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The role of presynaptic activity in monocular deprivation: Comparison of homosynaptic and heterosynaptic mechanisms

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ABSTRACT **Although investigations in computational neuroscience have been extensive, the opportunity (that has made such a marked difference in physical sciences) to test detailed and subtle quantitative consequences of a theory against experimental results is rare. In this paper, we outline a testable consequence of two contrasting theories of synaptic plasticity applied to the disconnection in visual cortex of the closed eye in monocular deprivation. This disconnection is sometimes thought to be the consequence of a process that stems from a competition of inputs for a limited resource such as neurotrophin. Such a process leads to what we call spatial competition, or heterosynaptic synaptic modification. A contrasting view—exemplified by the Bienenstock, Cooper, and Munro (BCM) theory—is that patterns of input activity compete in the temporal domain. This temporal competition is homosynaptic and does not require a conserved resource. The two mechanisms, homosynaptic and heterosynaptic, are the distinguishing characteristics of two general classes of learning rules we explore by using a realistic environment composed of natural scenes. These alternative views lead to opposite dependence on the level of presynaptic activity of the rate of disconnection of the closed eye in monocular deprivation. This strong and testable consequence sets the stage for a critical distinguishing experiment. This experiment has been done and supports the second view. These results have important implications for the processes of learning and memory storage in neocortex.**

Although investigations in computational neuroscience have been extensive, the opportunity (that has made such a marked difference in physical sciences) to test detailed and subtle quantitative consequences of a theory against experimental results is rare (1). In this paper, we outline a testable consequence of two contrasting theories of synaptic plasticity applied to the disconnection in visual cortex of the closed eye in monocular deprivation (MD). This disconnection is sometimes thought to be the consequence of a process that stems from a competition of inputs for a limited resource (2, 3) such as neurotrophin (4). Such a process leads to what we call spatial competition, or heterosynaptic synaptic modification. A contrasting view—exemplified by the Bienenstock, Cooper, and Munro (BCM) theory (5)—is that patterns of input activity compete in the temporal domain. This temporal competition is homosynaptic and does not require a conserved resource. These alternative views lead to opposite dependence on the level of presynaptic activity of the rate of disconnection of the closed eye in MD. This strong and testable consequence sets the stage for a critical distinguishing experiment. This experiment has been done (6) and supports the second view. These results have important implications for the processes of learning and memory storage in neocortex.

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In this paper we present results using two different classes of learning rules, one that exhibits heterosynaptic synaptic modification and one (of which BCM is a member) that exhibits homosynaptic synaptic modification. These general classes of learning rules are characterized by their dominant method of stabilization—weight decay for the heterosynaptic class and a sliding threshold for the homosynaptic class. The dynamics of the closed-eye disconnection in MD enables us to draw an experimentally testable distinction between the two different classes. We use a visual environment composed of natural scenes that is realistic enough so that the simulations can meaningfully be compared with the experiment.

METHODS

We use 13×13 circular patches from 12 images of natural scenes to represent the visual environment. The images are processed either by a retinal difference of Gaussians, with the biologically observed $\approx$3:1 ratio of the surround to the center of the ganglion receptive field (8), or a whitening filter corresponding to the lateral geniculate nucleus response properties (9). The response of the cortical cell is given by $c = s(\mathbf{m}\cdot\mathbf{d})$, where $s(\cdot)$ is a rectifying sigmoid, which sets the minimum and maximum values of the postsynaptic response. Neurons with a particular learning rule are trained with natural scene stimulus to both eyes until we obtain binocular oriented receptive fields. To model deprivation, we continue training but present uniform noise to the deprived eye(s). To quantitatively measure the timing of the deprivation experiments, we measure the response of the neurons by using oriented stimuli and then estimate the characteristic half-time for the decay of neuronal response. The specific learning rules used are shown in *Learning Rules*. The details of the different classes of learning rules and how they are derived are given in Blais *et al.* (10).

RESULTS

In MD, one eye is deprived of patterned stimuli; this results in the loss of responsiveness of cells in kitten's striate cortex to stimulation through the deprived eye (11, 12). Because the loss of response is much more striking in monocular, as opposed to binocular, deprivation (13, 14), it is sometimes thought to be the consequence of a competitive process. We call such a process (generally arising through a subtractive term in the synaptic modification equation) spatially competitive. Mathematically it has the form

$$\dot{\mathbf{m}} = f(c)\mathbf{d} - g(c)\mathbf{m} \qquad [1]$$

where $\mathbf{m}$ is the vector of synaptic weights, $\mathbf{d}$ and c are the pre- and postsynaptic activity of the cell, respectively, and $f(c)$ and

Abbreviations: BCM, Bienenstock, Cooper, and Munro; MD, monocular deprivation; BD, binocular deprivation; PCA, principal component analysis.

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$g(c)$ are functions of the postsynaptic activity. This form includes most stabilized Hebb-like rules as well as some others we have explored (see *Learning Rules* and ref. 10). When the subtractive term plays the crucial role in stabilizing the system, a heterosynaptic learning rule is at work. This has the effect of decreasing some synapses if others increase to keep some measure (such as Σm_j or $|\mathbf{m}|^2$) constant. Thus, the strength of synapses can change even in the absence of presynaptic activity to those synapses. Not all heterosynaptic processes lead to the observed receptive fields or ocular dominance distributions (15, 16). When they do (as they have in all of the cases we have analyzed), the disconnection of the closed eye either decreases or remains constant as the presynaptic activity from the closed eye increases, and presynaptic activity from the closed eye is not required for the disconnection (Fig. 1*a*).

In contrast, in the BCM theory (5) and other homosynaptic rules we explored (see *Learning Rules* and ref. 10), synaptic modification leads to what we call temporal competition between input patterns. This results in the disconnection of the closed eye because of homosynaptic long-term depression driven by presynaptic activity from that eye. As the presynaptic activity from the closed eye increases the rate of disconnection increases (Fig. 1*b*). To illuminate the origin of this counter-intuitive result, as well as to display further consequences and precise parameter dependence, we present below a simplified analysis of MD according to the BCM theory.

The BCM theory (5) postulates synaptic modification of the form

$$\dot{\mathbf{m}} = \phi(c, \theta_M)\mathbf{d} \qquad [2]$$

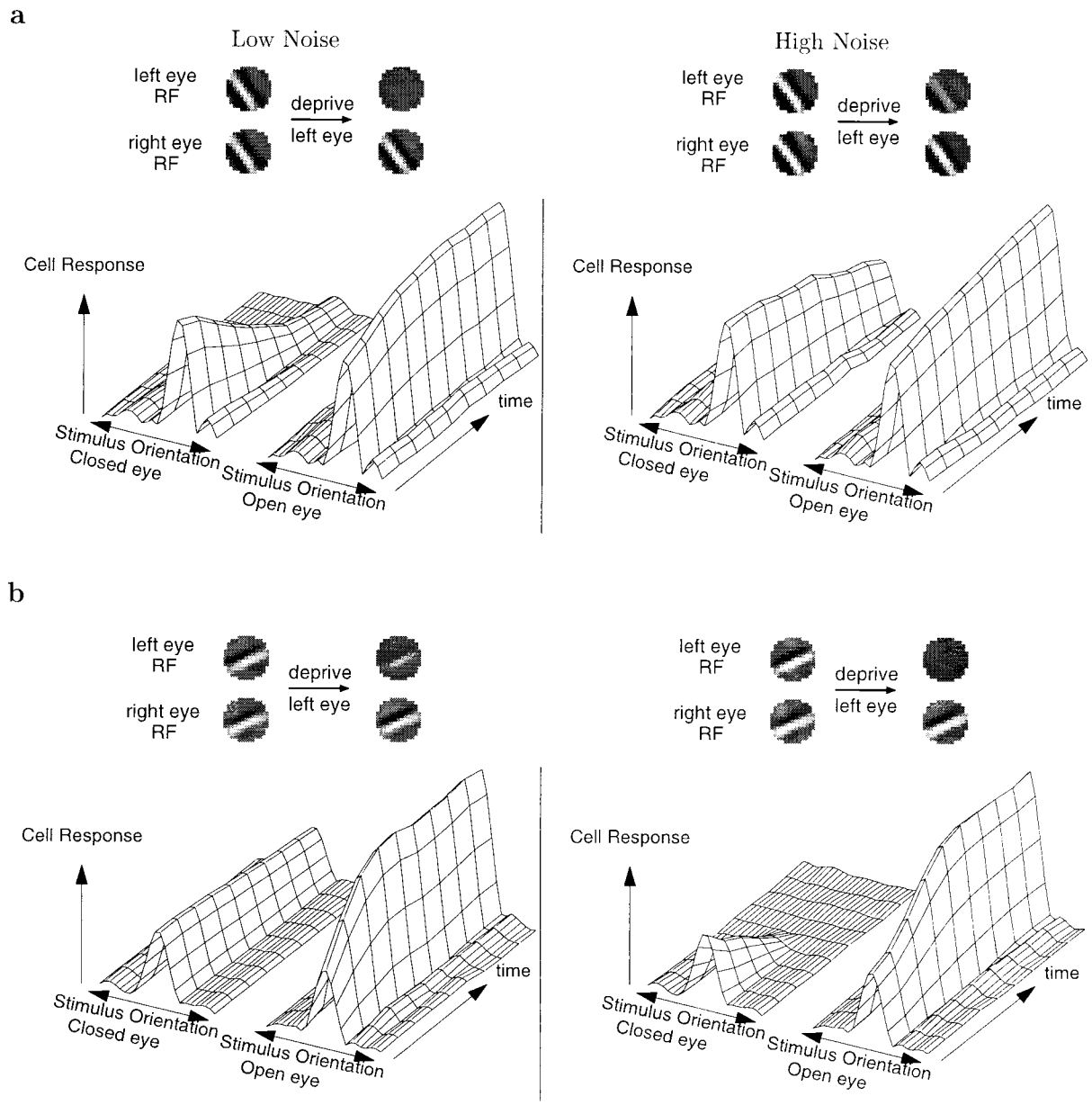

FIG. 1. The effect of noise from the closed eye on the disconnection of the closed eye in MD. (*a*) The heterosynaptic rule. K_2, as described in Blais *et al.* (10) and *Learning Rules*, is used to train a neuron in the natural scene environment to obtain binocular, oriented receptive fields (RF). Shown are the results of monocular deprivation starting from the binocular state. Left and right receptive fields (*Upper*), before and after depriving the left eye. Each pixel represents a point in space over the retina, where white and black correspond to strong and weak synaptic strengths, respectively, from that retinal input. The responses of the cell to oriented sine gratings (*Lower*) as a function of time during deprivation in a low-noise environment (*Lower Left*) and a high-noise environment (*Lower Right*). (*b*) The homosynaptic rule, BCM, is used to train a neuron. All of the conventions are the same as *a*. The two rules have the opposite dependence on the noise from the closed eye of the rate of disconnection of the closed eye in MD.

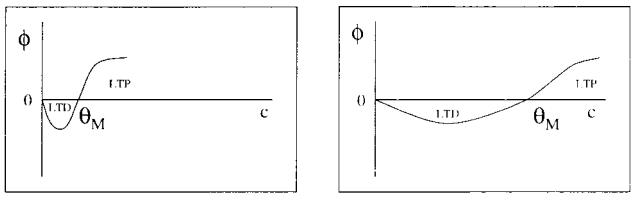

FIG. 2. BCM synaptic modification function. Shown is the function $\phi(c,\theta_M)$ as a function of c. This function determines the change in the weights, **m** (Eq. **2**). It is characterized by a negative region (LTD) for small postsynaptic depolarization, a positive region (LTP) for large postsynaptic depolarization, and a moving crossover point between LTD and LTP, θ_M.

where θ_M is the moving modification threshold and $\phi(c,\theta_M)$ is shown in Fig. 2. The moving threshold stabilizes the weights. The general form of BCM modification has been directly verified experimentally (17–19).

In normal visual environments, extensive simulations have shown that BCM synaptic modification leads to experimentally observed receptive fields (20) as well as to cells with varying ocular dominance (15, 16) and direction selectivity (21). Furthermore, such simulations have shown that in various deprived-visual environments, there is qualitative agreement between theory and experiment on the kinetics and final states of the receptive fields (21). Examples of BCM simulations in a visual environment composed of natural images (20) are shown in Fig. 3. These simulations illustrate how binocular BCM neurons develop in normal (Fig. 3, NR) and deprived visual conditions (see *Methods*). In these simulations, the closed-eye input is taken to be noise corresponding to the levels of lateral geniculate nucleus activity driven by input from the closed eye. A single set of parameters can be found such that both the final weight configurations and the time sequences are in qualitative agreement with experimental results for the various rearing conditions.

The effects of binocular deprivation (BD) are much less severe than those observed for MD (13, 14). This has led to the

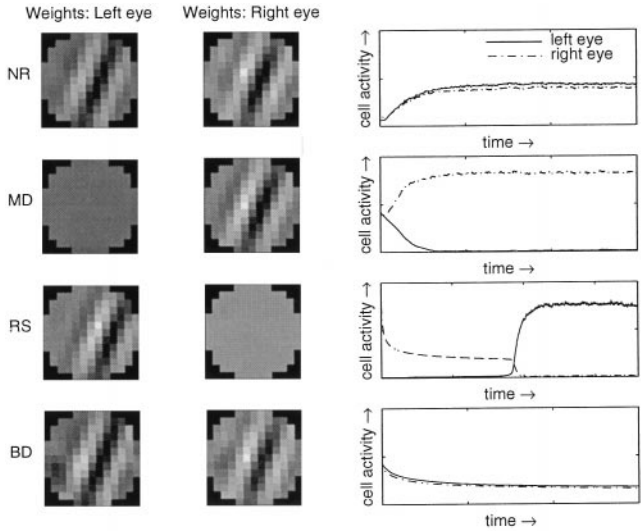

FIG. 3. Sample BCM Simulations. (*Left*) Final weight configurations, as described in Fig. 1. (*Right*) Maximum response to oriented stimuli, as a function of time. Simulations from top to bottom are as follows. Normal Rearing (NR): both eyes presented with patterned input. Monocular Deprivation (MD): after NR, the left eye is presented with noisy input and the right with patterned input. Reverse Suture (RS): after MD, the eye given noisy input is now given patterned input, and the other eye is given noisy input. BD: after NR, both eyes are given noisy input. It is important to note that if BD is run longer, selectivity will eventually be lost.

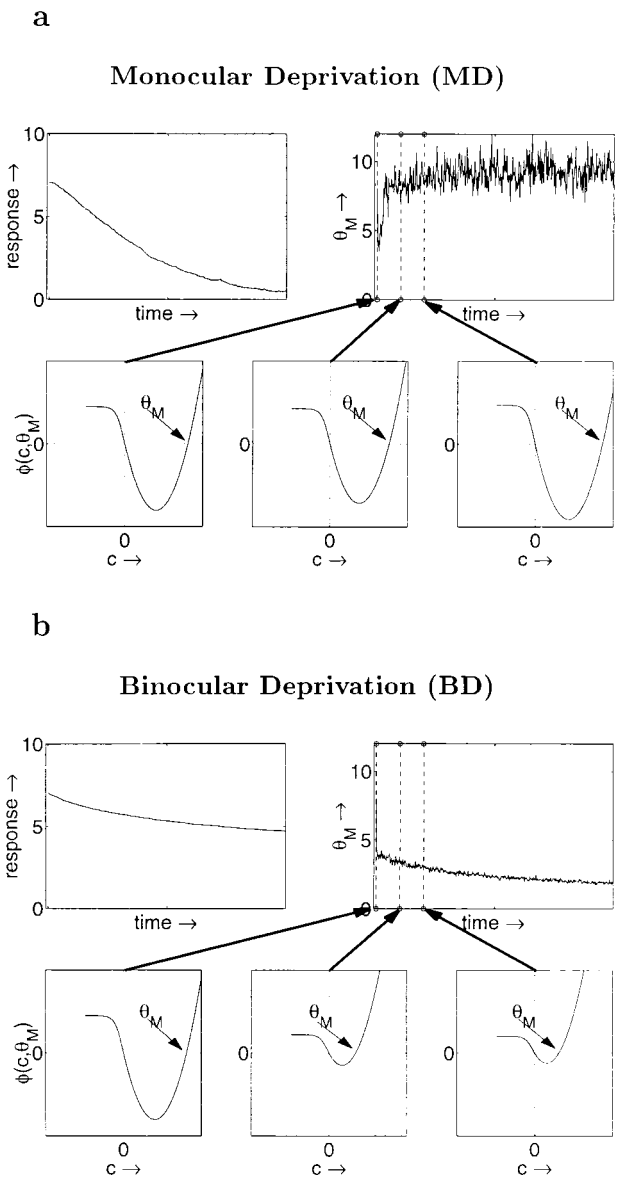

FIG. 4. Comparison between MD (*a*) and BD (*b*). (*a*) Shown is the response from the closed eye (*Upper Left*) and the modification threshold, θ_M (*Upper Right*), as functions of time during MD. Shown also is the modification function, $\phi(c,\theta_M)$ (*Lower*), sampled at three different time steps. During MD, the patterned input into the open eye keeps the modification threshold θ_M high, resulting in a more enhanced depression region of the modification function. (*b*) Same conventions as in *a*, but for BD. In BD, the unpatterned activity entering both eyes is insufficient to maintain the threshold at a high value, resulting in a significantly reduced depression. Eventually, binocularly deprived cells will lose orientation selectivity, but the time scale is much longer than that for the loss of response of cells to the closed eye in MD.

hypothesis that a spatially competitive process is at work. However, BD also can be produced by a homosynaptic mechanism. In the BCM theory, the difference between the rates of disconnection in BD and MD is the result of a moving threshold. This effect is illustrated in Fig. 4. During MD, the patterned input into the open eye keeps the modification threshold (θ_M) high, resulting in a large depression region of the modification function (Fig. 4*a*). In BD, the unpatterned activity entering both eyes is insufficient to maintain the threshold at a high value, resulting in a significantly reduced depression (Fig. 4*b*). Eventually, binocularly deprived cells lose orientation selectivity, but the time scale is much longer than for the loss of response to the closed eye in MD.

The noise dependence of the rate of disconnection of the closed eye in MD according to the BCM theory is obtained as follows. BCM modification (Eq. **2**) for the deprived channel in MD is.

$$\dot{\mathbf{m}}^{\text{closed}} = \phi(c, \theta_M)\mathbf{n}, \qquad [3]$$

where $\mathbf{n}$ is the presynaptic input from the closed eye and c is the postsynaptic response. By using a linear approximation, c becomes

$$c = \mathbf{m}^{\text{open}}\cdot\mathbf{d}^{\text{open}} + \mathbf{m}^{\text{closed}}\cdot\mathbf{n}. \qquad [4]$$

To best illustrate the effect, we calculate in the simplified situation in which the neuron has become selective to open eye inputs, so that $\mathbf{m}^{\text{open}}\cdot\mathbf{d}^{\text{open}} \simeq \theta_M$ or zero, and $c \simeq \theta_M + \mathbf{m}^{\text{closed}}\cdot\mathbf{n}$ or $\mathbf{m}^{\text{closed}}\cdot\mathbf{n}$, depending on whether the input to the open eye is a preferred or a nonpreferred pattern.

Near the two zero crossings, we can make a linear approximation to ϕ so that $\phi \simeq -\varepsilon_2 c$ near $c = 0$ and $\phi \simeq +\varepsilon_1(c - \theta_M)$ near $c \simeq \theta_M$. Here ε_2 and ε_1 are the slopes near zero and θ_M. Averaging over the noise input, for mean zero noise, we obtain for non-preferred input to the open eye

$$\dot{\mathbf{m}}^{\text{closed}} \simeq -\varepsilon_2\overline{\mathbf{n}^2}\mathbf{m}^{\text{closed}} \qquad [5]$$

and for preferred input to the open eye

$$\dot{\mathbf{m}}^{\text{closed}} \simeq +\varepsilon_1\overline{\mathbf{n}^2}\mathbf{m}^{\text{closed}}. \qquad [6]$$

For selective neurons, nonpreferred inputs greatly outnumber preferred inputs, so that

$$\log\left[\frac{\mathrm{m}^{\text{closed}}(t)}{\mathrm{m}^{\text{closed}}(0)}\right] \sim -\overline{\mathrm{n}^2}t. \qquad [7]$$

Thus, the rate of disconnection of the closed eye increases exponentially with increasing noise from that channel; faster disconnection occurs if the noise input from this deprived eye is greater. This is a subtle and counterintuitive consequence of the BCM theory. The results of this simplified analysis carry over into the more complex case of simulations using real images as input and learning rules of the homosynaptic class (Figs. 1 and 5).

DISCUSSION

We are thus capable of distinguishing between two contrasting points of view, both of which can account for the disconnection of the closed eye in MD but differ fundamentally in their dynamics and parameter dependence. Other rules have been proposed to account for segregation of ocular dominance columns (22, 23). These studies used environments and constraints that are not easily compared with the current work without the addition of extra assumptions. In most cases, however, when applied to the case of MD, these rules can be understood as correlational rules (24) and be categorized into the heterosynaptic class of learning rules.

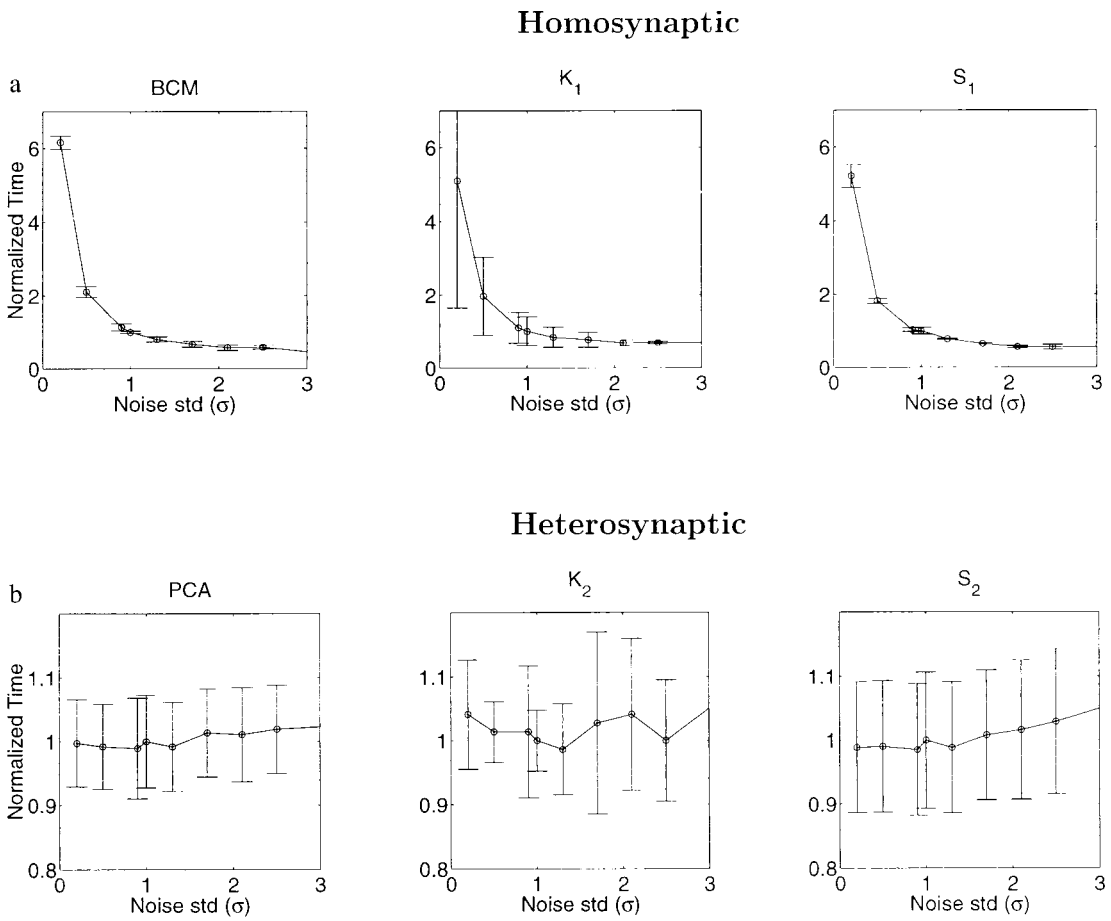

FIG. 5. Time for the disconnection of closed eye in MD as a function of the deprived-eye lateral geniculate nucleus activity (Noise). The times are scaled so that the time is set to 1 at a noise level of unit variance. (*a*) The rules in the homosynaptic class [Quadratic BCM, K_1, and S_1 as described in Blais *et al.* (10) and *Learning Rules*]. (*b*) The rules in the heterosynaptic class (PCA, K_2, and S_2). The homosynaptic class of learning rules have a faster loss of response to the closed eye for higher presynaptic activity levels in the closed eye channel. The heterosynaptic class of learning rules have the opposite behavior.

Recent experimental evidence (6) clearly is consistent with the predictions of the BCM theory and the other rules in the homosynaptic class.

It is important to note that these two classes of rules require different underlying molecular and physiological mechanisms. It is equally important that evolving experimental techniques will make it possible to determine the parameters of the theory with increasing precision. This will lead to deep insights into the mechanisms underlying learning and memory storage. In addition, these results may have clinical implications in the treatment of amblyopia (28).

LEARNING RULES

The following learning rules (derived in ref. 10) were explored.

Homosynaptic Class. *Quadratic BCM (25).*

$$\frac{d\mathbf{m}}{dt} = c(c - E[c^2])\mathbf{d}, \qquad [8]$$

where $E[\cdot]$ is approximated by the temporal average:

$$E[c^n(t)] \approx \frac{1}{\tau}\int_{-\infty}^{t} c^n(t')e^{-(t-t')/\tau}dt'.$$

Skewness 1. This learning rule is based on the statistical measure of skewness.

$$\frac{d\mathbf{m}}{dt} = c(c - E[c^3]/E[c^2])\mathbf{d}/E^{1.5}[c^2]. \qquad [9]$$

Kurtosis 1. This learning is based on the statistical measure of kurtosis.

$$\frac{d\mathbf{m}}{dt} = c(c^2 - E[c^4]/E[c^2])\mathbf{d}/E^{2}[c^2]. \qquad [10]$$

Heterosynaptic Class. *Skewness 2.* This learning rule is based on a different form of the statistical measure of skewness.

$$\frac{d\mathbf{m}}{dt} = c(c - E^{0.5}[c^2])\mathbf{d} - c^2(c - E^{0.5}[c^2])\mathbf{m}. \qquad [11]$$

Kurtosis 2. This learning is based on a different form of the statistical measure of kurtosis.

$$\frac{d\mathbf{m}}{dt} = c(c^2 - 3E[c^2]\mathbf{d} - c^2(c^2 - 3E[c^2]\mathbf{m}). \qquad [12]$$

Linear and nonlinear principal component analysis (PCA). This learning rule is a stabilized Hebb rule introduced by Oja (26) for performing PCA. The nonlinear version is a straightforward generalization of the original PCA rule.

$$\frac{d\mathbf{m}}{dt} = c\mathbf{d} - c^2\mathbf{m}. \qquad [13]$$

In all of the above learning rules, except for both versions of the PCA rule, the value of the activity of the cell is given by

$$c = s(\mathbf{m}\cdot\mathbf{d}), \qquad [14]$$

where $s(\cdot)$ is a nonlinear function of its argument. For linear, PCA the activity is given simply as $c = \mathbf{m}\cdot\mathbf{d}$. The nonlinear PCA rule uses a polynomial function, such as $s(\mathbf{m}\cdot\mathbf{d})^3$, which is not biologically plausible but has some nice mathematical properties (27). All of the other rules use the more realistic function

$$s(\mathbf{m}\cdot\mathbf{d}) = \begin{cases} s^+ \tanh(\mathbf{m}\cdot\mathbf{d}/s^+) \text{ for } \mathbf{m}\cdot\mathbf{d} \geq 0 \\ s^- \tanh(\mathbf{m}\cdot\mathbf{d}/s^-) \text{ for } \mathbf{m}\cdot\mathbf{d} < 0 \end{cases} \quad s(\cdot), \qquad [15]$$

where s^+ and s^- set the maximum and minimum activity levels, respectively.

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