & Wiesel, 1963)—begins at a significantly later postnatal stage: A comparative kinetic study of the development of orientation selectivity in area 17 of kittens submitted to different rearing conditions (Frégnac, 1979b) indicates that the cortical specification process becomes affected by the absence of visual input from around 18 days of age. This landmark corresponds precisely to the onset of the morphological maturation of the cortical neuropil (Cragg, 1972). The critical period seems to extend over the first 3–4 months of postnatal life of the cat (Hubel & Wiesel, 1970). Its ending should not be taken as occurring at a fixed time, since it depends both on the type of functional property for which dependence on visual experience is looked for (Daw & Wyatt, 1976), and on the past developmental history of the animal (Mower, Berry, Burchiel, & Duffy, 1981; discussion in Frégnac, 1985).

Another remarkable characteristic of functional epigenetic processes during the early postnatal life is the nonlinearity of the effects of visual experience throughout the critical period. A few hours of visual experience in 6-week-old kittens, previously binocularly deprived from birth, are sufficient to induce a level of specification in receptive-field properties, almost comparable to that observed in normally reared kittens of the same age (Imbert & Buissère, 1975). Delaying visual experience in kittens does not result in delaying a developmental process, but leads to the expression of functional changes that seem to have been masked up to this point by the absence of vision (Frégnac, 1979a). Evidence for occurrence of fast functional changes at the peak of the critical period motivates the “parti-pris” in this chapter to look for modifications which can be induced once the network is stabilized, simply by changing coupling gain between neuronal elements.

Epigenesis/Adult Plasticity

The understanding of cellular mechanisms of epigenesis can offer potential breakthroughs in the analysis of learning and memory. Particularly unknown, even in the invertebrate CNS, is the way in which different learning and memory processes emerge and become integrated during ontogeny (Carew, 1989). Recent demonstrations of visual cortical plasticity in response to imposed patterns of activity reveal impressive capacities of functional adaptation of central neurons even in adult life (Clark, Allard, Jenkins, & Merzenich, 1988; Frégnac et al., 1988). These findings provide support for the existence of links between developmental plasticity and learning processes in the adult vertebrate cortex. Although developmental plasticity in visual pathways is generally thought of as limited to a postnatal critical period (Wiesel, 1982), does this mean that adult neurons have altogether lost the capacity to change their properties (for instance,
by reduction or suppression of some active conductances (as shown in invertebrates) and/or of bursting behavior (Artola & Singer, 1987)? Or is it conceivable that their mature microenvironment provides the key that allows the functional expression of changes only under specific circumstances? This question is addressed in the last part of this chapter.

THE THEORETICAL APPROACH: IN SEARCH OF AN “ALGORITHM” OF SYNAPTIC PLASTICITY

The Network Level: Coactivity as a Rule of Formation of Cell Assemblies

Before considering the adaptive properties of its elementary components, let us start by defining some collective properties of the visual cortical network. A remarkable neuroanatomical characteristic of sensory neocortex is the potential for the formation of closed nets, where large numbers of elements emit recurrent collaterals (Purpura, Shofer, & Musgrave, 1964; Gilbert & Wiesel, 1981; Ferster & Lindström, 1985). This was already foreseen by Hebb in his original essay on cerebral organization (Hebb, 1949), where he proposed that cortical areas would be the ideal seat for the formation of cell assemblies. This prediction seems to apply best in primary visual cortex, since detailed study of its functional architecture in the adult, that is, corresponding to the final state, reveals a built-in tendency of the network to establish neighborhood relationships along various functional dimensions (von der Malsburg & Singer, 1988).

Intrinsic stabilized connectivity seems to obey a simple rule of association: Elements which are alike tend to be coupled together. And this rule would hold both in the spatial and the functional domains:

1. Spatially neighboring cells, situated in the same vertical column (orthogonal to the pial surface), tend to share similar afferents (Toyama, Kimura, & Tanaka, 1981a, 1981b; Tanaka, 1983; Toyama, 1988), and exhibit similar receptive-field properties, such as orientation preference and ocular dominance (Hubel & Wiesel, 1962). Direct vertical connections reinforce coactivity within this functional module (Toyama, 1988).

2. Cells, distant in the cortical tissue, but neighbors in the functional domain (i.e., which show similar orientation preference and/or ocular dominance), tend to be coupled by long-distance intracortical connections (Michalski, Gerstein, Czarkowska, & Taneki, 1983; Ts' O, Gilbert, & Wiesel, 1986; Eckhorn et al., 1988; Gray & Singer, 1989; Gray, König, Engel, & Singer, 1989).

In order to understand the spatial architecture of the cortical network, the spatial representation of these two properties can be studied in the plane of one lamina (for instance, the supragranular layers), and the use of voltage sensitive
dye techniques illustrates a general property of cortical organization (Blasdel & Salama, 1986; Grindvald, Lieke, Frostig, Gilbert, & Wiesel, 1986; Grindvald, Frostig, & Lieke, 1988). Visualization of coactive functional domains in response to the presentation of a unique orientation reveals a patchy but almost spatially periodic pattern (see Figure 5.1).

Figure 5.1. Coactivity and formation of cell assemblies
a. Schematic bidimensional representation of the cortical network considered as a single layer of neurons. In the initial state, before neuronal activity is propagated in the network, connectivity is presumed to be almost complete (every cell is connected to every possible neighbor within a range of a few hundred microns). This view is supported by the neuroanatomical description of long (up to several mm), bifurcating axon collaterals which...
Freund, Martin, Somogyi, & Whitteridge, 1985; Friedlander & Martin, 1989), but a given postsynaptic neuron may be the convergence site for at least several tens of LGN axons. These synapses are in their great majority asymmetric (type I), probably excitatory (Uchizono, 1965) and located on dendritic spines (in 70–90% of cases) (Garey & Powell, 1971; Levay & Gilbert, 1976; McGuire, Hornung, Gilbert, & Wiesel, 1984; Freund et al., 1985a, 1985b; Levay, 1986; Friedlander & Martin, 1989). More recent studies of transynaptic transport give a similar estimate, and rough calculations based on global numbers of axons and of cells lead to the conjecture that a typical layer V pyramidal cell would receive 500 to 1,000 contacts mediating visual activity relayed directly from the LGN (Friedlander, personal communication). The geniculate input in terms of synapses would represent only 10 to 20 percent of the mean number of synapses impinging on a cortical cell (Garey & Powell, 1971; Levay & Gilbert, 1976).

Although not much is known about the voltage amplitude of an average postsynaptic potential generated at the locus of an individual bouton, the assumption made by modelers that the simultaneous activation of only a few tens of contacts would lead to the firing of the target cell appears to be plausible (Abeles, 1982). Consequently, the distributed nature of the afferent connectivity (due to local convergence and divergence) supports the concept that the main function of a cortical neuron is to detect temporal coincidence in the firing of inputs.

The psychobiological approach. The hypothesis that coactivity controls the efficacy of synaptic transmission between neurons has deep historical roots, going back to the foundations of psychobiology, around 1890, when William James proposed the following principle of association (James, 1890): “When two brain processes are active together or in immediate succession, one of them, on reoccurring, tends to propagate its excitement into the other.”

However, posterity became oblivious of this earlier proposal, and most theoreticians and neurobiologists refer to Hebb’s postulate as the first principle of modification of the coupling between neural units (Hebb, 1949), although they could have attributed a similar paternity to some of his predecessors or contemporaries (Tanzi, 1893; Cajal, 1911; Wood-Jones & Porteus, 1928; Konorski, 1948). “When an axon of cell A is near enough to excite a cell B and repeatedly and persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A’s efficiency, as one of the cells firing B, is increased” (Hebb, 1949).

Hebb’s hypothesis requires spatial convergence of one neuron onto another, and provides a specific prediction: A period of maintained temporal correlation between pre- and postsynaptic activity will lead to an increase in the efficacy of synaptic transmission. In spite of an apparently precise neurobiological context,
originates mainly from layer II/III pyramidal cells and extend in the plane of layers II/III or V ("horizontal" connectivity). During the first three postnatal weeks in the cat, a steady increase is observed in the number of these "horizontal" connections, and no clustering is apparent (Callaway & Katz, 1990).

b. From the start of the critical period up to 7 weeks of age in cats, a gradual elimination of inappropriately projecting collaterals leads to the formation and the stabilization (final state) of periodic clusters of finer axon branches (Lumsden, Martinez-Millan, & Singer, 1986; Callaway & Katz, 1990). Temporal patterns of coactivity arising mainly through the influence of the spontaneous "dark discharge" in the retina, and from the asynchronous activation of ON and OFF pathways by visual input could be used by the cortical network to reinforce and stabilize connections within and between specific clusters.

c. Voltage sensitive dye techniques allow the visualization of spatially regular coactivity states in the adult (seen in the plane of the superficial cortical layers), which correspond to the distributed coding of a given parameter of the visual stimulation (orientation, ocular dominance) (drawing adapted from Blasdel & Salama, 1986). The patchy appearance of an isofunctional domain (shaded islets represent clusters of cells sharing the same orientation preference, e.g., horizontal) parallels that of the intrinsic horizontal connectivity arising from it, which tends to link spatially segregated clusters together (Callaway & Katz, 1990).

Theoreticians of visual cortical function have proposed that coding would no longer be expressed in the absolute firing of each neuron but in coactivity states distributed across members of given cell assemblies (von der Malsburg, 1981; Ballard, 1986; von der Malsburg & Bienenstock, 1986). A crucial question in the study of dynamic processing of visual information by neocortex is then to understand how instantaneous firing in different points in the cortex become related. The spatial regularity of the architecture of the final adult network, seen both neuroanatomically and functionally, may give a key answer, since it could be the result of long-term effects produced by intrinsic temporal correlations within the visual pathway, maintained from an early stage of postnatal development. If we assume that coactivity determines which connections are reinforced, the stabilized connections could be those where pre- and postsynaptic activities tended to be positively correlated during past functioning.

The Neuronal Level: A Temporal Coincidence Detector

One of the main functions of sensory neurons is to transmit information reliably. The integration of visual input at the cortical level is largely determined by the number and the location of synaptic contacts of geniculate origin onto a given target cell. Available neuroanatomical evidence concerning the convergence/divergence ratios between LGN and cortical neurons is limited. From serial reconstructions of HRP-filled LGN axons and Golgi-stained cortical cells in the cat, it was found that a given geniculate afferent makes only 1 to 8 synapses with the same postsynaptic cortical neuron (Freund, Martin, & Whitteridge, 1985;
the reader should be reminded of the generality of this principle, widely used on other grounds in system theory where the transfer function of a black box is made dependent on the product of input and output signals. In addition, implications in terms of structure and function are not addressed in this neurobiological postulate, since Hebb did not specify the site of the modification responsible for this reduction in "synaptic resistance" (Wood-Jones & Porteous, 1928; review in Brown, Ganong, Kairiss, & Keenan, 1990). According to his own words, "The assumption, in brief... about the structural changes that make lasting memory possible.... is that a growth process accompanying synaptic activity makes the synapse more readily traversed" (Hebb, 1949).

At that time, inhibitory connections were almost unknown, and Hebb referred exclusively to excitatory synapses, probably of axosomatic or axodendritic type. More recently, a symmetric version of Hebb's postulate has been proposed for the case of inhibitory synapses (Szent, 1973; see also von der Malsburg & Bienenstock, 1986), which assumes that their efficacy is reduced following maintained failure of the presynaptic axons to inhibit the postsynaptic cell, while this latter is activated by other excitatory inputs. But this second form of synaptic plasticity, derived from Hebb's postulate, has been ignored by most experimenters, who have since concentrated most of their efforts on the study of excitatory synaptic transmission.

The cybernetic approach. Although a cautious Hebb, 10 years later, was no longer thinking that his postulate could be addressed by experimenters (Hebb, 1958), it has been thought to have predictive value and has been tested electrophysiologically in various neuronal assemblies, from Aplysia to the mammalian brain (Wurtz, Castellucci, & Nusrala, 1967; Baranyi & Fehér, 1981a, b; Carew, Hawkins, Abrams, & Kandel, 1984; Kelso, Ganong, & Brown, 1986; reviewed in Sahley, 1985; Frégnac, 1986; Sejnowski & Tesauro, 1989).

A first limitation of Hebb's principle is that maintained temporal correlation between pre- and postsynaptic activities will eventually lead to a uniform saturation in the gain value of synaptic transmission (synaptic efficacy), and hence to a trivial connectivity state. This problem was solved in an almost ad hoc fashion by modelers, who introduced an additional normalization hypothesis (Marr, 1970; von der Malsburg, 1973). For instance, von der Malsburg proposed that the sum of the efficacies of all the synapses converging onto a given neuron should be kept constant. This is closely related to more neurobiological schemes, such as in the theory of selective stabilization (Changeux & Danchin, 1976), where a simplifying assumption is to consider a fixed pool of receptors, already present at the onset of activity in a "labile" or "stable" state (which limits the final quantity of receptors available for stabilization).

The consequence of these additional constraints is that competition between
active and inactive converging fibers will result in both selective increases and decreases in synaptic efficacy. A possible biophysical correlate was proposed by Stent, and assumes a selective decrease in the efficacy of synaptic transmission of afferent fibers which were inactive at the time when the postsynaptic neuron was discharging under the influence of other inputs. In spite of the lack of evidence for the proposed biophysical mechanism itself, the outcome of this postulate (Stent, 1973) finds strong support from cross-depression studies in visual pathways (Tsumoto & Suda, 1979), and correctly simulates the difference in the effects of monocular deprivation and binocular deprivation on cortical ocular dominance (Wiesel & Hubel, 1963).

Re-examination of Hebb's postulate. The use by modelers of nets of formal neurons (McCulloch & Pitts, 1943) connected through one ideal synapse should not be taken literally by the neurobiologist. Indeed, different biological implementations of the so-called Hebbian synapse have been proposed on the basis of recent data obtained in invertebrates and vertebrates. The historical view (Figure 5.2a) is to consider the ideal synapse as the set of direct synaptic contacts originating from one presynaptic neuron (neuron A in Figure 5.2) onto a postsynaptic neuron (neuron B in Figure 5.2). Some investigators using the invertebrate model (e.g., Hawkins & Kandel, 1984), might dispute this simplistic scheme, on the grounds that the only evidence for synaptic adaptation appears—at least in this invertebrate system—to act at the presynaptic level. Accordingly, if coactivity controls the gain between the two interconnected neurons, a plausible presynaptic amplification mechanism similar to that described in *Aplysia* could be obtained by transforming (through a feedback collateral) the postsynaptic neuron into a facilitatory neuron modulating the transmission of the presynaptic information (Figure 5.2b). Such a view might be thought of as an elegant sophism, since a classical Hebbian synapse can be found in this case between the postsynaptic neuron (now to be considered as the presynaptic partner) and the presynaptic fiber (now the postsynaptic structure) (see discussion in Frégnac, 1986). The main point nevertheless remains that temporal correlation between A and B will control the global gain of transmission. However a major difference with Hebb's postulate, not addressed here, is the requirement of a positive temporal delay between activity in neuron A and activity in the target neuron B in cellular analogs of alpha conditioning described in *Aplysia*. The last implementation of a Hebbian synapse is mainly inspired by neurobiological studies in *Hermisenda*, and introduces an intermediate circuit between the two neurons A and B, the excitability of which would be modulated by the associative procedure (Figure 5.2c). This scheme used by modelers after the first generation of perceptrons (Burke, 1966), and more recently by Tesaurro (1988), is often presented under the assumption of learning processes occurring without synaptic changes, but it could be considered as well as a third way of implementing the role of coactivity in the functional coupling of two neurons.
Figure 5.2. Neurobiological implementation of Hebb's postulate (adapted partly from Sejnowski & Tesavro, 1989).

a. Schematic representation of the historical viewpoint (Hebb, 1949). The modifiable synapse between cells A and B (dotted inset) is assumed to be purely excitatory and of axo-axonic or axo-dendritic type. The transmission gain of this connection (or "synaptic efficacy") is assumed to be regulated by the temporal coincidence in activity of both cells, detected at the postsynaptic site.

b. Connectivity scheme adapted from data obtained in the molluscan invertebrate Aplysia californica, where nonassociative (habituation, sensitization) and associative (alpha-conditioning) forms of behavioral learning are based upon presynaptic modulation of the transmitter release at direct synapses between sensory and motor neurons. The amplification of the synaptic gain is produced via the concomitant recruitment during classical conditioning of a facilitatory interneuron (activated by the unconditioned stimulus [US]) converging onto the active presynaptic sensory terminal (conditioned stimulus [CS]). This scheme may be adapted to the vertebrate brain in the following way (Hawkins & Kandel, 1984). In order to fulfill Hebb's postulate, the postsynaptic element (neuron B) is assumed to send an axon collateral which presynaptically controls the efficacy of the coupling between cells A and B. The modifiable synapse (dotted inset) here is the axo-axonic contact, where feedback from the
postsynaptic cell facilitates the transmission of its own sensory input. Consequently, the detection of the coincidence between pre- and postsynaptic activity occurs at the presynaptic site.

c. Connectivity scheme adapted from data obtained in the molluscan invertebrate H. crassicornis (review in Alkon, 1988), and in the CA3 field of the vertebrate hippocampus (Miles & Wong, 1987).

Cellular analogs of classical conditioning in H. crassicornis show that forced patterns of pre/postcoactivity can induce long-term changes in both passive and active parameters of neuronal excitability (Alkon, 1988). The modifiable Hebbian synapse is replaced by a polysynaptic chain of excitatory interneurons (I), the properties of which (internal excitability and threshold for initiation of action potentials) are presumed to be altered through functioning (see also Burke, 1966). In this scheme the interneurons are the site of detection of the coincidence of activity in cells A and B.

In addition, sustained patterns of afferent activity have also been reported to unmask latent unresponsive indirect pathways, at least in the vertebrate hippocampus, by removing the blocking influence of inhibitory parallel projections (filled symbols). Plasticity rules—symmetrical with Hebb's postulate (Stent, 1973; von der Malsburg & Bienenstock, 1986)—can be applied to inhibitory synapses, and predict a decrease in their efficacy following repeated failure to effectively block the postsynaptic activation of cells I and B. Both excitability changes in excitatory interneurons and decrease of feedforward inhibition will result in a long-term facilitation of the functional coupling between cells A and B.

Related findings have been reported in the vertebrate hippocampus and neocortex, and show that some indirect excitatory pathways can be functionally revealed or re-expressed following a high frequency stimulation train (Miles & Wong, 1987; see also the involvement of NMDA-dependent polysynaptic pathways in frontal cortex during long-term potentiation in Sutor & Hablitz, 1989a). In particular, in the CA3 field of the guinea pig hippocampus, the change in the functional coupling between neurons could be explained by a concomitant reduction in the efficacy of recurrent inhibitory circuits, due either to modifications per se of the efficacy of inhibitory contacts (see above), or to a reduction in the excitatory input to the inhibitory interneurons (Figure 5.2c adapted partly from Miles & Wong, 1987).

Learning Algorithms

The adaptive power. A classical view is to consider the neocortical neuron as a linear threshold unit. Its integrative function (passive mode) can be defined by stating that the postsynaptic potential (to be converted into firing frequency) is the summation of inputs weighted by the different synaptic efficacies, minus some threshold term (Table 5.1, equation 1.1). The second property of this kind of automaton (Brindley, 1967; Changeux et al., 1973) is modification of its transmitting properties as a function of past activity (adaptive mode, Table 5.1, equation 1.2).
Table 5.1. Integrative and adaptive powers of the formal neuron

a: integrative power

\[
y_j = \sum_{i=1}^{N} w_{ij} \cdot x_i - a_j
\]  
(eq. 1.1)

N presynaptic fibers converging on a target neuron j
x_i presynaptic activity in the ith fiber
y_j postsynaptic activity, a_i firing threshold of neuron j
w_{ij} synaptic efficacy between presynaptic fiber i and postsynaptic neuron j

b: adaptive power (Changeux & Danchin, 1976)

\[
\Delta w_{ij} = f(x_i, x_k, y_j, t')
\]  
(eq. 1.2)

x_k in the case of direct heterosynaptic interaction between afferent fibers, t' temporal delay in classical conditioning, \Delta w_{ij} change in synaptic efficacy

c: normalization rules (von der Malsburg, 1973)

\[
\sum_{i=1}^{N} w_{ij} = \text{Constant}
\]  
(eq. 1.3)

Cortical and hippocampal neurons, by the remarkable morphology of their dendrites and the relatively high level of convergence of the afferent connectivity, appear to offer the suitable hardware for "implementing" formal associative adaptive devices (such as those which are represented in Figure 5.3a). A simple form of unsupervised autoassociative learning (Figure 5.3a), where cells influence each other through their output signals, could even be realized neuronanatomically through the recurrent collaterals that a population of axons is potentially capable of making on the cells from which they originate (Figure 5.3b). In spite of the absence of quantitative neuronanatomical support for such an hypothesis, Figure 5.3b illustrates the finding of spiny pyramidal cells located in the supragranular layers of visual cortex, which often send recurrent collaterals of their descending axon in the direction of the pial surface, crossing their own basal and apical dendritic field. This umbrella-like coverage would be ideally suited to realize the internal feedback necessary for autoassociation (Figure 5.3a1).

More generally, the adaptive power of the formal neuron is characterized by the algorithm determining the dynamics of synaptic changes (Changeux et al., 1973; Changeux & Danchin, 1976). Equation 1.2 (in Table 5.1) expresses that each synaptic efficacy varies as a function of the presynaptic signal, of postsynaptic signal and of time. Temporal delays are introduced specifically in models of classical conditioning (review in Tesaur, 1986). Normalization hypotheses are added by certain modelers (equation 1.3 in Table 5.1).

Pre- and postsynaptic variables. Most algorithms used to model functional plasticity in neocortex (review in McGregor, 1987), and based on coactivity, may be summarized by the same general equation (Table 5.2) where the change of synaptic efficacy (or its derivative) with time is equal to the product of a control
Figure 5.3. Formal and Biological Neurons.
a. Formal neurons:
   a1. Auto-associative unit (von der Malsburg, 1973; reviewed in Cowan & Sharp, 1988). This McCulloch and Pitts neuron (McCulloch & Pitts, 1943) is driven by its own response to stimulus patterns, and will amplify small initial biases in its response. Such a mechanism has been used to model the emergence of orientation selectivity from slight biases in orientation preference already present at a subcortical level (Levick & Thibos, 1980; Vidyasagar & Urbos, 1982; Linsker, 1986b).
   a2. Hopfield's units with symmetric connections (Hopfield, 1982; reviewed in Cowan & Sharp, 1988). Units 1 and 2 excite one neighbor (open diamonds) and inhibit another (filled diamonds).
b. Biological neurons:
   Camera lucida drawing of a spiny pyramidal cell injected in vitro with biocytin, in layer II of
a visual cortical slice taken from a 4-week-old kitten (Grant et al., 1990). The axon of the cell running on an axis perpendicular to the cortical surface (upper continuous line) could be followed in the same plane for more than 1.5 mm (not shown). In its proximal part, only a few tens of microns from the soma, the axon sends recurrent projections to upper layers. These ascending collaterals towards the pial surface (upper bold line) apparently cross the spiny dendritic tree of the same pyramidal cell, which could result—as assumed in the case of formal neurons (see a1 and a2)—in a re-entry of the output signal on to the input lines. Inspection under light microscope at high magnification (×100) shows close proximity of axon and spiny dendritic processes (<2 μm), suggestive of the presence of synaptic contacts. Moreover, in these particular regions (circles) the axon collaterals show varicosities or swellings which may constitute possible boutons. This umbrella-like arborization pattern of the axon was observed in several spiny pyramidal cells of the supragranular layers. Scale marker: 50 μm.

factor C, a presynaptic term, and a postsynaptic term. The control factor C is used by the modeler to adjust the speed of convergence of the state of the system. Too high values could lead to oscillatory behavior. The second term represents presynaptic activity, for example, the activity in the considered afferent fiber. It can be expressed in different ways, as the instantaneous discharge frequency (see most models of the 1970s, and 1980s; von der Malsburg, 1973; Nass & Cooper, 1975; Bienenstock et al., 1982), or as time-average variables linked to afferent activity (see models of classical conditioning). Even in schemes supposedly determined only by postsynaptic factors (Finkel & Edelman, 1987), the rule governing synaptic change depends on hidden presynaptic variables; in this last model, the concentration of a modifying substance in the postsynaptic membrane reflects presynaptic activity. The third term corresponds to postsynaptic variables, such as the instantaneous discharge frequency of the target cell, or the summed postsynaptic potential of the membrane (in the case in which the model makes use of continuous variables). Interestingly, this term in Finkel and Edelman’s model represents the dendritic potential created locally by neighboring competing fibers, and it can be used to introduce heterosynaptic plasticity and cooperativity. In the case where postsynaptic variables are chosen to reflect local activity, no feedback or retrograde signal has to be assumed from the global postsynaptic output to the locus of modification itself.

The covariance hypothesis. Hebb’s principle, as presented in equation 2.1 of Table 5.2, presents the obvious limitation that predicted changes in synaptic efficacy will always be positive and lead to progressive saturation of the efficacy of all the synapses in the network. The type of algorithm of synaptic plasticity introduced by Sejnowski in 1977 in cerebellum (Sejnowski, 1977a, 1977b), and later by Bienenstock and coworkers in visual cortex (Bienenstock et al., 1982) (equation 2.2 in Table 5.2), overcomes this problem. The so-called “covariance hypothesis” replaces the pre- and postsynaptic terms by the departure of pre- and postsynaptic activities from their respective average values over a certain
Table 5.2. Coactivity and algorithms of synaptic plasticity

<table>
<thead>
<tr>
<th>Algorithm</th>
<th>Synaptic Change</th>
<th>Presynaptic</th>
<th>Postsynaptic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Associative memories:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hebb's postulate</td>
<td>$\Delta w_{ij}$</td>
<td>$C \ast x_i$</td>
<td>$y_j$</td>
</tr>
<tr>
<td><strong>Covariance algorithm</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C$, control parameter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$x_i$, instantaneous presynaptic activity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>or modifying substance concentration linked with afferent activity,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$y_j$, postsynaptic activity, or postsynaptic membrane potential, or local dendritic potential</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\bar{x}$, $\bar{y}$, time averaged values of $x_i$ and $y_j$</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Algorithm</th>
<th>Synaptic Change</th>
<th>Presynaptic</th>
<th>Postsynaptic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Memory with temporal contiguity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Rescorla and Wagner, 1972)</td>
<td>$\Delta w_{ij}$</td>
<td>$C \ast \bar{x}_i$</td>
<td>$y_j(y'(\bar{y}))$</td>
</tr>
<tr>
<td><strong>(Sutton and Barto, 1981)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\bar{x}_i$, CS stimulus “trace”</td>
<td>$\Delta w_{ij}$</td>
<td>$C \ast \bar{x}_i$</td>
<td>$\Delta y_j$</td>
</tr>
<tr>
<td>$y_j(t')$, postsynaptic response imposed by US following CS with delay $t'$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\bar{y}$, mean output predicted by the summation of the postsynaptic effects generated by the CS signals</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\Delta w_{ij}$ and $\Delta y_j$ changes in synaptic efficacy and in postsynaptic response</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Window of time. This covariance term, which allows the convergence towards nontrivial states, predicts both increases and decreases in synaptic efficacy.

Hebb's and Sejnowski's schemes of synaptic plasticity suppose that the biological net will function as an associative memory, and the modification rules use instantaneous pre- and postsynaptic variables. In the case of classical conditioning, the same equations are applied using an additional time parameter (equations 2.3 and 2.4 in Table 5.2), which will account for the needed temporal contingency between the CS and the US stimuli (Barto, Sutton, & Anderson, 1983; Tesauro, 1988). The presynaptic term usually reflects a trace of past activity and the postsynaptic term is either a covariance term or the difference between the actual value and the expected value of the output. Actually, however, and in spite of the amnesic tendencies shown by some theoreticians of behavioral learning (review in Klopf, 1988a, 1988b), all these equations may be considered as more or less simple variations on the same original basic algorithm (see also Table 5.3).
Table 5.3. Coactivity and prediction tables

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>0</th>
<th>1</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presynaptic</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Postsynaptic</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Change in</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Covariance</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>=</td>
</tr>
<tr>
<td>Change in</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synaptic gain</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>=</td>
</tr>
<tr>
<td>Protocol</td>
<td>$S'$</td>
<td>$S'$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presynaptic</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Postsynaptic</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>HEBB</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STENT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group Selection</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>=</td>
</tr>
<tr>
<td>BOLTZMANN</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>/HOPFIELD</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Covariance</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothesis</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>=</td>
</tr>
</tbody>
</table>

a: The covariance hypothesis assumptions:
1) the initial (unperturbed) level of covariance between presynaptic and postsynaptic activities is assessed during a control period on a preset number of pre- and postsynaptic events. Covariance between $X$ and $Y$ being defined as the mean value of the product $(X_i - \bar{X}_j)(Y_j - \bar{Y}_j)$ where $\bar{X}_i$ and $\bar{Y}_j$ are the mean values of $X_i$ and $Y_j$ respectively. Each activity process ($X$: pre, $Y$: post) is regarded as a 0- or 1-valued series on a discrete time-scale. This initial covariance level will be recomputed each time the pre- or the postsynaptic neuron fires (i.e. takes a "1" value), or when both fire together;
2) the pairing procedure "repeatedly and persistently" imposes a specific pattern of pre- and postsynaptic activity, given by one of the four situations described in the first two rows of each column, which results in a maintained change in covariance when compared with the control situation.

Under these assumptions, the predicted sign of synaptic change (4th row) is given by that of the covariance change imposed during pairing (3rd row).

b: Comparison of different synaptic modification algorithms:
The sign of synaptic change predicted by different models of synaptic plasticity (Hebb, 1949; Stent, 1973; theory of neuronal group selection in Edelman, 1978; Edelman & Finkel, 1984; Finkel & Edelman, 1987; Boltzmann/Hopfield model in Ackley et al., 1985) is given for the four patterns of pairs of pre- and postsynaptic activity detailed in the first two rows.

A simple way of illustrating the basic difference between Hebb’s postulate and the “covariance hypothesis” is to plot the right-hand term in equations 2.1 and 2.2 as a function of postsynaptic activity (Figure 5.4). In both cases, the dependence is linear. The line crosses the X-axis either at the origin (Hebb’s hypothesis), or at a positive value (Sejnowski’s scheme). In the latter case, depending on how the postsynaptic firing level compares with this threshold, a
Figure 5.4. Comparison of the Hebbian and the Covariance algorithms.

a. The changes in synaptic efficacy predicted by Hebb's postulate (eq. 2.1 in Table 5.2) and by the covariance algorithm (eq. 2.2 in Table 5.2) are plotted for a given input level, as a function of postsynaptic activity. Hebb's postulate predicts only positive changes in synaptic efficacy, which increase linearly with postsynaptic activity. In contrast, the covariance hypothesis predicts either increase or decrease in synaptic efficacy, depending on where the instantaneous postsynaptic activity reaches a fixed threshold value (Sejnowski, 1977a, b). Bienensnock and collaborators proposed a slightly different plasticity algorithm, where the threshold deciding for the sign of the synaptic modification is floating and depends on past activity of the cell, which avoids too rapid divergence of the synaptic gain towards extreme values following maintained periods of very low or high postsynaptic activity.

b. Same diagram as in (a) showing the behavior of the modification function used by Bienensnock et al. (1982) for two levels of mean postsynaptic activity ("low" and "high"). These authors assume that the modification sign threshold increases ("high") or decreases ("low") faster than the mean postsynaptic activity (Bienenstock et al., 1982).
decrease (if it is lower) or increase (if actual firing is above this threshold) in synaptic efficacy will be predicted. Cooper and collaborators introduced several refinements in the covariance algorithm (Bienenstock et al., 1982; Bear, Cooper, & Ebner, 1987), in which the threshold value itself is made "floating" and depends non-linearly on the past activity of the cell. The dependence relationship is chosen such that, for high levels of firing, the threshold increases faster than the mean activity of the cell. Consequently, in the case of the iterative presentation of a given stimulus initially causing a gain in synaptic efficacy, the cell’s response will eventually saturate or regress because the threshold will exceed the mean activity of the cell and become too high to allow a positive change in synaptic efficacy. Conversely, if the mean activity of the cell decreases to almost vanishing values (as would be the case during visual deprivation), the threshold is supposed to decrease faster than the mean activity of the cell. Under these assumptions, restoration of visual input will cause the neuron to increase the synaptic weight of activated synapses. This prediction agrees with the observation of an increased rate of cortical specification in previously deprived animals re-exposed to a visually structured environment, when compared with the normal process observed in nondeprived animals (Imbert & Buisseret, 1975; Frégnac, 1979c, 1985).

Since these first attempts to explore the consequences of synaptic modification rules mainly through numerical simulations, and to validate the chosen algorithm from the comparison of predictions with electrophysiological observations, a more systematic approach has been developed by Linsker (Linker, 1986a,b,c. 1988). With proper normalization of the changes in synaptic efficacies, a totally unsupervised Hebbian learning scheme is shown to produce center-surround receptive fields and orientation selectivity. A remarkable consequence—using this rule of learning based upon afferent competition—is that the neural network (properly interconnected) does not require a structured input (under the influence of vision) for the formation of almost spatially periodic isofunctional domains. In spite of the fact that it is not clearly understood why maximizing the covariance of the weighted coactivities of all possible pairs of input lines to a given unit create receptive fields similar to those described in visual cortex, the small number of the generic parameters makes this theoretical approach remarkable (review in Hinton, 1987).

Among other types of algorithm used recently in artificial net models, it is worthwhile to note the similarity between the learning rules used in the Boltzmann machine (Ackley, Hinton, & Sejnowski, 1985) and the “covariance hypothesis” (see Table 5.3), In this statistical formulation of Hopfield’s nets (Hopfield, 1982), an assembly of formal neurons is supposed to be partitioned into two functional groups—a nonempty set of “visible” units forming the interface with the environment (that we can assimilate to “input” and “output” cells in a biological multilayer network), and a possibly empty set of “hidden” units (hidden layers or association areas). These units are connected to each other
by bidirectional links, and each of them becomes active or silent with a probability dependent on the states of its neighbors and on the synaptic efficacies of the corresponding links. The Boltzmann machine follows a learning rule by matching coactivity probabilities between the environment and the network: During a "training phase" the environment clamps both the input and output units, and the probability that two units i and j are in the same state is estimated at equilibrium (p_i). During a "testing phase," input units are clamped (although this is not mandatory), and the output and hidden units are left in a free-run mode, so that a new probability of coactivity (for the same pair of units) is estimated (p'_i). All synaptic efficacies in the network are incremented by the same step, with the sign of the increment being determined by the sign of the difference between the two probabilities (p_i-p'_i). The statistical nature of the model ensures that connection strengths between formal units are modified in such a way that the whole network connectivity captures the underlying constraints in the structure of its environment. Striking parallels with the "covariance" scheme of synaptic plasticity are that the learning rule of the Boltzmann machine uses also only locally available information, and that both algorithms predict similar signs in the changes in efficacy of a given synapse depending on the relative fluctuations in coactivity of the two units it connects (Table 5.3; see also activity clamping protocols in a later section).

DO VISUAL CORTICAL NEURONS NEED AN EXTRARETINAL "TEACHER"?

The Paralysis/Anesthesia Paradox

Ever since neurobiological evidence first suggested that receptive-field properties at the cortical level could be profoundly remodeled by visual experience, Hebbian synapses have been proposed as a likely candidate for explaining functional changes occurring during epigenesis (Cynader & Mitchell, 1977; Rauschecker & Singer, 1979; Rauschecker & Singer, 1981). However, a fundamental problem in trying to test Hebb's hypothesis at the single cell level is to overcome the freezing of cortical dynamics generally observed under paralysis and anesthesia. Indeed to most electrophysiologists, the functional properties of visual cortical cells appear remarkably stable in the acute preparation. The success obtained using the anesthetized and paralyzed preparation may be due in part to the fact—in addition to the suppression of eye movements—that receptive-field (RF) properties reflect only sensory experience given prior to the electrophysiology session, and not that given during RF exploration.

Consequently it is not surprising that most attempts to induce modifications of the integrative power of a single neuron by repetitive visual stimulation have been unsuccessful under those conditions in inducing long-lasting and reliable changes in orientation selectivity and ocular dominance (review in Frégnac & Imbert, 1984). Several types of experimental approaches (Kasamatsu & Pettigrew, 1976; Buisseret, Gary-Bobo, & Imbert, 1978; Freeman & Bonds, 1979;
Singer & Rauschecker, 1982; Singer, Tretter, & Yinon, 1982; Geiger & Singer, 1986) indicate in contrast that extraretinal activation is a necessary requisite to induce functional modifications, and that perhaps a certain threshold in the activity of the postsynaptic site must be reached in order to allow the expression of such changes (von der Malsburg, 1973). This requirement—which apparently is not met under paralysis and anesthesia—is probably fulfilled in the alert animal during a normal visuomotor task, through the activation of a diversity of extraretinal signals (see next section), which in turn gates adaptation of cortical responsiveness to incoming visual input. Long-duration chronic multunit recordings with floating electrodes have been attempted in alert kittens (maintained in a semirestrained condition, but free to move the eyes) during monocular occlusion. Although proper receptive-field characterization could not be achieved, ocular dominance changes in visual responsiveness could be followed at a given cortical locus for a period of several days of maintained unilateral eye closure (Mioche & Singer, 1989).

**Extraretinal Gating Factors**

The hypothesis of a threshold for gating visual cortical plasticity implied—at least in the neurobiologist’s mind—the identification of some “teacher” controlling the gating of specific cellular changes. However, Hebbian schemes of plasticity do not require an external reinforcement procedure or the explicit specification of the desired output signal for synaptic changes to occur. *Unsupervised* learning procedures capture regularities in their input without receiving any additional information (Beinenstock et al., 1982; Linsker, 1986a, b, c; Hinton, 1987). Neurobiological data seem in fact to indicate that a global evaluation by the cortical network is needed to decide when synaptic modification (whatever its sign, for example increase or decrease) should occur. The remaining question—still largely unanswered—is to understand how these hypothetical “print now” signals are generated and what is their functional nature. Visual cortical cells have been shown to become adaptive in a variety of physiological conditions, and the occurrence of these modifications appears to be context-dependent: Their expression is linked to the motivation and the attention state of the organism, and to the motor act or behavior that was involved in sampling the visual information. A brief overview of the experimental literature suggests that two kinds of *extraretinal gating* signals could be of importance in the expression of visual cortical plasticity.

The noradrenaline hypothesis. Kasamatsu and collaborators provided appealing but controversial evidence (review in Kasamatsu, 1983; Frégnac, 1987) suggesting that the ascending noradrenergic system might be involved in maintaining the sensitivity of visual cortex to monocular deprivation during the critical period. According to Pettigrew and Kasamatsu, the cortical noradrenaline (NA) level would control locally the degree of cortical plasticity by gating functional modification in response to visual input. An impressive series
of pharmacological and electrophysiological experiments gives strong support to the role of catecholamines in modulating the functional cortical effects of monocular deprivation (Kasamatsu & Pettigrew, 1976, 1979; Kasamatsu, Pettigrew, & Arv, 1979, 1981). The loss of response to the deprived eye, normally observed following lid suture of one eye, can be completely prevented if the kitten has been subjected shortly before the start of the visual deprivation to lesions of the noradrenergic projections (achieved by intraventricular or intracortical injections of a specific neurotoxin, 6-OHDA). The implication of the intracortical beta-adrenoreceptor adenosine-monophosphate (cAMP) system was furthermore suggested by the restoration of cortical sensitivity to monocular deprivation in 6-OHDA pretreated kittens. Following local perfusion of exogenous NA or cAMP in the cortical tissue itself (Pettigrew & Kasamatsu, 1978; Kasamatsu et al., 1979; Kasamatsu, 1982; Kuppermann & Kasamatsu, 1984). Final convincing evidence was the claim that sensitivity to monocular occlusion is blocked in untreated cortex after injection of beta-adrenergic blockers (d, l-propranolol or sotalol) but is still present after injection of alpha-adrenergic antagonist (phenotamine and phenoxybenzamine) (Kasamatsu, 1979; Kasamatsu, 1983; Kasamatsu & Shirokawa, 1985; Shirokawa & Kasamatsu, 1986).

However, recent experiments (Adrien et al., 1982; Daw, Robertson, Rader, Videen, & Coscia, 1984; Videen, Daw, & Rader, 1984; Adrien et al., 1985) have shed doubt on the initial conclusions of Kasamatsu and Pettigrew, or have at least shown their dependence on the mode of neurochemical lesion of the ascending noradrenergic pathway. On one hand, the blockade of cortical plasticity following intraventricular injections of 6-OHDA could not be replicated (Adrien et al., 1982; Trombley, Allen, Soyke, Beaha, Lane, & Gordon, 1983; Adrien et al., 1985; Daw et al., 1985b), although most authors agree that intracortical injection of the same neurotoxin blocks visual cortical plasticity. Techniques of NA deafferentation, such as in situ lesion of the ascending fibers (Daw, Videen, Parkinson, & Rader, 1984; Daw et al., 1985a), or of the noradrenergic cell bodies (Adrien et al., 1982, 1985), involving much smaller doses of the neurotoxin than those used originally by Pettigrew and Kasamatsu (1978), did not confirm the dependence of cortical plasticity on the NA level alone. However, data from Bear and Singer (1986) showed that the combined systemic destruction of the cholinergic and noradrenergic ascending pathways reliably reduces the sensitivity to monocular deprivation, even though massive lesions of either system was confirmed to be ineffective. Although these last findings have been presented as evidence that cortical plasticity is mediated through coactivation of several “gate factors” (acetylcholine and NA), it does not contradict the view that the cholinergic system could play a modulatory role secondary to the gating action induced by NA (Imamura & Kasamatsu, 1989).

This reinterpretation does not preclude a palliative role of the cholinergic projections in controlling cortical plasticity following a systemic lesion of the NA pathway (see discussion in Frégnac, 1987). An alternative which remains open is
that the early use of massive lesions may have obscured the possible specificity of the implication of NA at the cortical level, by putting into play global compensatory mechanisms between interdependent modulatory pathways. In contrast with systemic lesions of the locus coeruleus projections, in situ intracortical infusion of minimal doses of neurotoxin, agonist, or specific receptor blocking agents might prove to be the only way of assessing the involvement per se of NA in gating visual cortical plasticity. This view is supported by recent in vitro electrophysiological studies, done in cocultures of explants of LGN and visual cortex (Yamamoto, Kurotani, & Toyama, 1989), which show that NA infusion concomitant with electrical activation of identified geniculocortical axons can allow the induction of synaptic plasticity in an otherwise aplastic network (Toyama, personal communication).

Extraocular eye muscle proprioception. A second source of extraretinal information, that may influence the functional development of visual cortex, finds its origin in the eye movements normally associated with the exploration of the visual environment. For instance, restoration of orientation specificity in dark-reared kittens following a brief flash of visual experience has been shown to depend on ocular motility (Buissere et al., 1978). More recent experiments demonstrated the implication of extraocular muscle proprioceptive signals running through the ophthalmic branch of the trigeminal nerve (Trotter, Gary-Bobo, & Buissere, 1983). Bilateral section of extraocular proprioceptive inflow, when performed at the peak of the classical critical period, blocks the further development of visual cortical integration (Graves, Trotter, & Frégnac, 1987).

The role of extraocular proprioception might be not limited only to this gating process. controlling the expression of vision-dependent cortical changes. For instance, Trotter, Frégnac and collaborators described—both in normally reared and visually deprived kittens—a susceptibility of ocular dominance to the unilateral section of the ophthalmic branch of the trigeminal nerve (Graves et al., 1987; Trotter et al., 1987). The consecutive loss of binocular interaction, which is independent of visual experience, demonstrates the existence of extraretinal critical period(s) lying within the temporal limits of the classical cortical period of sensitivity to monocular deprivation (Hubel & Wiesel, 1970). Early imbalance in proprioceptive inflow appears to affect selectively binocular cortical processing of spatial disparity cues (Trotter, personal communication), and leads to a long-term impairment in depth perception performances. Furthermore, extraocular muscle proprioceptive signals have been shown to modulate retinal transmission to the visual thalamocortical pathway in a specific temporal and spatial pattern, even in the adult (Lal & Friedlander, 1989, 1990). These data suggest that extraocular proprioceptive inflow plays a role per se in the maintenance, maturation and plasticity of visual cortical receptive properties (review in Frégnac, 1987), and could possibly retain a modulatory action in the integration of binocular signals at the adult age.
CELLULAR ANALOGS OF VISUAL CORTICAL PLASTICITY

An *in vivo* Experimental Test of the Covariance Hypothesis

The data presented above provide support for the argument made earlier that Hebb's postulate does not apply *stricto sensu* in the anesthetized and paralyzed preparation, where the absence of appropriate gating signals precludes visual neurons from reaching an adaptive state (Figure 5.5b). In spite of early claims of positive findings (Pettigrew et al., 1973; Imbert & Buisseret, 1975), which have been since reinterpreted (see detailed discussion in Frégnac & Imbert, 1984, pp. 403-407), low temporal frequency presentation of a visual test-stimulus to which a cell is already responding does not produce long-term enhancement of the initial response (Frégnac & Bienenstock, 1981; Frégnac, 1982).

One of the few experimental paradigms in which changes in ocular dominance or in orientation preference of single cells have been reported during the time of recording was when visual stimulation was paired with passive eye movements or with global extraretinal stimulation (Frégnac & Bienenstock, 1981; Tsumoto & Freeman, 1981; Geiger & Singer, 1986). Tsumoto and Freeman, for instance, combined monocular deprivation with electrical stimulation of the internal medullary lamina of the thalamus while recording cortical units from anesthetized (but unparalyzed) kittens. They found significant changes in ocular dominance of individual cells towards the experienced eye (Tsumoto & Freeman, 1981). Another paradigm was used by Frégnac and Bienenstock in an anesthetized and paralyzed preparation, where variable spatial disparity between visual signals on the two retinas—produced by the association of a binocular visual stimulation with imposed unilateral passive eye movements—was shown to induce long-term changes in the ocular dominance of visual cortical neurons considered individually. Transient changes in orientation selectivity were also reported (Frégnac & Bienenstock, 1981). However, one should note that these associative procedures concerned the whole cortex where all neurons were probably conditioned at the same time.

Another type of approach used in order to change the functional properties of individual visual cortical cells is to locally mimic the gating action of extraretinal signals which are lacking in the anesthetized and paralyzed preparation, by modulating the temporal correlation between the afferent visual activity and the postsynaptic activity of the recorded cell. In order to test predictions of the covariance algorithm, in collaboration with Elie Bienenstock and Simon Thorpe we developed an electrophysiological paradigm which allowed us to produce, during the time of recording of one cell, functional changes analogous to those classically described during visual cortical development (Frégnac, Shulz, Thorpe, & Bienenstock, 1988, 1992; Frégnac & Shulz, 1989; Frégnac, Shulz, & Debanne, 1989; Shulz & Frégnac, 1992). The control of the temporal correlation between the afferent visual message and the postsynaptic activity was obtained by the association of an iontophoretic current (in most
PASSIVE

SPONTANEOUS

EVOKE

ADAPTIVE

COVARIANCE  PRE  POST  SYNAPTIC CHANGES

+  

+  

+  

=  

=  

Figure 5.5. Neurobiological implementation of the covariance hypothesis (reproduced from Frégnac & Shulz, 1989, with permission).

Temporal patterns of pre- and postsynaptic activities are represented during two modes of functioning of a formal neuron.

Top of the Figure: passive mode. Left, two visual afferent pathways and the target cell on which they converge are spontaneously active. Right, the postsynaptic neuron responds to visual activation. Extraretinal modulation (indented bouton) is absent.

Bottom of the Figure: adaptive mode. The changes in covariance between pre- and postsynaptic activities imposed by extraretinal gating (when indented bouton is active) result in long-term modifications of synaptic efficacies. Left column, sign of the covariance change in each visual pathway. Middle column, postsynaptic activity pattern resulting from modulation by gating signals. Right column, induced long-term changes in synaptic efficacies (positive if bold, negative if dotted).

Predictions of the covariance hypothesis (see right column) are illustrated for two types of visual afferent activity: upper row, when both pathways are active (Hebb's postulate); middle (Stent's postulate) and bottom rows, when only one pathway is active. Extraretinal gating action is supposed to facilitate (upper and middle rows) or to block (lower row) postsynaptic activity.
cases less than \( \pm 10 \) nA) through the extracellular recording electrode (2-20M Ohm, 3M KCl) with the presentation of a given stimulus within the receptive field of the cell (see also next section).

Two types of control of covariance between pre- and postsynaptic activity were sought: (a) a positive change in covariance (upper row, Figure 5.5b) was imposed for a given characteristic of visual input, by increasing postsynaptic firing, that is, by applying concomitantly a positive current pulse (which in most cases depolarized the target cell, as a result of the current action itself and of the increase of extracellular potassium). (b) Alternately, for a different visual input message, a negative change in covariance (lower row, Figure 5.5b) was imposed by reducing or blocking the postsynaptic response, i.e., by applying a negative current pulse (hyperpolarizing the cell via an extracellular field effect). The consecutive adaptation of four different properties intrinsic to visual cortical organization was tested in response to this differential pairing procedure: ocular dominance (Figure 5.6), orientation selectivity (Figure 5.7), interocular orientation disparity (Figure 5.8) and spatial sensitivity profile of the receptive field (Figure 5.9). The cellular analog approaches devised for each of these properties are detailed in the next section, and their outcome is compared with schemes of plasticity already derived from classical developmental studies based on population analysis techniques.

Ocular Dominance Plasticity

The monocular deprivation paradigm. Activity-dependent changes in ocular dominance are probably among the most documented electrophysiological phenomena (Hubel & Wiesel, 1970), for which surprisingly no direct evidence had yet been given at the cellular level (review in Movshon & Van Sluyters, 1981). Knowledge so far relies on the comparison of properties of populations of neurons recorded in different animals and are based mainly on the following observations.

From eye opening (between the first and the second week of age in kitten; Blakemore & Cumming, 1975) most cortical cells are binocularly driven (Hubel & Wiesel, 1963). Unilateral eye closure by lid suture performed from the third postnatal week quickly produces a dramatic change in cortical binocularity; for example, most visual cortical neurons respond exclusively to the open eye (Wiesel & Hubel, 1963). This sensitivity of area 17 to monocular deprivation extends from the third postnatal week to three months of age in the cat (Hubel & Wiesel, 1970; Olson & Freeman, 1980). In contrast, total binocular deprivation by dark rearing does not produce any change in the cortical ocular dominance distribution, although one should note that other receptive-field properties such as orientation selectivity are altered by the absence of vision (Blakemore & Van Sluyters, 1975; Buisset & Imbert, 1976; Frégnac & Imbert, 1978; Leventhal & Hirsch, 1980; Mower et al., 1981). This implies that the
Figure 5.6. Plasticity of ocular dominance.
Left panel. Population analysis: comparison of ocular dominance histograms in normally reared and monocularly exposed kittens (data adapted from Trotter et al., 1983, 1987). In 6-week-old kittens, most cells are binocularly activated under normal rearing or binocular deprivation conditions (classes 2 to 4 in NR histogram), whereas monocular vision imposed for a few hours at that age results in most cells being dominated by the open eye (classes 1 and 2 in MD histogram).

Right panel. Single cell analysis: modification of the ocular dominance of a single cell, recorded in the visual cortex of an anesthetized and paralyzed animal. This cell, recorded in a 4-week-old kitten, was initially dominated by the right eye (middle histograms, before pairing). During pairing (not shown here) the left eye stimulation was associated with an increase in activity imposed by a positive current pulse passed through the KCl recording electrode (+5 nA, S+). For this particular cell, negative current (S-) had no effect on its firing level, and consequently no iontophoretic current was applied during right eye stimulation (S-). After pairing (lower histograms), in the absence of iontophoretic current, the cell showed an increased responsiveness to the stimulation of the eye which was associated previously with a reinforced level of activity (S+). The modification of the visual response was limited to the subzone of the left eye receptive field where iontophoretic action was achieved (dark bar below each PSTH). (Data adapted from Frégno et al., 1988.)
Figure 5.7. Plasticity of orientation selectivity.

Left panel, Population analysis: comparison of the distribution of preferred orientations in visual cortex following normal rearing and exposure to a vertically striped environment (top). Each radius line on the polar plot (middle and bottom) corresponds to the preferred orientation encoded by a given cell. Under normal rearing conditions, all orientations are equally represented in area 17 (middle). After a few hours of selective exposure to vertical orientations, most visual cortical cells show a preferred orientation (bottom row) attuned to that which was experienced during the rearing procedure. (Data adapted from Blokemade & Cooper, 1970.)

Right panel, Single cell analysis: modification of orientation selectivity of a single cell, recorded in the visual cortex of an anesthetized and paralyzed kitten. The polar tuning curves indicate the level of firing in response to the presentation of a bar of light as a function of its orientation (expressed on a 360° scale, since each given orientation corresponds to two
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opposite directions of sweep). For didactic purposes, the original polar tuning curves have been rotated by the same angle (90°), so that “reinforced” orientation (S+, right panel) is vertical, as is the case in the experiment depicted in the left panel. The conditioned cell, recorded in a 6-week-old visually deprived kitten, was initially nonorientation selective, i.e., it responded to every orientation (middle, before pairing). Responses for S+ and S− orientations were averaged over 80 presentations in control runs. During pairing (not shown here) the alternate presentations of a vertical (90°) and a horizontal (0°) orientation were associated respectively with a high (+5 nA, S+) and a low (−5 nA, S−) level of response. After pairing, the cell became tuned to the positively “reinforced” orientation (S+), and the response to the horizontal orientation (S−) was totally depressed. The lower polar plot (after pairing) shows that the change in orientation tuning is selective not only for the orientation, but also for the direction of movement of the oriented bar which was previously associated with an imposed increase in postsynaptic activity (i.e., 90°). This change was still present two hours after the end of the conditioning procedure. (Data adapted from Frégnac et al., 1988.)

abnormally low level of binocular interaction in the monocularly deprived cats cannot be explained simply on the basis of disuse of the deprived eye. Binocular competitive interaction between visual inputs for dominance of central connections appears to be a major mechanism involved in the monocular deprivation effects at the cortical level.

A more analytical way of studying afferent activity dependence requirements in the maintenance of binocular interaction is to control artificially and independently the pattern of activity originating from each eye. Stryker and coworkers have combined the silencing of each retina by the intraocular injection of a sodium channel blocker (teerodotoxin [TTX]; Reiter, Wartzman, & Stryker, 1986), and the individual stimulation of each optic nerve. They studied at the cortical level the effects of “in phase” and “out of phase” stimulation volleys on the segregation of ocular dominance bands formed by geniculate afferents, and on the binocularity of the target cells (Stryker & Strickland, 1984). This elegant experimental approach correctly simulates the effects of monocular occlusion and demonstrates once more that binocularity at the cortical level depends on the temporal synchrony of activation through each eye, within a given temporal window (see also Blasdel & Pettigrew, 1979; Altmann, Luhmann, Greuel, & Singer, 1987).

Coming back to more classical deprivation paradigms, the comparison of ocular dominance distributions—recorded in animals subjected to various periods of unilateral eye closure starting at the same age—suggests that the loss of binocular cells is larger the longer the duration of the monocular deprivation (Movshon & Dürsteler, 1977). Remarkably, the amount of binocular imbalance needed at the peak of the critical period (4–6 weeks of age) to produce a significant disruption of cortical binocularity appears to be of the order of a few hours in both normally reared kittens (Movshon & Dürsteler, 1977; Freeman,
Figure 5.8. Plasticity of interocular orientation disparity.

Left panel, Population analysis: comparison of the distribution of the difference in orientation preferences seen through each eye, in normal kittens (IOD = 0°) and in kittens reared with prisms imposing an optical rotation between each visual field (IOD = -16°). Under normal rearing conditions (or rearing with neutral goggles: 0°) most cells in primary visual cortex show an IOD centered around a null value (middle histogram). Conversely, if the animal experiences binocular vision though prisms imposing a -16° disparity (lower histogram) during its early life, most cells in cortex show a preferred IOD centered on the imposed disparity. (Data adapted from Shinkman & Bruce, 1977.)

Right panel, Single cell analysis: modification of interocular orientation disparity selectivity of a single cell recorded in visual cortex of an anesthetized and paralyzed kitten. This binocular orientation biased cell had been recorded for 5 hours and 45 minutes in a 9-week-old normally reared kitten. Initially the cell was tuned to the 0° disparity (broken line), and
comparable levels of binocular responses were obtained when pairs of oriented stimuli (see top cartoon) corresponding respectively to $-16^\circ$ and $+16^\circ$ disparities (middle graph, dotted lines) were presented simultaneously in each receptive field. During pairing (not shown here), the $-16^\circ$ and $+16^\circ$ disparities were associated respectively with high ($+25$ nA, S+) and low ($-9$ nA, S-) levels of imposed activity. After pairing (lower graph), the cell's binocular response became tuned to the reinforced disparity (i.e., $-16^\circ$), and a loss in responsiveness occurred concomitantly around the S- disparity (i.e., $+16^\circ$). (Data adapted from Shulz & Frégnon, 1992.)

1979; Freeman & Olson, 1979) and previously dark reared kittens (Schechter & Murphy, 1976; Trotter et al., 1983). The “capture” of the visual cortical response by the open eye after a short period of imbalance imposed between inputs from both eyes leads one to conclude that the relative inability of cortical cells to respond to the deprived eye in this experimental situation occurs too rapidly to result from anatomical disconnection of the deprived afferents. A favored explanation is activity-dependent changes in the efficacy of transmission at synapses mediating visual activity. Consequently, the monocular deprivation effect in the striate cortex is generally thought of as a two-step mechanism. First, rapid reversible synaptic changes take place which result in the functional silencing of the inputs from the deprived eye without a physical loss of synaptic contacts. This process itself might be more complex than originally thought. In a recent series of chronic multunit recordings, Mioche and Singer described a rather unexpected temporal sequence (Mioche & Singer, 1989): At a given cortical locus, a down-regulation of the responses evoked by the closed eye occurs within a few hours after the start of the eye occlusion, followed by a loss of responsiveness through both eyes, before the open eye becomes the more efficient in triggering cortical activation (1 to 3 days later). Longer periods of monocular deprivation will produce changes in geniculocortical axon arbor (Friedlander & Martin, personal communication, 1989) and eventually in an irreversible anatomical disconnection of some of the inputs of the closed eye (Blakemore, Van Sluyters, Peck, & Hein, 1976; Van Sluyters, 1978).

Additional support in favor of these stepwise mechanisms comes from studies on the effect of acute removal of the experienced eye following various periods of monocular deprivation. An almost 50 percent increase in responsiveness to the initially deprived eye was reported within a few hours following the acute enucleation of the experienced eye in 5-week-old normally reared kittens subjected to 10 days of monocular deprivation (Van Sluyters, 1978). In contrast, a much more limited reversal of the effects of eye-lid suture was observed after removal of the experienced eye in adult cats reared monocularly from birth (Kratz, Spear, & Smith, 1976; Spear, Langsetmo, & Smith, 1980). In both cases the acute recovery of response from the deprived eye suggests that at least part of
Figure 5.9. Plasticity of the spatial organization of visual cortical receptive fields. Left panel, Population analysis: Unusually large receptive fields with two distant zones of discharge have been reported in a previously binocularly deprived kitten, exposed selectively (12 hours) to a grating of fixed orientation and spatial frequency (Spinelli et al., 1972; Singer & Tretter, 1976). In some cells PSTHs, obtained in response to a single slit of light moving across the RF, show two or more discharge areas separated by a distance which corresponds exactly to the spatial period of the grating experienced during the restricted exposure. (Data adapted from Singer & Tretter, 1976.) However, no quantitative study is available concerning the statistical significance of these quasiperiodic receptive fields (when compared to their occurrence level in normally reared or deprived kittens of the same age). Uncommon receptive fields were also described after selective exposure of animals to planetarium-like environments (Pettigrew & Freeman, 1973), and these findings were thought to be supportive of a reorganization of the spatial structure of cortical RF during visual functioning. Right panel, Single cell analysis: modification of the relative levels of ON and OFF responses of a simple cell recorded in the primary visual cortex of a 27-week-old cat. Before
The inability of the closed eye to drive cortical neurons results from a tonic inhibition exerted by maintained retinal activity ongoing through the open eye (Duffy, Snodgrass, Burchfield, & Conway, 1976; Tsumoto & Suda, 1978). However, it remains unclear if this abnormally high interocular inhibition is the result or the cause of a decreased efficacy of the excitatory connections subserved by the deprived eye.

Nevertheless, other studies in monocularly deprived kittens, using evoked potentials and current source density techniques, reveal only a reduction of the short latency excitatory responses to electrical stimulation of the deprived optic nerve (Singer, 1977; see also Mitzdorf & Singer, 1980). Although one cannot rule out involvement of discrete changes in inhibitory transmission, it is admitted that changes in the efficacy of synaptic transmission of the excitatory connections are largely responsible for both the "capture" of the cortical response by the experienced eye and for the decreased influence of the deprived eye.

The cellular analog approach. In spite of the coherence of experimental observations based on population analysis and of theoretical schemes of synaptic plasticity (Rauschecker & Singer, 1981), it still remains to be proved if cells do individually change their ocular dominance following monocular deprivation. If one is to understand the activity requirements that prevail during ocular dominance shift, the demonstration in acute preparations of functional changes during the time of recording of a single cell is more appropriate than comparisons between the initial and final functional states of the entire cortex after a global manipulation of the visual input. The former strategy allows the determination of the conditions required to modify the integrative power of a single neuron.

Initially, Pettigrew and coworkers (Pettigrew et al., 1973) reported that repetitive visual stimulation of one eye induced a weak change in responsiveness in favor of the stimulated eye in a limited number of cells (4 out of 60 cells), but
the use of noninterleaved protocols and the absence of study of intrinsic variability made these data difficult to interpret. The low percentage of success following this “conditioning” procedure is supportive of our working hypothesis, since no change in the covariance between pre- and postsynaptic activities would be expected from the stimulation of visual afferents alone (upper row, Figure 5.5a).

More convincing evidence for acute changes in binocularity was provided by Kasamatsu who reported a long-term change in ocularity after total blockade of transmission of input from one eye following local application of an anesthetic to its optic nerve (Kasamatsu, 1976). The loss of responsiveness through the silenced eye persisted beyond the duration of the local anestheisa, which suggests induction of a long-term decrease in synaptic efficacy. It is noteworthy in this experiment that the observed changes still support the covariance hypothesis: During binocular vision, the cortical cells are active under the influence of the intact eye while the treated optic nerve remains inactive; the synapses linked to the silent eye are consequently subjected to a negative change in covariance (see column 2 of Table 5.3.1. and middle row in Figure 5.5b).

Another way of decreasing covariance is to diminish the output signal of the cell while maintaining its input unchanged (lower row, Figure 5.5b). In the protocol detailed in the right upper panel of Figure 5.6, we artificially helped the cell to respond to the presentation of the preferred stimulus to one eye and blocked the cell’s firing while presenting the same stimulus to the other eye. We could demonstrate, by repeating 40 to 80 times this differential pairing procedure, the induction of significant long-lasting changes in ocular dominance in about 30 percent of the cells (Frégnae et al., 1988; Shulz & Frégnae, 1992). The great majority of these changes were in favor of the “positively reinforced” eye, as predicted by the covariance hypothesis, and they could last from several tens of minutes up to several hours. It should be noted, however, that the pairing procedure could not install de novo responses, but induced enhancement or depression of already existing responses. Figure 5.6 illustrates one of the rare cases where the PSTH’s shape itself—in addition to the magnitude of the response to the “reinforced eye”—was altered: A new peak appeared as the result of an increase in responsiveness and was restricted to the subzone of the receptive field where iontophoresis had been applied concomitantly with visual stimulation. This finding, which is reminiscent of the modifications of PSTH’s shape reported by Shinkman and collaborators (Shinkman, Bruce, & Pfingst, 1974) using operant conditioning, supports the temporal contingency specificity and the associative nature of the underlying processes.

Orientation Selectivity Plasticity

The delayed visual experience paradigm. A second property of visual cortical cells, for which the development has been shown to depend on visual
experience, is orientation selectivity (review in Frégnac & Imbert, 1984). Cells in visual cortex not only integrate information from both eyes but also respond to slits of light correctly oriented within the receptive field (Hubel & Wiesel, 1962, 1963). Orientation selectivity appears at around eye opening and thereafter increases gradually (review in Figure 5.2 in Frégnac & Imbert, 1978). Until 18 days of age, the kinetics of development of orientation selectivity seem to be the same in normally and dark reared animals (Frégnac, 1979a). From this age, which is to be considered as the start of the critical period, the process of maturation becomes dependent on visual experience. Deprivation of vision from birth until 6 weeks of age leads to an almost complete loss of orientation selectivity. However, at 6 weeks, 6 hours of normal visual experience are sufficient to re-express an almost normal maturation level (Imbert & Buisset, 1975).

This strong nonlinearity in visual experience sensitivity explains the success of early studies on restricted visual exposure (Blakemore & Cooper, 1970; Hirsch & Spinelli, 1970; but see also Stryker, Sherk, Leventhal, & Hirsch, 1978). Animals, reared otherwise in total darkness, were exposed during a few hours every day to striped environments (see Figure 5.7). Comparison of the distributions of orientation preference of cortical cells recorded before and after the restricted visual experience showed the induction of a significant bias of representation in favor of the orientation to which kittens had been exposed. Two different interpretations concerning the processes involved in these effects were proposed, namely selective versus instructive mechanisms (see above). However, in view of the inherent limitations of analysis based on the comparison of populations of neurons recorded in different animals, no definitive answer could be given.

The Cellular Analog Approach

In order to address this question more directly, we applied the same protocol of associative conditioning to demonstrate plasticity of orientation selectivity during the time of recording of single cortical cells. The response of the recorded neuron was artificially reinforced during the presentation of a given orientation (S+) and suppressed while presenting a different (but fixed) orientation (S−) through the same eye (see Figure 5.7). Following several tens of pairings, about 40% of the conditioned cells showed a significant change in their relative preference between the two orientations, and in more than 90% of these cases the shift was in favor of the orientation associated with a high level of response during conditioning. Changes were found both in kitten and adult visual cortex, but the largest ones were observed in nonoriented cells recorded in deprived kittens at the peak of the critical period (Frégnac et al., 1988; Frégnac, Shulz, Thorpe, & Bienenstock, 1992).

The orientation preference paradigm allowed us to study the generalization of the effects of stimuli other than those used during the conditioning (see Figure
5.2). As already observed in the case of the study of ocular dominance plasticity, adaptation of orientation selectivity resulted in the long-term modulation of previously existing responses. Modifications in orientation tuning consisted of a displacement of the peak, often incomplete, towards the reinforced orientation, or of the onset of a significant polar asymmetry favoring the S+ region. Such changes could also be induced at the adult age, so long as the two stimuli used in the pairing procedure remained in the initial orientation spectrum of the recorded cell. The amplitude of the orientation shift was related to the initial selectivity of the neuron: The probability of observing large changes in orientation preference was significantly higher in initially poorly oriented neurons than in already selective ones.

These modifications in tuning selectivity appear to be linked to the competitive imbalance imposed between the two orientations presented during pairing: As a general rule, and independently of their angular separation, a gain in responsiveness was observed around the “positively reinforced” stimulus, whereas a loss of competence was observed around the “negatively reinforced” one. This pattern of orientation dependence contrasts with the eventual changes of visual excitability occurring spontaneously (“iceberg effect” which affects responses to all orientations similarly, in Frégnac & Bienenstock, 1981), or reported during bicuculline iontophoresis (“iso-orientation inhibition” in Albus & Baumfalk, 1989).

Interocular Orientation Disparity Plasticity

Interocular matching of orientation preference and the goggle rearing paradigm. Most cells in the primary visual cortex of the adult cat are binocularly activated, that is, they receive excitatory and/or inhibitory information from both eyes (Hubel & Wiesel, 1962; Kato, Bishop, & Orban, 1981; Gardner & Raiten, 1986). Furthermore, interocular comparison of specific functional properties of visual cortical neurons showed that the organization of the two receptive fields is very similar (Hubel & Wiesel, 1962; Skottun & Freeman, 1984). When assessing the response independently through each eye, a remarkable match was found between the number and the spatial sequence of dynamic subregions of each receptive field (Maske, Yamane, & Bishop, 1984), in the sharpness of orientation tuning (Nelson, Kato, & Bishop, 1977; Nelson, 1978; Skottun & Freeman, 1984), in the direction selectivity (Maske et al., 1984), and in the optimal spatial frequency (Skottun & Freeman, 1984).

Despite these similarities, there remain intrinsic differences between the processing of the visual message through each eye. The most documented example is probably the level of ocular dominance or the relative strength of the excitatory response elicited by the stimulation of each receptive field (Hubel & Wiesel, 1962). Besides ocular dominance, to which different functional roles
have been ascribed (Gardner, Douglas, & Cynader, 1985; Gardner & Raiten, 1986), the existence of spatial differences between the receptive-field positions established for each eye—or positional disparity—could be the physiological basis for stereopsis and binocular depth discrimination (Barlow, Blakemore, & Pettigrew, 1967). A much less studied parameter, on which binocular depth perception could also depend, is the difference in the orientation seen by each eye (interocular orientation disparity: IOD). Although this is affected by dynamic changes in cyclotorsion, it is mainly linked to the horizontal separation of the two eyes, and is experienced during normal vision when an object initially in the horopter is tilted in a sagittal plane towards or away from the observer. This has been shown, at least in humans, to be independent of positional disparity (Von Der Heydt, Haney, & Dursteler, 1980). However, two necessary conditions have to be met in order to use IOD as an additional cue for the perception of stimuli tilted in depth: (a) Cells should be sharply tuned for orientation disparity, and (b) the range of preferred disparities should cover all the possible values experienced during normal viewing conditions (± 20° according to Bishop, 1979). These requirements are partly fulfilled in the adult cat (Blakemore, Fiorentini, 1972; Nelson & Maffei, 1978; Kato et al., 1981), and interocular orientation disparity has been proposed as a second possible separate mechanism for binocular depth discrimination (Blakemore et al., 1972; Von Der Heydt et al., 1980).

In normal adult cats, most cortical cells show a null IOD, that is, both eyes prefer the same orientation; however, the range in the distribution of IODs extends across ± 15 degrees (Blakemore et al., 1972; Nelson et al., 1977; Kato et al., 1981). Studies on the development of the IOD in young kittens are rare, mostly because orientation selectivity is difficult to define clearly, and because cells which are orientation selective in the 3-week-old kitten are generally monocularly driven (Frégac & Imbert, 1978; Blakemore, 1979). The only attempt to determine IOD distributions in the developing animal showed that in 3–4-week-old normally reared kittens the distribution is quite similar to that observed in adult cats (± 20°). In contrast, bilateral lid sutured kittens (9 to 72 days old) showed a very broad IOD distribution reaching values up to ± 50° (Blakemore & Van Sluyters, 1975). Similar ranges in IOD distribution have also been reported in kittens reared with alternate occlusions, which never experienced simultaneous stimulation through both eyes (Blakemore, Van Sluyters, Peck, & Hein, 1975; Movshon, 1976).

These developmental studies suggested that binocular visual experience is a requisite for matching functional selectivity between the two eyes. This is not surprising since the relative position of the eyes in the orbits and their separation change progressively until 10 weeks of age. Further evidence for functional adaptation came from experiments imposing some degree of restriction in the binocular correspondence of monocular images (Shinkman & Bruce, 1977; Dursteler & Von Der Heydt, 1983). Shinkman and colleagues extensively studied
the cortical effects of rearing kittens with a fixed imposed IOD (review in Shinkman, Isley, & Rogers, 1985). Kittens were raised in total darkness from eye opening, and from 4 to 12 weeks they received 1 to 2 hour daily sessions of visual experience with prisms which optically rotated (around each ocular axis) the visual fields of the left and the right eye in opposite directions. Subsequent electrophysiological characterization of visual cortical RFs analysing the representation of the center of gaze showed that the distribution of IODs was centered around the disparity imposed by the prism (Shinkman & Bruce, 1977). This effect was permanent since re-exposure of the animal to a normal visual environment did not change the mean IOD (Shinkman, Isley, & Rogers, 1980). For prolonged periods of dark rearing, the susceptibility to the optical manipulation decreased, and after 4 to 5 months of age no residual plasticity was observed (Shinkman, Isley, & Rogers, 1983).

The ability of the cortical network to adapt to these manipulations of the binocular coherence of visual input was dependent on the actual value of the imposed IOD angle. For imposed optical rotations between monocular images less than or equal to 24°, a shift of the IOD distribution toward the experienced rotation was observed. However, if the rotation was larger (i.e., 32°), there was a breakdown of binocularity corresponding to a U-shaped ocular dominance distribution. In the latter experimental situation most cells presented non-oriented receptive fields, as is the case in visually deprived kittens in the middle of the critical period (Buisseret & Imbert, 1976), and were monocularly activated. The few remaining binocular cells did not show matching of the orientation preference seen through each eye, and the mean IOD did not reflect that imposed by the prism. Interestingly, many monocular orientation selective cells showed a preference for horizontal and vertical orientations (Isley, Rogers, Podell, & Shinkman, 1980; Isley, Rogers-Ramachandran, & Shinkman, 1990). This last finding supports an earlier hypothesis of “differential modifiability” (Frégnac & Imbert, 1978), in which it was proposed that monocular horizontal and vertical detectors are more resistant than other cells to alterations of visual input or to visual deprivation (Leventhal & Hirsch, 1977; Frégnac & Imbert, 1978; Leventhal & Hirsch, 1980).

The cellular analog approach. The above series of experiments showed elegantly that the cortical representation of IOD can be modified during the critical period by independent manipulations of each visual field. Since effects were analyzed in the central region of gaze where rotation along the visual axis does not introduce spatial disparity, these changes were attributed only to IOD manipulation. However the inference of a change in the correspondence of receptive-field properties was indirect since it was established using a population analysis strategy, that is, comparing the mean IOD averaged within populations of neurons recorded in control and experimental animals.

In order to test the activity dependence of such functional changes more directly, we developed a cellular analog of IOD plasticity, and tried by a local control of the covariance level between pre- and postsynaptic activities to induce
long-term changes in IOD selectivity during the time of recording a single cell (Frégnac et al., 1989; Shulz & Frégnac, 1992). During binocular viewing, the response of the recorded cell to the dichoptic presentation of two monocular oriented stimuli, rotated symmetrically away from the preferred orientations of the two receptive fields—thus corresponding to a fixed-orientation disparity—was artificially increased. Alternately the response for an opposite-orientation disparity was artificially decreased or even blocked. The same procedure was repeated several tens of times before proceeding to control assessment of IOD selectivity.

Statistical comparison of the binocular responses observed for the two test disparities before and after pairing demonstrates induction (in almost 50% of cases) of significant long-lasting changes in binocular interaction. According to the covariance hypothesis, the differential control of the postsynaptic response during pairing should produce competitive changes in the selectivity profile of the IOD tuning curve in favor of the disparity associated with increased responsiveness (compare with orientation selectivity, see above). In agreement with this prediction, the relative IOD preference shifted in most cases (71%) in favor of the “positively reinforced” disparity. Additional information on the associative nature of the induced changes was gained by comparing modifications of the binocular responses (which had been artificially modulated during the pairing procedure) with eventual alterations of the monocular responses to each element of the dichoptic stimulus configuration. If binocular integration is more than the linear summation of responses to monocular activation, and if induced changes were truly associative, one would expect the conditioning procedure to preferentially affect binocular processes put into play during the external control of activity. Indeed a differential evolution was found between changes observed in the binocular responses and in the monocular responses, and in a restricted number of cells, functional modifications were shown to be expressed only in the viewing condition used during the external control of coactivity (i.e., dichoptic stimulation). A relative gain in responsiveness was found in the S+ region and a loss was confined to the S− region for the binocular responses, whereas monocular responses indicated no change in the preferred IOD. In a more restricted number of cases, competitive changes in IOD selectivity could correspond not only to modification of the preferred disparity but also to a change in the type of binocular interaction (occlusion transformed into facilitation for the “positively reinforced” disparity, see Shulz & Frégnac, 1992). Changes could be induced from the 7th to the 15th week of age, and no age dependence in the amplitude of the effects was observed during this period. As in the two other protocols (ocular dominance and orientation selectivity) no change was observed following IOD pairing procedures which had been ineffective in modulating postsynaptic activity of the recorded cell during iontophoresis.

Implications for cortical binocular adaption. How similar are these effects described at the single-unit level with the global modifications of cortical
selectivity induced by restricted rearing procedures? Our artificial procedure of local conditioning was intended to mimic the protocol of "environmental surgery" devised originally by Shinkman and colleagues (review in Shinkman et al., 1985; see above). By comparison of the largest IOD to which binocular cortical cells can adapt, with the extreme values of the IOD distribution observed in the normal adult cat, it is possible to determine the limits to which the orientation network can integrate discordant information from both eyes. This boundary seems to be around 15–20°, which interestingly is the total angular deviation of the images in the two eyes which can be reached in the cat in some extreme viewing conditions (Bishop, Elekesy, & Nelson, unpublished data quoted in Nelson et al., 1977). The disparities used in our experiments were within this limit, and by extrapolation from Shinkman and colleagues' findings, no breakdown of the binocularly was expected. Our study of the adaptive capacities of binocular interaction using a simultaneous recording of monocular and binocular responses leads us to conclusions which are additional to those already reached by Shinkman and collaborators, who limited their analysis of binocular integration to ocular dominance assessment. The first sign of adaptation of the cortical response was found in most cases in binocular interaction, which was affected to a much greater extent than monocular responses. In some cases we could demonstrate a complete independence in the temporal evolution of the binocular response from that of the monocular responses. However, in view of the limited time of recording from our cells in the acute preparation (2 to 7 hours), one cannot rule out that this remarkable adaptation of binocular interaction precedes a more permanent modification of the monocular responses, possibly resulting in a differential shift of the preferred orientations seen through each eye, such as that described by Shinkman and coworkers (Shinkman & Bruce, 1977; Shinkman et al., 1983; Shinkman et al., 1985). Note that this last effect was observed, following a fixed interocular disparity imposed for periods longer than 50 hours, and distributed over a 1 to 2 month period.

Spatial Receptive-Field Organization Plasticity

Induction of anomalous receptive fields by restricted visual experience. The three paradigms discussed above mimic at the cellular level rearing situations known to profoundly affect the functional organization of visual cortex. However, there is a lack of quantitative evidence demonstrating that the spatial organization of the cortical receptive field itself can be modified by visual experience.

Unusual shapes of receptive fields have been reported following long periods of visual deprivation (Singer & Tretter, 1976), after exposure to planetarium-like (Pettigrew & Freeman, 1973) or to striped environments (Singer & Tretter, 1976; Singer, 1983). In some cases, experimenters have described, in addition to a
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classical normally sized receptive field, ectopic zones of weak responses which locally disrupt the precision of the retinotopic mapping (Singer & Tretter, 1976; Milleret et al., 1988). It has been suggested that the adult stabilized receptive field originates from a much wider envelope of discharge zones, and results from the regression of retinotopically incorrect projections which occur at an early stage of development. This problem has been tackled in a more analytical way at a subcortical level in studies using selective blockade of afferent propagated activity by tetrodotoxin (see Archer, Dubin, & Stark, 1982; also see Chapter 3).

The shaping or refinement of receptive fields by "environmental surgery" should not obscure the fact that under normal conditions of visual experience where spatial features are randomly accessible, only two types of spatial organization ("Simple" and "Complex") will finally emerge. This dichotomy found in adult primary visual cortex is based on the spatial overlap of discharge zones in response to the static presentation ("ON") and ("OFF") of a visual stimulus (Hubel & Wiesel, 1962; Gilbert & Wiesel, 1979; Hegelund, 1986). These exclusive classes are thought (in the original scheme of Hubel & Wiesel) to result from a fixed hierarchical wiring.

However, very few attempts have been made electrophysiologically to justify this scheme by looking quantitatively at the development of the spatial arrangement of ON and OFF responses (Tsumoto & Suda, 1982; Albus & Wolf, 1984), whereas more and more models tend to solve this problem by a numerical simulation approach (Linsker, 1986a; Kammen & Yuille, 1988; Miller, Keller, & Stryker, 1989b; Yuille, Kammen, & Cohen 1989). It still remains to be understood why only two types of receptive fields (among all the possible arrangements of ON- and OFF-afferent arbors) will be stabilized, and whether or not the typology once acquired by a cell is fixed throughout life (theoreticians seem more aware of the importance of this issue; see for instance M. Arbib, p. 197 in Levy et al., 1985).

The cellular analog approach. Our fourth protocol addresses the above issue more directly (Shulz et al., 1989, in press; Frégnac et al., 1989), and in addition could help us to understand how modifications in the responses of cortical cells assessed with moving stimuli may be related to discrete changes in the spatial organization of their receptive field. Moreover, independent manipulations of the level of responses to the presentation (ON) and extinction (OFF) of a static stimulus in a fixed position of the RF are thought to lead to a better separation of inputs (in terms of activated synapses): It is known at least in the mink (Levy, McFall, & Luskin, 1987) and in the ferret (Zahs & Stryker, 1988) that ON and OFF pathways remain segregated to a significant extent up to the cortical level.

In the differential pairing procedure, the response of the recorded cell was increased during presentation of a static, optimally oriented bar of light (ON response in Figure 5.9) and decreased during the extinction of the same stimulus (OFF response in Figure 5.9). We could induce significant modifications in the
relative level of ON and OFF responses in a given position of the receptive field in about 50 percent of cells. Changes in the spatial profile were generally not uniform, and in about 40 percent of modified cells they were selectively restricted to the paired zone of the RF. In all but one case the relative ON/OFF preference shifted towards the characteristics of the visual stimulation (ON or OFF) associated with the imposed increase in responsiveness. In a restricted number of cells, it could be demonstrated that reorganization of the static responses across the RF resulted in changes in direction selectivity of the recorded cell. Significant changes could also be obtained in the adult cortex, indicating that although two distinct stable states in receptive-field organization are classically observed, it is possible by an artificial control of activity to reveal masked responses in subzones of the receptive field so that simple cells may come to exhibit some of the properties of complex cells.

Validation of the Covariance Hypothesis

Hidden assumptions. The cellular analogs of visual cortical plasticity presented above demonstrate that an endogenous control of postsynaptic activity can induce long-term changes in RF properties. The ionophoretic technique—imposing different levels of visual response for different characteristics of visual stimulation—was devised to produce selective changes in the covariance between pre- and postsynaptic activities. Although postsynaptic activity changes were monitored during pairing, one cannot rule out the possibility that afferent activity is affected by ionophoretic action. Only in the latter case could one be sure that the change in postsynaptic activity would impose the sign of the change in covariance.

Obviously, the possibility of ionophoretic current (mainly potassium ions) having a presynaptic effect cannot be excluded (see detailed discussion in Frégnac, Shulz, Thorpe, & Bienenstock, 1992). Moreover the time during which control of postsynaptic activity is achieved is long enough to modify activity in intracortical loops (Gilbert & Wiesel, 1979) or reverberating circuits (Ferster & Lindström, 1985), thus influencing the pattern of afferent activity within a short delay. These remarks should remind theoreticians of the limitations in delineating the role of postsynaptic activity in synaptic plasticity, due to the existence of intrinsic closed current circuits.

Predictive power. Let us assume nevertheless that the different ionophoretic techniques reported here predominantly affect postsynaptic activity. If the observed functional modifications were not specifically linked to covariance changes, one would expect that the pairing procedure would produce an outcome independent of the sign of the imposed control of activity. Such a possibility can be refuted by the finding that 67–96 percent of the changes (depending on the
studied RF property) are observed in the expected direction: The change in the relative responsiveness between the two stimuli shown during pairing is in favor of the "positively reinforced" one.

Recently, Greuel and colleagues (Greuel et al., 1988a) confirmed our earlier findings by reporting persistent changes in ocular dominance of single cells during the time of recording, produced by the association of visual stimulation with combined iontophoresis of noradrenaline, acetylcholine, glutamate and/or N-methyl-D-aspartate. The rate of success of the pairing procedure was independent of the drug combination, which probably indicates a common control mechanism of plasticity for all these drugs. Eighty percent of changes favored the stimulus paired with the gating substances, and since the drugs which were applied during pairing had a predominantly facilitatory effect on postsynaptic activity, their results can be interpreted using our theoretical scheme, that is, in terms of covariance changes imposed by the applied drug. Among the cells that showed decreased responsiveness for the paired stimulus after conditioning, it is remarkable that blockade or reduction of postsynaptic activity was already observed during iontophoresis of the drug cocktail (see Greuel, Luhmann, & Singer, 1988b). This suggests—although the authors did not carry out this analysis themselves—that changes in relative responsiveness could be predicted to a significant extent by the type of control of activity (increase or decrease) imposed pharmacologically, and not by the nature of the drug (NA, Ach, NMDA, glutamate) applied during pairing.

Stimulus separability. In order to interpret the functional changes in terms of alterations in synaptic efficacies, an additional assumption must be made. The differential pairing procedure used in our protocols requires that the two stimuli used in alternation during pairing should activate separate sets of synapses. For modelers, separability between the two inputs is often imposed by assuming orthogonal input vectors. For biologists, validation of this requirement is more difficult.

Concerning each property, a specific type of synaptic set is predictably susceptible to the differential pairing procedure. For ocular dominance, the most plausible interpretation of our results is that the observed functional changes reflect maintained modifications in the efficacy of synaptic transmission between geniculate afferents and the cortical target cell (Figure 5.10a). First-order cortical cells, which receive separate information from each eye, represent a particularly good substrate for interocular competition. Note that cortical cells receiving exclusively binocular afferents are not thought to be modifiable since the same group of synapses will be activated during both positive and negative current iontophoretic periods.

The orientation paradigm potentially addresses another type of connectivity. By comparing the various modifications found in cells for which orientation tuning could be established before and after pairing, a striking relationship
Figure 5.10. Stimulus separability and putative loci of synaptic competition. Schematic representation of the different synaptic loci in the geniculo-cortical and intracortical network, which could account for competition and stimulus separability. In all four types of protocols, the two stimuli configuration used during pairing (i.e., $S_+$ and $S_-$) should activate distinct synaptic subsets in order to allow spatial separation in their respective locus of modification. Cells are represented by their receptive fields, symbolized as concentric disks (filled center/open surround) for geniculate cells, and by rectangular dark bars indicating the preferred orientation for cortical neurons. Pathways which are predominantly and alternately
activated during pairing are schematized by bold solid and broken lines. Modifiable excitatory and inhibitory synapses are indicated respectively by open and filled triangles. All other connections are indicated by thin solid lines.

a. Ocular dominance: Separate geniculate inputs from left and right eyes are assumed to converge on first-order cortical neurons, where synaptic competition should take place. Notice that second-order cortical neurons receiving already binocular inputs are less likely to be the locus for competition; in the latter case, the same set of synapses is activated during the stimulation of each eye, and is associated consequently with both opposite regimes of covariance.

b. Orientation selectivity: Nonoriented geniculate inputs converge onto first-order cortical neurons. The intracortical network responsible for orientation selectivity will allow competition only between second- or higher-order cortical cells, each of which conveys an input signal that has already been filtered according to its orientation content. Although horizontal connectivity has been shown to be progressively restricted during development to cells sharing neighboring orientation preferences (see Figure 5.1c; and Luhmann et al., 1986; Calloway & Katz, 1990), the concomitant increase in selectivity of the input filters (i.e., the neighboring orientation columns projecting on the recorded cell) will still maintain a residual substratum for competition. This scheme agrees with our observation that stimuli which were effective in the pairing procedure applied to adult cortical neurons have to have an orientation belonging to the initial tuning competence of the conditioned cell.

c. Interocular orientation disparity: For most binocular and orientation-selective cortical cells, the preferred orientations seen through each eye (double symbol) are the same (null IOD). However, even in the normally reared animal, a significant proportion of cells prefer different orientations through each eye (see normal rearing distribution in Figure 5.8). Input separability could be achieved in a way very similar to the orientation case (see section b) if we assume that IOD selective cells tuned to different nonnull disparities converge on to the recorded cell (which initially codes for a null disparity). This scheme is supported by our observation that most functional modifications were expressed only under binocular viewing conditions.

d. Receptive-field spatial profile: This scheme represents the connectivity for both ON and OFF simple cortical cells, receiving direct input from LGN. Presentation and extinction of a light bar in a given position of the receptive field will asynchronously activate ON and OFF channels, which are thought to be segregated at the LGN level (Wässle et al., 1981; Schiller, 1982). The activated ON center (filled disk) and OFF center (stippled disk) geniculate receptive fields are slightly separated for the sake of clarity, but they receive information from the same portion of the visual field. Considering that the target cortical cell is simple and unimodal ON, activated pathways are indicated by an open asterisk. The presentation of a light bar will excite the target cell via direct excitation of the ON center LGN cell. Extinction of the same stimulus will inhibit it indirectly by the activation of the OFF center LGN cell feeding a cortical interneuron which is thought to inhibit the target cell (Ferster, 1988). A similar reasoning can be applied to the case of an OFF unimodal simple cell (filled asterisk). Both networks can be superimposed in the case of overlapping ON and OFF subregions of a cortical receptive field. Separability of input provided by this wiring scheme supposes that modifiable synapses are the excitatory and inhibitory contacts on the first-order cortical neuron.
emerges: The observed shift in orientation preference is on average positively correlated with that imposed during pairing (Frégnac, Shulz, Thorpe, & Bienenstock, 1992). This finding has two implications: (a) adaptation occurs with a displacement in the peak of the orientation tuning curve in the direction of the reinforced orientation; (b) there exists a threshold of angular separation below which no significant modification is generally observed. This value (around $12^\circ$) fits with that of the half width at half height of orientation tuning (Orban, 1984), and suggests that cortical columns encoding distinct orientations must first be activated in order to increase the selectivity of each input channel before competitive processes occur at the level of the recorded cell (Figure 5.10b).

Concerning IOD, since adaptation of the cortical response was found in most cases to be specific to binocular interaction (which was affected to a much greater extent than monocular responses), the competition can be thought to arise between binocular cells which are tuned to different disparities (Figure 5.10c).

The last protocol was undertaken in order to benefit from the natural asynchrony in activation between ON and OFF pathways. Recent work by Stryker and colleagues, injecting muscimol in adult cat visual cortex, reveals a remarkable spatial separation of the RFs of ON and OFF afferents of certain simple cells: In the presence of muscimol the cortical cell's firing is selectively blocked without disturbing the afferent activity in geniculate fibers, which are known to be devoid of GABA$_A$ receptors. The recorded subfields corresponding to the same type of input (either ON or OFF) appear in addition to be aligned along an axis, which corresponds precisely to that of the silenced cortical RF (Chapman, Zahs, & Stryker, 1991). These findings support the view that part of the visual input, at least at the level of first-order synapses, activates separately ON and OFF pathways (Figure 5.10d).

The diversity of possible synaptic loci as potential seats for competitive modifications, and the absence of laminar specificity found in our data, plead for a rather generalized potential for plasticity within visual cortex. This activity susceptibility appears to be largely independent of the specialization of the hardware responsible for the processing of the particular visual feature under study and of the functional type (simple or complex) of the recorded cell.

A SUBCELLULAR LEVEL APPROACH: PUTATIVE BIOPHYSICAL MECHANISMS

The Covariance Model

A first conclusion gained from the experimental test of the "covariance hypothesis" is that imposed temporal correlation between postsynaptic activity and given characteristics of the visual message induces functional modifications in receptive-field properties which are analogous to those observed during
epigenetic development. A second conclusion, more unexpected, is that visual cortical neurons—under artificial conditions of forced coactivity—are able to adapt their functional specificity even at the adult age. The covariance algorithm and the experimental data presented above suggest that these changes are based on increases or decreases in the efficacy of activated synapses. The fact that no modifications of receptive-field properties were induced following visual stimulation alone suggests the existence of plasticity thresholds dependent on the membrane potential of the postsynaptic neuron which are not trespassed under normal transmission of sensory signals.

Synaptic Potentiation

Several lines of evidence in the in vivo and in vitro literature support the assumption that area 17 synapses can undergo potentiation when the covariance level between pre- and postsynaptic activity is increased.

Visual cortical plasticity and long-term potentiation (LTP). A first indirect demonstration was obtained by Tsumoto and Suda who showed that persistent changes in evoked cortical potentials could be induced by repetitive electrical stimulation of one optic nerve at medium frequencies (2Hz) and applied continuously during several hours (Tsumoto & Suda, 1979). Responses were enhanced at the visual cortex level in response to stimulation of the conditioned optic nerve, and were cross-depressed in response to stimulation of the nonconditioned optic nerve. A similar long-term potentiation of evoked potentials was found following trains of repetitive stimulation of LGN or optic chiasma at slightly higher frequencies (10 Hz) in area 17 of anesthetized but unparalyzed 4-week-old kittens (Frégnac & Baranyi, unpublished observations). These reports show in vivo that active visual pathways may sustain potentiation.

The fact that potentiation of evoked potentials could be obtained by stimulation of the visual pathway alone (i.e., without any extraretinal signal) does not contradict the hypothesis that extraretinal gating systems are normally necessary for the expression of cortical plasticity (see above). The massive and sustained electrical stimulation at different levels of the visual pathway is an artificial laboratory situation which is difficult to compare with natural visual input experienced in the everyday life of the animal. The former kind of stimulation (in contrast to selective visual activation) might produce significant changes in the covariance between pre- and postsynaptic activities by cooperativity-like mechanisms, which would not otherwise be recruited with a more physiological visual stimulation. The repetitive, synchronous and long-lasting stimulation of one optic nerve probably produces a massive activation of the postsynaptic cortical cells, so that the afferents from the nonstimulated eye are mainly silent while the target cell reaches a critical threshold of depolarization under the cooperative influence of the many fibers subservient to the other eye. Consequently, competition processes of the kind proposed by Stent (1973) or by
the covariance hypothesis (column 2 in Table 5.3) could lead to both homosynaptic potentiation of active synapses and heterosynaptic depression of inactive ones (see also Lynch, Dunwiddie, & Gribkoff, 1977; White, Levy, & Stewart, 1988 in hippocampus).

The finding that repeated trains of afferent stimulation produce long-lasting enhancement in the efficacy of geniculo-cortical and intracortical excitatory synapses has been confirmed by in vitro studies, using evoked potentials and current source density techniques (Komatsu et al., 1981; Toyama, Komatsu, Maeda, & Sakaguchi, 1982; see also Perkins & Teyle, 1988). One hour of continuous stimulation of the optic radiations at 2 Hz, in 4-week-old kittens, was shown to induce a moderate but significant effect in the granular layer, where most geniculate afferents terminate, leading to a twofold increase in excitatory synaptic sinks. Potentiation was more prominent in the supragranular layers, where an eightfold increase of late polysynaptic currents developed progressively after cessation of the “conditioning” train of stimulation. Significant reductions in the poststimulation latency of monosynaptically and polysynaptically evoked extracellular activity were noted as well (Komatsu et al., 1981). Although the frequency of stimulation chosen by Toyama, Tsumoto, and coworkers was later shown to be optimal to recruit a specific type of slow postsynaptic potential (Komatsu & Toyama, 1988; Kimura, Nishigori, Shirokawa, & Tsumoto, 1989) (see section above), most visual cortical electrophysiologists have switched progressively to much higher frequency of electrical stimulation of the white matter (Artola & Singer, 1987; Connors & Bear, 1988; Berry, Tyler, & Taizhen, 1989, up to 400 Hz in Lee, 1982) in order to reproduce the type of biophysical approach which has proved to be so successful in hippocampus (review in Brown et al., 1990). Under these sometimes less physiological conditions, and after decreasing the level of inhibition in vitro by adding small doses of the GABA_A antagonist bicuculline to the artificial cerebrospinal fluid (ACSF) perfusion, they have been able to produce long-term potentiation following a brief tetanus, and have carried out its analysis at the intracellular level in slices of the visual cortex of developing and adult rats (Artola & Singer, 1987; Connors & Bear, 1988; Kato, Artola, & Singer, 1991; Kimura et al., 1989). However, reports in other cortical areas, such as frontal cortex, of mixed effects on PSP amplitude (potentiation and depression) produced by high-frequency trains of intracortical pathways (Hirsch & Crépel, 1990) makes one wonder if the outcome of tetanizing input on synaptic transmission in visual cortex could depend in a complex way on both the frequency of the stimulation and the type of afferent pathways (extrinsic or intracortical) which have been selected (see tentative parametric approaches in Connors & Bear, 1988; Komatsu & Toyama, 1988; Berry et al., 1989).

As classically shown in the CA1 field in hippocampus under situations where the inhibition level has been artificially reduced by infusion of picrotoxin, the cumulative membrane depolarization produced by the repeated activation of a
given afferent (homosynaptic plasticity) or by the conjunctive activation of converging afferents (cooperative heterosynaptic plasticity; see White et al., 1988, in hippocampus) is thought to relieve the magnesium block of the ionophore coupled with the postsynaptic N-methyl-D-aspartate (NMDA) receptor (review in Collingridge, 1985; Collingridge & Bliss, 1987; Nicoll, Kauer, & Malenka, 1988). Calcium entry through this unmasked channel could then trigger second-messenger processes (review in Collingridge, 1987) leading to long-term increase in synaptic efficacy even in the adult (see Figure 5.11). This scheme is supported in visual cortex by the finding that selective blockade of NMDA receptor with its antagonist DL-2-amino-5-phosphonovaleric acid (APV) prevents the induction of LTP (Artola & Singer, 1990; Connors & Bear, 1988; Komatsu, Fuji, Maeda, Sakaguchi, & Toyama, 1988; Kimura et al., 1989).

**NMDA, a developmental "plastifier"?** The involvement of NMDA receptors in the functional epigenesis of visual cortical neurons described during a critical postnatal period appeared attractive to many experimenters, since their activation was found both in amphibians and vertebrates to play an unexpected role in the development of ocularity domains or in the refinement of retinotectal maps (see Chapter 3) during nerve regeneration. For instance, in the tectum of *Xenopus*, following the graft of a supernumerary eye, NMDA intratectal perfusion appears to sharpen the borders between bands of retinal afferent axons of different ocular origin (Scherer & Udin, 1990). In contrast, chronic perfusion of APV delays the sorting-out process of ocular dominance stripes and disrupts their maintenance (Cline, Debski, & Constantine-Paton, 1987).

The specific role of NMDA in mammalian visual cortical plasticity is furthermore suggested by a large variety of converging studies. Although NMDA receptors are still present at the adult age, visual responses of cortical neurons were reported to be dramatically suppressed by APV iontophoresis in kitten when compared with the adult (Hagihara, Tsumoto, Sato, & Hata, 1987; Tsumoto, Hagihara, Sato, & Hata, 1987). These authors concluded that NMDA receptors are more effective in immature cortical neurons and could be involved in triggering synaptic plasticity during postnatal development. Further relationships fitting with the time course of the degree of environmental susceptibility described during the critical period comes from physiological observations which suggested that APV perfusion performed at the peak of the critical period protects cortical neurons from the effects of monocular deprivation (Kleinschmidt, Bear, & Singer, 1987), or of reverse suture (Gu, Bear, & Singer, 1989). The intracortical injection of APV not only prevented the shift in ocular dominance of visual cortical cells in favor of the eye which remained open during the APV treatment, but at the same time it protected geniculate cells in the ipsilateral deprived LGN lamina from ulcerior morphological shrinkage (Colman & Bear, 1990), which is classically observed following long periods of monocular deprivation (review in Hubel, 1988). As a biochemical counterpart,
Figure 5.11. Neurobiological "implementation" of a Hebbian synapse.

a. Passive mode: Hypothetical and simplified representation of the passive mode of functioning of a visual cortical neuron (see Figure 5.5). During visual stimulation both excitatory and inhibitory synapses are activated together. It is assumed that the resulting increase in the K⁺ and Cl⁻ ionic conductances of the GABA, channel reduces depolarization of the postsynaptic membrane produced by putative excitatory transmitter (glutamate?), and prevents the removal of the Mg⁺⁺ ion block from the NMDA channel. Most Ca⁺⁺ voltage dependent channels remain closed (0). For the sake of clarity, only NMDA, GABA, and voltage-dependent channels are represented.

b. Adaptive mode (partly adapted from Artola & Singer, 1987): Under particular conditions of extraretinal activation associated with visual input (Geiger & Singer, 1986), or when inhibition is removed locally (Artola & Singer, 1987), the efficacy of transmission of the
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Synapse can be potentiated. During this adaptive phase, we assume that the additional presence of extraretinal modulatory signals (see Figure 3.12) allows postsynaptic depolarization by increasing sensitivity of NMDA receptors or possibly interfering with GABA_a channel. For instance, a reduction in the efficacy of the GABAergic shunt could allow the expression of a membrane depolarization strong enough to remove the voltage-dependent blockade of NMDA receptors by Mg^{2+}. The concomitant activation of these receptors opens their coupled ionophore channels. The resulting Ca^{2+} entry in the postsynaptic neuron via NMDA channels, and possibly additional voltage-dependent channels, could initiate a cascade of still unknown second-messenger processes, leading ultimately to an increase of NMDA and possibly non-NMDA components of the excitatory postsynaptic response.

Binding studies revealed a peak in the density of NMDA receptors at the onset of the critical period (Bode-Greuel & Singer, 1989), which agrees with gross electrophysiological measurements of LTP susceptibility, showing that maximal potentiation could be produced early in development (at 4 weeks of age in kitten visual cortex; Komatsu et al., 1988), before it diminishes by at least a factor of two outside the critical period (Perkins & Teyler, 1988; Teyler, Perkins, & Harris, 1989). In addition, NMDA uptake was shown to be reduced following binocular deprivation (Feldman, Sherin, & Bear, in press), although this finding is less readily interpreted in terms of the postulated role of the NMDA receptor in developmental plasticity.

An electrophysiological criterion for an activity-state dependent scheme of plasticity was proposed by Artola and coworkers, who tentatively explained the absence of potentiation seen in vitro (in standard ACSF conditions) in adult neurons. Stable neurons were found to be of the “regular spiking” type (Connors, Gutnick, & Prince, 1982), whereas the rarely encountered modifiable neurons were those which spontaneously exhibited a “bursting” behavior (Artola & Singer, 1987). An artificial way to reveal NMDA-dependent activation and to revive plasticity in otherwise stable cells was to force “regular spiking” cells into a “bursting” mode, by removing intracortical inhibition (by adjunction of bicuculline in the bath). Consequently, the main developmental difference in activity dependence between kitten and adult cortical neurons should be attributed to the higher proportion of neurons spontaneously in the “bursting” mode, that is, susceptible to undergo potentiation, which was found early in development when compared outside the critical period (Kato et al., 1988). However, this preliminary report has not been confirmed, and most cells recorded in normal ACSF perfused slices of 4-week-old kitten area 17 appear in fact to be of the “regular” type (Frégnac, Smith, & Friedlander, 1990; Grant et al., 1990).

This view of NMDA as the perfect developmental “plastifier” for strengthening synapses (Bear et al., 1987; Bear & Cooper, 1989) has been recently challenged by the finding that this receptor also participates in the normal
process of synaptic activation by visual experience in the adult cortical neuron (Jones & Baughman, 1988; Miller, Chapman, & Stryker, 1989a). Sustained visual responses which are the major carriers of current in the cell involve the activation of NMDA receptors. These receptors are present throughout life in the supragranular layers of cortex (Fox, Sato & Daw, 1989), and technical differences might explain why certain authors using local iontophoresis in deep layers previously reported a lack of NMDA sensitivity, especially if receptors were not located in the same layer as the cell body (compare discussions in Miller et al., 1989a, and Bear, Kleinschmidt, Gu, & Singer, 1990). The second strong criticism comes from more detailed studies of the action of APV on neuronal activity: The NMDA blocker has been shown in particular to interfere with the mechanism of spike initiation (Sah, Hestrin, & Nicoll, 1989), which could give a trivial activity-dependent interpretation to the loss of orientation selectivity observed in kitten visual cortex perfused with APV using osmotic minipump (Kleinschmidt et al., 1987).

In spite of the absence of a clear demonstration of a role of NMDA limited to a critical period of postnatal development, its possible involvement in visual cortical plasticity may be summarized as follows: (a) its activation above a certain potential of the postsynaptic membrane allows the amplification of postsynaptic responses and the recruitment of late NMDA-dependent excitatory postsynaptic potentials (Artola & Singer, 1987); (b) it would lead to the strengthening of the gain of active synapses. (c) its potency would be improved by other neuromodulators, such as NA and acetylcholine (Bear & Singer, 1986; Connors & Bear, 1988; Artola & Singer, 1989), and finally, (d) it would protect active synapses from depression (see below).

The dominant view of NMDA activation as a necessary step to trigger synaptic potentiation should be reexamined in the near future, since NMDA dependent processes are certainly not the only events responsible for synaptic potentiation in neocortical and hippocampal structures. Recent findings in the CA3 field of hippocampus seem to indicate that potentiation may also occur in networks lacking NMDA receptors (synapse between mossy fiber input and CA3 pyramidal neurons, Jaffe & Johnston, 1990). The common linking step at first inspection of all cases of potentiation in these neuronal structures seems to be a massive calcium entry into the postsynaptic cell due to the temporal continguities between two processes, namely the depolarization of the target cell (produced by intracellular cathodic current or by blockade of local inhibitory processes) and the synaptic activation of a certain class of receptors (Malenka, Kauer, Zuker, & Nicoll, 1988, seen also in CA3 Williams & Johnston, 1989). In some cases a single presynaptic event is not sufficient, and a high frequency train has to be paired with the postsynaptic depolarization to open NMDA channels and/or voltage gated channels (Jaffe & Johnston, 1990; Friedlander, Sayer, & Redman, 1990). This view is supported by associative conditioning experiments in visual cortex based on gross mesencephalic reticular stimulation, where transient
decreases in the calcium concentration of the extracellular medium were shown to be reliable indicators of the onset of visual cortical plasticity (Geiger & Singer, 1986).

In summary, interpretation of our electrophysiological recordings in terms of synaptic changes—where potentiation seems to be observed for stimulus characteristics paired with high extracellular potassium concentration and postsynaptic depolarization—might indeed correspond to a generalized form of synaptic plasticity (involving both NMDA and non-NMDA-dependent processes). It is interesting to note that situations used in our protocol S+ are probably associated with large transient increases in intracellular calcium (Katz, personal communication). These conclusions are supported by a large variety of results obtained in different neocortical areas: motor (Baranyi & Feher, 1978), frontal (Sutor & Hablitz, 1989a, 1989b), visual (Artola & Singer, 1987) and associative (Bindman, Murphy & Pockett, 1988) cortices and hippocampus (Kelso et al., 1986; Wigström, Gustafson, Huang, & Abraham, 1986; Bindman et al., 1988; Jaffe & Johnston, 1990) of the adult vertebrate. In these central structures, low frequency pairing of afferent stimulation (single pulse or weak tetanization) with depolarization of the target neuron—a situation equivalent to the S+ condition of our protocol—produces long-lasting enhancement of excitatory postsynaptic potentials (see also Friedlander, Sayer, & Redman, 1990).

The cerebellar paradox. This simplifying line of reasoning is obviously of limited predictive value: Calcium entry paired with intracellular second-messenger activation triggered by a selective synaptic input does not imply necessarily potentiation of the active synapses. The outcome of the secondary messenger processes which are engaged clearly differs from one structure of the CNS to another, and the sign of the modification may be the opposite, as found in the cerebellar cortex. In cerebellum, a 2-4 Hz pairing of parallel fiber activation with forced activity of a postsynaptic Purkinje cell leads to long-term depression of the parallel fiber / Purkinje cell synapse (Ito & Kano, 1982; Ito & Sakurai, 1982; Ekerot & Kano, 1985; Sakurai, 1987; Crépel & Krupa, 1988; Ito, 1989). Parallel fiber input can be produced or mimicked in different ways: (a) electrically, by direct stimulation of a beam of parallel fibers, or by indirect activation through stimulation of granule cells (from which parallel fibers originate), or mossy fibers (afferent to granule cells); (b) by natural or electrical stimulation of the vestibular nerve (sensory input to the granule cells); (c) and finally biochemically, by an iontophoretic pulse of the presumed neurotransmitter of parallel fibers (glutamate), applied locally in the dendritic tree of the Purkinje cell. Concomitantly the imposed period of postsynaptic firing—which will be paired with the synaptic activation of the adaptive pathway (parallel fiber input)—can be produced electrically by suprathreshold stimulation of climbing fibers or of inferior olive (from which these fibers originate), or can be induced
by a strong intracellular depolarization (recruiting calcium spikes and plateau depolarization) of the target cell. Biochemical stimulation of the climbing fiber input can be also mimicked by ionophoresis of its putative neurotransmitter, aspartate.

In order to explain why depression occurs when potentiation is predicted by Hebbian schemes of plasticity, one could be tempted to assume that the sign in the change of the synaptic modification depends on the type of neurotransmission (excitatory/inhibitory) that the postsynaptic neuron will exert on other neuronal targets. In contrast with presumably excitatory pyramidal cells of the neocortex, or of CA1 and CA3 fields of hippocampus, Purkinje cells are the inhibitory output neurons of the cerebellar cortex. Although a biological basis is still lacking to support this hypothesis, its implications sound very attractive in terms of system theory, since forced coactivity would produce the same type of global positive gain control whatever the neuronal structure under study, either by increasing the transmission of the selected input through a purely excitatory loop (Marr, 1969), or by reducing the excitation fed into the inhibitory efferent pathway (Albus, 1971).

**Synaptic Depression**

Much scarcer experimental evidence is available concerning the effects of pairing afferent stimulation with hyperpolarization of the target cell, which would constitute a situation equivalent to the S— condition in our protocol (Frégnac et al., 1988).

**Visual cortical plasticity and long-term depression (LTD).** In the numerous studies of LTP in neocortex and hippocampus, as already pointed out in the last subsection, the local postsynaptic potential at the site of synaptic activation appears to be a crucial variable. Current clamp and single electrode voltage clamp techniques have been applied to demonstrate that postsynaptic hyperpolarization or clamp of the postsynaptic potential near its resting level during a tetanus of input fibers can block the induction of LTP in the afferents that terminate close to the site of the current injection (Baranyi & Feher, 1981b; Douglas, Goddard, & Rives, 1982; Wigström, McNaughton, & Barnes, 1982; Kelso et al., 1986; Malinow & Miller, 1986; Baranyi & Szente, 1987).

Similarly, in the study of visual cortical plasticity, there is general agreement that postsynaptic activation of the neuron is a necessary requisite for any plastic change to occur (Rauschecker & Singer, 1981; Shaw & Cynader, 1984). However, recent work by Reiter and Stryker (1988) demonstrates cortical plasticity in the absence of postsynaptic firing. For this purpose, these authors used a GABA<sub>A</sub> agonist, muscimol, which blocks activity of the cortical cells, but not of the geniculate afferents (which have only GABA<sub>B</sub> receptors). Inactivation of cortical cells by infusion of muscimol, performed concomitantly with monocular occlusion, seemed paradoxically to put the closed eye at a competitive advantage.
over the experienced eye: Most cortical cells, recorded in the region of perfusion (once the muscimol blocking effect was relieved), responded only through the deprived eye. A similar finding has been reported since by experimenters using NMDA instead of muscimol, and is consistently observed near the cannulation site, where the concentration of the injected drug is very high and also leads to inactivation of the target cell (Bear, Kleinschmidt, Gu, & Singer, 1990). These surprising results are in fact fully predicted by our own working hypothesis, according to which a maintained period of failure in synaptic transmission induces a selective weakening of the efficacy of the active synapses. This situation is comparable to that imposed locally in our experiments, during an imposed negative change in the covariance level (S−) produced by the blockade or reduction of the response of the recorded cortical neuron (see lower row in Figure 5.5b and Table 5.3).

Recent in vitro studies both in hippocampus (Sejnowski, Chattarji, & Stanton, 1989; Stanton & Sejnowski, 1989) and visual cortex (Frégnac et al., 1990; Friedlander et al., in press) suggest that hyperpolarization paired with afferent stimulation may lead to synaptic depression in a significant number of cases. Input specificity has been demonstrated in CA1, and temporal contingency was studied in visual cortex. The induction of this effect could be blocked in hippocampus by AP3 perfusion - dl-2-amino-3-phosphono-propionic acid—which is thought to interfere with inositol triphosphate (IP3) turnover and possibly block as a partial agonist the normal activation of the metabotropic quisqualate receptor (Sladeczek, Recasens, & Bockaert, 1988)—but was unaltered in the presence of APV. A preliminary conclusion could be that this type of depression does not depend on NMDA receptor activation, but involves a different second-messenger process, probably linked to the phosphoinositide metabolism triggered by activation of quisqualate metabotropic receptors (Sladeczek et al., 1988). These findings are further supported by an independent biochemical study by Palmer, Monaghan, and Cotman (1988) suggesting that second-messenger systems linked to NMDA and non-NMDA ("ibotenate") receptors could be antagonistic. NMDA would inhibit phosphoinositide turnover (stimulated by excitatory amino acids) in a calcium-dependent fashion.

Interestingly, biochemical studies of the glutamate-stimulated phosphoinositide turnover in kitten visual cortex show a close dependence with age, which fits with the time course of the period of susceptibility to monocular deprivation (Dudek & Bear, 1989; Dudek, Bowen, & Bear, 1989). According to Bear, changes in synaptic efficacy would result from changes in a balance between NMDA receptor mediated calcium entry and non-NMDA receptor mediated phosphoinositide turnover (Bear & Cooper, 1989). Other authors propose, on the basis of pharmacologically induced depression and potentiation of geniculo-cortical PSPs following application of microdoses of bicuculline in the presence or absence of APV, that geniculo-cortical synapses would be reinforced or punished depending on the availability of NMDA-dependent
processes during postsynaptic depolarization (Artola & Singer, 1990) (see below).

Re-examination of the cerebellar paradox. The finding that hyperpolarization paired with afferent input leads to decreased synaptic efficacy of active synapses (Stanton & Sejnowski, 1989; Frégnac et al., 1990, Friedlander et al., in press) suggests a functional role for physiologically produced inhibitory potentials. Hyperpolarization in a target neuron can be obtained during normal functioning through direct inhibitory transmission, or during the consecutive phase following a period of intense afferent depolarizing activity (AHP or “out of phase” inhibitory rebound). An example can be found in associative LTD, recently demonstrated in CA1, following a low-frequency test input negatively correlated in time with a high-frequency conditioning input. Synapses of the pathway which was stimulated “out of phase” of the tetanus show a significant decrease in efficacy (Chattarji et al., 1989; Sejnowski et al., 1989); a tentative explanation is that LTD results from the conjunction of the AHP with the stimulation of the untetanized pathway.

A similar reasoning may be applied to heterosynaptic depression occurring after intense cellular activation. In the case of the cerebellar LTD, the climbing fiber activation of a Purkinje cell results in a “complex” spike, which depolarizes the cell so strongly that regenerative calcium spikes follow a fast Na-dependent spike, and their action in the dendrites are prolonged by persisting potassium conductance changes. A long-lasting hyperpolarization develops and is thought to be confined to the spines (Llinas & Sugimori, 1980a, b). At the somatic level the complex spike is followed by a period of membrane inactivation lasting 12–18 ms (Bloedel & Roberts, 1971). In some Purkinje cells this phase extends over several additional hundreds of milliseconds, probably through the retroaction of climbing fiber collaterals on inhibitory interneurons (basket and Golgi cells) of the cerebellar cortex. This hyperpolarization is sometimes seen directly following olivary stimulation applied at an intensity below threshold for triggering a “complex” spike. Duration of the hyperpolarization phase increases with the intensity of the stimulation applied to the climbing fibers (Murphy & Sabah, 1971). More remarkably, repeated stimulation of these fibers induces a long-lasting hyperpolarization (LLH), which may extend over several minutes. This lasting effect has been shown to be linked with the calcium component of the climbing fiber response (Houngaarda & Midgaard, 1989).

A provocative reinterpretation of the phenomenon of cerebellar LTD would be to naturally associate depression of the parallel fiber input not with the plateau depolarization produced in the Purkinje cell, but with the temporal contiguity of the hyperpolarization phase or LLH which builds up during the repetitive activation of the afferent climbing fiber. Our interest in suggesting this hypothesis comes from the fact that the cerebellar paradox could still be explained by the covariance hypothesis if one assumes that the critical parameter
characterizing postsynaptic activity is the membrane potential (and not postsynaptic firing).

This interpretation differs from that derived from a pharmacological dissection of LTD in the cerebellar cortex, presented briefly earlier, which suggests that desensitization of the ionotropic quisqualate receptor in Purkinje cell operates through the coactivation of protein kinase C by concomitant calcium entry (due to climbing fiber activity) and diacylglycerol increase (due to phospholipase C activation produced by parallel fiber input) (Crépel & Krupa, 1988). Although this phenomenon is typically presented as an example of adult plasticity (but see techniques in Crépel & Krupa, 1988), it may be worthwhile noting that LTD might be easier to induce at an immature stage of development, when NMDA receptors are still transiently expressed in Purkinje cells. If we compare this scheme with that proposed by Bear in kitten visual cortex (Bear & Cooper, 1989), a strong parallel could be established between LTD in hippocampus and visual cortex, and that demonstrated in cerebellum. Such a unifying hypothesis could be tested at the biochemical level by investigating if blockade of the phosphoinositide pathway (for instance by AP3) prevents—in a similar way in the three structures—the occurrence of depression produced by pairing synaptic activation with postsynaptic hyperpolarization.

**Postsynaptic Membrane Potential and Thresholds of Synaptic Plasticity**

Although it has been thought in the past 10 years that there is a unique membrane potential threshold above which a neuron switches from a relay mode to an adaptive state (Baranyi & Feher, 1981a; Brown, Chapman, Kairiss, & Kleeman, 1988), and that inhibition blocks cellular plasticity (Baranyi & Feher, 1981b; Malinow & Miller, 1986; Baranyi & Szente, 1987), demonstration of homosynaptic depression following periods of postsynaptic inactivation opens new theoretical possibilities.

A first thesis is defended by Artola, Bröcher, and Singer (1990), who assume that two successive thresholds for plasticity may be reached during postsynaptic depolarization: a) *low threshold LTD*: during respectively moderate postsynaptic depolarization, calcium entry signal without NMDA activation would produce synaptic depression, and b) *high threshold LTP*: during strong postsynaptic membrane depolarization, calcium entry through ionophores linked with the activated NMDA receptors would lead to synaptic potentiation. Synapses that are able to activate their NMDA receptor-dependent conductance in this latter situation would protect themselves from heterosynaptic depression.

As briefly presented in the last section, our own data and the findings of Sejnowski's group support a different scenario, where there would be an intermediate range of membrane potential (around the resting level) where neurons could be transiently excited and inhibited, and at the same time continue to transmit information in a replicable way. However, changes in
membrane potential from the resting level below or above certain threshold values would lead to adaptation of postsynaptic integration via antagonistic NMDA and non-NMDA dependent second-messenger processes, which respectively would lead to decrease or increase in the efficacy of recently activated synapses. The molecular processes involved in synaptic plasticity could differ according to the specificity of receptors put into play by synaptic transmission (compare CA1, visual cortex, and CA3), but the phenomenology of the PSP changes would follow the outcome predicted by the covariance rule.

Intrinsic Limitations in the Specificity of Synaptic Changes

A major advance in in vitro experiments compared to the in vivo approach is a better characterization of biochemical processes and activity patterns of both pre- and postsynaptic neurons required in inducing changes in synaptic transmission. But surprisingly the internal coupling within the network seems to beat this technical refinement. In particular, it was shown that pairing afferent activity with neighboring glia is sufficient to induce potentiation in the recorded postsynaptic cell (Sastry, personal communication; Sastry, Goh, & Huyet, 1986). This finding may have important consequences in the understanding of visual cortical plasticity. Detailed intraglial recordings show that these non-neuronal elements function as potassium sensitive electrodes (review in Kuffler & Nicholls, 1976) and share—as shown by their graded membrane potential selectivity—the functional preference for the column in which they are located (Kelly & Van Essen, 1976). Conversely, it might be plausible that the glial environment is able to extend the voltage change of depolarized neurons spatially across small patches of cortical tissue. Since the same cortical input is generally distributed to neighboring cells, synaptic plasticity processes under the control of coactivity may address a larger ensemble of neurons than the one defined by the initial voltage changes.

In addition, this intrinsic amplification in the locus of synaptic modification is not the sole result of the propagation of changes in potential on the postsynaptic side. Recent in vitro studies suggest in the case of LTP that additional synaptic modifications could affect the presynaptic side. Experiments using a slice/culture preparation (Gähwiler, 1984) have recently demonstrated that pairing of presynaptic activity with strong depolarization of an identified target cell enhances the synaptic efficacies of other contacts made by the same stimulated fiber onto neighboring but uncoupled cells (Bonhoeffer, Staiger, & Aertsen, 1989). Such an effect—if its generality is confirmed—indicates that pairing at one synaptic locus induces a synaptic recruitment extending over more than 150 μm of axon around the primarily enhanced synapse (i.e., around the depolarized neuron). However, this could still indirectly result from modifications occurring primarily in the target paired neuron, and diffusional models of retrograde factors released by the postsynaptic neuron and captured by neighbor-
ing presynaptic terminals have been recently put forward (the NO hypothesis in Gally, Read-Montague, Reeken, & Edelman, 1990; Garthwaite, Charles, & Chess-Williams, 1990; Bult et al., 1990; or the arachidonic acid hypothesis in Williams et al., 1989). In conclusion, the degree of specificity in the location of the putative synaptic changes produced by coactivity somehow appears diluted spatially within the cortical network, both on the pre- and postsynaptic sides.

CONCLUSION: COACTIVITY AND SYNAPTIC PLASTICITY

Role of Coactivity During Early Development

Propagation of nervous activity within the visual pathways may have a two-fold influence on the development of the visual system: In an early phase of postnatal maturation, tonic afferent activity may participate in transcribing at higher levels of integration a functional specialization present at the periphery. The development of the receptive fields of ganglion cells does not seem to depend itself on propagated activity, since it is not affected by blockade of sodium mediated spikes (following intraocular injection of tetrodotoxin). In contrast, retinal dark discharge has been shown to be a key factor in the regulation of layer segregation and in the maintenance of cellular integrity at upper levels of integration in CNS, that is, in the lateral geniculate body (Dubin, Stark, & Archer, 1986; Shatz & Stryker, 1988), and even at the cortical level (Chapman, Jacobson, Reiter, & Stryker, 1986; Stryker & Harris, 1986). A possible reason for the appearance of activity-dependent processes at these latter stages of visual processing is that ganglion cell integration depends mainly on summation of local graded potentials, whereas geniculate relay cells as well as cortical cells will fire as a function of coactivity arising between converging afferent axons.

Indeed a functional basis exists for such a scheme operating in the retinogeniculo-cortical pathway. The projection from retina to LGN seems at first inspection to arise from a random matrix of ganglion cells, but if selection of the afferent pathway is limited only to retinal cells which have a similar RF type—for instance, X-like (beta morphology) and ON center—the input matrix appears nonrandom and consists of a regular array of cells, the soma of which occupy the summits of contiguous hexagons (Wässle, Boycott, & Illing, 1981). In addition neighboring ganglion cells of a given type are found to be coactive even during spontaneous firing (Mastronarde, 1983a, b, 1989). Consequently a general property of early activity-dependent processes in visual pathway could be that coactivity—even of spontaneous origin—reinforces synaptic coupling between neurons that will later share the same functional specificity during development.

Such mechanisms could ensure the sharpening of precise topographical maps from one relay to the next, and even produce differentiation of separate ON and
OFF channels in the geniculo-cortical pathway. Although strongly dependent on intrinsic coactivity levels, the corresponding phase of development during which these processes occur can be considered to be independent of visual experience. Consequently the major role of spontaneous activity during an early phase of development would be to generalize within the central nervous system endogenous constraints already expressed at the retinal level in the coactivity pattern of ganglion cells.

Role of Coactivity During Later Postnatal Development

A second role of activity in the development of the visual pathway appears later during a postnatal period when the phasic component of the retinal message reflects interaction with the visual environment. This phase is usually referred to as the "critical period" during which evoked activity has a great influence on the functional development of sensory nervous structures. Interestingly, as noted earlier, the neurons which are the most sensitive to visual experience are found in relays where levels of spontaneous activity are low. Most experiments of cellular conditioning reported earlier were done in kitten visual cortex, at the middle of the critical period, or at the adult age. During this later part of postnatal life, propagated activity originates mainly from interaction with the visual environment, and activity-dependent plasticity may alter fine details of the functional architecture of the visual cortex in a precise way. For instance, evoked coactivity during visual activation could help to select by "resonance" among preformed assemblies those which are best suited to detect regularities of the everyday environment (Heidmann, Heidmann, & Changeux, 1984). Consequently, the intrinsic horizontal connectivity, which will be finally stabilized at the adult age, may reflect constraints which are endogenous to the network as well as functional links due to persistent coherence in the perception of certain attributes in the outside world.

Role of Coactivity During Learning

Functional changes induced by forced coactivity, and described in this chapter, have been reported in the adult as well, although they are of smaller amplitude than during the critical period. This surprising level of adaptation may be an argument for distinguishing the type of neural plasticity revealed in our experiments from natural changes occurring during epigenesis, since a decline in the degree of functional malleability of visual cortex is normally expected with age. This last conception might be in fact totally misleading, and care should be taken to distinguish between the potential available for plasticity and its degree of expression. It is in fact highly plausible that our artificial iontophoretic technique—adding an external "teacher" to a normally unsupervised system—uncovers a plasticity process which is not normally permanently
activated in the adult. This remark could apply also to the findings of Kasamatsu, Watabe, Hegelund, and Scholler (1985), who showed changes in the global binocularity state in the adult by the association of monococular deprivation performed well beyond the end of the so-called “critical period” (Hubel & Wiesel, 1970), with imposed electrical stimulation of the locus coeruleus.

**Relationship between developmental and adult plasticity.** Rather than assuming irreversible regression of the adaptive capacities of neocortical neurons during postnatal life, our findings lead us to propose that there exist both a fixed intrinsic potential for plasticity and a strong age-dependence in the mechanisms regulating its expression.

A first type of modulatory mechanism could be linked to the level of inhibitory constraints in the network. Inhibition could control for instance the probability that a neuron switches from a “passive relay” mode to an “adaptive mode” of transmission. Most neurons in the adult neocortex are found to be regular spiking neurons (Connors et al., 1982; McCormick, Connors, Lighthall, & Prince, 1985), and are rarely susceptible to synaptic potentiation when the intensity of afferent stimulation is high enough to recruit inhibitory collaterals (Sutor & Hablitz, 1989a). However, if inhibition is removed by intracortical infusion of bicuculline (in slices), regular spiking neurons exhibit burstlike behavior (Artola & Singer, 1987), and can be forced in this particular state to change their integrative properties. Another example of inhibitory control could be the expression/suppression of latent excitatory polysynaptic pathways revealed by changes in the synaptic efficacy of inhibitory collaterals (Miles & Wong, 1987).

A second major modulatory factor could be age-dependent agents released by the glial environment. A fascinating report by Müller and Best (1989) suggests that the graft of astrocytes taken from kitten visual cortex into adult cortex could restore plastic sensitivity to visual experience outside the critical period.

A third possibility is that all the machinery for cellular plasticity is still operational, but that the gating signals necessary for the expression of visual cortical plasticity, and which are extraretinal in nature, are no longer present in the adult cortex (Frégnot, 1987). There is, for instance, some evidence that the laminar pattern of noradrenergic projections in visual cortex may vary with age (Jonsson & Kasamatsu, 1983; Aoki, Kauffman, & Rainbow, 1986; review in Frégnot & Imbert, 1984). A crucial problem in understanding the decline of plasticity during development would then be to define the time dependencies with which different types of “external” events (extraretinal, humoral, hormonal [Daw et al., 1992], glial) control the transition of the internal state of a neuron from a passive relay mode to an adaptive mode. Although such an experimental approach might prove to be tantalizing, partial answers are already available and concern classical putative neuromodulators. Quantitative studies of
the laminar location of receptor binding sites during the course of postnatal development show that for almost all types of receptors studied so far, their distributions are far from constant, and in a restricted number of cases are affected by extrinsic activity arising from the periphery. A promising prospective approach has been engaged by Cynader and coworkers in trying to delineate the existence of "suspicious periods" where putative neuromodulatory systems would coincidently affect extrinsic fiber (i.e., presynaptic) and neuronal (i.e., postsynaptic) activities in the same cortical lamina (Aoki et al., 1986; Shaw et al., 1988; Van Huizen, Strosberg, & Cynader, 1988; Cynader et al., 1989).

**Control of covariance by extraretinal gating signals.** Cellular mechanisms by which neuromodulatory gating signals may amplify or reduce covariance between visual input and postsynaptic activity of cortical cells are still a matter of conjecture. Our hypothetical scheme assumes that developmental or context signals arising in the CNS during interaction with the environment control covariance between activities of specific retinal afferents and postsynaptic activity, by imposing maintained periods of increased and decreased visual responsiveness. Very limited conclusions have been reached concerning the role of neuromodulators like NA and acetylcholine in controlling the expression of functional selectivity at the cortical level. Most studies concern conflicting analysis of signal/noise ratio of the sensory response measured for the initially most potent stimulus (Kasamatsu & Heggeland, 1982; Foote, Freedman, & Oliver, 1984; Videen, Daw, & Rader, 1984; Metherate, Tremblay, & Dykes, 1987; Sato, Fox, & Daw, 1989). In the case of noradrenaline for instance, beta-adrenoreceptors are described to have both suppressive and facilitatory actions on both spontaneous and evoked activities of visual cortical neurons. In an unpublished work, suggestive evidence has been presented in favor of an increase in orientation selectivity during NA iontophoresis (Madar, 1983). Our own theoretical hypothesis, detailed in Figure 5.12, predicts the long-term maintenance of this effect following repeated pairing of sensory stimulation with noradrenaline. Although a direct experimental test has yet to be attempted, the biphasic covariance gain control exerted by this neuromodulator on the input/output integration of hippocampal and neocortical neurons may be an illustration of how the same "gating" factor can produce either synaptic potentiation or depression depending on the initial level of firing ("weak" or "strong" in Figure 5.12), or on the visual specificity of the selected input (if one assumes that input firing already codes for an attribute of the visual stimulus).

**Parallels between neuronal plasticity and behavioral learning.** The discovery of a significant potential of functional plasticity in the adult is certainly not specific to the primary visual cortex, since it is consistent with at least two recent studies showing functional changes in the somatosensory cortex (Merzenich et al., 1984; Clark et al., 1988), and the auditory cortex (review in
Figure 5.12. Covariance gain control by extraretinal signals (from Frégnac & Shulz, 1989, with permission).

a: Adapted freely from Madison and Nicoll (1986, p. 236). Two levels of hypothetical afferent activity ("weak" and "strong" spike trains in lowest row) are equated respectively with the action of a ramp and a step of current (third row) applied intracellularly in the target neuron. Postsynaptic responses are shown during control (upper row) and during neuromodulation by a putative extraretinal gating factor (NA, second row). Note the biphasic action of noradrenaline, resulting in a blockade of the response to the "weak" input (due to a hyperpolarizing effect), and in an increased response to the "strong" input (due to a loss of accommodation). Temporal evolution of postsynaptic firing following NA increase in the extracellular medium (underlined in bold) is represented in response to both inputs.
b: Upper graph, hypothetical input/output curves during the passive (Control) and adaptive (NA) modes of functioning (see Figure 5.5). Lower graph, change in the covariance between pre- and postsynaptic activities imposed during Noradrenaline action and plotted as a function of the level of presynaptic activity. Note that, according to the terminology used in our pairing experiments, modulation by the gating factor is analogous in that case with an S− pairing for the "weak" input and with an S+ pairing for the "strong" input. The covariance hypothesis predicts that the transmission efficacy of synapses activated by the "weak" (active pathway in lowest row of Figure 5.5) and "strong" input (active pathway in middle row of Figure 5.5) should be reduced and increased respectively.

Weinberger & Diamond, 1987) of adult animals. But in contrast to our artificially imposed procedures of cellular conditioning, these two sets of experiments describe adaptation of topographic mapping of the sensory input and of the functional specificity of the sensory analyzer as a result of learning processes in the normal behaving animal.

Although based on the comparison of sensory maps rather than on changes described at the single neuron level, a large functional reorganization has been demonstrated by Merzenich and coworkers (Merzenich et al., 1984; Clark et al., 1988), in the topography of cortical cutaneous receptive fields in the somatosensory cortex of the adult monkey. Dynamic changes in somatotopy could be traced following manipulation of the peripheral afferents (by amputation or fusion of digits of the monkey's hand) or following learning periods where a particular peripheral region (tip of one digit) was continuously stimulated during an attentive task. A second example of adult plasticity which is well-documented concerns cellular correlates of classical conditioning in the secondary auditory cortical area of the cat: During chronic recordings neurons were shown to develop frequency-specific plasticity in their frequency receptive field, concomitantly to the acquisition of a pupillary dilation conditioned defensive response (Diamond & Weinberger, 1986). Taken together with the results of our own study, these changes emphasize the adaptive capacities of primary sensory cortical networks in the adult animal, which can be functionally expressed during selective phases of learning.

A possible relationship between activity-dependent forms of neural plasticity and the cellular basis of behavioral learning can be further supported in comparing the reorganization of functional selectivity (orientation, IOD) demonstrated at the cellular level during conditioning of the neuronal response, with that of behavioral performances following classical or operant conditioning. Although a demonstration of causal links is still lacking in the vertebrate brain, tuning curves in neocortical neurons may indeed be considered as the neuronal version of generalization gradients of behavioral responses produced by conditioning. Similar changes in selectivity are observed following a differential
pairing of neuronal responses (Frégnac et al., 1988) and a differential conditioning of global responses of an organism (Hanson, 1959). Both the peak of the tuning curve of selectivity of the neuronal response to a parameter of the visual stimulation (expressed on a continuous scale) and the optimum of the behavioral gradient shift towards the reinforced stimulus (S+ or CS+) after conditioning; concomitantly a reduction in the relative responsiveness appears selectively for the response-suppressed (S−) or differential (DS or CS−) stimulus. It is thus conceivable that the same type of competition mechanisms could be implemented both at the cellular and at the behavioral or perceptual level. Support for this unifying scheme can be found in the study of cellular correlates of classical conditioning in auditory cortex (Diamond & Weinberger, 1986), where changes in sensory receptive fields have been described by gain and loss curves analogous to the ones derived from our study.

Role of Coactivity During Form Recognition Processes

In addition to Hebbian principles of synaptic plasticity applied to developmental or learning processes on a “slow” time scale (minutes to days), a less intuitive role has been recently ascribed to coactivity in dynamic processes involved in sensory coding and form recognition at the cortical level. According to the theory of correlation in the brain (von der Malsburg, 1981), internal representation of a mental object or of a percept would be encoded by the occurrence of temporally correlated activities among restricted neural subnets (von der Malsburg, 1981; Abeles, 1982; von der Malsburg & Bienenstock, 1986). If one assumes that Hebbian rules of plasticity also hold on a much faster time scale than classically thought (in the order of a second or less), the coactivation triggered by elaboration of mental processes (John, Tang, Brill, Young, & Ono, 1986) could produce a synchronized focus of activity, which by spreading as a “synfire chain” would lead to almost instantaneous changes in synaptic efficacy. This organized stream of activity would result in the selective activation of transient graphs of coupled neurons. The theory assumes that invariance in perception for different positions in space or deformed perspectives of the same visual object is unrelated to the physical locations of coactivated neurons, but depends on the existence of homeomorphisms between graphs formed by the neurons firing in synchrony, that is a consequence of the topological properties of the active assemblies (Bienenstock & Doursat, 1989; Bienenstock & von der Malsburg, 1987).

Such a concept elaborated by brain theoreticians is compatible with the earlier proposal by psychologists that representation in CNS of various visual properties of objects in the outside world are combined only transiently during perception (Treisman, 1977). A first neurobiological mechanism was proposed by Crick (1984) on the basis of the “searchlight hypothesis” (Treisman, 1977), and
Figure 5.13. Cellular analogs of generalization gradients

Left upper panel. Behavioral learning: Generalization curves following an operant conditioning, without (dotted line) and after (solid line) discrimination training (adapted from Hanson, 1959; quoted in Woody, 1982a). The dotted curve represents the generalization gradient of the effects of a positively reinforced stimulus (CS+) (pigeons are pecking a cue stimulus of a given wavelength). The solid curve illustrates the alteration of the gradient following the concomitant introduction of a negative discriminative stimulus (CS-) during training. This differential learning procedure results in an asymmetry and a higher selectivity in tuning, with a shift of the maximal response away from the negative stimulus (CS-). The modification of the generalization gradient is stronger the shorter the distance between CS+ and CS-.

Right upper panel. Cellular correlate of classical conditioning: Frequency tuning curves of a single unit in secondary auditory cortex (area A11), recorded before (dotted line) and after (solid line) conditioning of a pupillary response. Prior to training, the neuron was excited
assumed that bursting activity of neurons of the thalamic reticular nucleus would link all cortical neurons activated by different attributes of the same perceived object. Other scenarios could be invoked without requiring a subcortical “teacher,” and are further supported by the recent finding of phasic episodes in visual cortical areas, where local field potentials and cellular firing recorded in distant isofunctional domains (up to several millimeters apart) exhibit a remarkable temporal coherence or phase-locked coactivity patterns (Eckhorn et al., 1988, 1989; Gray et al., 1989; Gray & Singer, 1989; review in Stryker, 1989). Rhythmicity appears to be internal to cortical areas, since these oscillations have been reported to be absent at the LGN level (Gray & Singer, 1989). It is not yet clear, however, how much phase or temporal frequency of these oscillations (in the range of 40-50 Hz) are dependent on global characteristics or on the perceptual signification of the visual input and the preattentive state of the organism, but these pioneering experiments constitute a first line of evidence supporting a role of coactivity in figure/ground extraction processes.

Although the cellular basis for these oscillations in visual cortex is still a matter of debate (but see Alonso & Llinás, 1989, in entorhinal cortex), an attractive possibility is that autorhythmic electrical properties of neocortical neurons could form the basis of a “functional coordinate system” providing internal context to sensory input (Llinás, 1988), and helping to stabilize connectivity. Coherent but distributed coactivity in the cortical network could characterize temporal periods when synaptic changes are functionally expressed. The “print now” signal may consequently be an emerging property of self-organizing processes occurring on a “fast” time scale in the network.
Concluding Remarks

In summary, Hebbian models of synaptic plasticity appear to be highly relevant to functional plasticity described on a "slow" time scale during epigenesis and during selective phases of learning occurring at the adult age. Electrophysiological evidence, established in vivo and in vitro, supports the hypothesis that dynamic changes in coactivity, or in the level of temporal correlation between pre- and postsynaptic activities, locally control the sign and amplitude of synaptic changes. Similar principles of synaptic plasticity could also apply to a much faster time scale domain, of the order of integration delays required during perceptive tasks. These "fast" changes would allow waxing and waning of oscillations across transient functional assemblies during attentive visual processing.

This dual role of coactivity suggests its participation in two types of basic operations: the first one, which is performed locally (at the neuronal level) and correspons to the detection of synchrony between converging and competing afferents, was already foreseen by James:

The amount of activity at any given point in the brain cortex is the sum of the tendencies of all other points to discharge into it, such tendencies being proportionate (1) to the number of times the excitement each other point may have accompanied that of the point in question; (2) to the intensities of such excitements; and (3) to the absence of any rival point functionally disconnected with the first point, into which the discharges might be diverted. (Chapter XVI in James, 1890)

The second one is global, and is an emerging property of the network, signalling that an ordered state has been reached. In spite of limited direct neurobiological evidence, coherence of firing within assemblies could lead to internal evaluation by the assembly of a "print now" order and authorize local synaptic changes, or to the retrieval of perceptual invariances. This last concept echoes thoughts of the French philosopher Henri Bergson, who wrote in L'énergie spirituelle (1912) the following statement:

Si vraiment mon souvenir visuel d'un objet était une impression laissée par cet objet sur mon cerveau, je n'aurais jamais le souvenir d'un objet, j'en aurais des milliers. (...). Tel est le rôle du cerveau dans l'opération de la mémoire: il ne sert pas à conserver le passé, mais à le masquer d'abord, puis à en laisser transparaître ce qui est pratiquement utile.

If my visual memory of an object were the trace that it printed in my brain, I would never have the memory of one object, but thousands (...). Such is the role of the brain in the process of memory: its function is not to store the past, but first to mask it, and then to let emerge only what is practically useful.
Thus, coactivity in the visual pathway could be involved in different forms of synaptic plasticity leading to the formation of distributed memories, and to the dynamic expression of functional links inherited both from endogenous constraints and regularities in our perceptual world.

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