Full-length review

Evidence for the Hebbian hypothesis in experience-dependent physiological plasticity of neocortex: a critical review

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Abstract

Over the past decade, the number of experimental papers reporting physiological plasticity in primary neocortical regions, following certain types of controlled sensory experience, have increased greatly. These reports have been characterized by specific changes in receptive fields of individual neurons and/or the distributions of receptive fields across cortical maps. There is a widespread belief these types of plasticities have underlying Hebbian/covariance induction mechanisms. This belief appears to be based mainly on: (a) indirect evidence, largely from experiments on the kitten visual cortex, indicating that Hebbian induction mechanisms could be involved in neocortical plasticity; (b) the observation that some types of plasticity in systems other than neocortex follow Hebbian rules of induction; and (c) the adaptability of Hebbian induction mechanisms to models of neural plasticity. In addition, some experiments have directly tested the role of Hebbian induction mechanisms in experience-dependent neocortical plasticity. The present review critically analyzes these (and related) experiments, in order to evaluate the evidence for the Hebbian Hypothesis in experience-dependent physiological plasticity of neocortex. First, we present a set of criteria to show the involvement of a Hebbian process in any form of plasticity. Next, we compare evidence from each primary neocortical region to these criteria. Finally, we examine unresolved issues. While selected developmental studies are included, emphasis is placed on plasticity in the adult neocortex. It is concluded that there is some evidence meeting the criteria for the Hebbian hypothesis in neocortical plasticity. However, this evidence is quite limited considering the popular belief in the validity of the Hebbian hypothesis.

Keywords: Neocortical; Cortical; Cortex; Covariance; Hebb; Synaptic plasticity

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1. Introduction

1.1. Receptive field changes in adult neocortex are induced by experience

A major challenge facing neuroscience is understanding how behavioral experience alters the functional circuitry of the mammalian neocortex, and consequently modifies the way it processes information. It is assumed that understanding such changes will help clarify our knowledge of adaptive processes that engage neocortex (e.g., perception, learning and memory). An area of research that directly addresses this issue is the study of experience-dependent neocortical physiological plasticity. Throughout the past decade it has become increasingly well established that controlled sensory experience, such as partial sensory deafferentation or learning, can induce systematic physiological changes in the neocortex of adult animals. In primary sensory and motor areas, these changes have been characterized as `receptive field plasticity' — i.e., specific alterations in the receptive fields of individual neurons and/or the distributions of receptive fields across cortical maps (reviewed in [65,86,113,163]). For example, the experience of associative learning modifies receptive fields (RFs) of cells in adult auditory cortex, increasing cellular responses to tone frequencies that signal behaviorally important events (food or shock), and decreasing responses to other frequencies (reviewed in [162]).

1.2. Induction of receptive field plasticity: the Hebbian hypothesis

The present review concerns itself with the issue of induction of neocortical RF plasticity. The specific focus will be on one `theory' that has been extremely pervasive throughout the literature surrounding induction mechanisms. This theory is referred to as the `Hebbian' [75,151] or `covariance' (reviewed in [146,60]) hypothesis. It postulates the involvment of particular types of intercellular interactions in the induction of particular types of synaptic plasticity. Modern manifestations of the Hebbian hypothesis generally state that: (a) temporal correlation of pre- and postsynaptic activity will lead to synaptic strengthening and (b) lack of correlation will lead to synaptic weakening. In the case of neocortical RF plasticity, postsynaptic cells would consist of the cortical cells that express the plasticity, and presynaptic cells would consist of the subcortical and cortical afferents that project to those cells. The Hebbian hypothesis can be broken down into three separate `rules', based on the activity of the pre and postsynaptic elements, during potential plasticity-inducing events (see Fig. 1).

(1) The Hypothesis predicts that a synapse will be strengthened when its pre- and postsynaptic elements are simultaneously active (indicated by upward arrow, No. 1, upper left of matrix). This prediction will be referred to as the `pre and post' rule — meaning both pre and postsynaptic elements are active.

(2) The Hypothesis predicts that a synapse will be weakened if its presynaptic element is active while its postsynaptic element is inactive (indicated by No. 2, lower left). This prediction will be called the `pre not post' rule — meaning the presynaptic but not the postsynaptic element is active.

(3) The Hypothesis also predicts that a synapse will be

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1 We recognize that the term `plasticity' refers to the inherent property of nervous tissue to change. However, this term is now generally used to refer to the expression of the change rather than to the capacity for change. Our use of `plasticity' is in accord with this common usage. Thus, whenever a statement indicates that an experience induces receptive field plasticity, it means that the experience caused the receptive field to change, and not that the experience endowed the neuron with the capacity for the change.
weakened when its postsynaptic element is active while its presynaptic element is inactive (No. 3, upper right). This will be called the ‘post not pre’ rule.

One generally accepted contemporary variation of the Hypothesis is that the changes in synaptic strength are not based on deviations in covariance from zero levels. Instead, a non-zero threshold of covariance is generally employed, above which potentiation would occur, and below which depression would occur.²

The original formulation of the Hebbian hypothesis (which included only rule No. 1 above — i.e., the ‘pre and post’ rule) [75] provided a simple neural mechanism to explain associations that occur during learning and perceptual development. This clear relationship between psychological phenomena and neural implementation undoubtedly contributed to some of its initial popularity. Independent of whether or not the original support for the Hebbian hypothesis was well founded (see [64] for a critical discussion), its modern manifestation, the ‘Covariance Hypothesis’ above, remains extremely popular as a potential mechanism of induction for synaptic changes occurring during neocortical RF plasticity. This current popularity is due in part to the adaptability of the hypothesis for models of neural plasticity, [21,140,146,6,1,99] and the fact that some forms of plasticity in systems other than neocortex follow Hebbian rules of induction [169,25,39,104]. More importantly, there is some indirect and direct evidence supporting the involvement of Hebbian processes in RF plasticity for several regions of neocortex, including each primary neocortical area. Some of the strongest of that evidence will be reviewed shortly.

This paper is divided into two major sections. First, the general evidence implicating Hebbian induction processes in neocortical RF plasticity will be reviewed. This will begin by examining the logic required to show the involvement of a covariance process in induction. With that logic in mind, relevant experiments from visual, somatosensory, auditory, and motor cortex will each be presented in turn. Emphasis will be placed on experience-dependent types of plasticity in the adult. The next section will discuss unresolved issues, challenges, and problems with Hebbian induction mechanisms. The goal of this paper is to thoroughly and critically examine the current evidence (through September, 1995) relating Hebbian mechanisms to experience-dependent neocortical plasticity. It will not be an exhaustive review of all potentially relevant papers, but rather will focus on critical papers that may satisfy criteria to either support or refute the hypothesis. It is hoped this will provide the reader the context necessary to make informed evaluations of relevant experiments in the future.

2 Evidence implicating Hebbian processes in receptive field plasticity

2.1 Logic required to show the involvement of Hebbian processes

2.1.1 Demonstrating covariance changes in the ‘normal’ situation is required

In order to show the involvement of Hebbian processes in RF plasticity, an obvious first step is to demonstrate that the kinds of experiences that normally induce RF plasticity are accompanied by appropriate changes in pre/postsynaptic covariance, as indicated by the Hypothesis (above). It will become clear from the following discussion that several plasticity-inducing experiences cause such changes. Appropriate alterations in covariance by themselves however do not provide strong evidence for Hebbian mechanisms — other conditions must be met.

2.1.2 Experiments in the Aplysia provide an example of the importance of demonstrating necessity and sufficiency

An illustration of this point comes from experiments in the invertebrate Aplysia where an analog of learning has been shown to result in an increase in the synaptic efficacy between two neurons: a presynaptic sensory neuron and a postsynaptic motor neuron. Potentiation of the synapses connecting the sensory and motor neurons could ‘normally’ be induced by pairing the activation of the sensory neuron (in the behaving animal the sensory neuron is activated by light touch), with stimulation of a modulatory nerve (activated by aversive stimuli in the behaving animal). Stimulation of this nerve caused a burst of action potentials in the postsynaptic motor neuron. Thus, pairing the activation of the sensory and modulatory pathways caused strong increases in the covariance between the presynaptic (sensory) and postsynaptic (motor) neurons during the learning analog. Because the increased covariance produced subsequent synaptic potentiation, a Hebbian explanation seemed plausible.

Carew et al. [29] went further by asking whether the increased pre/postsynaptic covariance observed was sufficient and/or necessary for the plasticity. To test sufficiency, they temporally paired action potentials in the pre- and postsynaptic neurons, at the levels that occurred during standard induction of plasticity. However, the postsynaptic action potentials were initiated by directly injecting depolarizing intracellular current, in the absence of the modulatory stimulus. The experimenters found no increase in synaptic strength following this protocol, indicating that the increased pre/postsynaptic covariance alone was not sufficient for induction of plasticity. However, it still remained possible that the increased covariance observed during normal induction was necessary for plasticity.

In the next experiment they tested for necessity by pairing sensory neuron activation with the modulatory stimulus (that normally induced plasticity), while hyperpo-

² The exact value of the threshold may be a pre-set value, or based on previous activity levels of the synapse or cell in question. Some ideas for determining possible threshold values will be discussed explicitly in Section 3.
larizing the motor neuron to prevent postsynaptic spiking. By preventing postsynaptic activity, the hyperpolarization prevented the increase in covariance. In this case, the plasticity still occurred, indicating that increased covariance was not necessary for plasticity. It was concluded from these and other experiments (e.g., see [74]) that the induction of potentiation in this system does not involve activity of the postsynaptic motor neuron. Therefore, the induction is not ‘Hebbian’.

The *Aplysia* example was selected to draw attention to the possibility that non-Hebbian explanations are quite possible even in situations where there are appropriate and obvious changes in covariance (between pre- and postsynaptic elements) during ‘experiences’ that induce plasticity. This emphasizes the importance of demonstrating the necessity and sufficiency of ‘covariance’ in a particular system of experience-dependent plasticity, before accepting a Hebbian model of induction for that system.

### 2.1.3. Is covariance necessary and sufficient for plasticity in the cerebral cortex?

Similar logic has been applied to hippocampal long-term potentiation (LTP) to demonstrate that positive pre/postsynaptic covariance is both necessary and sufficient for LTP [170,91,142,111] (for reviews see [169,25,23]). The role of Hebbian processes in the induction of neocortical RF plasticity is much less clear. However there are positive reports both from studies of developmental and adult plasticity. The next sections will review the evidence for each primary sensory and motor neocortical area. Emphasis will be placed on direct tests where they exist, sometimes deferring to more indirect evidence in systems where direct tests are unavailable. The goal for this first section is to provide the strongest data available implicating Hebbian induction in cortical plasticity, so that an informed critical analysis in Section 3 can follow.

### 2.2. Hebbian processes in visual cortical plasticity

#### 2.2.1. Introduction

Many of the experiments to be reviewed for the visual cortex (VCx) come from work on developmental plasticity. There are two reasons for their inclusion, despite our primary interest on adult plasticity. First, the original rationale implicating Hebbian processes in cortical plasticity were based on findings from the mid-1960s on visual development [151]. Second, recent visual developmental studies have provided clear and direct tests of necessity and sufficiency of Hebbian processes in plasticity (reviewed in [60,155]). Data that are most pertinent to these two issues will be emphasized below. However, it should be stated that important contributions to this area were made between the times of original experiments of the 1960s and the later direct tests (e.g., Rauschecker and Singer [131]). Such studies not only provided indirect evidence relevant to Hebbian mechanisms in visual cortical plasticity, but were also crucial in encouraging the more direct tests. For example, a review of these early studies, compiled in 1984 (Fregnac and Imbert [58]), clearly suggested the need for the types of direct tests of sufficiency that were subsequently conducted by Fregnac and colleagues (discussed below in subsections 2.2.6–8). While the ‘indirect’ literature is not discussed in great detail here, the reader is encouraged to consult several excellent reviews ([43,58,35,129]).

#### 2.2.2. Stent, Hubel and Wiesel provide the original rationale for invoking the Hebbian hypothesis in experience-dependent neocortical RF plasticity: the development of binocular integration

Three classic discoveries of Hubel and Wiesel provided the empirical foundation that allowed Gunther Stent to recognize that a Hebbian algorithm could be operating in the development of binocular connections to VCx. The first of these was the observation of ocular dominance changes during monocular deprivation. When a kitten is deprived of vision through one eye during the first four months of life, most cells in primary VCx come to respond only to stimulation through the non-deprived eye (greater than 85%) [168]. In contrast, most cells in the VCx of normal animals respond to both eyes (about 80%), and the preferences for one eye vs. the other are approximately even [167].

The second important discovery was that the loss in number of neurons responsive to the deprived eye was not simply a result of atrophy following disuse. This was demonstrated by depriving kittens of vision to both eyes for the same periods as in the monocular deprivation experiment. If the nearly complete loss of response to the closed eye in the original monocular deprivation experiments had been due to disuse, then the binocular deprivation should have produced a nearly complete loss of response to both eyes. However the actual result was that most cells (71%) remained visually responsive [168]. This discovery, combined with corroborating anatomical data (e.g., Guillery [69]), led to the idea that there was an active competition between converging inputs for functional connectivity onto cortical cells. A decrease in the activity of one input relative to another would put the less active input at a disadvantage (at least during a period of relatively strong postsynaptic activity). During binocular deprivation, all inputs were equally inactive, so that there would be no differential depression.

The third major discovery revealed that it was not only the relative amount of activity between inputs from the two eyes that was important; equally critical was the temporal relationship between the (presynaptic) inputs from the two eyes. Hubel and Wiesel [78] found that

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1. However there is recent evidence indicating that neurons in this circuit may be capable of ‘Hebbian plasticity’ (Lin and Glanzman [104]).
raising a kitten with artificially induced squint caused most visual cortical cells to become monocular (80% monocular, 20% binocular, almost no unresponsive neurons).

The following rationale was used to relate the artificial squint results to presynaptic temporal patterns. In a normal animal, homologous parts of the retina from each eye are stimulated by the same small area of visual space, and eventually provide input to the same region of Vcx. As a result of this organization, normal vision produces nearly synchronous input onto visual cortical cells from the two eyes. In squint animals, a given point in visual space will not stimulate homologous parts of the retina, preventing their simultaneous activation. On average two homologous retinal regions, and their corresponding projection to Vcx, will be activated about equally, but they will rarely be activated at the same time. Because cortical cells receive input mainly from homologous regions of the two retinae, these cortical cells would ‘see’ only asynchronous input from the two eyes. From this it was reasoned that temporally asynchronous presynaptic activity from the two eyes was responsible for the loss of the binocular connections.

Stent [151] recognized that presynaptic temporal asynchrony from the two eyes could be detected postsynaptically. He believed that presynaptic mechanisms of detection would be unlikely, because the large number of axon collaterals required would be excessively complicated — every axon would have to contact every other axon that shared a common target. Instead he postulated that, “the activity of the synapse of cell A (a presynaptic cell) upon cell B (a postsynaptic cell) is manifestly asynchronous with the activity of synapses of other cells converging on cell B if most of the impulses that arise in cell B occur while the synapse of cell A is inactive.” With this logic in mind, Stent concluded that the problem of weakening asynchronous inputs to a cell could be solved if the synapses of inactive inputs were weakened whenever the postsynaptic cell fired. This is basically the ‘post not pre’ rule, as delineated in the Introduction. He also postulated that the synapses of a presynaptic cell would be protected from weakening if that cell fired synchronously with the postsynaptic neuron [151].

Stent went even further and proposed sub-cellular mechanisms of induction and expression for the effects observed. While the details of these proposals have not received support, the general concept of heterosynaptic depression and protection of active inputs during postsynaptic activity has been demonstrated in some systems (e.g., see [39] for neuromuscular junction and [30] for hippocampus).

One point should be emphasized before proceeding — Stent did not explicitly propose a mechanism of enhancement of synaptic efficacy by temporal synchrony because: (a) such a mechanism had previously been proposed for another system, the cerebellum [112]; and (b) visually inexperienced animals have binocular connections (reviewed in [151]). However, more recently it has been demonstrated that enhancement in the number of neurons responsive to both eyes (above control values) can be produced by extended synchronous stimulation of inputs from the two eyes [156,154]. Therefore a corollary ‘pre and post’ mechanism of detection of presynaptic synchrony and enhancement of synaptic strength could be postulated for ocular dominance plasticity.

The Hebbian interpretations proposed by Stent, and inferred from the synchronous stimulation experiments provide a means of explaining the observations of plasticity in Vcx following manipulations of visual input. Experiments that could be considered direct tests of these interpretations will be examined next.

2.2.3. Postsynaptic activity is necessary for normal ocular dominance plasticity

While the manipulations that produce ocular dominance plasticity involve alterations in patterns of presynaptic activity, the mechanisms of induction proposed to account for them (the ‘post not pre’ rule and the ‘pre and post’ rule, above) require postsynaptic activity as well. Thus, one way to test for the necessity of the proposed rules would be to interfere with postsynaptic activity during the plasticity-inducing events. If either of the two Hebbian ‘rules’ mentioned directly above are involved in ocular dominance plasticity, then postsynaptic interference during monocular deprivation should prevent the shift toward the open eye. This is the same logic employed in the Aplysia experiments of Carew et al. [29] discussed above. Several strategies have been employed with this end in mind, all of them reporting success in at least partly blocking the normally induced ocular dominance plasticity. One experiment increased tonic postsynaptic cortical activity with chronic infusion of excitatory neurotransmitter agonists. This largely eliminated any difference in detectable postsynaptic response to inputs coming from the open and closed eyes [147]. Some experiments blocked specific types of excitatory transmission in order to block the postsynaptic response or perhaps block the detection of the covariance itself (e.g., [16,130]; discussed below). Finally others attempted to block postsynaptic action potentials or depolarization using TTX [135] or GABAergic agonists [134].

In a clear example of the latter strategy, Reiter and Stryker [134] blocked postsynaptic activity by infusing the GABA_A receptor agonist muscimol into part of the Vcx of kittens. During this postsynaptic activity blockade, the
kittens were deprived of vision to one eye for 5 days. Following this period, the muscimol infusion was discontinued and cortical cells were tested for bincularity (following recovery from the acute effects of the drug). The authors found that within the area that had been previously silenced by muscimol,ocular dominance not only failed to shift toward the open eye, but instead shifted significantly toward the closed eye (Fig. 2). These results support the necessity of postsynaptic activity in the ‘normal’ ocular dominance shift toward the open eye. They are also supportive of the ‘pre not post’ rule — it appears that relative strengths of synapses from the open eye were weakened when they were active in the absence of postsynaptic discharge.

Recently an anatomical parallel of these physiological results has been reported [73]. The manipulation just described (except 2–4 weeks of treatment rather than 5 days) resulted in a relative increase in the layer-4 visual cortical area covered by thalamo-cortical arbor corresponding to the closed eye. These anatomical results, besides being interesting in their own right, add a new level of confidence to the original conclusions drawn from the physiology.

2.2.4. Testing the necessity of the ‘covariance signal’: blockade of N-methyl-D-aspartate receptors during monocular deprivation

Another way to test for the necessity of postsynaptic function is to apply antagonists of receptors believed to be involved in transmission to postsynaptic cells. One such receptor is the N-methyl-D-aspartate (NMDA) receptor, which is found on cortical neurons that have soma or dendrites in the upper layers of cortex in adults, and seems to be involved in excitatory transmission to neurons of all visual cortical layers in young animals [36,56,40,158,126]. An experiment testing for the necessity of NMDA receptors in ocular dominance plasticity will be presented after briefly discussing the possible role of these receptors in the detection of covariance.

If the level of pre/postsynaptic covariance is the ‘true’ signal determining the direction and degree of changes in synaptic strength, then there must be a way of detecting that level of covariance. One prominent candidate for this role, which has received support from experiments in the hippocampus, is the NMDA receptor/channel complex (see [169,25] and [33] for reviews). Briefly, the NMDA receptor is a glutamate receptor with an associated voltage dependent ion channel that is permeable to calcium. The voltage dependence results from a blockade of the channel by Mg$^{2+}$ when the membrane potential is near the resting potential, and a progressive removal of the Mg$^{2+}$ blockade at more depolarized levels (reviewed in Ref. [7]). Activation of the NMDA receptor/channel complex has been found necessary for some types of long-term potentiation (LTP), a form of synaptic facilitation shown to obey Hebbian-like rules of modification. In order for the NMDA receptor/channel complex to be activated and conduct calcium, it requires both excitatory neurotransmitter (as occurs during presynaptic activity) and postsynaptic depolarization (as occurs near the action potential threshold). Thus, if one could ‘read’ the level of calcium flowing through the NMDA receptor associated channels at a given synapse, then the degree of coincidence of pre- and postsynaptic activity for that synapse might be determined.

NMDA mediated calcium currents on their own could only ‘inform’ the postsynaptic cell that a positive correlation had just occurred (e.g., large Ca$^{2+}$ surge) or perhaps that there had been a presynaptic signal with a moderate postsynaptic depolarization (small Ca$^{2+}$ surge), but no NMDA mediated Ca$^{2+}$ current would flow (at an inactive synapse) from a strong depolarization alone. From the point of view of the NMDA mediated Ca$^{2+}$ current at an inactive synapse, strong postsynaptic activity ‘looks’ the same as no postsynaptic activity.
covariance signals mediate VCx plasticity, and the NMDA receptor/channel complex is a detector of those signals, then blocking NMDA receptors should disrupt VCx plasticity.

Several experiments have tested for the necessity of NMDA receptor activation in experience dependent VCx plasticity (see [55] for a review). For example, Bear et al. [16] blocked the NMDA receptors of one visual hemisphere in a group of 3–5-week-old kittens with chronic infusion of the selective antagonist APV (using osmotic mini-pumps). During the infusion period (7 days) the contralateral cortex was infused with saline and the contralateral eye sutured closed. Following the treatment, neurons of both visual hemispheres were checked for ocular dominance. Results indicated that 50 μM APV significantly disrupted the shift in ocular dominance for the infused hemisphere, while the control hemisphere shifted normally. One group of kittens was recorded during the infusion along with the post-infusion recordings. It was found that at distances greater than 3 mm from the cannulae (this was the distance recorded in the results above) 86% of the neurons encountered were driven by visual stimuli — a figure not significantly different from the control hemispheres. On the basis of this evidence, the authors argued that it was unlikely that the lack of ocular dominance shift was the result of a general blockade of excitatory transmission, but was more likely to be an NMDA-specific effect.

In a related experiment, Rauschecker et al. [130] also infused APV (100–200 μM) into the VCx during monocular deprivation. They found that the antagonist caused a significant reduction in responses to visual stimulation, which is in agreement with most other studies (reviewed in [40] and [55]), but somewhat in contrast to the Bear et al. [16] findings (above). Furthermore, Rauschecker et al. [130] found that the degree to which ocular dominance changes were prevented appeared to be directly related to the reduction in postsynaptic responsiveness. In the regions closest to the drug cannulae, postsynaptic responses were most reduced and so was the ocular dominance shift. The regions far from the cannulae showed near normal responsiveness, and ocular dominance shifted normally. Finally, in the middle ranges, responsiveness was somewhat attenuated, and the ocular dominance shift was moderate.

In summary, the results of the two NMDA antagonist experiments described above appear to be somewhat conflicting. The Bear et al. [16] results suggest that the NMDA receptor blockers reduced the ocular dominance shift through a specific effect on plasticity itself (perhaps by interfering with the detection of covariance levels), without significantly reducing postsynaptic responses. In contrast, the Rauschecker et al. [130] results suggest that the effects of NMDA receptor antagonists on plasticity are dependent on, and proportional to, their ability to block postsynaptic responses. Determining which of these interpretations is valid will be critical for a complete understanding of the role of NMDA receptors in VCx plasticity. Nonetheless, by supporting the necessity of normal transmission to postsynaptic visual cortical cells in the induction of ocular dominance changes, both studies provide support for Hebbian induction mechanisms in this system.

2.2.5. Limitations of chronic population studies, and acute alternatives

In the preceding group of experiments chronic manipulations were implemented, after which responses from populations of neurons were recorded, to determine whether or not plasticity had been expressed. The manipulations tested the necessity of postsynaptic ‘activity’. Because all of these experiments blocked the shift to the open eye in the regions of decreased transmission or postsynaptic responsivity, the assertion that normal postsynaptic activity is necessary was supported. This supports the notion that covariance is necessary because blocking the postsynaptic activity also blocks covariance. However, it is obvious that the manipulations could block plasticity in ways independent of the effect on covariance. Support would be much stronger if the evidence just mentioned could be combined with a demonstration that covariance changes on their own are sufficient to produce ocular dominance plasticity.

It might be possible to carry out tests of sufficiency of covariance using a chronic manipulation, followed by a population analysis. However, a limitation of chronic experiments of this kind is the difficulty in knowing how the treatment influences individual postsynaptic cells. This makes a clear understanding of the process difficult. For example, Reiter and Stryker [134] (above) could not definitively determine whether the active synapses had become weakened or the inactive synapses had become strengthened, because the measurements were only taken after the changes had occurred.

An alternative strategy is the acute within-cell approach, in which a single postsynaptic cell is recorded before, during and after a treatment. For a test of sufficiency, the treatment could involve imposing an increase or decrease in the relative activities of a presynaptic input and a postsynaptic cell. Because the activity of the postsynaptic cell would be recorded continuously throughout the experiment, any treatment-induced change in its response properties could be assessed directly. In the VCx, these types of experiments have been conducted in vivo, using natural (visual) presynaptic activation [20,61,68,59,148] as well as in vitro [96,76,57,92,171]. We consider these next.

2.2.6. Demonstration of the sufficiency of covariance changes for inducing ocular dominance and orientation plasticity in single acute neurons, in vivo

One group of experiments testing the sufficiency of covariance changes in an acute preparation in vivo, was conducted by Fregnac and collaborators [20,61,59,148].
During the treatment periods of these experiments, covariance levels were manipulated by altering the magnitude of postsynaptic responses to constant presynaptic inputs. Specifically, Shulz and Fregnac [148] controlled the activity of single postsynaptic cortical cells with direct juxtacellular current stimulation through the recording electrode. Two different populations of presynaptic afferents were activated by separately presenting visual stimuli to the two different eyes. This natural afferent stimulation allowed direct examination of changes in receptive field properties, making possible comparisons with plasticity observed following pure manipulations of experience.

The experimental protocol was as follows. First, a baseline period was conducted in which stability of responses to alternating visual stimulation of each eye was determined. Second, a pairing treatment was delivered, in which visual stimulation of one of the eyes (the S+ eye) was repeatedly combined with directly overlapping excitatory (positive) current to the postsynaptic cell. This created a period of enhanced covariance between the postsynaptic cell and afferents from the S+ eye. In alternation, during the same period, visual stimulation of the second eye (the S− eye) was paired with inhibitory (negative) postsynaptic current. This created a decrease in the covariance between the S− afferents and the postsynaptic cell. At least 40 pairing trials were accomplished for each polarity stimulus. Finally, following the pairing treatment, relative responses for the two eyes were re-determined (without any juxtacellular current) to examine effects of the treatment.

The imposed change in covariance during the pairing treatment induced a subsequent expression of post-pairing plasticity, in the direction predicted by the Hebbian hypothesis (i.e., a relative increase for the CS+ compared with the CS−), for 7/24 (29%) neurons. Only one neuron shifted its preference in favor of the CS−. The modifications were not restricted to kittens: 4/7 neurons that were modified in the predicted direction were from adult cats. All of the modifications lasted at least 10 min, and in two cases the plasticity lasted for the duration of the experiment (100 min). However, in 5/7 modified cells, the responses returned to the control values within 100 min. Fig. 3 shows the results of an exemplar cell.

Fregnac et al. [59] accomplished analogous experiments using stimuli of two different orientations for the S+ and S−, delivered to a single eye. These orientation selectivity experiments produced a similar probability of success as the ocular dominance experiments, but involved larger numbers of cells: 27/87 (31%) cells had significantly modified orientations following pairing, with a time course similar to the ocular dominance experiments. All of the modified cells were changed in the predicted direction. Three adult cells were studied, one of which was modified. Finally a pseudo-pairing protocol, in which the postsynaptic current was specifically unpaired with the visual stimuli, was carried out for 32 cells. This produced only 1 significantly modified cell.

In summary, the in vivo experiments of Fregnac and colleagues demonstrate that changes in the covariance between presynaptic afferents and postsynaptic visual cortical neurons are sufficient to produce specific plasticity of ocular dominance and orientation selectivity that agree with the Covariance hypothesis. The probability of obtaining these effects was about 30%. The probability of observing the effects in adults was as great as in kittens, although the total number of modified adult cells was small (n = 5). The authors found no differences according to cortical depth. This finding, together with the similarity of results for ocular dominance and orientation selectivity (which are likely to be mediated by different groups of synapses) [60], led Fregnac and Shulz to propose that the

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6 In the juxtacellular configuration, a KCl pipette can activate neurons with low levels of positive current (<15 nA) and prevent spontaneous and evoked discharge with low levels of negative current (also <15 nA).
operation of Hebbian rules may be a general property of visual cortex and not confined to a specific anatomical subset of synapses or cells [60].

2.2.7. Limitations of in vivo extracellular recording for assessing plasticity of functional synaptic strength

A limitation of the in vivo experiments directly above is their ambiguity regarding which specific Hebbian ‘rules’ are supported by the results. The pairing treatments involved both increases in pre/postsynaptic covariance for the S+ afferents, and decreases for the S- afferents, all within the same cell. The increase to the S+ during the treatment produced ‘pre and post’ activity for the S+ afferents, as well as ‘post not pre’ activity for the S- afferents. In addition, the decrease in covariance to the S- produced ‘pre not post’ activity. Taken together, any combination of the three Hebbian rules could have been responsible for the observed plasticity. These limitations could be partially overcome by presenting either the S+ or the S- protocol alone, with an unpaired rather than an oppositely paired control input (see [57] below).

A second, related, limitation stems from the use of extracellular discharge as a measure of functional synaptic strength. According to Fregnac et al. [59], there is considerable spontaneous variability, across minutes or hours, in the absolute extracellular spike responses in Vcx, to sensory inputs. This variability is thought to be due to general changes in excitability rather than to specific alterations in synaptic strength. This is because changes in a visual cortical cell’s response to inputs mediated by one set of synapses (e.g., synapses carrying information from the contralateral eye) are usually accompanied by correlated changes in response to inputs mediated by other synapses (e.g., synapses carrying information from the ipsilateral eye). In order to control for these general changes, the authors employed a relative measure of functional synaptic strength. The measure that they used was calculated as: relative measure = (spikes to S+ stimulus)/(spikes to S+ stimulus + spikes to S- stimulus).

This relative measure can only detect changes in response to the S+ or S- stimuli if those changes are different from one-another in polarity or magnitude. Thus, the measure is largely unaffected by general changes in postsynaptic excitability. This relative measure does not allow one to determine which of the two sets of synapses (the S+ synapses vs. the S- synapses) are modified. For example, an increase in the relative measure could be due to an absolute increase in the S+, a decrease in the S-, or both. In summary, extracellular methods can be used to measure relative changes in synaptic strength, but may not be well suited to measuring absolute changes, due to potential changes in postsynaptic excitability. Intracellular recording, which permits independent assessment of postsynaptic excitability (by measuring membrane properties), is required to properly determine absolute changes in synaptic strength. The next experiment to be discussed accomplishes this.

2.2.8. Independent support for all three Hebbian rules from intracellular experiments in the visual cortical slice

Fregnac et al. [57] performed an in vitro intracellular analog of their previous in vivo, extracellular work, using kitten (n = 4 cells) and adult guinea pig (n = 25 cells) visual cortical slices. Of course in vitro preparations do not permit the measurement of RF properties, which may limit the applicability of the results to RF plasticity, the mechanisms of which are being sought. The authors tested the effects of positive and negative covariance treatments on separate groups of neurons. Afferent pulses (to either white matter or layer 2/3, 0.2–1 Hz) were paired with either depolarizing or hyperpolarizing intracellular current (±2–8 nA, 50–80 ms, starting 5–10 ms after presynaptic pulse) injected into a postsynaptic cortical cell recorded in layer 2–4 (65–200 trials). For each experiment, only one input was ever paired with postsynaptic current, and the other (when present) served as an unpaired control. However, more than one experiment was conducted on most cells (n = 22). Membrane potential and resistance were continuously monitored to control for changes in postsynaptic excitability. With the exception of there being only a single paired input, this in vitro protocol is conceptually similar to the in vivo work (above).

Results revealed that 36% (8/22) of the experiments on cells undergoing positive covariance treatment (afferents paired with postsynaptic depolarization) had significant post-pairing increases in response to the paired inputs (homosynaptic potentiation), and 41% (13/32) of the experiments on cells undergoing negative covariance treatment (afferents paired with hyperpolarization) had significant post-pairing decreases in response to paired inputs (homosynaptic depression). No cells changed significantly in the non-predicted direction.

There was no significant group change in postsynaptic membrane properties, indicating that the changes in evoked responses were true synaptic modifications, and not the result of non-specific changes in postsynaptic excitability. Furthermore, for 68% (17/25) of the experiments in which control inputs were presented, responses to these control inputs were unchanged. Control responses of the cells in the remaining experiments changed in a direction opposite to that predicted for their associated paired input; following positive covariance treatments, control responses became depressed (heterosynaptic depression, n = 6), and following negative covariance treatments control responses became potentiated (heterosynaptic potentiation, n = 2).

These results provide independent support for the suffi-
ciency of all three Hebbian rules. First, the ‘pre and post’ rule predicted the homosynaptic potentiation of paired synapses seen following the positive covariance treatment. Second, the ‘pre not post’ rule predicted the homosynaptic depression of the paired synapses observed following the negative covariance treatments. Third, the ‘post not pre’ rule predicted the heterosynaptic depression of the control synapses for the neurons undergoing the positive covariance treatment.

A potentially important observation of this experiment is that the synaptic plasticity observed was reversible. First, it decayed in a relatively short time without any overt manipulation (10–15 min). Second, a potentiated input could become depressed if a negative covariance protocol followed, whether the second treatment was delivered before or after the eventual spontaneous decay of the first. Potentiation of a formerly depressed input could also be achieved. Furthermore, synaptic weight could be significantly increased and decreased several times within a session. It is possible that such reversible balancing of synaptic weight may be an important property of neocortex, allowing for continuous adjustment, based on recent patterns of input. It is also possible that the absence of long lasting cortical effects may be the result of the protocol used. These two possibilities are not mutually exclusive. The issue of duration of plasticity in visual cortex will be discussed next.

2.2.9. A Hebbian protocol can induce long lasting potentiation in the visual cortical slice following the use of specific protocols

A potentially important paper relating to the duration of potentiation was presented by Malenka and colleagues [77]. They describe a protocol for inducing short-term potentiation (STP) in the hippocampal slice that is similar to the protocol used by Fregnan et al. [57] in the VCx slice. In this protocol a trial consisted of pairing a 400–800 ms depolarizing current pulse with a single afferent stimulus (0.1 Hz, 30 pulses total, current pulse started 5–10 ms before each afferent stimulus). Following pairing, a transient synaptic potentiation was induced which lasted less than 10 min.

In the same slices but with different inputs, Huang et al. [77] induced LTP with a slightly different protocol that could also be considered ‘Hebbian’. Here they continuously depolarized the postsynaptic cell for 2 min (to between −20 and 0 mV), during which time an afferent was stimulated once every 4 s. Strong potentiation resulted (200% of control value), which was non-decremental (greater than 30 min), and input specific.

These experiments remind us that within a single system, long and short-term plasticity can be differentially induced, depending on subtle differences in protocol. Moreover, the STP protocol in the hippocampus is similar to that used by Fregnan et al. [57] — a protocol that produced short lasting plasticity in VCx. By extension, these data suggest that a method similar to the LTP-inducing protocol of Huang et al. [77] might produce LTP in the VCx.

Kirkwood and Bear [92] provide data that are effectively a successful test of this suggestion. Like Huang et al., they continuously depolarized a postsynaptic cell (located in layers 2/3 of the VCx, in vitro) for 90 s, during which single stimuli were delivered to presynaptic afferents in layer 4, at 1 Hz. Following pairing, significant non-decrementing LTP was observed (an increase of 25% above control values). Depolarization alone or the afferent stimuli alone did not produce potentiation. These results make it tempting to conclude that the absence of long-lasting effects in the Fregnan et al. experiments was due to the protocol, and not to the limited potential of the system. However, there is one caveat — Kirkwood and Bear stimulated layer-4 afferents while Fregnan et al. stimulated the white matter. It may be that these two groups of afferents have a different capacity for covariance-induced potentiation. In fact, Kirkwood and Bear [92] state that they were unable to obtain LTP by pairing depolarization with white matter stimulation (see also [94]).

Synapses from intracortical afferents other than layer 4 can also become potentiated in the VCx in vitro. For example, Yoshimura and Tsumoto [171] were able to produce potentiation of the EPSC elicited in a layer-3 pyramidal cell from stimulation of another layer-3 pyramidal cell (less than 100 µm distant), by pairing a continuous intracellular voltage step of the postsynaptic neuron (to −20 mV), with 1 Hz activation of the presynaptic neuron. Therefore at least connections between a pair of layer-3 neurons can also be potentiated in VCx. The reasons for the differences between white matter and intracortical stimulation loci for obtaining LTP are unknown at present (but see [92] for an interesting hypothesis relating to differences in the capacity of the circuits that are activated at the differing loci to bypass inhibitory processes on their way to the recorded targets).

2.2.10. Summary of involvement of covariance in visual cortical plasticity

Three original discoveries of Hubel and Wiesel [78,167,168], on plasticity of ocular dominance, provided some of the first evidence for the involvement of a Hebbian mechanism in cortical plasticity. The findings impli-
cated temporal asynchrony of input from the two eyes in the reduction of binocular cortical responsiveness. Stent [151] proposed a Hebbian detection and induction mechanism to account for these effects.

The proposed Hebbian rules required postsynaptic function. Several experiments [134,16,130] were presented that provided support for the notion that postsynaptic cortical activity is necessary for ocular dominance plasticity. However blockades of postsynaptic activity could have effects that are not related to changes in pre/postsynaptic covariance. Therefore tests of sufficiency of pre/postsynaptic covariance manipulations were also examined. Fregnac and co-workers [20,61,59,148] tested sufficiency in vivo, and found general support for the covariance hypothesis in both adults and juveniles, although there were smaller numbers of adults tested. The in vivo results would have been predicted by all or any of the Hebbian rules proposed in the Introduction. To distinguish among the three possible rules, an in vitro analog by Fregnac et al. [57], was examined. That study demonstrated independent support for each of the three Hebbian rules, but almost no long-term plasticity. Subsequent experiments showed that the VC×s is capable of long lasting covariance-induced plasticity following certain protocols, although perhaps only for intra-cortical afferents [92,171] (but see also [76]).

In conclusion there is some evidence supporting the necessity (in development) and significant evidence supporting the sufficiency (during development and adulthood) of alterations in pre/postsynaptic covariance in the induction of visual cortical plasticity. The next section will undertake a similar analysis for somatosensory cortical RF plasticity, with emphasis on the adult.

2.3. Hebbian processes in somatosensory cortical plasticity

2.3.1. Receptive fields in adult somatosensory cortex are influenced by temporally correlated inputs

With regard to RF plasticity, the somatosensory cortex (SC×) has been one of the most extensively investigated systems (reviewed in [86]). While the phenomenology is rich, experimental investigations into the mechanisms of plasticity in this region are sparse. However, there has been considerable speculation about the nature of such mechanisms, and many of the phenomenological observations have been interpreted as supporting Hebbian processes (reviewed in [114]).

One such experiment that was particularly relevant to this issue was conducted by Merzenich and colleagues in adult monkey SC× (specifically, Clark et al. [31]). In normal monkeys the cortical representation of the glabrous skin for any two adjacent digits is ‘discontinuous’; that is: (1) there is a fairly sharp border between the two representations; and (2) very few neurons respond to more than one digit. Clark et al. [31] suggested that the discontinuity arises from a lack of temporally coincident input from separate digits onto common neurons. The implication is that if neurons in cortex were synchronously stimulated by inputs from two digits (consistently), then a greater number of neurons would have double digit receptive fields. The idea is analogous to that presented for ocular dominance (above). For example, the visual cortical cells in animals reared with artificial squint [78] received little temporally coincident input from the two eyes, and rarely responded to inputs from both eyes. However visual cortical cells in the normal animals received considerable coincident binocular input and nearly always responded to both eyes.

To test the role of temporal contiguity of inputs on the cortical representation, Clark et al. [31] surgically fused adjacent digits 3 and 4, in an attempt to increase the amount of synchronous stimulation of their skin. Following recovery for 4–5 months, the authors examined the RFs of the cortical neurons in and around the representations of digits 3 and 4. Critical data came from two monkeys in which the formerly fused digits were separated just before mapping; this made it fairly certain that any effects observed at the level of the CNS would not be the result of a passive propagation of peripheral effects. The authors reported a cortical representation of the pair of fused digits that was similar to the representation of a single digit. This included many cortical loci that were responsive to both of the formerly fused digits (at least 20 in one monkey and 14 in a second monkey). In contrast, only one site sampled from the borders with the two adjacent digits (2/3 and 4/5) had double digit RFs, providing a within-animal control. [31]

These experiments support the hypothesis that temporally synchronous input from two sets of afferents onto a postsynaptic neuron allows that neuron to develop and/or maintain robust functional responses to both sets of afferents. Likewise, asynchronous input prevents the postsynaptic cell from responding to one set of afferents. This is almost exactly the situation observed by Hubel and Wiesel [78] when comparing the results of animals reared with squint vs. those reared with normal vision, as described above. Aside from differences in sensory modality, the main differences are that the SC× work was done in the adult, and several facts that were known for ocular dominance plasticity are not yet known in the SC×. For example, although changes in response properties of somatosensory cortical neurons to peripheral inputs do occur as a result of the chronic digital fusion, it is not certain whether the actual mechanistic changes are localized in cortex itself or sub-cortically.

The same potential Hebbian explanation proposed by Stent for VC× [151] could be posited for the SC× findings. Moreover to validate that hypothesis, the same types of experiments testing necessity and sufficiency would need to be done. This has not yet been accomplished for the digit fusion experiments.
However two experiments in the rat barrel cortex, that are analogous to Clark et al. [31], provide some additional information about mechanism and therefore will be discussed next. In the first of these, Diamond and colleagues [46] recorded in somatosensory cortical barrel D2 of the anesthetized rat following chronic ‘whisker pairing’. This ‘pairing’ consisted of trimming all but two whiskers (D2 was always left intact, as well as either D1 or D3), and then allowing the animal to live normally for 1–3 days before recording. They found that responses of neurons in the D2 barrel were usually enhanced for the adjacent intact whisker compared to the adjacent trimmed whisker. The interpretation is similar to that presented for the digit fusion experiment; synchronous input from the two intact whiskers would occur frequently, while synchronous input from D2 and the clipped whisker would occur infrequently. It is proposed that these differences in synchrony are detected postsynaptically, producing the differences in functional connectivity through a Hebbian mechanism [46].

Diamond and colleagues provide two findings on time course which indicate that the origin of this plasticity is cortical rather than sub-cortical. First, plasticity is only seen in the portion of the neuronal discharges that occur more than 10 ms after the stimulus onset. The thalamically induced portion of the cortical response is thought to have a latency of less than 10 ms, so the authors argue that any changes exclusively appearing later than 10 ms are not passively relayed from thalamic sources [47]. Second, in the initial 24 h of the manipulation, only non-granular neurons express the plasticity [47]. If the observed plasticity were being passively relayed from sub-cortical sources, then granular neurons (the primary recipients of thalamic input) should develop plasticity no later than non-granular cortex.

In a related experiment in the acutely prepared awake rat, Delacour et al. [42] recorded responses of single barrel cortical neurons to stimulation of two whisker stimuli (S1 and S2) before, during, and after a different type of ‘whisker pairing’. Before the pairing, S1 (stimulation of a single non-dominant whisker) elicited a weak response or no response from the recorded neuron. On the other hand S2 (stimulation of a bundle of ten whiskers) elicited a strong response initially. Pairing consisted of stimulating S1 followed 500 ms later by S2. After 30–100 pairings, significant increases in the response to S1 compared with S2 emerged for 36% of the neurons. This experiment overcomes some of the limitations of the studies previously discussed for the SCx. First, it shows that sensory stimulation alone, rather than injury or surgery, can induce RF changes. Second, the stimulus control allows for calibration of the amount of afferent pairing required to obtain plasticity. It also provides some data on the inter-stimulus intervals that are sufficient for the induction of RF plasticity in this system (discussed in Section 3 below). Finally, because individual neurons were recorded throughout the experiment, this study shows that the RFs of individual neurons in SCx can be modified by experience, whereas this was less clear in the previous population studies.\footnote{The changes in distributions of RFs across populations might be explained by selective survival of cells with specific RFs rather than changes in the RFs of any individual cells.}

2.3.2. Mechanisms of somatosensory cortical receptive-field plasticity are poorly understood

The experiments presented thus far are supportive of the claim that temporally correlated inputs to somatosensory cortex become favored by postsynaptic cortical neurons. If one were to assume that the temporally coincident inputs cause strong postsynaptic responses during the inducing events, it could be concluded that these data are consistent with the Hebbian/covariance hypothesis. However it should be emphasized that this conclusion is based on the above assumption, and that postsynaptic responses were not directly measured during the treatments for two of three experiments discussed thus far (i.e., Clark et al. [31] and Diamond et al. [46]). Furthermore, even if enhanced pre/postsynaptic covariance (during the induction process) was ultimately shown to exist, this would not prove that the enhanced covariance itself was the critical factor responsible for the induction of the RF changes — direct demonstrations that the enhancement in covariance is both necessary and sufficient to induce the RF changes would be required. This is the same logic employed by Carew et al. [29] to try to determine whether or not the synaptic potentiation observed in the Aplysia was the result of a Hebbian process (discussed in subsection 2.1.2 above).

To our knowledge, no tests of necessity exist for types of adult SCx plasticity that are induced by increasing afferent synchrony (e.g., digit fusion and whisker pairing). However, Kano et al. [87] have tested the necessity of ‘postsynaptic’ cortical activity in a type of plasticity in adult cat that is induced by removal of a hind limb. In normal cats, hind limb amputation produces a physiological reorganization within 18 days so that the hind limb representation becomes responsive to stimulation of the trunk. Kano et al. found that chronic cortical infusion of APV prevented this reorganization so that neurons in the hind limb cortical region were completely unresponsive to somatosensory stimulation after 18 days. The effect of the APV was reversible; reorganization would occur within 3 weeks of drug removal. At the concentrations used by Kano et al., the APV significantly attenuated evoked cellular discharge in SCx. Thus, this experiment suggests that normal ‘postsynaptic’ SCx activity is necessary for the induction of plasticity that is normally induced by selective removal of specific sensory inputs.

Schlaggar et al. [144] and Jablonska et al. [82] have found results consistent with the Kano et al. [87] findings in studies of plasticity in rodent barrel cortex. In the Schlaggar et al. [144] experiment, chronic cortical APV
administration prevented anatomical reorganization that was normally produced by removal of a row of whiskers early in development (see [18] for a description of the normal plasticity). In the Jablonska et al. [82] study, chronic APV infusion prevented physiological reorganization that is normally produced in the adult, following removal of all but one row of whiskers.

All three of these discoveries relating to the necessity of postsynaptic cortical activity are interesting and important for understanding the mechanisms of deafferentation-induced plasticity. However, their relevance to understanding the role of Hebbian mechanisms in experience-dependent plasticity is unclear. For example, the role of sensory experience, as opposed to injury-related processes, as well as the nature of afferent activity patterns remain unknown. Moreover, the loci of the ‘plastic synapses’ are also uncertain for these types of plasticity. Therefore from a Hebbian perspective it is impossible to know whether or not the APV infusions blocked ‘postsynaptic’ activity selectively.

To our knowledge there has been only one experiment that directly tested sufficiency of covariance changes in the induction of SCx plasticity. In that study, Craig and Malenka [37] used a thalamocortical slice preparation that included monosynaptic projections from ventrobasal thalamus (VB) to primary somatosensory (‘barrel’) cortex of rats. The authors paired continuous intracellular depolarization of a postsynaptic cell located in cortical layer 4 (depolarized to between −10 and 0 mV) with repeated low frequency stimulation of presynaptic afferents located in VB (100 stimuli at 1 Hz). In young animals (postnatal day 3–7), this treatment resulted in robust potentiation of the thalamocortical synapses that were activated during pairing. This could be considered support for the ‘pre and post’ rule \(^{11}\). However, in slices from more mature animals (at least postnatal day 8), no potentiation resulted. Thus, at least in the in vitro slice preparation, it appears that positive covariance is not sufficient to induce potentiation of thalamocortical transmission to layer 4 of primary SCx of animals more than 1 week of age. Craig and Malenka provide evidence that the reduction in plasticity in older animals is due to a reduction in NMDA-receptor mediated synaptic currents [37]. It will be interesting to determine whether the same decrease in plasticity will be found in other layers that receive intracortical inputs and maintain reasonably high levels of NMDA receptors in mature animals [36,56,40,158,126].

Several other tangentially related studies of mechanism have been carried out in adult SCx. For example, Lee et al. [101] and Lee and Ebner [100] demonstrated intracortical and thalamo-cortical LTP respectively, using novel and potentially physiologically relevant induction protocols. In both cases disinhibition was used to produce cortical potentiation \(^{12}\). In a separate line of inquiry, Recanzone et al. [132] and Dinse et al. [48] stimulated the middle layers of SCx at a low frequency, and were able to induce ‘expansions’ of SCx maps that resembled plasticity seen following injury. This could be important because it shows that local manipulations within the SCx are capable of producing RF plasticity in the cortex \(^{13}\).

2.4. Hebbian processes in auditory cortical plasticity

2.4.1. Receptive-field plasticity in adult auditory cortex results from behavioral classical conditioning; a Hebbian model has been proposed for induction

Like the VCx and SCx, the auditory cortex (ACx) also develops RF plasticity following chronic partial deafferentation. Neurons in deafferented zones of the cortical frequency map become responsive to frequencies corresponding to intact cochlear regions after chronic deafferentation during development and in the adult [138,70,127,145]. Perhaps more interesting for the present review is the extensive body of work on learning-induced changes in ACx receptive fields. The first studies that examined the effects of learning on RFs reported that classical conditioning produces highly specific changes in the receptive fields for frequency (‘frequency tuning curve’) in the auditory cortex of adult cats [44] and guinea pigs [10]. RFs were determined before and after a brief training session in which subjects were presented with a tone followed by a foot shock (10–45 tone/shock pair-

\(^{11}\) Again, as noted for the VCx experiments, in vitro methods do not allow for measurement of RF properties. Therefore one should be cautious in concluding that covariance processes that are sufficient to induce synaptic plasticity in the SCx slice, are also sufficient to induce RF plasticity in the in vivo SCx.

\(^{12}\) In the cortical slice, Lee et al. used low frequency stimulation (0.5–8 Hz) of the white matter combined with low levels of magnesium (designed to enhance the NMDA response) to produce potentiation of intracortical connections. The potentiation continued after the return of normal magnesium levels. The authors speculate that functionally (although not mechanistically) similar disinhibition in the intact animal could occur by reduction in cortical GABAergic transmission. In fact it is clear that reduced GABA function does occur following some types of deafferentation (reviewed in Jones[84]). Using a different tactic, Lee and Ebner disinhibited a small area of somatosensory thalamus (VPM) in intact animals by iontophoretic application of bicuculline. Stimulation of a whisker at the theta rhythm during the disinhibition produced dramatic increases in thalamic and cortical single unit responses to the stimulated whisker. (In the thalamus they recorded near to the iontophoresis electrode, and only included neurons that responded to the ‘stimulated’ whisker prior to the disinhibition.) The thalamic increase subsided when the bicuculline wore off, but the cortical increase to the stimulated whisker lasted until the recorded neuron was lost. The authors propose that a similar effect might be produced in natural situations by inhibition of the reticular nucleus of the thalamus (the main source of inhibition to VPM) through ascending cholinergic inputs.

\(^{13}\) Moreover, the Dinse paper demonstrates that there is an increase in cross-correlation between clusters of neurons exclusively in the reorganized cortical zones, which argues that the expression (as well as the manipulation) for this type of plasticity can be localized cortically.
ings). The frequency of the tone (conditioned stimulus, CS) was selected to not be the best frequency (peak of the tuning curve, BF) to determine if learning could shift tuning. Behaviorally, subjects acquired typical signs of conditioned fear to the CS. After training, neuronal responses to the frequency of the CS were generally increased, whereas responses to the BF and other non-CS frequencies were often reduced. The opposing changes between the CS frequency and the BF were sometimes so large that the frequency of the CS became the new BF (See also [49]). This learning-induced RF plasticity is associative, that is, it requires stimulus pairing because control subjects that received unpaired tone and shock developed general increases in response to all frequencies; there was no CS specificity [44,10,9]. Subsequent studies have shown that this CS-specific RF plasticity develops rapidly (within five trials) [52], shows a high degree of CS specificity during two-tone discrimination [53], and is retained indefinitely (tested to 8 weeks) [165]. Moreover, it is robust across brain states; it can be induced in waking, behaving animals and expressed subsequently while they are under general anesthesia [165]. Thus it is not a reflection of arousal to the CS stimulus during post-training RF determination (see also Diamond and Weinberger [45]). The types of learning-induced receptive field changes described above might be expected to yield an increased representation of the paired tone across the frequency map of the auditory cortex. Such effects have been reported in both rodents [66] and primates [133] (but see [143]).

Weinberger et al. [164] have proposed a model of how ACx RF plasticity develops during learning, that involves a Hebbian mediated increase in the strength of synapses coding for the CS tone and a decrease for other tones (Fig. 4). In the model, presynaptic CS input arrives at the ACx through a projection from the ventral division of the medial geniculate nucleus (MGv) — the main acoustic

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**Fig. 4.** Weinberger et al. [164] model of ACx RF plasticity. The hypothesis models a relative increase in response of an ACx neuron to a CS tone during classical conditioning. The final synaptic changes responsible for the changes in cortical response occur at the synapses connecting the MGv to the ACx. The changes are induced by an increase in covariance between the cortical cell and the MGv input activated by the CS tone. The increase in covariance results from convergent excitatory drive on the ACx neuron from the MGm and the Bas F during conditioning. Synaptic weights are indicated by the diameter of the circles at the projection terminals. Operation of the model can be divided into three separate steps. Step A: before conditioning the ACx neuron is tuned so that it responds best to tone 2 and less well to tones 1 and 3, as indicated by the synaptic weights on the cortical neuron’s apical dendrite. Step B: tone 3 is chosen as the CS for classical conditioning, and is paired with an US. The convergence of the CS and US at the MGm produces an increase in synaptic weight for the CS synapses at the MGm, via a Hebbian mechanism (note the larger circle on the MGm for tone 3 in step B vs. step A). Step C: the increased response to tone 3 by the MGm is projected up to the ACx, producing enhanced cortical excitability. In addition, the US activates the Bas F, increasing ACh release onto the cortical neuron, producing more excitability. Together these two sources of converging excitation cause enhanced covariance between presynaptic MGv inputs coding for the CS tone, and the postsynaptic cortical neuron. This results in an increased synaptic strength for the CS synapses on the cortical neuron from the MGv via a ‘pre and post’ rule (note the larger circle on the cortical cell for tone 3 in step C vs. steps A and B). In addition, the synapses for tones 1 and 2 are silent during this strong postsynaptic cortical activity, producing synaptic weakening via the ‘post not pre’ rule.
relay in the thalamus. The response of the postsynaptic corticall neuron to CS input is facilitated during the learning experience though two other converging inputs, both of which receive excitatory input from the US. These are direct excitatory input from the medial division of the medial geniculate (MGm) and neuromodulatory input from the basal forebrain (Bas F), which releases acetylcholine (ACh) onto cortical neurons. The facilitation of postsynaptic response produces an increase in pre/post synaptic covariance for those inputs from the MGv that are activated by the CS tone. This, in turn, results in an increase in strength of those CS activated synapses via a "pre and post" rule. In addition, inactive synapses from the MGv that code for the non-CS tones are predicted to decrease in strength by the "post not pre" rule.

Of the ideas presented so far in this paper that relate experience to changes in covariance, the Weinberger et al. model is distinctive in that it involves an enhancement in postsynaptic cortical response by convergence of indirect polysynaptic input (the US input), and that one of the mechanisms of that enhancement is through a neuromodulator (ACh).

2.4.2. A novel test of sufficiency in auditory cortex using acoustic stimuli to control postsynaptic activity and cross-correlation for a measure of synaptic strength

At the heart of the Weinberger et al. model are two Hebbian induction rules. First, the active CS synapses coming from the MGv become strengthened by the "pre and post" rule. Second, the inactive synapses coming from the same nucleus weaken by the "post not pre" rule. As discussed above, necessity and sufficiency of these covariance rules need to be demonstrated in order to clearly show their involvement in the experience-dependent plasticity. No tests of necessity have yet been done. On the other hand, there have been at least two tests of sufficiency.

In the first of these, conducted in awake behaving monkeys, Ahissar et al. [2] estimated the functional synaptic strength between two neurons in ACx (by measuring the cross correlation of their activity) before, during, and after a pairing paradigm designed to either increase or decrease covariance. During pairing, a spike in one neuron (nominally, the presynaptic neuron) was followed by a sound that either excited or inhibited the other neuron (the postsynaptic neuron). The authors found that in cases where the sound excited the postsynaptic neuron, so that the covariance between the two neurons would be held at an increased level during pairing, the cross correlation remained elevated for a time after termination of pairing. In cases where the sound inhibited the postsynaptic neuron, the cross correlation remained weaker for a time (1–13 min). This effect is represented in Fig. 5. Clearly there is a strong positive correlation between the imposed change in covariance during pairing vs. the subsequent change immediately after termination of pairing. The increased cross-correlation levels observed after the imposed increases are consistent with the "pre and post" rule. Likewise, the decreased cross-correlation levels seen following the imposed decreases are consistent with the "pre not post" rule. The findings of this novel and ingenious study are generally supportive of the Hebbian hypothesis. However, there are some potential limitations that will be noted next. The critique that follows is clearly not meant to undercut the importance of the Ahissar et al. findings. In fact, as shown below, one of the principal limitations that we will discuss was ultimately controlled for by Ahissar and coworkers. Instead, the critique is meant to: (a) illustrate some of the difficulties in obtaining clear data about

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14 They included only neurons in the analysis that were positively coupled prior to any manipulation.

15 A second important finding relating to behavioral gating of plasticity will be discussed in Section 3 below.
the covariance hypothesis; and (b) provide concrete ideas about how to address these difficulties (a more general discussion of unresolved issues and difficulties is presented in Section 3).

The first potential limitation on the Ahissar et al. findings stems from the possibility that changes in responses of cortical neurons to synaptic inputs could occur as a result of changes in postsynaptic excitability alone. If this were the case, then observing a change in cross correlation between a pre and a postsynaptic cortical neuron would not necessarily indicate that a specific change in the strength of the synapses linking these neurons had occurred. In support of this possibility. Fregnac et al. [59] have indicated that absolute levels of responsiveness of cortical neurons to synaptic inputs change spontaneously across time. Furthermore, results from ACx in our laboratory show that the spontaneous changes in cellular responses that occur at one time point, compared with a previous baseline, are a good predictor of subsequent changes that will be seen at later time points (on a time scale of approximately 10–15 min, Fig. 6A). The data in Fig. 6A share some qualitative similarities with the Ahissar et al. results, except the X-axis represents ‘spontaneous change’ in response at a middle time period rather than ‘imposed change’ during a treatment at a middle time period. It is likely that the spontaneous changes observed in our laboratory were due to changes in postsynaptic excitability, rather than synaptic strength for the test input, because the responses to other test inputs (different tone frequencies) within the same postsynaptic cells had correlated changes (Fig. 6B). Together, these data seem to indicate that the relationship observed in the Ahissar et al. experiment, between: (a) the imposed change in pre-postsynaptic cross correlation during the treatment; and (b) the subsequent change in pre-postsynaptic cross correlation after the treatment, could be partly due to spontaneous drifting of postsynaptic excitability. This would weaken the support that the experiment provided for the Hebbian/covariance hypothesis in auditory cortical plasticity.

There are at least two controls that could help determine whether the observed changes were due to alterations in postsynaptic excitability or to covariance-induced synaptic affects. First, the cross correlation between the postsynaptic cell and an unpaired control presynaptic cell could be measured in addition to the paired presynaptic cell; a ‘Hebbian’ interpretation would be considerably buttressed by showing that changes in cross correlation are specific to paired cells. Second, it could be determined whether or not the spontaneous change in cross correlation at a middle time point (around the time that the treatment would have occurred in the original experiment) predicts the change that occurs at a later time point (around the

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16 This spontaneous variability provided the basis for their use of a relative measure of synaptic strength (above).
17 However, one might argue that the likelihood of this possibility is reduced by the quantitative differences between the spontaneous changes observed in our laboratory and the (stronger) changes following the treatment observed by Ahissar et al. [2]. See also the control results below.
The second limitation comes from the use of orthodromic stimuli (sound) to control the activity of the postsynaptic cell. Recall that whenever the presynaptic neuron fired, a sound was presented to either increase or decrease the activity of the postsynaptic cell. To clearly interpret the results in terms of the Hebbian hypothesis requires that the sound must affect the postsynaptic cell independently of the pathway by which the presynaptic cell influences the postsynaptic cell. However, there are potential routes of action that the sound input could take that involve the pathway from the pre- to postsynaptic cell. These would allow for non-Hebbian explanations of the findings. One such explanation is presynaptic modulation — similar to that found during sensitization and classical conditioning in Aplysia. A simplified diagram of this schema, as well as two others (including one ‘Hebbian’ schema) are provided in Fig. 7. The alternatives are not meant to be exhaustive or even the most likely, but only to illustrate that simple non-Hebbian explanations could account for some of the results. One way to be more certain that the method of controlling postsynaptic activity does not influence the pathway from the pre to the postsynaptic cell, would be to control the activity of the postsynaptic cell directly rather than orthodromically. Although this is difficult to accomplish using extracellular methods in vivo, one possible solution is to stimulate in a juxtacellular fashion as in Fregnac et al. [59] above.

In summary, Ahissar et al. [2] tested the sufficiency of covariance induction mechanisms in ACx plasticity by measuring changes in cross correlation between two cortical neurons after a pairing protocol that also changed the covariance between their activities. They obtained results that were consistent with the Hebbian hypothesis. However, some potential limitations were noted. Possible solutions were also discussed. The next section describes an experiment conducted in our laboratory that attempts to address these issues further, and could be considered complementary to the Ahissar et al. experiment. In addition, the experiment examined the sufficiency of covariance processes in the induction of RF plasticity per se, by examining RF properties directly.\footnote{Technically, in order to determine whether or not covariance processes are sufficient to induce RF plasticity, RF properties must be measured. (An ‘auditory RF’ in this case is the receptive field for acoustic frequency, sometimes called the ‘frequency tuning curve’.) In the ACx experiment of Ahissar et al., RF determinations were not made because the authors did not intend to study RF plasticity specifically. Similar qualifications were previously noted when discussing the in vitro experiments conducted in the VCx and SCx.}

2.4.3. Test of sufficiency in auditory cortex using direct juxtacellular postsynaptic control, and measuring receptive-field properties

Our experiments in the ACx [38] were similar to the in vivo experiments of Fregnac and colleagues in the visual
system (above). Like Fregnac, we controlled the activity of single postsynaptic cortical neurons with direct juxtacellular current to avoid the interpretational limitations inherent with orthodromic postsynaptic control (i.e., sound stimuli as discussed above). Two acoustic stimuli of differing frequency were presented as a method of activating two different populations of presynaptic afferents. They were on opposite sides (lower and higher) of the best frequency, and always elicited excitatory responses. During a treatment period, one of these stimuli (called the CS+) was repeatedly paired with excitatory postsynaptic current to enhance the covariance between the activated afferents and the postsynaptic cell. The second presynaptic/acoustic stimulus (the CS−) was repeatedly paired with inhibitory postsynaptic current to decrease pre/postsynaptic covariance (60 trials of each stimulus, interleaved, current level ≤±15 nA). This ‘discrimination’ design was employed so that synaptic specificity of any pairing-induced changes

Fig. 8. Example cell in ACx for which an imposed change in pre/postsynaptic covariance is sufficient to induce RF plasticity in the direction predicted by the Hebbian hypothesis. Results were from Cruikshank and Weinerberger [38]. Peri-stimulus time histograms (PSTs) and associated raster plots are presented for the CS + (top row) and the CS− (middle row). Relative responses to the CS + vs. CS− are shown in the bottom row (the relative response index is defined on the Y-axis, and will hereafter be called the ‘relative index’). Measurement periods are labeled along the bottom. The PSTs are divided into 10 ms bins on the X-axis and normalized to spikes/s on the Y-axis. Each dot in the raster plot represents a spike. Successive trials for a given period are stacked in rows upon one-another. The raster for the treatment periods have more rows because they represent the responses to 60 trials rather than 20 trials. For this neuron, the CS− response was consistently weaker than the CS− for the three baseline periods, resulting in a low mean relative index value (baseline = 0.17 ± 0.03 S.E.). There were no differences between the three blocks of index scores in the baseline (P > 0.9). During the first 60 pairing treatment trials, a significant increase in the CS + response, and a significant decrease in the CS− response produced a significant increase in the relative index (P < 0.0001, index value = 0.76 ± 0.04, Y-axis is discontinuous in graph to enhance the resolution of the upcoming post vs. baseline comparison). During pairing trials 61−120, even greater changes were imposed for both stimuli (P < 0.0001, index value = 0.95 ± 0.01, again Y-axis discontinuous). Immediately post-treatment, the CS− response was about equal to the baseline, but the CS + response had significantly increased (P < 0.001). This resulted in a significant increase in the relative index (P < 0.0001). By 15 min, the CS + response had begun to decline, but was still significantly larger than baseline (P < 0.03), as was the relative index (P < 0.02). The significant post-pairing increases in the relative index indicate that, for this cell, the covariance pairing treatment was sufficient to induce RF plasticity in accordance with the Hebbian hypothesis. See associated text for group results.
could be differentiated from potential changes in general levels of postsynaptic excitability (discussed above). In addition it allowed explicit examination of RF properties, which could permit quantitative comparison with learning-induced RF plasticity in the future.

The protocol consisted of the following. First there was an initial characterization, in which the acoustic and current stimuli to be used in the subsequent periods were chosen. Second, a 15-min period of baseline recordings was obtained to insure stability of the relative responses to the two acoustic stimuli. Third, the covariance pairing treatment (described above) was administered. Following pairing, the effects on functional synaptic strength were examined, by presenting the CS+ and CS− without current, as had been done during the baseline period. The results were compared with the predictions of the Hebbian hypothesis — the hypothesis predicts that the response of the CS+ should increase relative to the CS−, assuming there was sufficient control during the treatment.

The relative response between the two acoustic/presynaptic stimuli was measured for each trial in each period — similar to the measurement used by Fregnan and collaborators (above). During the pairing treatments (in the presence of the postsynaptic current stimuli) the responses to all 22 neurons that underwent 120 pairing trials were significantly controlled, so that each had a significant increase in response to the CS+ relative to the CS− (P < 0.05, treatment vs. baseline, t-test). Following the treatment trials, 7/22 (32%) cells had significant increases in the response to the CS+ relative to the CS− (post vs. baseline), while none had significant decreases. Significant effects were maintained in 6/7 neurons at 15 min, and in 2/4 neurons at 30 min (three of the significant cells became mechanically unstable before the 30-min measure). While this shows promise for long-term effects, strong conclusions will require larger samples. An individual example of a significant relative CS+ increase following 120 pairings is shown in Fig. 8. There was also a significant group increase in the CS+ relative to the CS− that was maintained at least 15 min (P < 0.03).

In summary, it was found that there was a population of neurons in ACx (about 32% of the sample) for which 120 covariance trials were sufficient to induce statistically significant post-pairing RF plasticity in the direction predicted by the Hebbian hypothesis, while no cells changed significantly in the direction opposite that predicted by the hypothesis. Effects were maintained at least 15 min.¹⁹

2.5. Hebbian processes in motor cortical plasticity

2.5.1. Plasticity in adult motor cortex results from experience, and is implicated in motor learning

Adult primary motor cortex (MCx), like the primary sensory cortices, exhibits plasticity following peripheral manipulations. These include non-invasive manipulations such as postural adjustments [141], as well as more drastic perturbations such as peripheral or central nervous system lesions and amputations (see [86] for a review). In the sensory cortices there were fairly obvious ways in which the patterns of external stimuli that produced RF plasticity could also produce pre/postsynaptic covariance changes. In fact this obvious correspondence was one of the reasons that Stent proposed a Hebbian mechanism for ocular dominance plasticity in the first place (above). However, the MCx is not a sensory area, and as such the routes by which sensory stimuli arrive there are more indirect. Consequently, explanations of how external stimuli produce covariance changes are complex and can be somewhat unsatisfying. Therefore we will examine this topic only briefly, by presenting the data and ideas behind one particular hypothesis that provides some indication of how learning could produce covariance-induced modifications of MCx. On the other hand, the more robust data on cellular mechanisms of MCx plasticity will be presented in detail, especially focusing on experiments that test sufficiency of positive covariance for potentiation.

One prominent set of ideas relating MCx plasticity to environmental events comes from Asanuma and coworkers. A goal of their work is to understand the role of MCx plasticity in the acquisition and retention of motor skills (e.g., [90]). Recently, they proposed that learning may involve potentiation of the projection from the ventrolateral nucleus of the thalamus (VL) to MCx, through a cooperative interaction with SCx. For our purposes, their hypothesis will be divided into two steps. First, early in motor learning, high levels of activity in the SCx (and potentially other unspecified factors) allow potentiation of its projection to MCx. Second, later in learning, the strong potentiated input from the SCx arrives at the MCx simultaneously with the VL inputs. This could produce an increase in covariance between presynaptic neurons in VL and postsynaptic neurons in MCx [81]. Consequently, from a ‘pre and post’ rule, potentiation of the VL input is produced. Thus, rather than enhancing covariance to one peripheral stimulus through simultaneous input from another (such as temporal contiguity of two eyes, two digits, two whiskers), Asanuma and colleagues propose the convergence of two different central afferent pathways, which could potentially carry parallel information about a single external stimulus. This is similar to the parallel CS tone information carried by the MGv and MGm inputs to ACx in the Weinberger et al. [164] model discussed above (Fig. 4).

¹⁹Besides studying the main effects just described, we also asked whether there were ‘factors’ that influenced the degree to which the covariance treatment was effective at inducing plasticity. Two factors found to be significantly related to plasticity were EEG state of the cortex during the pairing treatment, and the temporal relationship between the presynaptic input and the postsynaptic facilitation during the treatment. They will be discussed in relevant parts of Section 3 below.
The Asanuma model is based on effects of SCx lesions on motor learning, as well as LTP experiments in MCx. Evidence that the SCx is involved in motor learning comes from the finding that lesions of SCx before training produce difficulty in acquiring new motor skills (discussed in [81]). Furthermore, the projection from SCx to MCx is ‘plastic’, and capable of tetanically induced homosynaptic LTP [89]. This LTP is dependent on postsynaptic depolarization [90]. These findings suggested that the nature of the SCx involvement in learning could relate to the plasticity in its projection to motor cortex. However, removal of SCx after learning does not abolish previously learned skills, indicating that the plasticity in the SCx to MCx connection is probably not a permanent substrate for the storage of learned information. Therefore it might serve some other purpose. One hypothesis is that plasticity in the SCx projection could facilitate plasticity in other pathways that converge on MCx, as a way of consolidating motor learning. A possible beneficiary of such convergent cooperation is the projection from the VL to MCx. In support of this idea, it was found that paired VL and SCx tetani produced potentiation of the VL to MCx pathway, while tetanic stimuli to VL alone resulted in no plasticity [80,81].

2.5.2. Strong postsynaptic responses paired with presynaptic input is sufficient to induce potentiation in motor cortex

Showing that the MCx is capable of experience-dependent plasticity is important, and the data-driven hypothesis of Asanuma and colleagues provides a theoretical framework for thinking about how behavioral treatments could produce covariance plasticity in MCx. However, the most important asset of the MCx for the present review is the rich database examining sufficiency of positive covariance treatments for synaptic potentiation. In one of the earliest experiments of this type, O’Brien et al. [124] repeatedly (225 times) paired antidromic stimulation of single extra-cellularly recorded pyramidal tract neurons (the postsynaptic cell) with a mild hind paw shock designed to activate mixed afferents to the MCx (paired inputs). Unpaired stimulation of the contralateral hind paw was used as a non-associative control. O’Brien et al. found significant changes in 24/32 neurons in favor of the paired input, in the absence of changes in thalamic evoked potentials. Group data revealed that the responses to the two inputs decreased to almost equal levels following 75 unpaired presentations, although the authors did not determine whether time alone could produce this decay.

The antidromic pyramidal tract stimulus was relatively large [21] and could have had effects that were unrelated to postsynaptic activation, especially considering that the animals were awake. While the authors devised an interesting control (see methods, [124]), a more direct approach to insure postsynaptic specificity would be to stimulate the postsynaptic cell directly, either with low level juxtaglial current (above) or intracellular depolarizing current. The latter method has been employed extensively in MCx, by Baranyi and associates, over the last 15 years (e.g., [11–13]). In one of the most widely referenced examples of this strategy, Baranyi and Szente [12] recorded intracellularly from cells in the MCx of anaesthetized cats. They measured sub-threshold excitatory postsynaptic potentials (EPSPs) elicited by stimulating one of the recorded neuron’s afferent inputs (either thalamic, callosal, SCx, or a peripheral nerve) before, during, and after a pairing protocol. Pairing consisted of stimulation of the afferent, followed 0–200 ms later by strong postsynaptic depolarization (enough to elicit action potentials), repeated 150 times, at 0.1–0.2 Hz.

The authors found that 149/533 (28%) cells were significantly facilitated. In 106 neurons the facilitation lasted 40 min or more. From this result, it appears that positive covariance is sufficient for long lasting synaptic facilitation. In a second set of experiments within the same paper, they began to investigate the intracellular postsynaptic signals involved in this covariance plasticity. As a first step they examined the role of calcium by injecting EGTA (a calcium chelator) into 53 postsynaptic neurons 5 min before pairing. The EGTA blocked potentiation (despite higher excitability to current injection during pairing), showing the necessity of postsynaptic calcium in this form of plasticity (for an earlier example of this strategy, applied to hippocampus, see [107]).

One limitation of the experiment just described is that it fails to demonstrate that the effect is a synaptic change for the paired afferents. Only the paired test stimulus was presented; therefore it is possible that the observed changes might have been the result of non-specific postsynaptic effects (similar logic was presented in the discussion of the Ahissar et al. [2] results, above). This problem is partly addressed in a later experiment [13], using a similar paradigm but testing an unpaired control pathway as well as the paired pathway, within individual neurons. In this later experiment, the probability of significant potentiation to the paired pathway was approximately 57%, while no cells had significant increases on the control pathways. Thus, it is likely that the increases in EPSP amplitude in the previous (and present) experiments were due to specific potentiation of the paired synapses.

In addition to providing assurance of specificity, Baranyi

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21 They stimulated at > 15 V using a macro-electrode (probably 100,000 Ω maximum resistance), producing currents > 150 μA.
et al. [13] also addressed several other issues. First, they showed that awake cats had approximately double the probability of significant LTP compared with anesthetized animals for the same protocol: 58% (47/81) for awake vs. 28% (above) for anesthetized. Second, they found a clear relationship between the probability of LTP and the inter-stimulus interval (ISI) of the pre and postsynaptic stimuli: as the ISI was increased beyond 50 ms, there was a progressive decrease in the chance of observing LTP (discussed in Section 3 below). Third, they showed that sodium spikes were not required. In past experiments, Baranyi and associates had injected strong depolarizing current during pairing that always elicited action potentials. In this study, they blocked firing by injecting the local anesthetic QX-314 into the recorded cell before pairing. During pairing, enough current was injected to get greater than 30 mV depolarization. This resulted in potentiation to 171% of control amplitude. Finally, the probability of inducing LTP using a tetanus protocol (80–200 Hz, 5–15 s) was compared to the previously characterized probability using the covariance protocol. It was found that tetanization of pyramidal tract afferent collaterals resulted in potentiation, that was not different from the covariance protocol. However no LTP was produced by tetanizing VL using the same protocol.

Bindman et al. [22] have carried out experiments similar to Baranyi et al. [13] in vitro, using rat sensori-motor cortex slices. Intracortical cortical EPSPs from layer-5 neurons, elicited by stimulation of two pathways (one in the white matter medial to the recording electrode, and one lateral), were measured before, during, and after a covariance protocol. Like Baranyi et al, the treatment protocol included intracortical postsynaptic depolarization (here adjusted to produce 6–13 spikes) paired with stimulation of one of the test pathways. The pairing was repeated 25–50 times, and then the effects were assessed. Potentiation of the EPSP for the paired test input occurred in 4/28 (14%) neurons. The unpaired inputs showed no significant changes.

The lower probability for potentiation in these in vitro experiments (14%) compared with both the anesthetized (28%) and awake (58%) in vivo experiments is striking, and leads to the question of the nature of the differences. For example, are the intact vs. slice preparations fundamentally different with respect to this type of plasticity, or can some methodological differences explain the observed distinctions. In all cases layer 5 of MCx was recorded.

Although Bindman et al. [22] presented fewer initial pairing trials (25–50 vs. 150), Baranyi et al. [13] reported that potentiation was usually observed within about 40 trials. Moreover, when Bindman et al. [22] failed to get potentiation, they repeated the pairing protocol. After close inspection, one is led to believe that similar stimuli were being delivered to similar neurons using similar protocols. If this is true, then the differences in plasticity have to be explained by differences in the preparations themselves. One potentially important factor is the reduced extrinsic modulatory influences on cortical neurons in the slice. For example ascending basal forebrain cholinergic as well as brainstem noradrenergic inputs are literally cut off from neocortical neurons in vitro.

In accordance with this idea, Nowicky et al. [123] tested whether or not bath application of norepinephrine (NE) could restore the full potential for plastic changes to the MCx slice (i.e., to levels observed in intact animals). Unfortunately, no increase in the probability of potentiation was found, leading to the conclusion that the differences observed were not due simply to a lack of NE in the slice. It remains to be tested whether other neuromodulators, interactions between neuromodulators, or other factors, are responsible for the observed differences in plasticity (see discussion of gating factors in Section 3 below).

2.5.3. Summary of the evidence for Hebbian induction of motor cortex plasticity

The unresolved differences between preparations should not overshadow the important discoveries made in the MCx concerning covariance plasticity. Foremost is the consistent demonstration in all preparations that low frequency presynaptic stimulation, paired with simultaneous strong postsynaptic activation, is sufficient to induce significant synaptic potentiation for some population of MCx cells. The same types of stimuli that induce the potentiation when presented simultaneously do not induce changes when unpaired, indicating the importance of temporal covariance. Moreover it has been shown that in MCx, like the hippocampus, potentiation requires postsynaptic calcium and strong depolarization, but not action potentials [107,91]. Thus the MCx provides some of the best cellular data available on sufficient conditions for Hebbian potentiation in neocortex.

In contrast, no explicit tests of the role of negative covariance in synaptic depression have been reported. However all of the experiments that had simultaneous recording of a positively paired and unpaired control input provide indirect evidence for the failure of the ‘post not pre’ rule (also see discussion in Section 3). For example, O’Brien [124], Baranyi [13] and Bindman [22] all reported no change in their control pathways following strong postsynaptic depolarization (i.e., after pairing of the `experimental’ inputs with excitatory postsynaptic current).

In addition, no clear tests of the necessity of positive covariance in experience-dependent MCx RF plasticity are
available yet. The fact that these tests have not been done could be largely due to the indirect relationship between environmental manipulations and MCx activity. As discussed earlier, it is not obvious that the types of behavioral or surgical manipulations that produce RF plasticity in MCx, also produce changes in covariance between postsynaptic MCx neurons and their presynaptic afferents (during the manipulations). Therefore there has been no compelling reason to test for the necessity of covariance in the induction of that plasticity. However, now that hypotheses potentially linking these phenomena are emerging (above), and the sufficiency of ‘covariance’ in MCx plasticity has become clear, perhaps some tests of necessity will soon be undertaken.

3. Empirical challenges, possible solutions, and other unresolved issues

The preceding review was designed to emphasize the strongest experimental results that support Hebbian processes in neocortical plasticity. We now present a more critical analysis. This section will begin by discussing the logical criteria required to refute the Hebbian hypothesis. It will then be shown that results from experiments on plasticity of ocular dominance in the developing VCx satisfy some of these criteria. Following this, possible ways of reconciling the apparently contradictory data with the Hebbian hypothesis will be explored. Finally, other unresolved issues will be discussed.

3.1. Criteria needed to refute each of the three Hebbian rules

There are three potential ‘positive’ results, that are complementary to the three original Hebbian rules, that would provide refutations for each. These refutations and their corresponding ‘rules’ are:

1. Strong post/prepostsynaptic covariance resulting in synaptic depression (would refute the ‘pre and post’ rule).
2. Strong presynaptic activity without postsynaptic activity resulting in synaptic potentiation (would refute the ‘pre not post’ rule).
3. Strong postsynaptic activity without presynaptic activity resulting in synaptic potentiation (would refute the ‘post not pre’ rule).

A ‘negative’ result that could also be considered a type of refutation would be a situation in which either strong positive or strong negative pre/postsynaptic covariance resulted in no change in synaptic strength. However, this type of result is rarely reported as a refutation, even when it exists in the same paper as data considered supportive of one or more of the Hebbian rules. For example, in the experiments presented above examining synaptic potentiation in MCx, there was a lack of a change in strength for the unpaired ‘control’ synapses. This result could be considered a failure of the ‘post not pre’ rule because control synapses that were inactive during strong postsynaptic activation underwent no change in strength. Such an interpretation might seem excessively rigid if it were not for the fact that support for the ‘post not pre’ rule on its own (without homosynaptic potentiation) is sometimes considered a positive incidence of Hebbian plasticity (e.g., [39]). However, it is conceded that this type of ‘negative’ refutation is qualitatively weaker than Refutations Nos. 1–3, and as such will be set aside in order to devote attention to the stronger ‘positive’ refutations.

The core question posed in the present section is whether or not strong refutation criteria can be satisfied for forms of RF plasticity that otherwise appear to have good evidence implicating Hebbian induction mechanisms. In Section 2, the strongest evidence for Hebbian mechanisms was presented for ocular dominance plasticity in the developing VCx. Therefore in the present section, ocular dominance plasticity will be considered first.

3.2. Problem of differences in thresholds for plasticity

3.2.1. Potentiation without postsynaptic action potentials: is this a refutation of the ‘pre not post’ rule or an inappropriate definition of postsynaptic activity?

Direct support for Refutation No. 2 (a contradiction of the ‘pre not post’ rule) can be found in a few different types of experiments examining plasticity of the developing VCx (reviewed in [14]). The most common of these experiments/protocols is referred to as ‘Reverse Suture’. In this protocol a developing animal is first exposed to a period of monocular deprivation. By the end of that period, nearly all the cells of its VCx are unresponsive to the deprived eye. Next the suture is reversed, such that the formerly closed eye is opened (and allowed normal visual input), while the formerly open eye is sutured closed. Subsequently there is a robust and rapid (hours) shift in ocular dominance to the newly opened eye (reviewed in [129]). The cortical cells don’t discharge to the newly opened eye immediately after the reversal of ocular deprivation, yet the synapses in the VCx that are activated by inputs from the newly opened eye seem to potentiate.

The results of the ‘Reverse Suture’ experiments would appear to be a direct contradiction of the ‘pre not post’ rule, unless the definition of postsynaptic activity is broadened to include sub-threshold depolarization. Consequently the question of whether it would be appropriate to adopt such a broad definition of activity emerges. There are clear precedents from work in the hippocampus and MCx to consider LTP to be ‘Hebbian’ when it is induced by pairing presynaptic inputs with postsynaptic depolarization, in the absence of postsynaptic action potentials (e.g., [91,13]). However in those cases the depolarization was strong enough to elicit action potentials, and postsynaptic discharge did not occur because the experimenters had pharmacologically blocked sodium channels. The situation
in the ‘reverse suture’ experiments is therefore qualitatively different because the EPSPs are actually of sub-threshold magnitude to elicit action potentials.

3.2.2. If sub-threshold excitatory postsynaptic potentials are considered responses, then what is the lack of a postsynaptic response?

If we accept a definition of postsynaptic activity that includes depolarizations below action potential threshold, then the question arises as to the lack of postsynaptic activity. All inputs that release excitatory neurotransmitter will cause some type of EPSP. Therefore, would there always be postsynaptic ‘activity’ (as used in the context of the Hebbian hypothesis) following a presynaptic action potential? If so, then the ‘pre not post’ rule becomes logically impossible. If postsynaptic ‘activity’ always occurs in response to a presynaptic input, then according to the ‘pre and post’ rule, all active inputs would be facilitated. We know that this is not the case. Considering this, how might we interpret the discovery of Reiter and Stryker [134] (discussed above), that decreases in synaptic strength occur for inputs that are active during postsynaptic inhibition, relative to inputs that are inactive? Are we to assume that the pharmacological inhibition of postsynaptic activity (with muscimol) completely blocked EPSPs?

Artola et al. [5] provide a possible resolution to these seemingly conflicting issues by demonstrating differential thresholds for LTP and long-term depression (LTD) in VCx. Briefly, they found that EPSPs that are extremely weak cause no change in synaptic strength, while large EPSPs cause increases. Moreover, they found that EPSPs that are midway between the two in amplitude, produce depression. Thus, there could be three different EPSPs delivered to a dendrite, all of which are below the threshold for cellular discharge, that could cause either no change, a decrease, or an increase in efficacy, depending on their amplitudes. These results could be incorporated into a modified set of ‘Hebb-like’ rules resembling the following: (1) presynaptic activity with a ‘very weak’ postsynaptic response causes no change in synaptic strength; (2) presynaptic activity with a ‘moderate’ postsynaptic response causes depression; (3) presynaptic activity with a ‘strong’ postsynaptic response (but not necessarily supra-threshold) causes potentiation.

The solution just described would be difficult to test experimentally (especially in vivo) because the graded potentials would need to be measured intracellularly. Despite the practical difficulties, the Artola et al. ideas seem logically valid and could provide predictive value if the thresholds for depression and potentiation were consistent. However, it will be seen in the next section that this does not seem to be the case.

3.2.3. Fixed thresholds for plasticity cannot account for the available data

There is considerable evidence that in some situations the threshold for potentiation in the neocortex is above, rather than below, the action potential threshold (reviewed in [58, 14, 129]). Some cases even exist in which a decrease in efficacy occurs despite eliciting supra-threshold responses in cortical postsynaptic cells. An example of this is the correlate of habituation that occurs in ACx. When an acoustic stimulus that is effective in eliciting action potentials from a cortical cell is presented repeatedly, there is a decrease, rather than an increase, in response by that cortical cell to the repeatedly presented input [34]. This is despite the high levels of depolarization required to initiate action potentials. The result just described could be considered support for Refutation No. 1 above, which is a contradiction of the ‘pre and post’ rule.

In summary, it appears that the levels of postsynaptic activation that occur during induction of depression in some cases, are higher than the threshold levels required to produce potentiation in other cases. Therefore covariance models that contain fixed thresholds cannot account for these data. However, if the threshold levels of covariance required to induce plasticity (either potentiation or depression) were themselves dynamically regulated, then a covariance model might still work. By implementing dynamically maintained thresholds, a given level of depolarization (perhaps a low level) might be sufficient to induce potentiation under one set of circumstances, while that same level of depolarization might be too weak for potentiation (but sufficient for depression) under a different set of circumstances. Despite the differences in thresholds between circumstances, it may still be that the threshold for depression is lower than for potentiation within any given circumstance. This reasoning could account for the available data while maintaining the central characteristic of covariance models; i.e., that high levels of covariance induce potentiation and low levels of covariance induce depression, within any given situation.

Two basic approaches have been proposed that allow for this type of dynamic regulation. These are: (1) models that allow the threshold for plasticity itself to ‘float’; and (2) invoking some type of external ‘gate’ on the induction, so that plasticity only occurs when a ‘gating factor’ is present and proper levels of pre- and postsynaptic activity occur. Both of these ideas will be examined, beginning with ‘floating thresholds’.

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25 Perhaps future optical imaging with high spatial and temporal resolution will aid in such tests (see [122] for an example of in vitro imaging of small dendritic regions; [63] for an example and technical description of in vivo imaging; and [62] for a more general discussion of the utility of in vivo optical imaging).

26 Habituation in the auditory cortex develops in the absence of subcortical changes (Weinberger et al. [166]). Therefore, habituation response decrements in the ACx are likely to involve cortical mechanisms.
3.3. Floating thresholds

3.3.1. Bienenstock–Cooper–Munro model adjusts thresholds for plasticity according to mean recent postsynaptic activity

The preceding discussion provided a rationale for invoking models in which thresholds for plasticity are allowed to ‘float’. At this point an example of an actual model, the ‘BCM’ model (Bienenstock, Cooper and Munro [21]), will be presented in order to clarify how a ‘floating threshold’ covariance model might operate. The BCM model, which is one of the most widely referenced theories of its kind, will first be described according to its basic features and operation. Afterward it will be compared with related ideas and alternative strategies 27.

The threshold value of postsynaptic activity governing synaptic plasticity in the BCM model is called \( \theta_M \). The model predicts that potentiation of an active synapse will occur when instantaneous postsynaptic activity reaches a level above \( \theta_M \), and depression will occur when postsynaptic activity falls below \( \theta_M \). This threshold (\( \theta_M \)) is usually about equal to the mean level of postsynaptic activity (averaged over minutes or hours), and is allowed to ‘float’ with that mean level. Therefore, if mean postsynaptic activity increases, then \( \theta_M \) increases. If mean postsynaptic activity decreases, then \( \theta_M \) decreases.

The basic BCM equation is:

\[
\text{change in the strength of a synapse} = \phi \times d.
\]

The value of \( d \) represents instantaneous presynaptic activity. Therefore, the change in synaptic strength in this equation is linearly related to presynaptic activity; zero levels of presynaptic activity produce no change, and progressively higher levels result in proportionally greater change, for a constant value of \( \phi \). The value of \( \phi \) relates to postsynaptic activity, and determines the polarity (and to some extent, the magnitude) of synaptic change, as indicated below. The authors provide a graph of the function \( \phi \) (adapted in Fig. 9A,B), and indicate that any mathematical definition of \( \phi \) must have the characteristics of the graphed function [21].

Fig. 9A illustrates that \( \phi \) directly relates to instantaneous postsynaptic activity (X-axis). For example, zero levels of instantaneous postsynaptic activity (c) produce zero values of \( \phi \) (far left, Fig. 9A). Zero values of \( \phi \) would, in turn, result in zero change in synaptic strength, as calculated from the basic BCM equation (i.e., change in strength = \( \phi \times d \)). Low positive levels of instantaneous postsynaptic activity (c), would produce negative values of \( \phi \), and would therefore result in decreases in synaptic strength, by the BCM equation (change in strength = \( -\phi \times d \)). At approximately 2/3 of the maximum level of \( c \) shown, the function \( \phi \) crosses back over the

\[\text{depotisn/potentiation threshold (at } \theta_M; \text{ Fig. 9A). At higher levels of } \phi \] levels of instantaneous postsynaptic activity (c), would produce negative values of \( \phi \), and would therefore result in decreases in synaptic strength, by the BCM equation (change in strength = \( -\phi \times d \)). At approximately 2/3 of the maximum level of \( c \) shown, the function \( \phi \) crosses back over the

\[\text{ The function } \phi \text{ is indirectly related to the mean postsynaptic activity because it 'floats' (is either 'stretched' or 'compressed' along the X-axis) as a non-linear function of mean postsynaptic activity. For example, } \phi \text{ would be compressed during a period of lower than 'normal' mean activity (Fig. 9B), and the threshold for potentiation (} \theta_M \text{) would decrease 28.}

27 Bear, Cooper and Ebner [14] nicely explain the model in physiological terms, so their diagrams, equations, and conventions have been adapted here.

28 Bear et al. (1987) state that in a 'simple situation', \( \theta_M \) equals the square of the mean postsynaptic activity: \( \theta_M = (\text{mean postsynaptic activity})^2 \). The faster than linear function ensures that \( \theta_M \) will accelerate beyond the changes in mean activity, preventing runaway plasticity.
It has been claimed that the BCM model could account for the differences in thresholds for plasticity observed between different types of experiments, by virtue of its floating threshold [14,32,99]. For example in the ‘reverse suture’ experiment described above, the threshold immediately preceding the reversal would be quite high due to the strong postsynaptic activity produced by inputs from the open eye. Following reversal, the threshold would begin to drop, because there would be very weak inputs from the newly opened eye (which had been rendered ineffective by the previous suture) and no patterned inputs from the newly closed eye. Once the threshold fell below the level produced by the open eye, the synaptic strength for the open eye would begin increasing. The resulting increased response would cause the threshold for potentiation ($\theta_u$) to increase. Eventually a new equilibrium state would be achieved in which the cortical cells would be driven only by the open eye and the mean postsynaptic firing rate would be near $\theta_u$ (adapted from [14]).

One potential limitation of the BCM model is the lack of a provision for heterosynaptic depression: whenever there is no presynaptic activity $d$, the resulting change in efficacy is always zero ($\phi \times 0 = 0$). A second potential weakness is that homosynaptic change is predicted to occur whenever there is any pre- and postsynaptic activity (except at the threshold crossing point), because the threshold level of postsynaptic activity required for depression is always set to zero (Fig. 9A,B). This is a potential weakness because some workers (e.g., [5]) have observed no plasticity within a fairly broad range of weak (but non-zero) depolarization values, and have found synaptic depression only with higher (although still moderate) levels of depolarization.

3.3.2. Artola–Brocher–Singer model modifications

In a recent review, Artola and Singer [6] address some of these limitations by proposing another model, which they refer to as ABS (for Artola, Brocher and Singer). This model is similar to the BCM model with a few important modifications (adapted in Fig. 9C).

One of the most obvious differences is that the function for determining synaptic change has been moved to the right (on the X-axis) so that very low levels of postsynaptic activity result in zero change in synaptic strength. A second important difference is that the Y-axis represents change in synaptic strength, and is simply a function of postsynaptic response, as measured by an intracellular calcium surge (approximately proportional to postsynaptic depolarization). Unlike the BCM model, the ABS model does not directly consider presynaptic activity, nor does it require any presynaptic activity for synaptic change to occur. Therefore it allows for heterosynaptic depression. Artola and Singer [6] reason that similar levels of calcium would be present near an inactive synapse during strong overall depolarization as near an active synapse during weak depolarization. In the ABS model, the moderate calcium surge in both cases would initiate events ultimately leading to depression of synapses in the local area.

The model is difficult to test because measuring somatic membrane potential and calcium concentration are inadequate — the local calcium concentrations near synapses are critical. To truly test these ideas, and not simply apply them in a post-hoc manner, the calcium levels of small dendritic compartments would have to be tracked, and related to subsequent changes in strength of local synapses. Furthermore, unlike the BCM model, the ABS model has no direct provision for adjusting floating the thresholds for synaptic change. However the authors mention that many “factors will influence the shape and the position of the function” that relates levels of postsynaptic calcium response to changes in synaptic strength [6]. In any event, the ABS model as presented here, does not permit quantitative predictions, reducing its utility. However a hybrid, combining the best features of the BCM and ABS models, may be useful.

3.3.3. Thresholds may depend on mean recent synapse-specific activity

One particularly interesting experiment (Malach and Van Sluieters [110]) poses a direct challenge to any model in which the threshold for plasticity is determined by the mean activity of the postsynaptic cell. The authors combined two of the classic Hubel and Wiesel experiments into one. First an ocular bias was induced by exposing kittens to 2 days of monocular deprivation. After these 2 days, the visual cortical cells were driven almost exclusively by the open eye. Next, they surgically produced an artificial squint (by sectioning the tendon of the rectus muscle of the eye that was previously sutured closed), followed by 3–5 months of cross-eyed but otherwise normal development. The animals showed a complete recovery so that approximately equal numbers of neurons were driven by each of the two eyes, just as in the artificial squint experiments of Hubel and Wiesel (discussed earlier). There was no obvious effect of the previous monocular deprivation.

The Malach and Van Sluieters results would not be predicted by a BCM-like model because the threshold for potentiation would never have decreased; the originally open eye remained open, and presumably continued activating visual cortical cells very strongly during the period of artificial squint. Without the decrease in postsynaptic activity, there would be no decrease in threshold, and therefore the weak inputs from the newly open eye would never become potentiated. Somehow the weak inputs became potentiated despite the continued strong asynchronous activation by the eye that had always remained open. Moreover the strong inputs from the continuously opened eye did not seem to potentiate further. These data suggest that the important factor for determining the threshold of plasticity might be related to mean level of activity at individual synapses rather than the postsynaptic
cell as a whole. If this were the case, then the threshold of activation for the weak inputs from the newly opened eye would have been initially low, allowing for potentiation. The thresholds for the strong inputs from the previously opened eye would have been high, preventing further potentiation.

Huang et al. [77] found support for this hypothesis in hippocampal field CA1. They found that an initial strong stimulation of an afferent pathway, which was sufficient to produce short-term potentiation (STP) but not LTP, could partially prevent subsequent LTP of that pathway. More important for the present discussion was the discovery that the inhibition of LTP was synapse specific; a second pathway projecting to the same cell, that had previously only received weak test inputs, expressed normal LTP with standard stimuli. Interestingly, in the ‘blocked’ pathway, LTP could be induced if the LTP treatment was repeated two or three times. From this, the authors suggested that a true blockade of LTP had not occurred, but rather that the threshold amount of activation for these particular synapses had been increased (Huang et al. [77]).

3.4. Non-specific modulation as a way to ‘gate’ when covariance induces plasticity

3.4.1. Rationale for non-specific gating

The preceding discussion revealed that ‘floating threshold’ models might provide a way to account for inconsistencies in the threshold levels of activity required for induction of synaptic plasticity, while maintaining the central properties associated with Hebbian models. An alternative to floating thresholds is a system of ‘gating’ by some non-specific external system. The idea is that a non-specific gating system could ‘instruct’ synapses in sensory cortex when to ‘pay attention’ to the degree of pre/postsynaptic covariance. This could be accomplished in an absolute fashion (analogous to a switch), so that the ‘gate’ on plasticity would be either ‘open’ or ‘closed’. Alternatively, gating could be graded, so that an adjustment in gain on a synapse would be proportional to the amount of a ‘gating factor’. In a certain way then, the latter mechanism would allow threshold levels of covariance necessary for plasticity to ‘float’ in a way similar to the BCM model. However, instead of threshold levels being determined by mean postsynaptic or synaptic activity, these thresholds would be determined by the amount of a ‘gating factor’ present. Candidate ‘gating factors’ include neuromodulators that are released from diffusely projecting subcortical systems.

These modulatory systems receive input from limbic afferents that could, in turn, signal the ‘behavioral relevance’ of a situation (discussed below). It could be hypothesized then, that the amount of ‘gating factor’ (neuromodulator) might be related to the type of behaviorally relevant cues to which the modulatory system has access. An example of how this might operate is in the ACX during acoustic habituation [34]. During such habituation, acoustic stimuli are repeatedly presented without any behaviorally salient stimuli, so that one might predict low levels of neuromodulators. If this were true, then the gain on auditory cortical synapses would be low during acoustic habituation (assuming the amount of neuromodulator is positively related to ‘gain’). Consequently no potentiation would occur despite strong covariance between the acoustic afferents and postsynaptic auditory cortical cells.

The two neuromodulatory systems that are most widely proposed as ‘gating factors’ are the cortically projecting cholinergic and noradrenergic systems. While it is not at all certain that these two systems are involved in the gating of covariance-induced plasticity, they have been so widely investigated that no discussion of gating would be complete without including them. Unfortunately an adequate treatment would require an extensive review article for each. Therefore only the generally agreed upon major points relating the two systems (and their respective modulators) to cortical plasticity will be covered, first considering ACh and then very briefly NE.

After the general overview, we will concentrate on the logic of how a ‘non-specific gating factor’ such as a neuromodulator might exert its effect on covariance plasticity in a sensory system. Finally some data that supports the concept of gating of covariance plasticity by ‘state’ will be presented.

3.4.2. General evidence implicating acetylcholine in cortical plasticity

The anatomy of the basol forebrain cholinergic system (Bas F) is one of the key features making it attractive as a gating system for cortical plasticity. First, it has been demonstrated that diffuse projections from the Bas F provide the primary cholinergic input to all areas of neocortex. For example, lesions of the Bas F produce significant decreases in cortical levels of both choline acetyltransferase [102] and acetylcholinesterase [139]. Moreover, stimulation of the Bas F causes increases in ACh release in cerebral cortex [97]. The inputs to the Bas F include limbic structures such as hypothalamus, amygdala, nucleus ac-

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29 Of course another possible explanation for the latter could be a saturation of synaptic strength.

30 Here ‘non-specific’ is used to refer to a neural system that is not involved in processing a particular modality of sensory stimulus (e.g., visual, auditory, somatosensory). Instead the non-specific system would be involved in providing specific systems with extrinsic information (e.g., such as information about ‘state’ of the animal).

31 In the VCs, proprioceptive information from the eye has also been implicated in gating of plastic changes (reviewed in [79]). However, here we will concentrate on the neuromodulatory systems because of their generality to all sensory cortical systems.

32 Due to the length of this paper, the lesser investigated cortical neuromodulators such as dopamine and 5HT will not be considered.
cumbens, septum, entorhinal and medial temporal cortices. The input/output connectivity therefore would make the Bas F ideal as a relay for transmitting behaviorally relevant limbic information to the neocortex [115].

In accordance with the view just described, Richardson, DeLong and colleagues have found evidence that the neural activity in the Bas F is related to reinforcement (reviewed in [136]). The relationship between discharge in the Bas F and learning is strengthened by the observation that cells in the Bas F itself develop discharge plasticity, changing responsiveness to acoustic CS stimuli during classical conditioning [137,109].

Application of ACh or other muscarinic agonists onto sensory neocortical neurons, through iontophoresis [41,117] or by stimulation of the Bas F, [116,51] has generally been reported to cause atropine sensitive enhancement of cortical responsiveness to synaptic input during the application, sometimes accompanied by a decrease in background activity (reviewed in [149]). Moreover, if a sensory input is repeatedly paired with ACh or Bas F stimulation, then long-lasting plastic effects can develop for the paired input. Sometimes experiments have produced mainly increases to the paired input, [128,71] others mainly decreases [119] while still others have resulted in mixed effects [8]. The fact that the changes exhibit specificity to the afferent input that is paired with the muscarinic agonists indicates that they do not reflect general changes in excitability. However, the fact that the direction of the changes is not always the same indicates that this approach has not yet accomplished adequate control or understanding of the systems under investigation.

An indirect line of reasoning relating the Bas F to gating of sensory response and plasticity is the increasingly documented involvement of ACh in cortical activation. Cortical activation is the process of changing from a state of large amplitude slow wave EEG activity (synchrony) to low amplitude fast wave EEG activity (desynchrony). It has been known for some time that cortical activation profoundly alters cortical responsiveness (e.g., [106]) and is associated with states of arousal and behavioral readiness — states in which learning and cortical plasticity are most likely to occur (reviewed in [83,121,152,129]). It is now becoming clear that ACh, released onto the neocortex from the Bas F, is important for this activation. For example stimulation of the Bas F can produce intensity dependent desynchronization of the EEG [118,51]. Local application of ACh onto cortical neurons can shift their activity patterns from the type seen during synchrony to that seen in desynchrony (reviewed in [153]). Moreover, Bas F lesions cause resistance to desynchronization in undrugged animals [27]. Finally, local application of atropine can prevent the local desynchronization that could otherwise be induced by Bas F stimulation [118]. The fact that ACh alone can produce changes in cortical responsiveness and produce phenomena that resemble cortical activation, is a strong clue that the responsiveness changes seen during natural cortical activation may be mediated though cholinergic mechanisms.

The experiments discussed so far, relating ACh to cortical modulation, have focused on whether ACh application onto cortical neurons is sufficient to induce modulatory effects. Demonstrating the necessity of ACh and/or the Bas F in modulatory effects would strengthen the argument for their normal involvement. With this in mind, Webster et al. [161] demonstrated that Bas F lesions could block the physiological reorganization normally seen in rat hindpaw representation of SCx following sciatic nerve section. However, not all cortical plasticity is blocked by cholinergic depletion alone. Bear and Singer [17] found that ocular dominance plasticity in the developing kitten could only be blocked by lesions of both cholinergic and noradrenergic systems — a lesion of either system alone was ineffective. In conclusion, the Bas F is well suited both anatomically and physiologically as a modulator of cortical responsiveness. Moreover, several experiments have clearly implicated ACh, the Bas F, or both in physiological plasticity of the neocortex. Therefore it is quite possible that ACh, released from the Bas F, could be important for gating covariance plasticity. Possible routes of action for this gating will be briefly discussed at the end of this subsection.

3.4.3. General evidence implicating NE in cortical plasticity

Many of the same characteristics that make the Bas F a good candidate gating system are shared by the locus coeruleus (LC), the cortical source of NE (Rauschecker [129] provides a brief yet balanced review of the evidence implicating the LC in cortical plasticity). There has been considerable controversy over the necessity of NE in ocular dominance plasticity. Basically, one method of depletion (intraventricular infusions of 6-OHDA) tended to block plasticity, while most other methods did not (reviewed in [129]). This controversy was partly solved by the Bear and Singer [17] experiment, discussed above. They showed that the 6-OHDA lesions (which were originally thought to selectively lesion the NE system) actually interfere with the action of ACh on cortical neurons as well as interfering with NE. Thus, when workers blocked cortical plasticity with 6-OHDA lesions, it was likely that the combination of interference on processes mediated by both neuromodulatory systems caused the deficits.

As was the case with the Bas F, there are many indirect lines of evidence that may be pertinent to the role of the LC in cortical responsiveness and plasticity. Two of these issues will be examined next. First, the effects of NE agonists on cortical responses to sensory stimuli are quite different from those of ACh. ACh is generally reported to have an excitatory effect on cortical neurons (above), while NE tends to be more inhibitory. The popular consensus from in vivo reports is that NE tends to depress spontaneous activity more than evoked activity. This has
led to the idea that NE release causes an increased ratio of ‘signal-to-noise’ in sensory cortex (e.g., [54,160,159], discussed in [50]).

Given the different effects on sensory responsiveness between NE and ACh, it is surprising that the relationship between NE and cortical activation appears to be very similar to that of ACh. For example, activation of cells in the LC is sufficient to produce neocortical activation [19]. Moreover, local application of NE onto cortical neurons tends to shift these neurons from the bursting pattern characteristic of slow wave sleep, to a smooth firing pattern reminiscent of the awake state (reviewed in [153]). For example, Armstrong-James and Fox [4], found that 1 min of NE iontophoresis could produce the shift to the awake-like state for up to 1 h. While the potential role of cortical activation in plasticity is fairly easy to imagine (above), the role of the activity-depressing effect of NE is not obvious. Perhaps some clarity can be gained in the next subsection, by stepping away from actual data for a moment, and using hypothetical examples to examine the logic of how a non-specific input could ‘gate’ covariance plasticity. Following this logical exercise actual data will be compared to the idealized cases.

3.4.4. Logic of a neuromodulatory ‘gate’ vs. direct affect on the level of covariance

There are at least two modes of action that non-specific input such as a neuromodulator could take to enhance covariance-induced synaptic plasticity. First, it might influence the level of covariance itself, by altering the activity of the post- and/or the presynaptic neurons. Second, it may in some way ‘gate’ synaptic modifications, independent of any direct effects on the covariance level itself. Fig. 10 illustrates these two possibilities for a hypothetical case in which depolarizing postsynaptic current is paired with stimulation of afferent input, in the presence or absence of a ‘gating factor’ (in this case a neuromodulator):

In case No. 1 (top) there is a significantly larger increase in covariance during pairing, when the neuromodulator is present, than without the modulator. The resulting potentiation is greater in the modulator group because we are assuming the level of covariance is important for synaptic potentiation. Note the shift of all the points to the upper right in 1B compared to 1A, but the similar slope and y-intercept. Note also that there are equal synaptic changes in regions where there were equal covariance increases during pairing (shaded regions).

Case No. 2 (bottom) is designed to illustrate a situation in which the modulators enhance synaptic change without directly affecting covariance levels during the pairing. Note that the distributions of points along the X-axis are similar for 2A and 2B. However the group with modula-

\[ \text{Covariance increase imposed during pairing} \]

Fig. 10. Two hypothetical effects of a neuromodulator on covariance plasticity: direct effect on covariance vs. gating. Hypothetical changes in synaptic strength (Y-axis) are shown as functions of increases in pre/postsynaptic covariance imposed during pairing treatments (X-axis). These changes in synaptic strength are greater when neuromodulators are present (part B, right) than without the neuromodulators (part A, left). Two different hypothetical mechanisms of the neuromodulator are postulated: case 1 (top) and case 2 (bottom). In case 1 the modulators directly affect the covariance levels that are imposed during the pairing treatment (note the shift to the right on the X-axis in case 1B vs. 1A). This results in an increase in the change in synaptic strength (higher Y-axis values in case 1B vs. 1A). In case 2 the modulators have a downstream gating affect, which increases the change in synaptic strength without influencing the covariance levels imposed during pairing (observe the higher Y-axis values in case 2B vs. 2A but similar X-axis values). See also text.

3.4.5. Examples of gating of covariance plasticity

The reason for considering the hypothetical roles that non-specific factors could have in enhancing covariance plasticity was to emphasize the difference between such factors as true ‘gating’ vs. more trivial alterations such as

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33 The ‘actual data’ will include the effects of ‘state’ but not NE explicitly.
increases in postsynaptic excitability. While either mode of action could be functionally important and effective, a clear understanding of their role in covariance plasticity requires being able to distinguish between them. In the present section, two findings that may be relevant to this issue will be discussed. These potential gating phenomena may or may not be exerted through neuromodulators.

Ahissar et al. [2], as explained above, showed that when the covariance between two cells was artificially altered for several minutes during a conditioning treatment, there was a subsequent change in the apparent synaptic effectiveness between the two cells. The direction and magnitude of the post-treatment changes were appropriate and proportional to the changes imposed during the treatment. Furthermore, the strength of the change was 'gated' (in the sense used in case No. 2 above) by the behavioral relevance of stimuli presented during the treatment. The plasticity observed was greatest, for a given level of imposed covariance, if the animal was required to attend to the stimuli used to control the activity of the cells. If the animal did not attend to the stimuli, the level of 'synaptic change', for a given level of imposed covariance, was reduced. Fig. 11 is adapted from Ahissar et al. [2].

Note the clear increase in slope for the 'behaving' cell group, with no associated change in the y-intercept. Importantly, the distribution along the X-axis (which represents the covariance change during the treatment) is not different for the two groups. Thus 'behavior' in this case exerted a pure amplification on the plasticity observed, and is similar to hypothetical case No. 2 above (without the additive effect). At present it is unknown what factors are responsible for the enhancement in plasticity seen in the behaving group, but it is tantalizing that at least one of the neuromodulatory systems implicated in gating (the Bas F system) exhibits high activity during behaviors similar to those used in the Ahissar experiments [2,136].

Findings from ACX obtained in our laboratory also exhibit apparent gating behavior. [38] In urethane-aneuritized animals, the cortical EEG alternates between periods of synchrony and desynchrony, even under deep anesthesia (as indicated by areflexia — see [108]). As reviewed above, it is known that shifts in cortical EEG have profound influences on cortical processing of sensory inputs [26,106] (reviewed in [152]). Moreover, the neuromodulators that are candidate 'gating factors' for plasticity [88,17,68,128,119,41,85,161] (also see above), are also involved in EEG shifts [27,19,118] (reviewed in [153]).

**A. Examples of EEG Categories**

1. Desynchronized

2. Synchronized

3. Transition

**B. Nonsynchronized EEG During Treatment Increases Probability of Plasticity**

<table>
<thead>
<tr>
<th>Significant Increase</th>
<th>Synchronized</th>
<th>Nonsynchronized</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Significant Change</td>
<td>2</td>
<td>5</td>
</tr>
</tbody>
</table>

χ² = 3.96, df = 1, p < 0.05

Fig. 12. Receptive field plasticity in auditory cortex induced by covariance treatment appears to be gated by the cortical state/EEG during the treatment. Results were from Cruikshank and Weinberger [38]. The experiment was described in subsection 2.4.3, above. A: representative examples of each EEG category. The top record (A1) is a desynchronized EEG, dominated by small amplitude (<100 μV), high frequency (>5 Hz) waves. The middle record (A2) is a synchronized EEG, characterized by large amplitude (>300 μV), low frequency (1–5 Hz) waves. The bottom record (A3) is a transition state, in which the EEG gradually shifted from a desynchronized to a synchronized state. Panel B: the χ²-table shows the probability of plasticity as a function of the cortical EEG/state during the treatment. Desynchronized and transition states were combined into a single 'non-synchronized' group and compared with the fully synchronized group. Recall that no significant decreases in the index occurred immediately after 120 pairing trials. Note the significantly higher probability of plasticity in the non-synchronized than the synchronized group. See text for relationship of these data to 'gating'.
Therefore we wondered whether cortical EEG state, during the covariance treatment (above), might influence how a cell is affected by that treatment. To examine this relationship, the EEG states of the animals during the pairing treatments were compared with the corresponding levels of functional plasticity observed after the treatment. EEG’s were categorized as synchronized, desynchronized, and transition (Fig. 12A). The desynchronized and transition groups were subsequently collapsed into one ‘non-synchronized’ group because there were only two completely desynchronized cases [38].

Fig. 12B shows that the probability of significant plasticity was greater if the cortical EEG was non-synchronized during the pairing treatment than if it was synchronized: 5/9 (56%) cells that underwent treatment when the EEG was non-synchronized were significantly affected, whereas only 2/13 (15%) that underwent treatment when the EEG was synchronized were so affected (χ² = 3.96, P < 0.05) [38].

We wanted to understand the nature of this relatively strong influence. For reasons already mentioned, it was important to determine whether factors associated with the non-synchronous EEG state affected the covariance itself or if it had a more downstream, gate-like effect. To determine this, we compared the changes in covariance imposed during pairing for the two EEG groups; there were no differences (P > 0.5, t-test; mean synchronous change = 0.50 ± 0.04, mean non-synchronous change = 0.53 ± 0.04) [38]. It therefore appears that covariance levels that were insufficient to induce plasticity during synchrony were sufficient to do so during non-synchrony. Thus, the cortical state/EEG seemed to truly ‘gate’ the covariance-induced plasticity in a manner similar to ‘behavior’ in the Ahissar et al. experiment [2,38]. It would be interesting to know the EEG states of the monkeys of the Ahissar et al. experiments during the behaving vs. the non-behaving conditions. It would also be interesting to test the roles of the classic neuromodulators NE and ACh in the EEG-related effects.

3.4.6. Possible mechanisms of action of gating factors (acetylcholine and norepinephrine)

In the last two sections a distinction was made between ‘true gating’ of covariance plasticity vs. direct effects on covariance itself. It should be emphasized that gating is not meant to imply some mysterious non-biological process. Perhaps a more mechanically relevant way of making the distinction would be to talk about the effects of a factor being upstream vs. downstream from the covariance treatment. What has been called gating would be downstream, and what has been called direct effects on covariance would be upstream. Downstream processes could directly or indirectly affect the chain of cellular events that are initiated by the imposed change in covariance. These could include long lasting subthreshold currents, 2nd messenger cascades and other processes involving consolidation of synaptic changes (discussed in [129]), among other things. For example Lisman [105] modeled LTP and LTD, and showed that it was quantitatively possible to get either synaptic depression or potentiation from a surge of postsynaptic calcium. The critical difference in Lisman’s model is that LTP requires a larger surge of calcium than LTD. If this model were valid, then it would be theoretically possible for a non-specific gating factor to exert its influence on plasticity by increasing the level of intracellular calcium entry (or release from intracellular stores) for a given level of depolarization. Thus, potentiation might be produced with only a moderate depolarization, if the modulating factor was present during that depolarization.

On the other hand, upstream modulation could also readily occur. For example, the neuromodulators NE and ACh could enhance postsynaptic excitability through their known actions on ligand, voltage, and calcium gated potassium conductances (discussed by Brocher et al. [24]). This could result in shifts in the resting potential, increases in membrane resistance, decreases in spike accommodation, and longer as well as larger EPSPs.

3.5. Other unresolved issues

Initially in Section 3, the criteria required for refutation of the three Hebbian ‘rules’ were delineated. It was then shown that results from several experiments in the literature satisfied some of these criteria. Analysis of potential solutions to these problems revealed that no covariance model which included fixed thresholds for potentiation or depression could account for the data. Therefore two strategies that incorporated dynamic thresholds were discussed. These strategies were: (1) covariance models based upon floating thresholds; and (2) ideas that incorporated some type of external ‘gating’ on the induction of plasticity. For the remainder of Section 3, two other unresolved issues relating to covariance plasticity will be discussed. The first of these involves a re-examination of the concept of covariance.

3.5.1. ‘True covariance’

3.5.1.1. A description of the issues. In a recent review, Ahissar and Ahissar [1] contrasted several common plasticity algorithms or ‘rules’, and pointed out that most do not consider changes in levels of pre/postsynaptic covariance during the inducing event. This is equally true of the models discussed so far in the present paper, which base their operation mainly on levels of postsynaptic activity. Recall, for example, that the plasticity predicted in the ABS model was determined exclusively by the local surge of postsynaptic calcium; the same levels of plasticity would be predicted for a synapse that ‘experienced’ a specified calcium surge, whether its corresponding axon terminal fired one spike or ten spikes. On the other hand, the output change that these models (e.g., the ABS, BCM, etc.) are
designed to determine is synaptic strength — an input/output function involving both sides of the synapse. Ahissar and Ahissar [1] found that the imposed change in pre/postsynaptic covariance, during a conditioning period, was appropriate for predicting the plasticity in their own experiments (data discussed above [2]). These types of models, that incorporate changes in covariance during the induction period for determination of subsequent plasticity, will be referred to here as ‘true covariance models’.

In the simplest case a synapse in a ‘true covariance model’ might start with a synaptic weight of 1.0 during a baseline period. This would mean that (on average) a given number of spikes in the presynaptic neuron would correlate with the same number of spikes in the postsynaptic neuron (e.g., five postsynaptic spikes would follow five presynaptic spikes: 5/5 = 1.0). Imposing a treatment in which there is strong postsynaptic inhibition but constant presynaptic activation might result in five presynaptic and two postsynaptic spikes. Thus the covariance ratio during this treatment would be 2/5 = 0.4. In a ‘true covariance model’, this reduction in covariance during the treatment would result in a subsequent decrease in synaptic strength. In the postsynaptically driven ABS model, the same decrease in synaptic strength might occur if, for example, the threshold (dividing potentiation and depression) was set to five postsynaptic spikes (Fig. 13A).

A. Example of the Same Synaptic Change with True Covariance vs. ABS Models

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Treatment</th>
<th>Synaptic Change</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>True Covariance Model</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td>Post/Pre = 5/5</td>
<td>1</td>
<td>Post/Pre</td>
<td>2/5 = 0.4</td>
</tr>
<tr>
<td><strong>ABS Model:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td># Post Spikes</td>
<td>= 2</td>
<td># Post Spikes</td>
<td>= 2</td>
</tr>
</tbody>
</table>

B. Example of Different Synaptic Changes with True Covariance vs. ABS Models

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Treatment</th>
<th>Synaptic Change</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>True Covariance Model</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td>Post/Pre = 5/5</td>
<td>1</td>
<td>Post/Pre</td>
<td>10/10 = 1</td>
</tr>
<tr>
<td><strong>ABS Model:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td># Post Spikes</td>
<td>= 10</td>
<td># Post Spikes</td>
<td>= 10</td>
</tr>
</tbody>
</table>

The changes in synaptic strength produced by ‘true covariance models’ vs. ABS types of models would be qualitatively different from one-another for situations in which presynaptic activity was not held constant, such as during a period of enhanced excitation to both pre- and postsynaptic cells. This might result in ten spikes for both cells, producing in a covariance ratio of 10/10 = 1.0. This is equal to the covariance ratio for the baseline period (5/5 = 1.0). Therefore, no change in synaptic weight would occur in the true covariance model, despite the doubling of postsynaptic activity. The ABS model, on the other hand, would produce an increase in strength because the postsynaptic threshold of five spikes would have been exceeded (Fig. 13B).

3.5.1.2. Difficulties with true covariance models. Potential problems with true covariance models might arise when presynaptic activity is adjusted in parallel with postsynaptic activity. For example, two spikes in the postsynaptic cell coincident with a single spike in a presynaptic cell produces the same ratio (2/1 = 2) as a train of 100 spikes in the post and 50 in the pre (100/50 = 2). Perhaps this could be remedied by weighting the synaptic change by the presynaptic activity.

Fig. 13. True covariance vs. ABS-type models. Panel A: true covariance type model (middle row of matrix) is contrasted with ABS type model (bottom row of matrix). For both models, average simultaneous pre- and post-synaptic spike trains are shown for a baseline period (left) as well as during a treatment period designed to induce plasticity. The resulting directions of synaptic change are shown on the far right. For the true covariance model, covariance ratios are calculated for both the baseline and treatment periods, and shown in the matrix (postsynaptic spikes divided by presynaptic spikes). For the true covariance model, the covariance ratio during the treatment is compared to the baseline. If there is an increase during treatment, then the resulting change in synaptic strength would be an increase. If there is a decrease during treatment, then the resulting change in synaptic strength would be a decrease. For the present case (panel A), the baseline covariance ratio was 5/5 = 1. The treatment covariance ratio was 2/5 = 0.4. This decrease in covariance during the treatment resulted in a decrease in synaptic strength. In an ABS-type model, the change in synaptic strength only involves the magnitude of the postsynaptic response during treatment, and does not take into account the ratios of the pre and post-synaptic responses. In the present example, we set the threshold for potentiation vs. depression at the average baseline postsynaptic spike rate, which was five spikes. If there were more than five spikes during treatment, there would be potentiation, and if there were fewer than five spikes, there would be depression. In the example shown, there were two spikes, producing depression. Thus, for the present case, decreasing the postsynaptic response during constant presynaptic input, resulted in synaptic depression for both the true covariance and ABS type models. Panel B: both pre and postsynaptic spike rates are doubled during treatment. This produces no change in the covariance ratio. Therefore, for the true covariance model, there is no resulting change in synaptic strength. On the other hand, for the ABS-type model, the increase in postsynaptic activity above the postsynaptic threshold of five spikes, produces synaptic potentiation. Thus, for the case shown in panel B, the same change in activity produces different results for the true covariance vs. the ABS-type models. See text for further explanation.
A related problem might occur with diminishing presynaptic activity. In a situation where very high levels of coincident pre- and postsynaptic activity normally occurs (e.g., 200 spikes each during a 1-s stimulus), the lowering of presynaptic activity levels, while maintaining normal postsynaptic activity levels (e.g., with other afferent inputs), would result in a covariance 'increase' as defined here. Eventually a point could be reached in which the presynaptic cell would fire one spike, while the postsynaptic cell continued to fire 200 spikes. This is the type of situation for which heterosynaptic depression might be expected (via the 'post not pre' rule), yet a true covariance algorithm, in its simplest form, would predict large homosynaptic potentiation. A final difficulty with true covariance rules is that a viable biological covariance detection mechanism has yet to be delineated, especially for neocortex [55,40].

3.5.2. Presynaptic / postsynaptic inter-stimulus intervals: what is temporal coincidence?

Up to now, the discussion has revolved around the magnitude of pre- and postsynaptic activity, with the implicit assumption being that the pre- and postsynaptic cells were firing either nearly simultaneously or very far apart in time. However in the real animal pre/postsynaptic inter-spike intervals would be on a continuum. This section will attempt to briefly review the data relating to fine-grain timing in cortical covariance plasticity.

While temporal constraints on synaptic plasticity have been the topic of research in the hippocampus for quite some time (e.g., [103,169,98,72]), in the neocortex this type of investigation is really just beginning. To this end, Baranyi, Szente, Woody [13] (also discussed above) attempted a temporal analysis in the MCx. They found that as postsynaptic depolarization followed presynaptic stimulation by progressively longer intervals, the probability of inducing potentiation decreased. Zero to 50 ms delays produced significant potentiation in 86% of tested cells. Fifty to 100 ms delays potentiated 58%, 100–150 ms potentiated 40%, and 150–200 ms potentiated 22%. The experimenters did not test any 'negative' delays, so it is unknown what would happen if postsynaptic stimulation preceded afferent input.

The previously discussed results of Fregnac et al. [57], in visual cortical slices, are also pertinent to the timing issue. Recall that weak presynaptic inputs from the white matter were paired with strong depolarizing or hyperpolarizing pulses, that preceded the presynaptic stimulus by 5–10 ms, and lasted 50–80 ms. Significant synaptic plasticity (both potentiation and depression) was observed for 36%–41% of paired cells. However, no such plasticity occurred in controls for which the intracellular current pulse followed the synaptic stimulus by 120 ms. To our knowledge, this is the first demonstration in the neocortex of precise pre/postsynaptic timing constraints on homosynaptic depression (see [150], [125], for experiments in the hippocampus relating to a similar issue).

Results from our laboratory also speak to the issue of fine-grain pre vs. postsynaptic timing (unpublished observations). In our experiment (the general protocol was described above) [38], the tones used to activate the presynaptic cells, and the current administered to the postsynaptic cell, were delivered simultaneously (100 ms each). However the latency of the maximally enhanced portion of the postsynaptic response, during the pairing treatment, varied from cell to cell. This latency was used to estimate the pre vs. postsynaptic delay during the treatment.

We found that when the maximally enhanced portion of the postsynaptic response occurred simultaneously with, or slightly after (> 100 ms) the estimated time of arrival of the presynaptic input, 91% of the cells (10/11) had a subsequent increase in the relative CS+ vs. CS− response (i.e., 91% in the direction predicted by the Hebbian Hypothesis). On the other hand, when the current enhanced portion of the postsynaptic response occurred before the estimated time of arrival of the presynaptic input, about equal numbers of cells had increases (6/11) as had decreases (5/11) (χ² = 3.67, P = 0.055). Therefore the function relating (a) the latency between presynaptic activation and postsynaptic enhancement with (b) plasticity was asymmetrical: there was greater tolerance for delays in which the presynaptic input led the postsynaptic enhancement. Explicit manipulation of the latency between pre and postsynaptic stimuli would be useful in exploring this issue further. Nonetheless, it is exciting that these preliminary findings of directional asymmetry are reminiscent of the results of Larson and Lynch [98] in area CA1 of the hippocampus, and Hashemzadeh-Gargari [72] in the dentate gyrus (see [67], [120] for theoretical treatments relating temporal order and asymmetry to synaptic plasticity).

The data presented in the preceding discussion seem to indicate that plasticity is greatly attenuated if the pre- vs. postsynaptic delay, during induction, exceeds ±150 ms. Further, there may be some asymmetry within this temporal window. Such narrow constraints would not have been predicted from experiments in which plasticity was induced by sensory experience alone. For example, recall that Delacour et al. [42] (discussed above) induced potentiation of somatosensory cortical responses to a weak whisker stimulus by repeatedly pairing the weak stimulus with a strong whisker stimulus. The inter-stimuli interval was 500 ms. Thus, any enhancement in postsynaptic response to the first stimulus, resulting from presentation of the second, was necessarily delayed by about 500 ms. Obviously, this is outside the range previously discussed.

In another example, Altmann et al. [3] raised kittens with shutter goggles that allowed vision to be alternated between the two eyes. The inter-eye interval was adjusted by the experimenter. Kittens reared with alternation rates as long as 400 ms had normal binocular responses in their visual cortical cells, while longer delays resulted in abnor-
mal binocular integration. If a pre/postsynaptic covariance mechanism was mediating the binocular development in the 400 ms delay group, then the enhancement in the postsynaptic response to one eye’s inputs, by stimulation through the second eye, could only have occurred at a 400 ms delay. Again, this is substantially longer than the effective delays found in the previously described experiments that tested the temporal constraints more directly (about 150 ms). Clearly more work has to be done if these discrepancies are to be resolved.

4. Conclusions

In this review we attempted to thoroughly and critically examine the evidence relating Hebbian induction mechanisms to neocortical RF plasticity. To accomplish this we first examined the logical criteria needed to show the involvement of a covariance process. The criteria involved showing the necessity and sufficiency of covariance processes in the induction of RF plasticity. In Section 2 we applied these criteria to each of the primary sensory and motor neocortical areas. From this it was concluded that for visual cortex, there was significant evidence supporting the sufficiency of covariance processes in the induction of RF plasticity in both developing and adult animals. It was further concluded that there was reasonable evidence demonstrating the necessity of covariance processes in ocular dominance plasticity during development. The evidence for Hebbian induction mechanisms in somatosensory cortical plasticity was weaker than for visual cortex. We were not aware of any clear tests of necessity for types of RF plasticity in somatosensory cortex that are strongly suspected to be mediated by Hebbian induction mechanisms. Moreover, only one clear test of sufficiency has been reported. The latter supported the involvement of Hebbian mechanisms in somatosensory cortex for very young animals, but found lack of support for animals older than 1 week of age. Two experiments were discussed that tested the sufficiency of covariance processes in adult auditory cortical plasticity. The methodologies of the two experiments were rather different from one another, yet both generated results that were supportive of the Hebbian hypothesis. To our knowledge, no tests of necessity have been conducted for auditory cortex. Finally, for motor cortex it was consistently shown that a period of positive covariance (i.e., repeatedly pairing strong postsynaptic activity with afferent stimulation) is sufficient to induce synaptic potentiation. To our knowledge, no explicit tests of the role of negative covariance in synaptic depression have been reported. Moreover, no experiments were available testing the necessity of either positive or negative covariance in any form of motor cortical RF plasticity.

Following the general review just summarized, a more critical analysis was presented. First, criteria for the possible refutation of the Hebbian hypothesis were delineated. Next, data were presented that satisfied some of those criteria. These data came mainly from experiments examining the plasticity of ocular dominance in the developing visual cortex — a type of experience-dependent plasticity for which the best case for Hebbian induction mechanisms had previously been made. Possible ways of reconciling the data with the Hebbian hypothesis were then discussed. It was postulated that if the threshold levels of covariance required to induce plasticity were dynamically regulated, then covariance models might be able to account for the known data. Two dynamic regulation approaches were extensively discussed. These included models that allowed the thresholds for plasticity to float, and ideas involving external gating of the induction of plasticity. Finally, two additional unresolved issues were discussed. In the first, comparisons were made between models that truly based their operation on levels of pre/postsynaptic covariance vs. other types of so called ‘covariance models’. The second issue addressed was the time interval between pre- and postsynaptic activity during induction.

A major objective of this paper has been to establish a set of criteria that can be used by researchers to determine whether or not a particular type of plasticity is likely to have an underlying Hebbian induction mechanism. We maintain that this is an important objective if only because of the pervasiveness of the Hebbian hypothesis in the literature. The review in Section 2 showed that when strict criteria for necessity and sufficiency were applied, there was less convincing evidence for the Hebbian hypothesis than might have been suspected. In Section 3 it was shown that even in situations for which reasonable support had been shown (i.e., the criteria of necessity and sufficiency were generally satisfied), further careful examination could reveal contradictions.

This discussion is not meant to imply that the Hebbian hypothesis is refuted. In fact, implicit throughout this paper has been the assumption that it makes little sense to talk about either global refutation or support for the Hypothesis. This assumption is based on the nature of the Hypothesis itself — it is a ‘theory’ that potentially explains the induction of various types of physiological plasticities; in the present context this includes RF plasticities in each of the primary neocortical areas, resulting from a wide array of sensory experiences. It is conceivable that each particular form of RF plasticity could have a distinct mechanism of induction. Thus, neither support nor refutation for a Hebbian induction mechanism in one type of RF plasticity would necessarily transfer to other types of RF plasticity.

34 Some might argue that similarities in architecture and processing among at least the primary sensory neocortical areas could imply similar plasticity mechanisms. Although we acknowledge this as a possibility (it provided part of the rationale for including these areas together in the present paper), we believe it is an overly broad logical leap, with insufficient basis at this time.
Based on this reasoning, and the fact that there is a minimal amount of strong evidence implicating Hebbian mechanisms in any form of neocortical RF plasticity (above), it would be extremely myopic to exclusively consider the Hebbian hypothesis at the expense of other hypotheses when investigating the induction of a particular type of plasticity. Unfortunately, the popular belief that there is strong general support for the Hebbian hypothesis, combined with the paucity of clear alternatives, often leads investigators to exactly such exclusive consideration. It is hoped that this review will provide some inspiration to generate and test alternative induction hypotheses. Perhaps the emphasis can shift away from testing the fit of a specific type of plasticity to a global theory, and more toward development of hypotheses that are based on the specific architectures and processing of the particular cortical systems under investigation, as exemplified by Stent [151] who advanced the original adaptation of the Hebbian hypothesis to visual cortical plasticity.

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References


