Review

A reassessment of the role of activity in the formation of eye-specific retinogeniculate projections

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ABSTRACT

In all mammalian species the projections from the two eyes to the dorsal lateral geniculate nucleus of the thalamus terminate in separate layers or territories. This mature projection pattern is refined early in development from an initial state where the inputs of the two eyes are overlapping. Here I discuss the results of studies showing that the formation of segregated eye-specific retinogeniculate projections involves activity-mediated binocular competition. I conclude that while retinal activity undoubtedly is involved in this process, the results of recent studies cast doubt on the prevalent notion that retinal waves of activity play an instructional role in the formation of segregated retinal projections.

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1. Introduction

Based on the stationary images Ramon y Cajal observed under his microscope, he was able to deduce a number of astonishing facts about the development and plasticity of neurons. Mostly everyone is familiar with his proposal that extension of developing axons occurs by means of growth cones sensing chemicals that signal their direction of growth. Today the discovery of these signals, and the means by which they regulate axonal growth and direction, is a major theme in molecular neuroscience. Perhaps less well known is the fact that Cajal also proposed the notion that early neuronal connections are often exuberant and that “exercise or use” promoted the formation of certain connections while disuse resulted in the loss of others (DeFilipe, 2006). Knowledge of neuronal physiology was primitive at the time, but Cajal's
widespread terminal arbors (Sretavan and Shatz, 1986a,b) as in the cat, there is evidence that retraction of initially exuberant retinal inputs. For instance, with respect to the cellular events underlying the gradual postnatal life. There also appear to be species differences where the inputs of the two eyes are overlapped. This proposal clearly presupposes that the activity of neurons is involved in the refinement of early exuberant connections. One hundred years after Cajal was awarded the Nobel Prize for Physiology and Medicine the fact that neuronal activity plays a role in the development of the nervous system has been unequivocally demonstrated by numerous studies at virtually every level of the nervous system. What is still debated, however, is what features of neuronal activity regulate which aspects of development, as well as the mechanisms by which such activity strengthens and weakens specific connections between neurons.

For many decades the visual system, and in particular, the connections between the two eyes and the visual centers of the brain, have served as a model for studies dealing with neuronal development and plasticity. Here I provide an overview of the literature dealing with the role of activity in the formation of segregated left and right eye inputs to the dorsal lateral geniculate nucleus. Until recently, the paramount role of neuronal activity in this developmental process seemed to be firmly established. But now, several studies have raised questions about the main tenets of this widely accepted premise.

This essay will be divided into four parts. First, I will provide some relevant background information on the organization and development of projections from the two eyes to the dorsal lateral geniculate nucleus (dLGN). Next I will summarize the results of some of the studies that support the notion that one particular type of activity, aptly described as retinal waves, plays an instructional role in the formation of segregated eye-specific retinal-dLGN projections. I will then discuss the results of studies that question this prevalent viewpoint, and also consider future research directions that could reconcile some of the seemingly diverse findings in this field. Readers are directed elsewhere for fuller accounts of this topic (Chalupa and Huberman, 2004; Huberman and Chapman, 2006).

2. Relevant features of developing retinogeniculate projections

Retinal ganglion cells from both eyes project to the dLGN in all mammalian species, and the territory innervated by the crossed retinal input is segregated from that of the uncrossed retinal input. Such segregation of retinogeniculate projections, which is a hallmark of the visual system of adult animals, is established during early development from an initial pattern where the inputs of the two eyes are overlapping. This progression from overlapping to segregated retinogeniculate projections was first described about 30 years ago in the fetal monkey by Rakic (1976), and since that time it has been observed in many other species (Chalupa and Dreher, 1991). The timing of this event differs in different species; in some animals, such as cat and monkey it occurs in utero, while in others, such as ferret and mouse, it takes place during postnatal life. There also appear to be species differences with respect to the cellular events underlying the gradual refinement of initially exuberant retinal inputs. For instance, in the cat, there is evidence that retraction of initially widespread terminal arbors (Sretavan and Shatz, 1986a,b) as well as the loss of inappropriately projecting retinal ganglion cells (Williams et al., 1983; Chalupa et al., 1984) is responsible for this process. By contrast, in the fetal monkey retinogeniculate terminals show no evidence of early exuberance (Snider et al., 1999), and ganglion cell loss is thought to be solely responsible for the shift from the overlapped to the segregated state.

This brief description of the sequence of events leading to the formation of the mature retinogeniculate pathway raises two related questions: why are retinal projections initially overlapping and what causes the inputs from the left and right eye to become segregated? The former can only be addressed meaningfully when an answer to the latter question becomes apparent.

3. Role of activity in formation of segregated retinogeniculate projections

The seminal studies of Wiesel and Hubel on the development of ocular dominance columns demonstrated in a dramatic fashion that balanced visual stimulation of the two eyes is required for this feature of the visual cortex to form normally (Wiesel, 1982). Their model of activity-based binocular competition appeared to follow Hebb’s (1949) postulate whereby cells that fire together wire together. It seemed logical to extend this powerful concept to the development of segregated retinogeniculate projections. The fact that binocular competition plays a role at this level of the visual system was demonstrated by the finding that removal of an eye in a developing animal, at a time when retinal projections from the two eye were overlapping, resulted in the maintenance of a widespread projection from the remaining eye (rat: Lund et al., 1973; macaque: Rakic, 1981; cat: Chalupa and Williams, 1984; ferret: Guillery et al., 1985). Shatz and Stryker (1988) obtained the first evidence that this binocular competition is based on neuronal activity. They showed that infusion of tetrodotoxin (TTX), the sodium voltage-gated channel blocker that abolishes action potentials, into the region of the optic tract of a fetal cat prevented the formation of eye-specific retinogeniculate projections. This was found to reflect an abnormal increase in the size of individual retinogeniculate arbors in the TTX-treated animals (Sretavan et al., 1988).

The next crucial piece of this story was provided by heroic studies from Lamberto Maffei’s laboratory in Pisa. These investigators made extracellular recordings from retinal ganglion cells of embryonic rats and discovered that ganglion cells periodically discharge spontaneous action potentials (Galli and Maffei, 1988); moreover the firing patterns of neighboring cells (recorded by one microelectrode) were found to be correlated (Maffei and Galli-Resta, 1990). This work was followed by multi-electrode recordings in Denis Baylor’s laboratory at Stanford, using an isolated retinal preparation obtained from developing ferrets. Such recordings revealed in greater detail the spatial–temporal pattern of spontaneous retinal discharges (Meister et al., 1991). It has now been shown in a number of species that the developing retina is characterized by periodic waves of activity whereby closely positioned ganglion cells fire in synchrony (Wong, 1999). Such
waves sweep across the retinal surface in seemingly random fashion. Thus, the pattern of activity in one eye is assumed to be entirely random with respect to the pattern of activity in the other eye.

These observations cemented the link between the Hebbian postulate and the processes underlying the formation of eye-specific retinogeniculate projections. During the developmental period when the projections from the two eyes are overlapping, dLGN cells that are binocularly innervated would receive correlated discharges stemming from one eye or the other, but these would occur at different times and be of unequal intensity. The inputs that are stronger functionally from a given eye would tend to more often depolarize the postsynaptic dLGN neuron so that connection would be strengthened, while the weaker functional inputs stemming from the other eye would be lost. Moreover, multiple lines of evidence suggested that Hebbian synaptic strengthening and weakening are mediated through NMDA receptors (Cline, 1987; Ramoa and McCormick, 1994).

Thus, a consensus was reached that retinal discharges, and in particular retinal waves, are responsible for the formation of eye-specific retinogeniculate projections. A number of review articles were published in influential journals making this point unequivocally. For instance, Katz and Shatz (1996) wrote, “the emergence of adult patterns of connectivity requires correlated neural activity among sets of inputs.” Others reiterated this point by stating “patterned neuronal activity is required for eye-specific segregation of inputs within the dorsal lateral geniculate nucleus” (Cohen-Cory, 2002). And more emphatically, it was written, “activity plays an instructive rather than permissive, role in the development of the dorsal lateral geniculate nucleus” (Sengpiel and Kind, 2002). A cogent review of this literature has been provided by Torborg and Feller (2005).

While such statements have been widely accepted, several contradictory findings and conceptual points remained to be addressed. From a conceptual perspective, it seems difficult to reconcile the idea that activity serves to instruct the formation of eye-specific retinogeniculate projections with the stereotypic organization of ipsilateral and contralateral projections evident at maturity in all members of a given species. Thus, layer A of the cat dLGN is always innervated by the contralateral eye (that is, ganglion cells situated in the nasal retina), while layer A1 is always innervated by the ipsilateral eye (temporal retina). The stereotypic pattern in eye-specific projections to the primate dLGN is even more remarkable, with layers 1, 4, and 6 innervated by the contralateral retina and layers 2, 3 and 5 by the ipsilateral

![Diagram of retinal ganglion cells](image)

**Fig. 1** Correlated activity of developing retinal ganglion cells. The photomicrograph shows two retinal ganglion cells that have been dye filled (red and green) in a postnatal day 1 ferret retina. The tracers in red and green show whole-cell patch-clamp recordings that were made from two pairs of such ganglion cells. Note that when one cell fired (in red) the other cell also discharged at virtually the same time (shown in green). To the right are cross correlation plots of membrane potentials from 15 pairs of such neurons at the ages denoted in the upper right hand corner of each plot. A combined plot for all 15 cell pairs is shown in the lower right hand corner in orange. As may be seen all cell pairs show a high temporal correlation in their discharge patterns.
retina. How could retinal activity instruct such species-specific retinogeniculate projection patterns? Clearly, this is not possible without some other factor(s) being at play. Moreover, for a Hebbian-type mechanism to be operative, during development of eye-specific projections, every single cell in a given layer of the dLGN would require a functionally stronger input from one eye or the other. This would seem to require some initial bias in the strength of synaptic contacts from a given eye to the region of the dLGN destined to be exclusively innervated by that eye. There is also the assumption, that during the binocular overlap period, individual dLGN neurons are innervated by axons from both eyes. Remarkably, as yet, there is no direct evidence for this basic tenet of the Hebbian model. Nor is it known what proportion of retinogeniculate terminal arbors form functional synapses during the time period when eye-specific projections are being formed.

There are also some empirical findings contradicting the notion that retinal waves via an NMDA-mediated Hebbian synapse are responsible for the formation of segregated eye-specific projections. Thus, Cook et al. (1999) used slow release of TTX to block action potentials in one or both eyes of developing ferrets, and found that contrary to expectation, this manipulation did not prevent eye-specific segregation. Rather, blockade of retinal activity made the boundaries between dLGN layers less distinct and delayed the formation of eye-specific labeling patterns. In an earlier study, Smetters et al. (1994) found that chronic blockade of NMDA receptors in the ferret dLGN, during the developmental period when eye-specific projections are normally formed did not appear to interfere with this developmental process. Interestingly, blockade of NMDA receptors, at a later time in development, was found to prevent the segregation of retinal afferents into On and Off sublaminae of the ferret dLGN (Hahm et al., 1999). Thus, evidence from two different laboratories indicated that in the developing ferret, neither blockade of retinal activity nor of NMDA receptors in the dLGN prevents the formation of eye-specific retinogeniculate projections.

Nevertheless, two subsequent studies from Carla Shatz’s laboratory, which relied on different methods to perturb retinal waves, reported that such activity is in fact responsible for the formation of segregated retino-dLGN inputs. In one study, Penn et al. (1998) relied on epibatidine, a cholinergic agonist that they reported blocks all ganglion cell discharges when applied in vitro. Binocular injections of this drug prevented eye-specific segregation, while monocular treatment with this drug caused the treated eye to occupy a smaller than normal territory within the dLGN, while the projections of the treated eye were found to be expanded. The latter finding, reminiscent of the effects of early monocular enucleation, suggested that activity-mediated binocular competition underlies the formation of eye-specific retino-dLGN projections. In a subsequent study, the spatio-temporal properties of retinal waves were modified by forskolin, a drug that increases the intracellular levels of cyclic AMP (Stellwagen and Shatz, 2002). Injections of this drug increased the frequency of waves in that retina, and this in turn resulted in that eye innervating a greater than normal amount of territory in the dLGN. The
results of this study extended the concept of activity-mediated binocular competition, by showing that the more active eye captured more territory in the target nucleus.

4. Dissociating retinal waves from retinal activity

A limitation of the foregoing studies is that they did not differentiate between retinal waves (that is, correlated discharges of spatially adjacent retinal ganglion cells) and retinal activity per se, in that, all manipulations designed to block or increase retinal waves also affected the overall discharge levels of retinal ganglion cells. Thus, in a traditional sense, these would be considered confounded experiments, since one manipulation (a given drug treatment) impacted two different variables (overall retinal activity as well as retinal waves). For this reason, a role for correlated retinal activity in the formation of eye-specific retinogeniculate projections remained to be tested. In this section, I describe the results of two recent studies from my laboratory designed to overcome this limitation.

One approach to resolve this issue is to attempt to perturb correlated activity without affecting the overall discharge levels of developing retinal ganglion cells (Huberman et al., 2003). During the time that eye-specific projections are being established, retinal waves in the ferret are driven by acetylcholine released by starburst amacrine cells (Feller et al., 1996; Zhou, 1998). We reasoned that partial depletion of these cholinergic interneurons from the developing ferret retina might provide a viable approach for disrupting correlated discharge patterns of retinal ganglion cells, without blocking overall firings levels. To deplete cholinergic amacrine cells we injected a novel immunotoxin designed to selectively target these neurons. This approach proved successful as described by Gunhan et al. (2002). Moreover, depleting a majority of cholinergic amacrine cells in newborn ferrets did decorrelate the firing patterns of adjacent ganglion cells during the time when eye-specific projections are normally formed, the first 10 postnatal days. To assess the correlated firing patterns of two recent studies from my laboratory designed to overcome this limitation.

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Fig. 3 - Development of segregated retinogeniculate projections. To the left are three pairs of photomicrographs showing the retinogeniculate projection pattern in a postnatal 1 ferret. The top pair of photomicrographs show the contralateral projection to the dorsal lateral geniculate nucleus on the left and right side of the brain, the photomicrographs in the middle show the ipsilateral projections, and those on the bottom combine these images to demonstrate the high degree of overlap in the projections from the two eyes. To the right, the three sets of photomicrographs show the equivalent projections at postnatal day 10. At this age the projections from the contralateral and ipsilateral eye are completely segregated.
developing ferret ganglion cells, we made dual patch-clamp recordings from spatially adjacent neurons. During these recordings, both cells were filled with different colored dyes; this revealed their morphology and enabled us to confirm unequivocally (by the presence of an axon) that recordings were made from ganglion cells rather than displaced amacrine cells. Fig. 1 shows a set of recordings made from two dye-filled cells in a control postnatal day 4 ferret retina, with the recordings of action potentials showing a high degree of temporal coincidence. Thus, when one cell discharged an action potential (shown in green) the other cell (shown in red) did so as well. To the right are cross correlation plots of membrane potentials from 15 pairs of cells recorded from control retinas at the postnatal (P) ages denoted in parenthesis on each plot. As expected, every cell pair at this age manifested discharges that were highly correlated. By contrast, Fig. 2 shows the results of comparable recordings carried out from ferrets at equivalent ages where the cholinergic amacrine cell populations were depleted by about 75% from normal levels. As may be seen, in these immunotoxin-treated retinas the discharges of spatially adjacent cells were not significantly correlated with each other. In fact, these cell pairs manifested firing patterns that were not significantly different from random. These results made it clear that immunotoxin treatment can effectively decorrelate the spontaneous discharges of developing retinal ganglion cells. Importantly, the overall discharge rates of ganglion cells in the immunotoxin treated retinas were not significantly different than normal.

To determine whether correlated retinal discharges are required to form segregated retinogeniculate projections, different tracers were injected into each eye allowing us to quantify the degree of binocular overlap in the ferret dglgn. Fig. 3 shows the retinogeniculate projections in a newborn ferret, where the left and right eye inputs are extensively overlapping and at P10 when the binocular inputs are completely segregated. The contralateral input on both sides of the brain is shown in the top row of photomicrographs, the ipsilateral projection is show in the middle, while the photos

Fig. 4 – Comparison of the effects of decorrelating with blockade of retinal activity. The conventions are the same as in the preceding figure. To the left are three sets of photomicrographs showing that the segregation of retinogeniculate projections is completely normal at P10 in a ferret that lacked retinal waves due to depletion of cholinergic amacrine cells by immunotoxin intraocular treatment at P1. To the right are equivalent sets of photomicrographs showing extensive overlap of contralateral and ipsilateral retinogeniculate projections in a ferret that received binocular injections of epibatidine from P1. This cholinergic agonist has been shown to block all discharge of retinal ganglion cells. See text for details.
on the bottom superimpose the two projections. In this study we also assessed the effects of treating the two eyes with injections of epibatidine. Recall that this is an agonist of cholinergic receptors that was shown to silence ganglion cells in the developing ferret retina (Penn et al., 1998). In Fig. 4 is depicted a comparison of contralateral and ipsilateral projections in two P10 ferret. To the left is the pattern of an animal that received binocular injections of the cholinergic immunotoxin at P1. Even those with limited familiarity with neuroanatomical tracings can appreciate that the projection patterns in the immunotoxin treated case are identical to those shown in the normal animal of the same age in the previous figure. This means that decorrelating the discharges of developing retinal ganglion cells had no appreciable impact on the normal segregation of retinogeniculate projections. By contrast, in the case of the animal that received binocular injections of epibatidine (right side of Fig. 2) it is obvious that segregated eye-specific projections failed to form. We interpreted these results as showing that while normal retinal activity (that is retinal waves) is not required for the formation of eye-specific retinogeniculate projections, retinal activity per se does play a vital role in this developmental process (details in Huberman et al., 2003). It is worth noting, however, that the effects of chronic treatment with epibatidine on the activity of developing retinal ganglion cells are yet to be established.

Another approach we employed to dissociate retinal waves and the formation of segregated retinogeniculate projections was to assess these two phenomena in the prenatal macaque monkey. In the species commonly used for studies of the developing visual system, such as the ferret and even more so the mouse, the time period during which connections in the visual system are made and refined is relatively brief. Many salient developmental events occur concurrently in these species, and as a consequence it is difficult to dissociate the links between them. For instance, refinements in retinotopy and formation of eye-specific projections are overlapping developmental events where retinal activity may play a role in both. By contrast, the developmental period when brain connections become established is much more protracted in the macaque monkey, so it seems reasonable to think that the salient features of visual system development could be more dispersed, and that makes it more likely that key events could be dissociated temporally from each other.

We began this venture by employing modern neuroanatomical methods to accurately delimit the time period during

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**Fig. 5** – Retinal waves in an embryonic monkey retina. Four panels showing recordings from an isolated retina of a fetal monkey more than 100 days before birth (at E60; gestation = 165) with an array of 61 microelectrodes. Within each panel each electrode shows 1 s of recordings. Note the presence of waves of activity spreading across the retinal surface that is evident in the panels at the upper right, lower left and lower right.
which eye-specific retino-dlgn projections are established in the fetal macaque monkey (Huberman et al., 2005a). This involved making intraocular injections of different tracers in each eye of fetal monkeys of known gestational ages. Subsequently, the extent of the binocular overlap within the developing dlgn was quantified using confocal microscopy and image analysis software. This study showed that about 100 days before birth at embryonic day 69 (E69), the projections from the two eyes were extensively intermingled in the dlgn. At E84 segregation of left and right eye axons was found to be essentially complete, with the 6 eye-specific domains that characterize the mature macaque dlgn clearly apparent. Thus, the segregation of eye-specific inputs occurs during a remarkably early and relatively brief in utero period in the macaque, taking about 14 days in a 165-day gestation period.

With the foregoing information in hand, we were anxious to establish how the developmental period when eye-specific projections are formed relates to the discharge patterns evident in the fetal macaque retina. To address this issue, we used multi-electrode arrays to record the activity from isolated retinas obtained from fetal monkeys of known gestational age (Warland et al., 2006). Before embryonic day 55 (E55) the fetal monkey retina was found to be essentially silent, with only a few cells manifesting occasional discharges. This means that the specific ingrowth of retinogeniculate axons into regions destined to form magnocellular and parvocellular layers, which occurs prior to E55 (Meissirel et al., 1997) is not dependent on retinal activity. Retinal waves of activity were found to be prevalent at E60, which is more than a week before segregation of retinogeniculate projections is first observed. Moreover, the incidence of retinal waves decreased progressively during the period when eye-specific projections become established (E69–E76). These findings in the fetal macaque monkey differ from the results obtained in other species where retinal wave activity has been reported to be robust throughout the period when segregated retinogeniculate projections are formed, with such activity declining after this developmental event becomes established (mouse: Demas et al., 2003; Torborg et al., 2005; ferret: Meister et al., 1991; Wong et al., 1993; Feller et al., 1996).

Thus, while the multi-array recordings from fetal monkey retina do not rule out the possibility that retinal activity plays a role in the formation of segregated retinogeniculate projections, they do indicate that retinal waves are most prominent at an earlier time in development than the period when eye-specific inputs are being established. One could still argue, however, that the limited correlated discharges observed during the segregation period are sufficient to trigger this process (Fig. 5).

5. Summary and future directions

The available evidence indicates that while retinal activity plays a role in the formation of eye-specific retino-dlgn projections, it is unlikely to operate by a Hebbian-type mechanism. Rather, it is more likely that retinal activity interacts with the expression of molecular factors along the retinal pathway as well as in the developing dlgn to promote the formation of eye-specific projection patterns. Recent studies point to a role for the ephrin As and their receptors (EphAs) in this process (Huberman et al., 2005b; Pfeifferberger et al., 2005), and it is likely that other molecules will soon be added to this list.

What then is the role of retinal waves in the development of visual projections? Refinements in the early projection pattern of retinal axons occur at several levels, from the elimination of gross topographic errors to the reduction of multiple retinal inputs onto single dlgn neurons, and retinal waves could clearly play a role in one of more of such developmental events. Interestingly, retinal activity has recently been shown to play a permissive role for ephrin signaling during the establishment of retinotopic maps (Nicol et al., 2007). Another possibility is that retinal waves provide an efficient means for increasing intracellular levels of calcium into developing retinal ganglion cells essential for the expression of genes controlling normal axon growth and proliferation, cellular events that are clearly required for retinal segregation. These alternatives are of course not mutually exclusive.

In closing, it is worth emphasizing that the answer as to what controls the formation of eye-specific projections, or for that matter most other features of the developing brain, is unlikely to be parcelled neatly into either activity-dependent or activity-independent events. Rather, the challenge we now face is to unravel how different types of neuronal activities interact with a cascade of molecular factors to form the exquisite circuitry that characterize the most complex organ in the known universe. One wonders what insights Ramon y Cajal could provide in tackling this daunting task!

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