

ROLE OF NEURAL ACTIVITY IN DEVELOPMENT AND PLASTICITY OF MAMMALIAN VISUAL CORTEX

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ABSTRACT

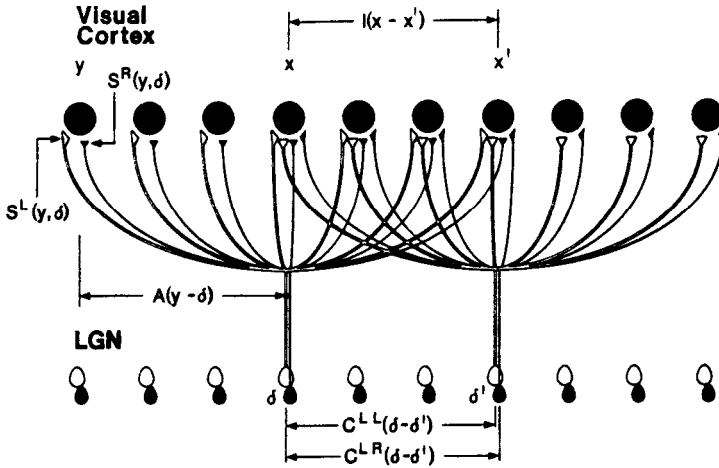
Previous experiments indicate that patterns of neural activity may guide the refinement of connections in developing visual cortex. Recent theoretical studies show that a Hebbian synapse at the input layer of the visual cortex can allow neural activity to guide the formation of ocular dominance columns, and that the widths of these columns are predictable from measurable biological parameters. New experiments show that neural activity in post-synaptic cortical cells plays a crucial role in the plasticity of ocular dominance columns.

Previous work has shown that ocular dominance columns in layer IV of cat visual cortex develop by a progressive segregation of geniculocortical afferents from an initial state of complete overlap at two weeks of age (20). During the period of segregation, and perhaps for a brief time afterward, the relative efficacy of the two eyes in driving visual cortical cells, and the sizes of ocular dominance patches in layer IV, may be influenced by alterations of neuronal activity (14, 34). We have shown that blocking neuronal activity by making repeated intraocular injections of tetrodotoxin (TTX) prevents ocular dominance segregation, but that vision is not required for segregation to take place (38). Instead, the maintained discharge of retinal ganglion cells in darkness is sufficient. These and other findings suggest that the correlated spontaneous discharge of neighboring retinal ganglion cells (23) acts to organize the central connections of their target cells, possibly through a Hebb-type synapse (reviewed in ref. 39, 40).

The notion that the visual cortex is a self-organizing biological system that re-

organizes itself under the influence of neural activity has prompted much experimental work and theoretical interest over the past 30 years. One approach we have taken toward understanding the properties of this network that allow it to organize itself is to construct a formal mathematical model of the system that incorporates the microscopic cellular properties that are believed to exist on experimental grounds. The mathematical model that we have constructed consists of a network of Hebbian geniculocortical synapses and various arrangements of fixed corticocortical synapses and afferent arbors (24, 25). The model has then been followed, from an initial state of diffuse connectivity through a stage of refinement to an ultimate stage of precise connectivity, by computer simulation and with analytic methods (21, 27).

The elements of the formal model, shown in Fig. 1, have been chosen so as to correspond to real biological features of the developing visual cortex (13). For this reason, the biologically realistic values of the important features of the model may be measured experimentally in kittens at the



$$\partial_t S^L(x, \delta, t) = \lambda A(x-\delta) \sum_{y, \beta} I(x-y) [C^{LL}(\delta-\beta) S^L(y, \beta, t) + C^{LR}(\delta-\beta) S^R(y, \beta, t)] - \text{DECAY}$$

$$\partial_t S^R(x, \delta, t) = \lambda A(x-\delta) \sum_{y, \beta} I(x-y) [C^{RR}(\delta-\beta) S^R(y, \beta, t) + C^{RL}(\delta-\beta) S^L(y, \beta, t)] - \text{DECAY}$$

Fig. 1 The elements of the model are illustrated in the above figure, from the manuscript by Miller and Stryker (27). 1) Afferents from the lateral geniculate nucleus ('LGN' in figure) project to the visual cortex. Afferents serving each of the two eyes, represented in the figure by the open and filled circles, make equivalent initial projections to the cortex. Synaptic interconnections between cortical cells are either excitatory (illustrated as more local, direct connections) and inhibitory (illustrated as more distant connections via inhibitory interneurons). 2) The afferents project in 'arbors', connecting to all cortical cells in a small region whose radius we call the 'arbor radius'; the strength of this arbor between a cortical point y and a geniculate point δ is given by the arbor function $A(y-\delta)$, which is zero outside the arbor radius. 3) The degree of correlation in firing among incoming afferents from retinotopic positions δ and δ' is represented by the correlation functions $C^{LL}(\delta-\delta')$, $C^{RR}(\delta-\delta')$ (not illustrated), and $C^{LR}(\delta-\delta')$ gives the correlation between a left eye afferent from δ and a right eye afferent from δ' , etc. 4) Each synapse has a physiological strength, which varies with time during development. This is illustrated by the functions $S^L(y, \delta)$ and $S^R(y, \delta)$. 5) Finally, there is some influence of activity at a cortical point x' on the strength of synapses at a cortical point x . This spread of influence, as a function of distance, is summarized in the corticocortical interaction function $I(x-x')$, which may be both excitatory and inhibitory at different distances. This influence is dependent on the biological particulars of one's cellular model of plasticity; hence, different biological models may yield different corticocortical influence functions, which in turn, via our mathematical model, may be seen to lead to different predictions as to the expected wavelength of the pattern of ocular dominance columns.

time ocular dominance columns begin to develop, allowing quantitative predictions of ocular dominance patch size. To date, however, most of these features have been measured only in adult animals, in which

the final patches in area 17 have a period of about $850 \mu\text{m}$ (1, 22, 33, 41). The four features model on which the model focuses are as follows:

1) The patterns of initial connectivity of

the afferents onto the cortical cells, incorporating the effects of the spread of afferent arbors and cortical dendrites. These are described by an 'arbor function'. Initial arbors may fill a region with diameter 1-1.5 mm (X-cells) or larger than 2 mm (Y-cells) (15, 19).

2) The patterns of activity in the geniculocortical afferents. For example, there is greater correlation between afferents from a single eye than between afferents from different eyes. These are described by a set of 'correlation functions'. In adult animals, afferents from a single eye appear positively correlated over distances of from 0.5 (X-cells) to 1.5 (Y-cells) of a geniculocortical arbor radius (23).

3) Influences acting laterally within the cortex, whereby synapses on one cell can influence the competition occurring on nearby cells. These influences may be described by a 'cortical interaction function' and may occur through corticocortical synaptic connections or diffusion of modulatory substances. Corticocortical synaptic interactions have been found to be excitatory at short range, and inhibitory out to about 400 μm (11, 12, 42).

4) Constraints on afferents or cortical cells, giving upper and/or lower limits to the total synaptic strength supported by a cell. The precise values of these constraints are unknown, but they may be estimated by measuring the variance of synapse sizes and numbers in normal development.

This model demonstrates that the proposed mechanism can give rise to the observed arrangement of ocular dominance columns (26). In addition, it reproduces the critical period of susceptibility to the effects of monocular deprivation (8, 14, 36, 44). We have also shown, however, that several different biologically reasonable synaptic mechanisms of plasticity may be reduced to the same mathematics, in which the terms of the formal mathematical model correspond to different aspects of the biological system. Therefore, agreement between the predictions of our initial model and the biological reality can not by itself be taken as strong evidence in favor of a particular synaptic mechanism of plasticity.

We have further explored the synaptic

mechanisms of plasticity in the developing visual cortex by concentrating on the role of postsynaptic cortical cell responses (32). The hypothesis about the mechanism of plasticity in development put forward by Hebb is that spike activity in the postsynaptic cell enhances the efficacy of recently active inputs (5, 9, 30, 37, 45). Hebb's hypothesis has been used to explain many instances of neural plasticity (6). This hypothesis stands in contrast to one favoring a purely presynaptic mechanism as was reported for classical conditioning in *Aplysia*, in which responses of cells were facilitated even while their somata were hyperpolarized by an intracellular microelectrode (4). In the visual (7, 17, 31, 35) and motor cortex (2), however, several types of evidence favor a mechanism of plasticity coupled to postsynaptic excitation.

Previous experiments in which a region of visual cortex was infused with tetrodotoxin (TTX) during a period of monocular deprivation demonstrated that activity at the level of the visual cortex is crucial for ocular dominance plasticity (31). Because TTX blocks pre- as well as postsynaptic activities in the visual cortex, these experiments could not answer the question as to which of the elements in the cortex need to be active in order for plasticity to occur. A logical approach to answering this question is to block just the postsynaptic elements involved in cortical synaptic plasticity. Since the neurotransmitter(s) used by the geniculocortical afferents are not known, we were unable to selectively block the postsynaptic effects of geniculocortical transmission. Instead, we emulated the *Aplysia* experiments of Carew *et al.* (4) and inhibited postsynaptic cortical neurons under circumstances in which, were these cells not inhibited, we would have expected plasticity. Unlike the *Aplysia* studies, in which inhibition was produced by an intracortical microelectrode, in the present experiments kitten cortical cells were inhibited pharmacologically. If the postsynaptic spike activity were a crucial element of the mechanism underlying ocular dominance plasticity, our expectation was that a selective blockade of this activity should prevent

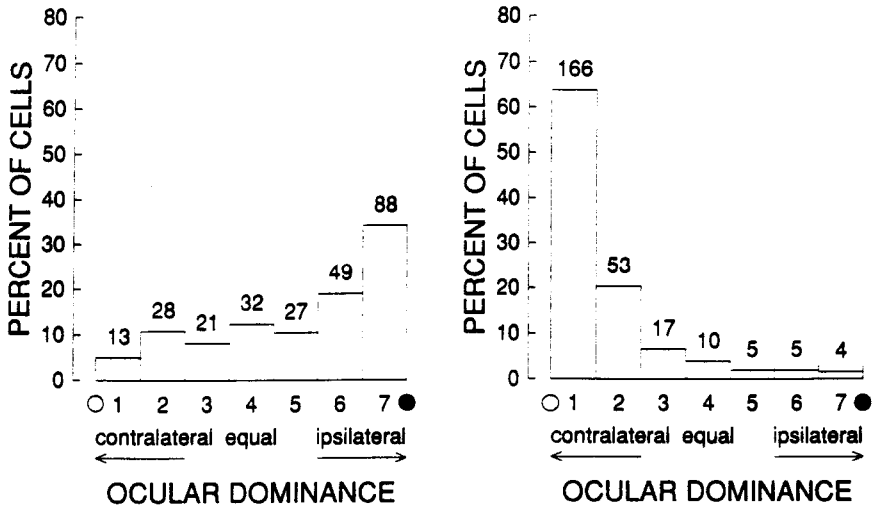


Fig. 2 Ocular dominance histograms compiled from single unit responses in area 17. Monocular eyelid closures were performed in different animals either ipsilateral or contralateral to the muscimol-infused hemisphere. Results are plotted as if the eyelid sutured was always ipsilateral to the treated hemisphere, and control recordings were obtained from unaffected regions of that hemisphere. That is, responses from single cells were plotted such that an ocular dominance of 1 indicates a cell driven only by the open eye; 7 a cell driven only by the closed eye; and 4 a cell driven equally by the two eyes. All animals received intracortical muscimol infusions for 8-10 days and were monocularly deprived for 5-7 days beginning 3 days after the onset of the muscimol infusion. The direction of ocular dominance shift within the area blocked by the muscimol infusion was the same in all animals tested and opposite to the direction of shift in control areas outside of the blockade. Left: Ocular dominance distribution of 258 visually responsive units recorded within the region of cortex in which discharges had been blocked by muscimol infusion during the period of monocular deprivation. Right: Ocular dominance distribution of 260 visually responsive units recorded in regions of cortex outside of the muscimol-induced blockade, including contralateral control hemisphere as well as unblocked areas anterior to the blocked region.

such plasticity.

To block postsynaptic activity selectively, we used the drug muscimol, an agonist of the inhibitory neurotransmitter GABA that is selective for the GABA_A-type receptor. GABA is the principal inhibitory neurotransmitter in cerebral cortex (16, 18). It is found in all layers (10), and it powerfully inhibits all or nearly all neurons (11). While the inhibitory action of GABA is generally associated with a direct postsynaptic effect (29), GABA has also been shown to have a presynaptic effect, namely that of reducing neurotransmitter release from presynaptic nerve terminals (3). In all cases, however, this activity has been shown

to be mediated through the GABA_B-type receptor, at which muscimol and other GABA agonists, such as THIP and 3-APS, are not or are only minimally active. In addition, muscimol binding can always be antagonized by bicuculline, a GABA antagonist active at the GABA_A-binding site, while the effects associated with binding to the GABA_B-receptor are completely or largely bicuculline-insensitive (3). In the kitten visual cortex, GABAergic inhibition is already present (43, 46), and muscimol appears to bind *only* to GABA_A-receptors (28).

We selectively blocked postsynaptic cortical cell discharges by using an osmotic

minipump to deliver a continuous intracortical infusion of muscimol during a period of monocular deprivation. As expected, this drug inhibited cortical cell discharges in a region of cortex extending 2–3 mm anterior to the cannula, with no apparent effect on the activity of their presynaptic geniculocortical inputs. Recording from single cortical cells after they had recovered from the muscimol-induced blockade, we found a consistent shift in the responsiveness of the visual cortex in favor of the less-active, *closed eye*, while the normal shift in favor of the more-active, open eye was evident in regions not affected by the treatment. These findings are illustrated in the ocular dominance histograms shown in Fig. 2. Such an inhibition-coupled expression of plasticity in favor of the less-active, closed eye cannot be explained by a non-specific disruption of cortical function. We interpret these results to indicate that, as postulated by Hebb, the postsynaptic cell is crucially involved in plasticity of the visual cortex. These results also suggest that the direction of cortical plasticity is controlled by postsynaptic membrane voltage or conductance. Finally, the results demonstrate that ocular dominance plasticity can occur in the absence of postsynaptic spike activity, suggesting that, contrary to Hebb's postulate, local responses rather than action potentials govern cortical plasticity.

The studies reviewed here were carried out principally by my students, Drs. K. D. Miller and H. O. Reiter, and constituted part of their Ph.D. dissertations. I am grateful to them for their energy and creativity.

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