

THE ROLE OF NEURAL ACTIVITY IN REARRANGING CONNECTIONS IN THE CENTRAL VISUAL SYSTEM

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Work in my laboratory has focused on the role of the electrical activity of young neurons in the development of the mammalian central visual system. What makes such a role likely is the fact that even the earliest processes of growing neurons are electrically excitable, capable of function long before there is anything obviously useful for them to do. In the visual system, for example, Shatz and Kirkwood (1984) have found effective retinogeniculate transmission during fetal life, when visual stimulation is completely lacking. Our experiments on the developing visual system are directed toward the hypothesis that the electrical activity of neurons plays a special role in early development, different from its role in later life. The evidence reviewed below suggests that patterns of spontaneous electrical activity, present even in the absence of an adequate stimulus, are involved in the refinement of neuronal connections that leads to the formation of the adult nervous system. Rubel (this volume) has evidence that similar principles may obtain in the developing auditory system; indeed, in that system, spontaneous activity appears to be necessary even for the survival of some central neurons.

Development of ocular dominance columns depends on electrical activity

For proper development of the visual cortex, the principal input neurons (from the lateral geniculate nucleus) must first grow their axons to the right area of the brain, and there they must form a single continuous retinotopic map. These earliest stages of development seem unlikely to depend on electrical activity. Rakic (1977) has shown that areal specificity is present during a prolonged waiting phase in which the geniculocortical afferents ramify within the cortical sub-plate; this takes place at a time before the neurons with which they will ultimately form their synaptic connections have migrated into the visual cortex. While there is as yet no direct evidence for the mammalian visual cortex, Harris (1981), reviewing evidence from the fish and amphibian retinotectal system, concludes that at least coarsely organized maps can form in the absence of electrical activity.

Next, the geniculocortical and local corticocortical connections must reorganize so as to endow the visual cortex with a single array of orientation columns, used in common by inputs from the two eyes. The role of visual experience in the development of orientation columns has been a topic of controversy over the years. Microelectrode recording studies, beginning with the report of Hubel and Wiesel (1963), have disclosed variable numbers of single neurons selective for stimulus orientation in very young, visually inexperienced kittens (see reviews in Fregnac & Imbert, 1984; Movshon and VanSluyters, 1981; Sherman & Spear, 1982). In neonatal monkeys, physiological recordings reveal an arrangement of orientation-selective neurons very similar to that in adult animals (Wiesel and Hubel, 1974), making it unlikely that visual experience plays an important role in the development of the orientation columns. Prolonged dark-rearing or bilateral lid-suture, however, causes many neurons to become poorly responsive to visual stimuli or unselective for stimulus orientation, leaving only a few selective neurons (see Hirsch and Leventhal, 1978, for review). This finding, and those of selective orientation-deprivation experiments, suggests a role for visual experience at least in the maintenance of orientation columns (Stryker et al., 1978). It is not yet known whether spontaneous electrical activity is important for the development of orientation columns.

Finally, and only after the retinotopic map and orientation columns have formed, the continuous and overlapping geniculocortical projections serving the two eyes must segregate within layer IV to form ocular dominance columns. A cartoon illustrating the organization and development of ocular dominance columns in the retino-geniculo-cortical visual system is shown in Figure 1. For the purpose of this discussion, we may simplify this system down to its essentials: the projection from the ganglion cells of half of each retina to adjacent laminae of the lateral geniculate nucleus (LGN) of the thalamus, the principal cells of which relay the visual signal to the major input layer, layer IV, of the visual cortex. Within layer IV of the visual cortex of many adult carnivores and primates, the geniculocortical projection takes the form of alternating patches or bands of inputs serving the two eyes; these bands constitute the basis of the ocular dominance columns.

These ocular dominance columns develop gradually, out of initially completely overlapping projections serving the two eyes. During the period in which afferents serving the two eyes are segregating, and for a short time thereafter, this system is strikingly plastic. At this critical period of life, even a brief period of unequal competition between the two eyes--produced, for example, by blurring or occluding the vision of one eye while the other eye continues to see well--results in the restriction of one eye's territory in the

visual cortex and the corresponding enlargement of the territory serving the other eye. After this critical period in early life, the effects of deprivation appear to be irreversible.

Hubel et al. (1977), LeVay and Stryker (1979), and LeVay et al. (1980) review evidence that such plasticity appears to be an abnormal outcome of the normal developmental rearrangement of axonal arbors and synaptic connections. While much of this development takes place in utero in the monkey (and presumably in humans), the normal segregation of geniculocortical axon arbors does not begin until after two weeks of postnatal life in the cat (LeVay et al., 1978), allowing easy experimental intervention. Stryker and Harris (1986) showed that, as expected from the findings in the monkey, ocular dominance columns formed in the absence of visual experience in dark-reared or bilaterally lid-sutured kittens. The columns did not form, however, when the spontaneous discharge of retinal ganglion cells in the two eyes was blocked by infusions of the voltage-sensitive sodium channel blocker, tetrodotoxin (TTX). The physiological effect of this blockade was to prevent neurons in visual cortex from coming to be dominated by one eye or the other, as they do in normal development and did in various control experiments illustrated in Figure 2.

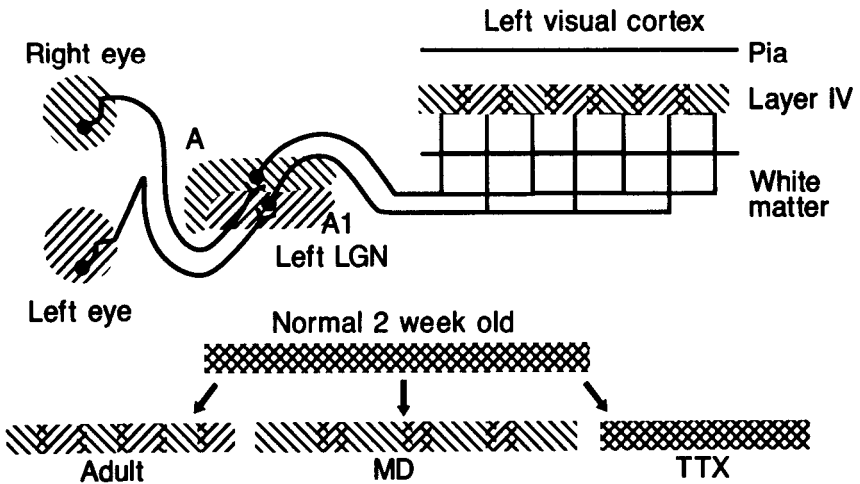


Fig. 1. Cartoon showing (top) the arrangement of the retino-geniculo-cortical projection to area 17 in the normal adult cat; (middle) the arrangement of geniculocortical afferents serving the two eyes in normal two week old kittens, before the beginning of binocular segregation; and in (bottom) normal adult animals, animals monocularly deprived of visual experience during a critical period in early life (MD), and animals deprived of impulse activity in both optic nerves (TTX) below. Regions serving the two eyes are indicated by different hatching. Note that the complete overlap of the two eyes' influences within cortex at two weeks of age persists only in the case of impulse blockade.

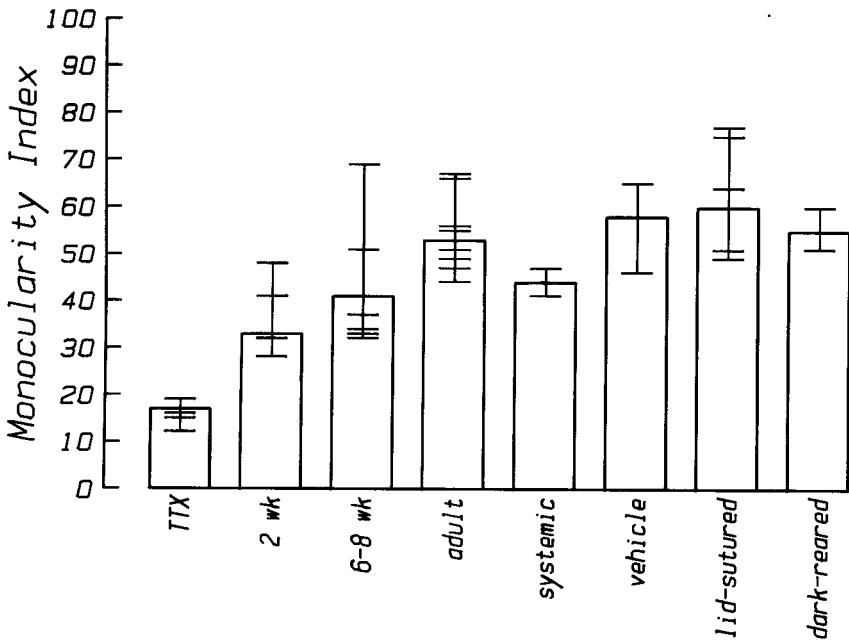


Fig 2. Monocularity indices, the physiological index of binocular segregation in visual cortex, calculated as described from 8 groups of animals studied by Stryker and Harris (1986). Histogram bars show the values of this index for the pooled data from each group. Data from individual animals are indicated by short horizontal lines; vertical error bars display the range of data within each group. 'TTX' indicates animals studied at 6-8 weeks of age following a period of complete binocular impulse blockade begun at about 2 weeks of age. '2 wk', '6-8 wk', and 'adult' show data from normal animals of the ages indicated. 'Systemic' control animals received more TTX than the experimental group but as a systemic dose so that impulse activity in the visual system was normal; 'vehicle' control animals received treatments identical to the experimental group except that the TTX was left out of the buffer solution in which it was normally suspended. 'Lid-sutured' and 'dark-reared' animals were completely deprived of visual experience until more than 8 weeks of age. Note that data from experimental group is out of the range of variation found in normal animals; while data from all control groups overlap with normal data.

What is the role of electrical activity in the development of ocular dominance columns?

The different effects of dark-rearing and retinal impulse blockade strongly suggest that the spontaneous electrical activity of retinal ganglion cells plays an important role in the development of ocular dominance columns in the visual cortex, for the presence or absence of spontaneous activity is major difference between these two treatments. Experiments by Mastrorarde (1983b) and others (Rodieck, 1967; Arnett, 1978; Arnett and Spraker, 1981) have revealed that the spontaneous discharge of retinal ganglion cells is not completely random. Instead, there are patterns of spontaneous discharge activity, even in

darkness. In uniform illumination, or even in total darkness, the discharges of neighboring ganglion cells of the same center type are closely correlated over a few to a some tens of milliseconds. There are also longer term (minute to few minute) fluctuations in the discharge rates of retinal ganglion and lateral geniculate neurons in darkness, in which the activity is correlated within one eye but not between the two eyes (Rodieck and Smith, 1966; Levick and Williams, 1964).

One may hypothesize that the spontaneous electrical activity in the developing visual system plays an instructional role. Under an instructional hypothesis, it is the pattern rather than the amount of activity that is important for development. Patterns of spontaneous discharge like those that are actually present in adult animals could be the source of the information that distinguishes the geniculocortical afferent terminals serving the left eye from those serving the right eye, allowing them to segregate into eye-specific patches. Thus, the pattern of spontaneous activity present in normal development could play an instructional role in the formation of ocular dominance columns if geniculocortical connections were to develop out of their overlapping state by aggregating the the terminals that were simultaneously active, and segregating those with different activity.

An alternative hypothesis is that the requirement for electrical activity in the development of this system is merely permissive. It is possible that the lateral geniculate nucleus and visual cortex are made generally dysfunctional by retinal activity blockade, and that the failure of ocular dominance segregation under these conditions is a nonspecific effect due to a reduction in the amount of impulse activity.

The instructional hypothesis is consistent with inferences made from studies of experimental strabismus and alternating monocular occlusion, in which binocular segregation appeared to be enhanced by projecting different images onto corresponding points in the two eyes (Hubel and Wiesel, 1965; Van Sluyters and Levitt, 1980). Such manipulations were presumed to disrupt the similarity between the discharge patterns of retinal ganglion cells in the two eyes that would ordinarily be produced by binocular visual stimulation. It has been hypothesized that the maintenance of binocular connections required such a similarity between the discharge patterns in the two eyes (Blasdel and Pettigrew, 1979). The notion of the "Hebb synapse", one in which the synaptic connection becomes stronger as a result of the correlation between presynaptic and postsynaptic activity, was proposed to account for such a loss of cortical binocularity upon disruption of binocular visual stimulation, and various physiological mechanisms were proposed for constructing such a correlation-sensitive synaptic connection (Stent, 1973; Changeux and Danchin, 1976).

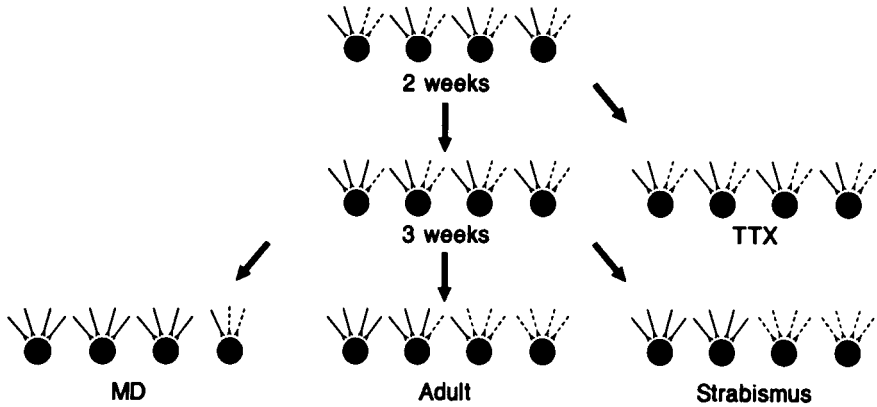


Fig. 3. Cartoon illustrating the process of binocular segregation in terms of presynaptic cortical terminals (dashed and solid lines) contacting cortical cells (black circles). 'Strabismus' refers to animals subjected to experimental strabismus during critical period; other labels as in Fig. 2. See text for discussion.

The instructional hypothesis is particularly attractive because it can be used to explain not only the TTX findings but also, at least in a general way, both the normal development of ocular dominance columns and all of the various forms taken by ocular dominance columns under different conditions of visual deprivation. Figure 3 shows a cartoon of the axon terminal rearrangements that are thought to underly the normal development of ocular dominance columns and their abnormal development resulting from early monocular visual deprivation (MD), experimental strabismus, and binocular impulse blockade (TTX). Under the instructional hypothesis, one can explain the various developmental outcomes as follows: At 2 weeks of age, terminals serving the left and right eyes are approximately uniformly distributed among the postsynaptic cortical cells. In normal development, small local fluctuations in the relative density of terminals serving the two eyes become magnified over the following weeks as, wherever one eye is slightly more effective than the other eye, the discharges of the terminals serving the more effective eye become more closely correlated with those of the postsynaptic cell, leading to a strengthening of their connection. Because the spontaneous discharges of the terminals serving one eye are correlated with one another, but not with those of the terminals serving the other eye, the terminals of the more effective eye on a particular postsynaptic cell reinforce one another; thus competing with those of the other eye for available synaptic space. Eventually in normal development, as the animal spends an increasing fraction of its time awake and alert, with proper eye alignment and simultaneous binocular vision, visual stimulation causes the

discharges to become correlated between the two eyes, ending the process of binocular segregation short of completion. In the case of experimental strabismus, visual stimulation would not cause the discharge activities of the two eyes to become correlated, and the segregation process is enhanced over that in normal development. In the case of monocular deprivation, the enhanced correlation of discharge produced by visual stimulation of one eye competes successfully against the lower level of correlated discharge in the occluded eye. In animals treated binocularly with TTX, rearrangement of terminals would not take place without discharge activity.

Experiments to test whether electrical activity plays an instructional role in the development of ocular dominance columns.

At least three experimentally testable predictions would follow from the instructional role hypothesized for electrical activity in the development of ocular dominance columns: (1) If the process is as simple as hypothesized, then monocular deprivation effects should be produced by any significant difference between the amounts of electrical activity transmitted to the brain from the two eyes; these effects should not require behaviorally significant visual stimulation. (2) The relevant electrical activity for ocular dominance plasticity should be that involving geniculocortical afferents and their postsynaptic cells in the cortex. (3) Controlled patterns of activity in the two eyes should produce different outcomes for the development of ocular dominance columns depending on whether the activity occurs simultaneously or asynchronously in the two eyes. Recent experiments have tested all three of these predictions, and the outcomes are in accord with an instructional role for electrical activity.

Ocular dominance plasticity without useful vision. In order to determine whether visual stimulation was necessary for plasticity of ocular dominance columns during the critical period, Chapman et al. (1986) reared kittens in which one eye was deprived of vision, but retained its spontaneous electrical activity, and the other eye was deprived of both vision and spontaneous electrical activity by intraocular injection of TTX. After a week of such treatment at the height of the sensitive period, the retinal blockade was allowed to wear off while both eyes were deprived of pattern vision, and microelectrode recordings were carried out to determine whether the ocular dominance had shifted toward the more-active visually-deprived eye. The left half of Figure 4 displays indices of the bias in the resulting ocular dominance distributions; these clearly show that pattern vision (in the case of the TTX-versus-lid-suture group) or, indeed, any vision at all (in the case of the TTX versus dark group) is not necessary for ocular dominance plasticity. Spontaneous activity alone was sufficient.

Activity blockade in cortex prevents ocular dominance plasticity. Many earlier studies had supported the notion that the activity of neurons in the cortex and their presynaptic inputs was necessary for the plasticity of ocular dominance columns (Cynader and Mitchell, 1977; Rauschecker and Singer, 1981; Shaw and Cynader, 1984; Carlson et al., 1986). One direct test of this notion was to see whether blocking electrical activity in the cortex would prevent ocular dominance plasticity. Reiter et al. (1986) carried out monocular deprivation on kittens in which electrical activity was prevented in a defined region of cortex by infusing it with TTX. The result of this experiment, illustrated in the right half of Figure 4, was that plasticity was completely prevented by the blockade of activity in the geniculate afferent terminals and cortical cells.

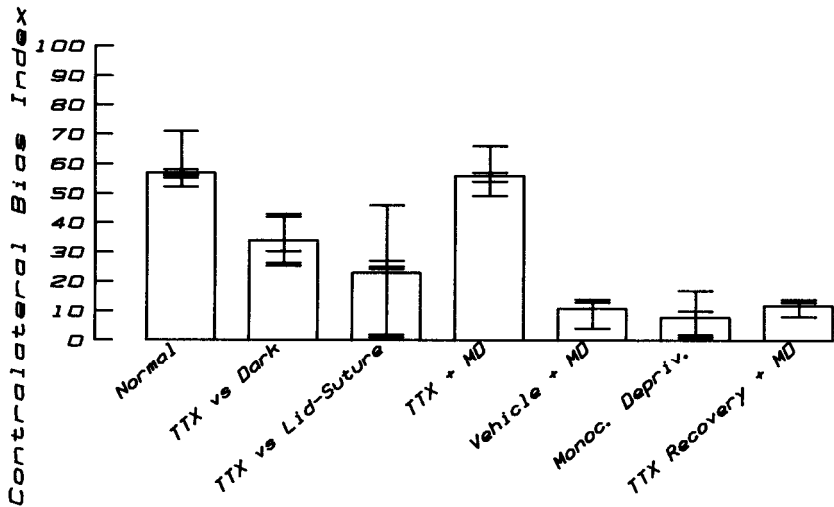


Fig. 4. 'Contralateral Bias Index' (calculated as described in Chapman et al., 1986) of ocular dominance plasticity on the ordinate, plotted like the monocular index of Fig. 2. The first three groups shown are from data of Chapman et al. (1986); the last four groups are from Reiter et al. (1986). Note that data from TTX-vs-Dark or TTX-vs-Lid-Suture experimental groups are out of the range of data from normal control animals, and that neither group of experimental animals was so strongly shifted as conventionally monocularly deprived ('MD') animals. In contrast, data from the 'TTX + MD' cortical blockade experimental group are indistinguishable from normal, and are very different from treatment with vehicle solution ('Vehicle + MD'), conventional monocular deprivation ('MD'), or monocular deprivation after recovery from the effects of a cortical TTX blockade ('TTX Recovery + MD').

Controlled patterns of activity. The previous two results demonstrate that electrical activity, rather than vision alone, in the cortex, rather than at some earlier stage, is crucially involved ocular dominance plasticity. But they are not strong tests of any particular mechanism by which activity might be responsible for the development of ocular dominance columns. The final

experiments attempt to control the patterns of activity in the developing visual system, and if the hypothesis of an instructional role for electrical activity is correct, thereby to control the development of ocular dominance columns. Because we do not know how to control the spontaneous electrical discharge in the retina, our strategy has been to eliminate all naturally-occurring discharge activity coming from the eyes to the brain. We then introduce controlled patterns of activity using stimulating electrodes in the optic nerves or tract.

We raised two groups of kittens with binocular impulse blockade during the period of cortical binocular segregation in normal animals, from 2 weeks until 6-8 weeks of age. We have previously shown that this treatment alone completely blocks binocular segregation. In one group of 3 kittens, cartooned in Figure 5, we placed chronic stimulating electrodes into both optic nerves. Through these electrodes we delivered electrical activity alternately to the two nerves in the pattern shown. Any mechanism for binocular segregation that depends on the correlation of activity within each eye or the lack of such correlation between the two eyes should proceed easily in these animals. In a second group of 5 kittens, cartooned in Figure 6, we placed a chronic stimulating electrode into the optic tract. Through this electrode we delivered electrical activity simultaneously to the retinal ganglion cell axons in the two optic nerves in the pattern shown. Any such correlation-sensitive mechanism for binocular segregation should fail under these conditions, since there is the same correlation between terminals serving the two eyes as there is within the population of terminals serving one eye. Because both nerve and tract electrodes delivered maximal X and Y volleys, the amount and pattern of activity within each optic nerve was exactly the same under the two conditions. Thus, if the role of activity is permissive, the two experimental conditions should have identical outcomes. If, on the other hand, the role of activity is instructional, one would expect opposite outcomes of the two conditions.

The predictions indicated in the cartoons were borne out by the results of these experiments. Figure 7 shows that these two experimental conditions have opposite outcomes for our physiological index of binocular segregation. The data from animals treated with simultaneous activation of afferents from the two eyes (O.T. Stim) is indistinguishable from those from animals treated with binocular impulse blockade alone (TTX), and more binocular than normal animals of the same age (6-8 wk). In contrast, the data from animals treated with alternate activation of the two optic nerves (O.N. Stim) is dramatically less binocular than was seen in any of the other experimental or control groups, and is similar to that found in animals subjected to experimental strabismus or alternating monocular occlusion. In the alternate stimulation group, ocular dominance columns were also evident in the clustering of neurons encountered

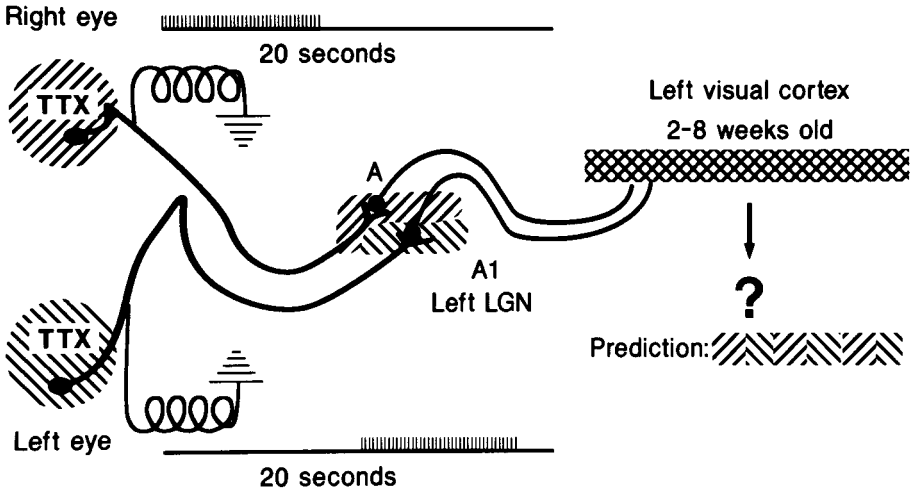


Fig. 5. Cartoon illustrating the placement of stimulating electrodes, time course of electrical stimulation, and predicted outcome for alternate optic nerve stimulation experiment described in text. Conventions as in Fig. 1.

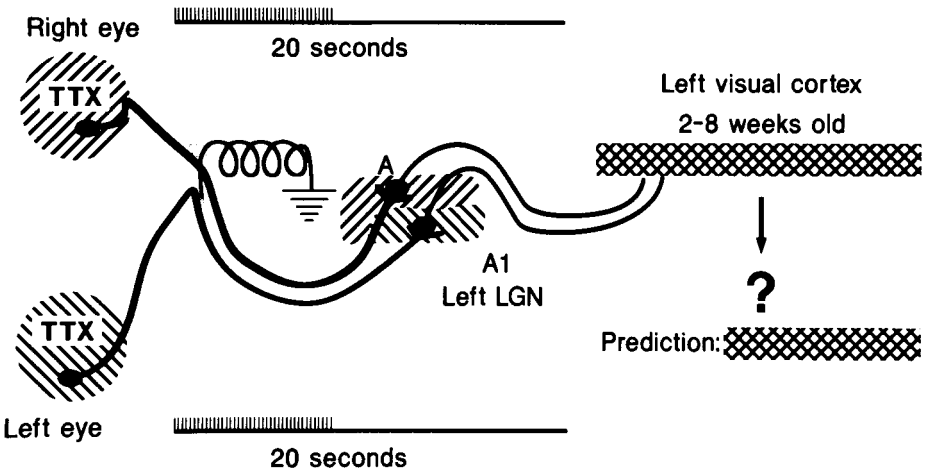


Fig. 6. Cartoon illustrating the placement of stimulating electrode, time course of electrical activation of the two optic nerves, and predicted outcome for experiment on simultaneous optic nerve activation through optic tract stimulation. See text for description. Conventions as in Fig. 1.

successively along electrode tracks according to eye preference; whereas nearly all neurons were equally driven by the two eyes in the simultaneous stimulation group.

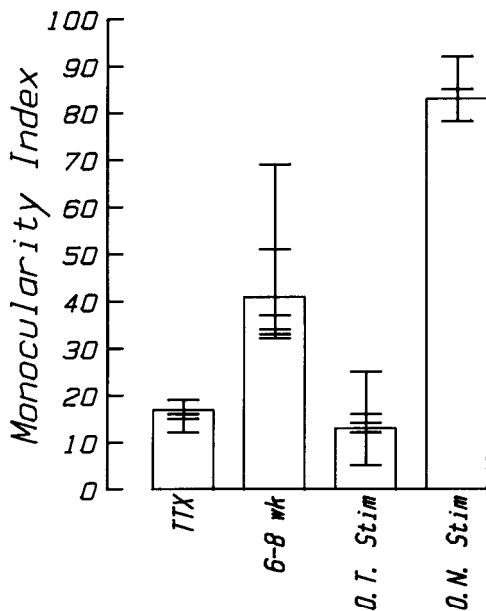


Fig. 7. 'Monocular Index' of binocular segregation like that shown in Fig. 2. See text for explanation.

Conclusion

These findings provide strong support for the notion that the timing of electrical activity plays an instructional role in the formation of cortical ocular dominance columns. It is tempting to speculate that the mechanisms underlying such activity-dependent synapse rearrangement may be quite general in the developing nervous system, and may be responsible for much of the specificity that is attained during fetal and neonatal life. The fact that spontaneous electrical activity appears to be sufficient, at least in some circumstances, to drive these mechanisms suggests that they could operate in utero. Recent findings on the developing retinogeniculate projection in fetal kittens support this notion (Shatz and Stryker, 1986).

We still know little, however, about the mechanisms that underly this process, other than their dependence on patterns of activity. To reveal the cellular basis of these mechanisms is a major new goal.

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