Retinal Waves: Implications for Synaptic Learning Rules during Development

DANIEL A. BUTTS
Department of Neurobiology
Harvard Medical School
Boston, Massachusetts

Neural activity is often required for the final stages of synaptic refinement during brain development. It is thought that *learning rules* acting at the individual synapse level, which specify how pre- and postsynaptic activity lead to changes in synaptic efficacy, underlie such activity-dependent development. How such rules might function in vivo can be addressed in the retinogeniculate system because the input activity from the retina and its importance in development are both known. In fact, detailed studies of retinal waves have revealed their complex spatiotemporal properties, providing insights into the mechanisms that use such activity to guide development. First of all, the information useful for development is contained in the retinal waves and can be quantified, placing constraints on synaptic learning rules that use this information. Furthermore, knowing the distribution of activity over the entire set of inputs makes it possible to address a necessary component of developmental refinement: rules governing competition between synaptic inputs. In this way, the detailed knowledge of retinal input and lateral geniculate nucleus development provides a unique opportunity to relate the rules of synaptic plasticity directly to their role in development.
NEUROSCIENTIST 8(3):243–253, 2002

KEY WORDS *Activity-dependent development, Spontaneous retinal waves, Lateral geniculate nucleus, LTP, Learning rules*

Over the course of development, the central nervous system accomplishes the monumental task of wiring an immense number of connections in the brain. Often, activity-independent processes set up an initial connection pattern (Tessier-Lavigne and Goodman 1996), and its refinement and maintenance requires neural activity (Katz and Shatz 1996). The latter activity-dependent processes may be a subset of the more general phenomenon of activity-driven rewiring of connections between neurons, which is thought to underlie such processes as learning and memory (Holscher 1999). As a result, there is broad-ranging interest in the rules that the nervous system employs that effect activity-dependent refinement of connections during development.

Knowledge of activity-dependent development is heavily reliant upon studies of *developmental plasticity*, where changes in the patterns of connection established during development were induced by blocking or altering the activity patterns normally present in the brain (Katz and Shatz 1996). It is thought that developmental plasticity is accomplished at the level of the individual synapse by particular *learning rules*, which specify how presynaptic and postsynaptic activity should translate into changes in synaptic efficacy. Although a variety of different synaptic learning rules have been observed in the developing nervous system (Malenka and Nicoll 1999), it is largely unclear how they might drive developmental plasticity. In most systems where synaptic plasticity has been studied, one or both of the following is not well understood: 1) the pattern of input that drives postsynaptic activity patterns and may underlie competition between the inputs and 2) how the developmental outcome should manifest on the synapse level. Thus, it is often unclear whether the known examples of synaptic plasticity are relevant to "natural" input patterns that would be observed in vivo and whether such plasticity underlies development.

The early development of the visual system provides a situation where the distribution of activity over the inputs is well characterized and the developmental importance of such input is known. Before the onset of vision, waves of spontaneously generated neural activity travel across the retina and are relayed to higher visual centers. *Retinal waves* are required for the refinement of retinal projections to the lateral geniculate nucleus (LGN) (Sretavan and others 1988; Penn and others 1998; Wong 1999) and superior colliculus (Thompson and Holt 1989; Simon and others 1992) and may play a role in visual cortical development as well (Weliky 2000). Due to their multiple developmental roles, the spatiotemporal properties of the retinal waves have been intensively studied, using multielectrode arrays (Meister and others 1991; Wong and others 1993) and calcium imaging (Wong and others 1995; Feller and others 1996, 1997).

This work was supported by the National Science Foundation Postdoctoral Fellowship in Biological Informatics. The author thanks Patrick Kanold, Lisa Boulanger, and Gene Huh for very helpful comments on the manuscript.

Address correspondence to: Daniel A. Butts, Ph.D., Department of Neurobiology, GB 405, Harvard Medical School, 220 Longwood Avenue, Boston, MA 02115 (e-mail: daniel_butts@hms.harvard.edu).

ISSN 1073-8584

Thus, during early retinogeniculate development, both the system-level input (retinal waves) and the developmental outcomes (synaptic refinement) are known. Furthermore, synaptic learning rules in the LGN are experimentally accessible (Mooney and others 1993), potentially in situations with naturally generated input (Mooney and others 1996). For this reason, this review will focus on predictions and conclusions about developmental learning rules reached through the study of the properties of retinal waves. Such discussion rests on the likely tenet that retinal waves provide instructive signals for brain development (Crair 1999; Wong 1999). If this is the case, then waves contain information about the spatial organization of the retinal afferents to the LGN. Knowing what information they provide leads to insights into the developmental processes that use this information, including rules governing changes in synaptic strength and those governing synaptic competition.

First, I will review what is known about the patterns of input to the LGN, the retinal waves. Under the standard dogma of Hebbian learning rules, it is apparent how many of the qualitative features of this activity might play a role in the refinement that takes place in the LGN. I will review work that quantifies the information transmitted by retinal waves in order to gain insight into the learning rules that may exist at the retinogeniculate synapse. Finally, I will discuss how competition between inputs is a necessary component of rules governing retinogeniculate refinement, and detail what is known about synaptic competition in the LGN.

Retinal waves are a subset of the spontaneous activity present in the brain that drives development (Katz and Shatz 1996; Yuste 1997), and the in-depth study reviewed here may have ramifications to a broad variety of systems where the inputs are not as well known and their developmental outcomes are less amenable to study.

The Spatiotemporal Properties of Retinal Waves

The existence of spontaneous retinal activity was predicted before waves were observed, owing to the dependence of retinogeniculate development on neural activity (Shatz and Stryker 1988). Direct evidence of spontaneous activity in the retina was first observed in the embryonic rat (Galli and Maffei 1988). Since then, retinal waves have been observed in the cat (Meister and others 1991), ferret (Meister and others 1991; Feller and others 1997), chick (Catsicas and others 1998; Wong and others 1998), mouse (Bansal and others 2000), rabbit (Zhou and Zhao 2000), and turtle (Grzywacz and Sernagor 2000). The most complete set of studies of the spatiotemporal properties of retinal waves has been performed in the ferret (Meister and others 1991; Wong and others 1993; Feller and others 1996, 1997; Stellwagen and others 1999, 2002; Wong and others 2000), which therefore will be the primary focus of this review.

Ferrets are born with a relatively immature visual system, and light cannot evoke neural activity in the retina until 3 weeks after birth. From embryonic day 35 (a week before birth) until eye opening at postnatal day 30 (P30), the retina is spontaneously active, generating activity that spreads across the retina in waves. Throughout this period of development, retinal afferents innervating the LGN undergo significant remodeling. Retinal afferents are initially intermixed at birth but segregate into eye-specific layers (Linden and others 1981) and later into sublayers specific to ON and OFF pathways (Hahm and others 1991). Retinal afferents also undergo retinotopic refinement (Sretavan and others 1988), where neighboring retinal ganglion cells (RGCs) ultimately project to neighboring LGN neurons such that a map of the retina is replicated in each of the layers of the LGN.

Because any instructive role that retinal waves play in development must rely on their patterns of activity, they have been studied in detail using both multielectrode arrays (Meister and others 1991; Wong and others 1993) and calcium imaging (Feller and others 1996, 1997). Both the spatiotemporal properties of the retinal waves (Bansal and others 2000; Wong and others 2000) and the mechanisms that govern them (Bansal and others 2000; Wong and others 2000; Zhou and Zhao 2000) change dramatically over development, so we will focus on waves observed in the ferret over the first 2 postnatal weeks.

Simultaneous recordings of 39 neurons are shown in Figure 1*A*, demonstrating the roughly 2-min periodicity of events that are nearly synchronous among most neurons (data from Meister and others 1991). This activity is composed of bursts of action potentials fired by RGCs, which comprise the output layer of the retina (Wong and others 1993). (Other neurons in the developing retina are known to be involved in retinal waves [Feller and others 1996, 1997], though they do not fire action potentials during waves [Zhou 1998].) When the timing of burst onset is plotted relative to position on the multielectrode array (Fig. 1*B*), it is clear that the retinal activity travels across the array as a wave from *right* to *left* in Figure 1*B*.

Calcium imaging experiments can visualize RGC bursting over much larger spatial scales and with better spatial resolution (Feller and others 1996, 1997). This technique cannot resolve individual action potentials but rather reveals the increased intracellular calcium concentrations resulting from RGC bursting (Fig. 2*A*, *right*). Figure 2*A* shows a retinal wave propagating to its full extent over 4 seconds. For comparison with the dimensions of the multielectrode array (Fig. 1*B*), the dark hexagons aligned along the wavefront demonstrate the spacing of electrodes and overall size of the array. Sequential fluorescence changes can be seen as the wave propagates through these positions (Fig. 2*A*, *right*), though note that calcium imaging reveals the other propagation directions at the same time.

Only after visualizing the large-scale dynamics in this way is it clear that retinal waves do not travel across the entire retina; instead, their propagation is limited to a "domain." These domains are not static features of the

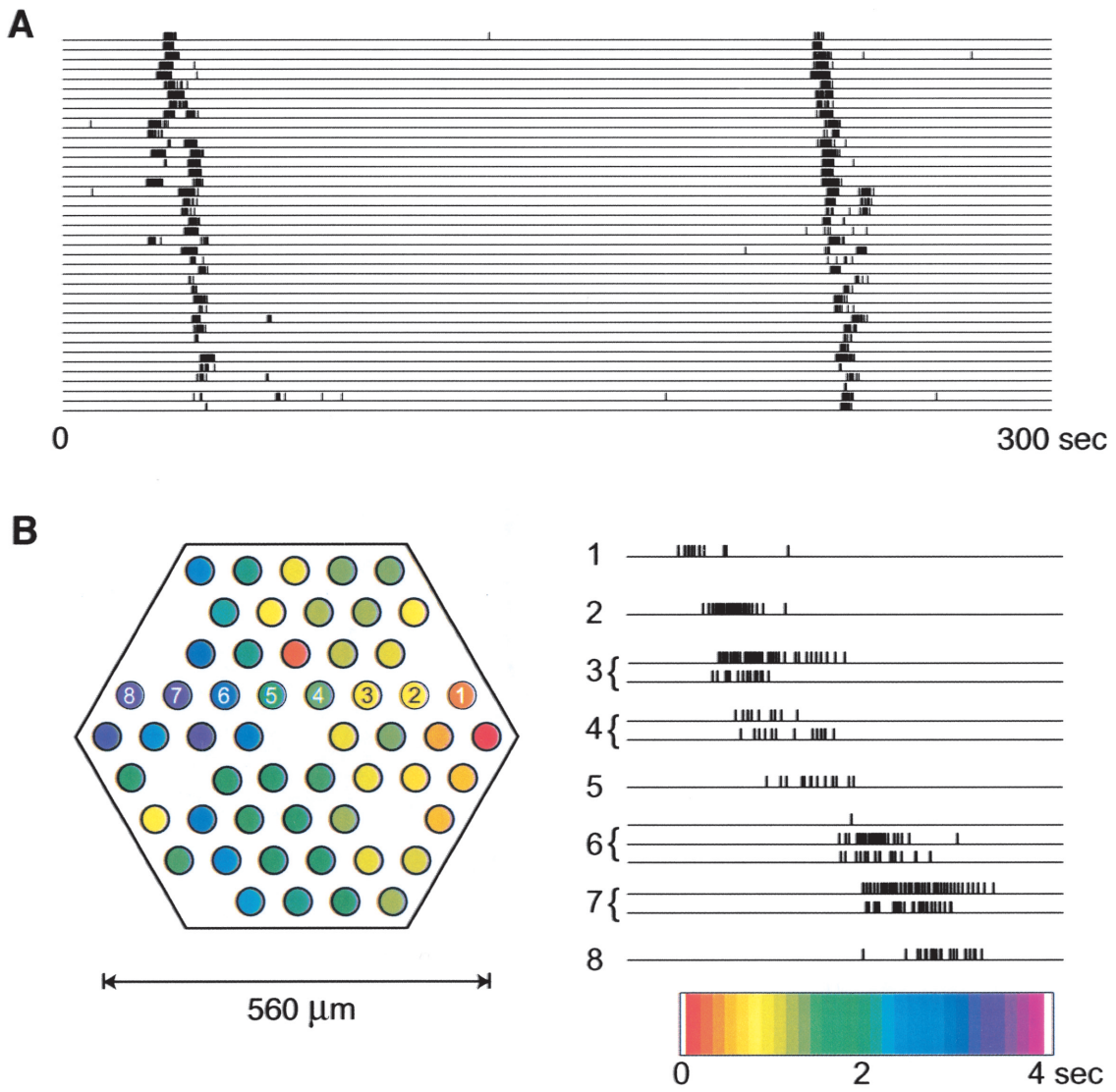

Fig. 1. Multielectrode recordings of retinal waves. *A*, The spike trains of 39 retinal ganglion cells of a P4 ferret retina, from data recorded by Meister and others (1991). In the 5 min shown, two wave episodes involve most of the recorded neurons, demonstrating the average interwave interval of roughly 2 min. *B*, The spread of wave activity over the multielectrode array. Colors correspond to the timing of the burst onset of individual neurons recorded from each electrode (*left*). Recordings from representative electrodes perpendicular to the wavefront demonstrate the near-sequential activation of neighboring retinal ganglion cells (*right*). Modified from Butts and Rokhsar (2001). Copyright 2001 by the Society for Neuroscience.

retina but rather occur with equal probability at each location, and ultimately tile the entire retina (Feller and others 1997). Figure 2*B* shows sequential domains of activation (*left* to *right*, then *top* to *bottom*), with each frame showing the next active domain within the experimental field of view. Wave boundaries can be explained in part by a 40-second *refractory period*, where RGCs active in a wave cannot participate in another wave within this amount of time (Feller and others 1996, 1997). A network model of the retinal waves links the causes of this refractory period to the variable propagation dynamics of retinal waves (Fig. 2*A*) and demonstrates how the simple retinal circuitry present at this time can generate these complex spatiotemporal patterns (Feller and others 1997; Butts and others 1999).

Synaptic Learning Rules and Development

In the first 2 postnatal weeks, retinal waves are required for eye-specific layer segregation (Penn and others 1998) and, to some degree, the refinement of retinotopy (Sretavan and others 1988) in the LGN and superior colliculus (Thompson and Holt 1989; Simon and others 1992). Because this developmental refinement is the only known role for retinal waves, it poses the question of the relationship between the particular (and peculiar) spatiotemporal properties of retinal waves and these developmental roles.

This question is intimately tied to the mechanisms at the retinogeniculate synapse that are thought to use this activity to instruct development, that is, the synaptic

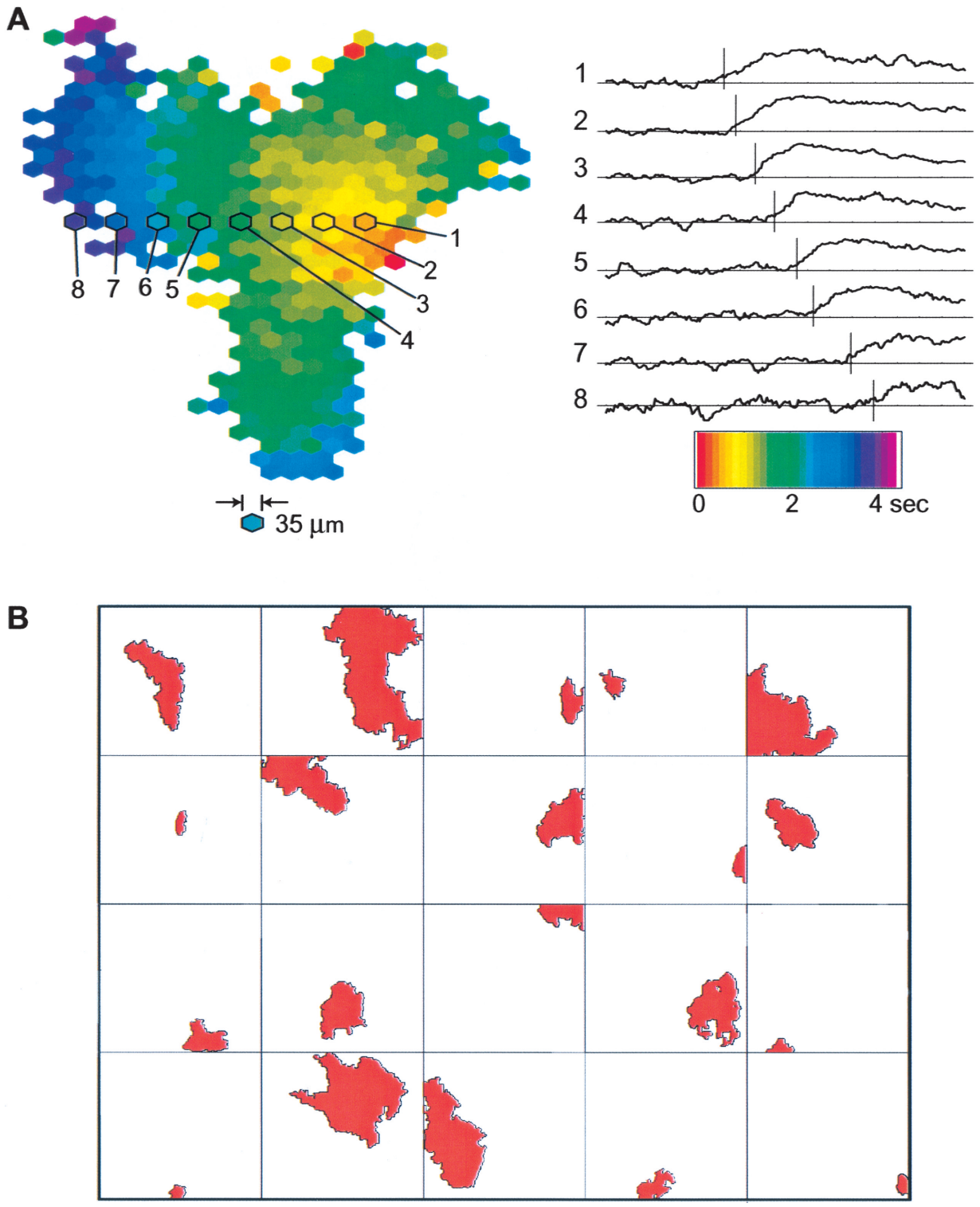

Fig. 2. Calcium imaging of retinal waves. *A*, The propagation of an entire wave, with color representing the onset of fluorescence resulting from burst activity. Example fluorescence traces are shown (*right*) for eight locations with the same spacing as individual electrodes in the multielectrode array (Fig. 1*B*). Modified from Butts and Rokhsar (2001). Copyright 2001 by the Society for Neuroscience. *B*, The patterning of waves over 2 min, with a new wave shown in each successive frame (*left* to *right*, then *top* to *bottom*). Each frame represents the field of view of the experiment: 1.4 mm × 1.2 mm. Boundaries do not repeat, and the entire retina is eventually tiled by overlapping domains of activation. Modified from Feller and others (1997). Copyright 1997, with permission from Elsevier Science.

learning rules. A starting place for this discussion is the seemingly ubiquitous developmental principle of Hebbian plasticity: "cells that fire together wire together" (Katz and Shatz 1996). Retinal waves synchronize

the activity of groups of retinal ganglion cells within the same eye, but retinal waves are unlikely to be synchronized between eyes, conceivably driving segregation of afferents from different eyes in the LGN (Meister and others 1991). Furthermore, wave propagation synchronously activates local clusters of neurons (in the wavefront) that could potentially segregate from neurons that are further away and, as a result, not synchronous, leading to retinotopic refinement (Wong and others 1993). Later in development, the further segregation of retinal afferents into ON/OFF sublayers in the LGN (Hahm and others 1991) occurs simultaneously with a change in the amount of synchrony of ON RGCs (Wong and Oakley 1996; Wong and others 2000), further suggesting the amount of synchrony is a crucial element of connecting to the same region of the LGN.

How might Hebbian principles—that reinforce synchronously active inputs—be implemented at the retinogeniculate synapse? The best candidate mechanism for this and other forms of developmental plasticity is *synaptic plasticity*, where specific patterned presynaptic stimulation is paired with postsynaptic depolarization, leading to a long-term change in efficacy at the involved synapse (Malenka and Nicoll 1999). Because synaptic plasticity is often inducible only during periods of developmental plasticity, and the expression of both forms of plasticity are sensitive to the same pharmacological agents, it is commonly believed that the observed synaptic plasticity underlies developmental plasticity (Katz and Shatz 1996; recent example: Boettiger and Doupe 2001).

The most common example of synaptic plasticity is long-term potentiation (LTP), which has been observed in a number of systems, both during development and in the adult (Malenka and Nicoll 1999). LTP can be induced through a variety of stimulation paradigms: one of the most common is tetanic stimulation, composed of high-frequency bursting (e.g., 100 Hz for 1 sec) induced in presynaptic inputs. LTP can also be induced with lower frequency stimulation (e.g., 1 Hz) coupled with postsynaptic depolarization, or even with repetitions of individual pre- and postsynaptic spikes paired at short latencies (reviewed in Abbott and Nelson 2000). In the latter case, known as *spike-time dependent plasticity* (STDP), changing the latencies between pre- and postsynaptic spikes on the order of milliseconds can dramatically affect whether the synapse will potentiate or depress.

Often, multiple stimulation paradigms that operate over multiple time scales can induce changes in synaptic efficacy at the same synapse. The situation is made more complicated by modulators of synaptic efficacy not directly related to LTP that could also act during development, such as neurotrophins, whose time scales of action are not known (Katz and Shatz 1996; Turrigiano and Nelson 2000). Thus, though the presence of LTP demonstrates that synaptic changes may be induced by activity at a given synapse, it is not often clear what types of activity lead to synaptic changes in vivo, and whether the rules governing the observed plasticity play any role in development.

At the retinogeniculate synapse, an increase in synaptic efficacy can be induced—over the time that segregation of eye-specific inputs takes place in the LGN—by optic tract stimulation with a tetanus (100 Hz for 1 sec) (Mooney and others 1993). In contrast, endogenous retinal waves are composed of RGC bursts with an average frequency of 10 Hz, and RGCs do not all fire simultaneously, but rather their firing is distributed over seconds (during the propagation of a given wave). Due to this mismatch, it is not clear that the changes in synaptic efficacy induced by tetanic stimulation actually occur under conditions of natural input. Furthermore, retinal waves have spatiotemporal features over multiple time scales, ranging from those of individual spikes (milliseconds) to the bursts (seconds) to the observed retinal refractory (40 seconds). What time scales might the relevant rules of synaptic plasticity rules act on? What aspects of retinal activity might be employed by these rules?

Information Transmission during Development

Because retinal wave activity is responsible for many aspects of synaptic refinement in the LGN and superior colliculus, the relevant aspects of retinal waves must be capable of instructing such refinement. As a result, their spatiotemporal properties must convey information, and the mechanisms at the retinogeniculate synapse responsible for developmental plasticity must be able to detect this information. Thus, detailed study of the information content of retinal waves has highlighted the information-carrying aspects of the retinal waves and placed constraints on learning rules in the LGN (Butts and Rokhsar 2001).

How does one quantify information transmission in the nervous system? Theoretical studies of information in the nervous system have been applied in many areas (Borst and Theunnissen 1999) including the adult retina (Nirenberg and others 2001) and LGN (Reinagel and Reid 2000). However, all of these studies investigate the information contained in neural spike trains in response to external stimuli. In contrast, retinal waves are spontaneously generated, and RGC spike trains contain information about the structure of the retina itself (Butts and Rokhsar 2001). As a result, the same theoretical framework of information theory is still applicable, but the specific application must be fundamentally different.

How can spontaneously generated activity carry information? The fact that waves have consistent spatiotemporal properties means that the spatial distribution of the inputs within the retina are translated into temporal features of input activity to the LGN (i.e., the RGC activity). Because eye-specific information about a given retinal afferent is not dependent on its retinotopic position, the patterning of activity within a given retina can only be useful for the refinement of retinotopy. Retinal waves have potentially relevant temporal features across many different time scales (Feller and others 1997); to name a few: the relative timing of spikes within the bursts, the timing of the bursts themselves, and the number of coincident spikes within a certain time window. The features

that convey information are those that depend on the separation between RGCs: the temporal features that do contain retinotopic information; those that do not depend on RGC separation convey no information.

For example, consider the relative timing of the onset of bursts of a pair of RGCs. From Figures 1*B* and 2*A*, it is clear that the burst onset time difference (BOTD) between the two RGCs changes as a function of the distance between them: RGCs that are close together have relatively small BOTDs, whereas RGCs separated by some distance have longer BOTDs. Unfortunately, there is not a strict relationship between BOTD and distance, owing to the random orientation of the wavefront, which can synchronize RGCs that are further apart but aligned along the wavefront, and the fluctuating propagation speeds (Feller and others 1997). As a result, to judge how much information is encoded by BOTD, it is necessary to calculate the overall distribution of BOTDs for each separation *r*.

The distribution of BOTDs is shown for pairs of RGCs recorded on the same electrode (Fig. 3, *upper left*), on adjacent electrodes (*upper right*), between RGCs separated by 280 microns (*lower left*), and 420 microns (*lower right*). The fact that these distributions change as a function of RGC separation means that burst onset timing encodes retinotopic information.

To quantify the amount of information encoded, note that if these distributions were more distinct from one another, a given observation of BOTD would more clearly correspond to a particular range of RGC separations, and more information would thus be conveyed by an observation of BOTD. The difference between groups of probability distributions (such as those in Fig. 3) can be quantified using a widely studied mathematical tool (Cover and Thomas 1991): the Shannon mutual information I[*r*, Δt]. Fortunately, understanding the mathematics behind the mutual information—though a life-enhancing experience—is not necessary to understand the following discussion. (For further explanation and discussion about Shannon mutual information and its application to neuroscience, see Borst and Theunnissen [1999].) What is important to understand is that the Shannon information is zero when the conditional distributions are the same, meaning an observation of Δt does not give any information about *r*. Furthermore, Shannon information is larger for conditional distributions that are more distinct from each other.

The use of information theory allows for comparisons between the ability of different aspects of retinal wave activity to instruct retinotopic refinement, unbiased by preconceptions about the important features of the activity. Butts and Rokhsar (2001) compared the information contained in BOTD with other timing measures and found that burst onset timing carries at least as much information than any other measure. For example, though there are an average of 11 spikes for each burst, the information contained in spike timing does not contain any more information than the overall burst timing. This implies that the organization of spikes within the burst contains no additional information, a finding that

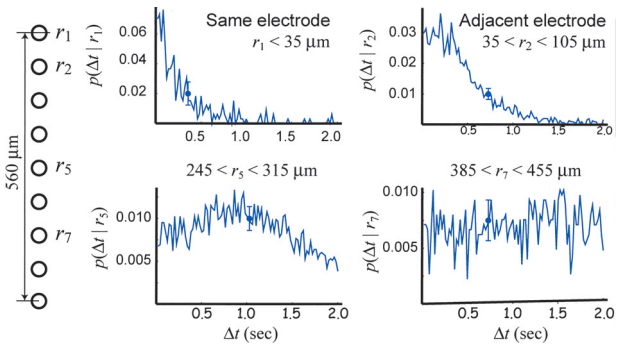

Fig. 3. Distributions of burst onset time differences (BOTDs) for pairs of retinal ganglion cells (RGCs). The conditional probability distributions $p(\Delta t|r)$ of BOTD Δt for RGCs separated by a distance *r* are shown for four separations in the multielectrode array (demonstrated on the *left*). For RGCs recorded on the same electrode (*upper left*), synchronous bursts are most likely, but the peak shifts away from zero for successively larger separations (*upper right* and *lower left*). Bursts between RGCs separated by 0.4 mm or more appear to be completely uncorrelated (*lower right*) because each BOTD is equally likely. Reprinted from Butts and Rokhsar (2001). Copyright 2001 by the Society for Neuroscience.

is consistent with earlier studies that found no fine structure-to-spike correlations between different RGCs during retinal waves (Meister and others 1991; Wong and others 1993). In addition to the lack of importance of spike timings within a burst, bursts with a larger number of spikes convey more information than bursts with a small number of spikes (Fig. 4). The smaller amount of information encoded by bursts with fewer spikes is likely explained by the occurrence of sporadic RGC activity that is not associated with waves (see Fig. 1*A*).

Given that the spike timing contains no additional information than burst timing, it is no surprise that the information contained in retinal waves is retained even at a remarkably coarse time resolution. This can be demonstrated by adding random offsets to the timing of each burst onset and recalculating the mutual information (Fig. 5*A*). The information measured from two experiments (from Wong and others 1993, from P0 and P4 ferrets) is plotted as a function of the average noise magnitude σ of the random offsets. The total information available can be seen when $\sigma = 0$ (0.125 bits), and this information is completely disrupted by very large temporal noise magnitudes ($\sigma > 0.5$ sec). However, once the timing of bursts is known to a precision of 100 ms (i.e., $\sigma = 100$), there is no more information to be gained by higher precision.

If small time scales do not convey additional information, what time scales are important for information encoding of retinal waves? Figure 5*B* shows the fraction of total information that the observation of a particular BOTD Δt contributes. Bursts that are synchronous or nearly synchronous ($\Delta t = 0$ ms) clearly contain the most information, and there is negligible information contained in time scales greater than 3 seconds. What is interesting is that a significant fraction of information is conveyed by rather large time differences: almost half the information is contained in measurements of BOTD

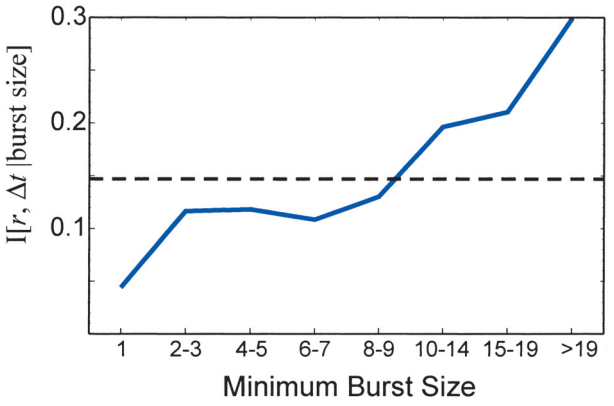

Fig. 4. The information of bursts with different numbers of spikes. Information contained in burst onset time differences (BOTDs) is plotted as a function of the number of spikes involved (in the smaller burst). Bursts with a small number of spikes carry less information, and the largest bursts have the most reliable timing signals. The average information about retinotopic separation contained in bursts is shown as a dotted line. Modified from Butts and Rokhsar (2001). Copyright 2001 by the Society for Neuroscience.

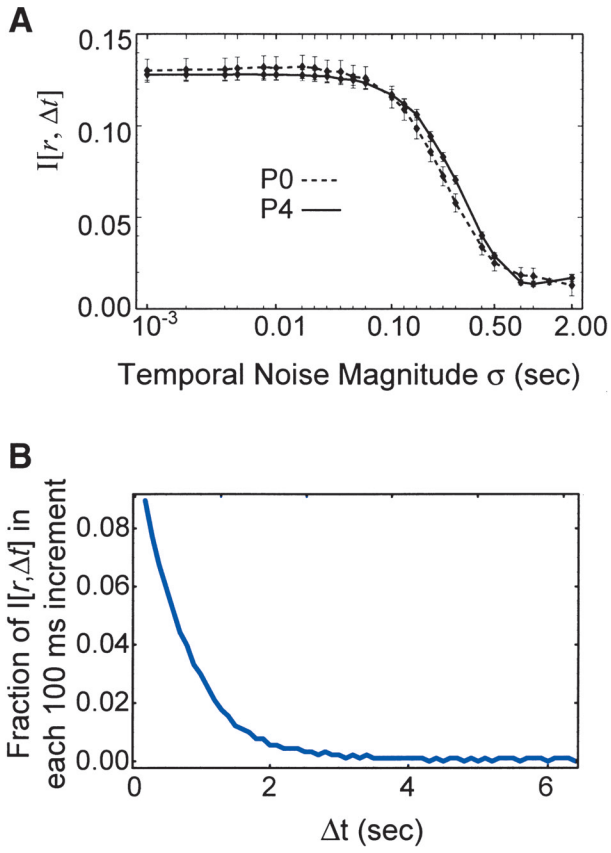

Fig. 5. The time scales of retinotopic information. *A*, The time resolution of information contained in retinal waves, calculated by adding noise with average magnitude σ to burst times and recalculating the mutual information I[*r*,Δt]. Because the information is constant from 0 to 100 ms, there is no additional information contained at these time resolutions. Reprinted from Butts and Rokhsar (2001). Copyright 2001 by the Society for Neuroscience. *B*, The fraction of the total information contained in each measurement of Δt. There is very little information to be gained by measuring large time differences, but there is a significant amount to be gained up to measurements of Δt = 2 sec. Simultaneous bursts (Δt = 0) contain the most information.

greater than 500 ms! This is surprising given that learning rules observed in other systems appear to operate much finer time scales, and given what is known about candidate intracellular mechanisms responsible for such synaptic plasticity (see reviews: Abbott and Nelson 2000; Malenka and Nicoll 2000).

The finding that synchronous activity (especially with a loose definition of "synchronous" that includes time differences up to 1 second) contains the most information (Fig. 5*B*) recapitulates our original Hebbian principle. Furthermore, for synchronous activity to convey information, RGC bursting must be localized to small regions of the retina. Were retinal waves to propagate over larger regions of the retina, synchronously bursting cells would be increasingly far apart as the wave expanded, providing significantly less information overall about interneuron separations. Thus, wave boundaries—and the underlying refractory period in the retina thought to be responsible for them (Butts and others 1999)—seem well-suited to preserve the information contained in coincident activity.

Implications for Retinogeniculate Learning Rules

The analysis of the information content of retinal waves makes clear predictions for synaptic learning rules at the retinogeniculate synapse. First of all, the fact that no information is conveyed by time scales smaller than 100 ms suggests that STDP, discussed above, although it may be observed at the retinogeniculate synapse, would not be useful in extracting retinotopic information. Along these lines, burst timing contains all of the available information, with larger bursts containing more information than smaller ones. Taken together, these findings argue that bursts are the unit of information transmission during development. This idea is consistent with the unreliability of immature synapses and the common inability to relay individual spike information in developing systems (Lisman 1997). Furthermore, developing LGN neurons do not seem well-suited for precise timing of postsynaptic spikes, because they express a large calcium current (Ramoa and McCormick 1994a) and their synaptic input is dominated by slow NMDA currents (Ramoa and McCormick 1994b).

In the meantime, the information analysis suggests that the ability to distinguish burst time differences on the order of seconds is necessary to extract the maximal amount of retinotopic information. Additional analysis reveals that a learning rule that simply distinguishes between BOTDs of less than 1 second ("coincident") and those greater than 1 second ("not coincident") can extract nearly all the information available in BOTD (Butts and Rokhsar 2001). Coincidentally, individual RGC bursts last on the order of a second, meaning that detection of a BOTD on the order of a second might be accomplished simply by detecting coincident spikes on a

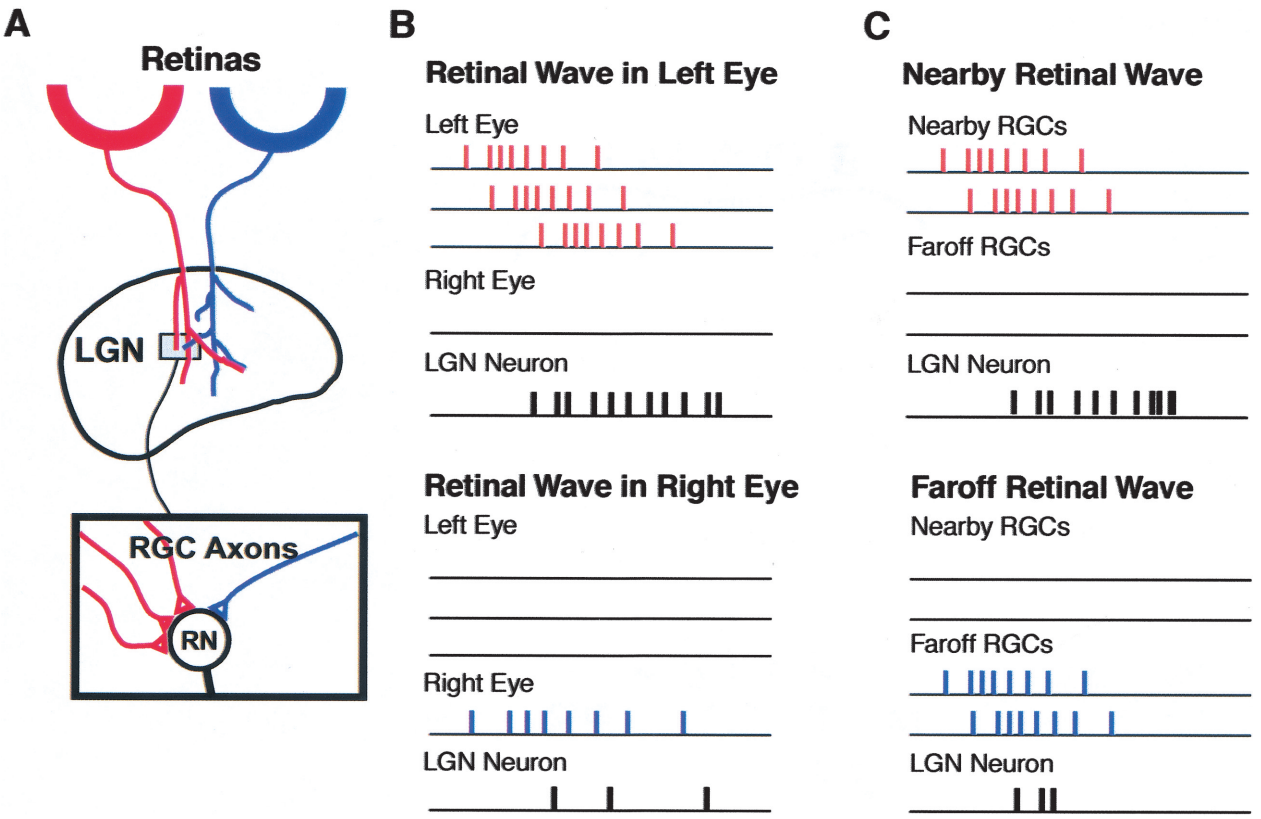

Fig. 6. Patterns of pre- and postsynaptic activity may instruct retinogeniculate refinement. *A*, A cartoon of the retinogeniculate synapse, demonstrating the initial intermixed state of retinal ganglion cells (RGC) afferents from both eyes in the LGN, and binocular innervation of lateral geniculate nucleus (LGN) relay neurons (RNs). *B*, Due to initial biases in the connection to an RN, a retinal wave in the left eye drives more postsynaptic firing (*top*) than a wave in the right eye (*bottom*). *C*, Likewise, within the same eye, a wave across an area that is initially more strongly connected to the RN (due to an initial retinotopic bias) will evoke more postsynaptic activity (*top*) than a wave in a different location on the retina (*bottom*).

more biophysical time scale. This coincident agreement of time scales might provide an additional reason for RGC bursting.

Thus, in providing a way to make unbiased comparisons between the information content of various aspects of retinal waves (both features like bursts and spikes, and time scales), information theoretic analysis predicts the existence of a learning rule governing development not unlike the original Hebbian principle of "cells that fire together, wire together," though on a time scale an order of magnitude larger than previously investigated! Due to this analysis, it is now known that such a rule can take advantage of the information contained in retinal wave activity, providing a potential link between synaptic learning rules and the development that they are thought to drive.

Competition Is Necessary for Hebbian-based Development

Information theoretic analysis thus suggests that a burst-based Hebbian learning rule with a time scale of seconds acts at the retinogeniculate synapse. Is such a learning rule (or any Hebbian learning rule for that matter) enough to explain developmental refinement at the synapse?

Consider the basic case of eye-specific layer segregation in the LGN. During the formation of eye-specific layers, many LGN neurons receive input from both eyes (Fig. 6*A*) (Shatz and Kirkwood 1984; Ziburkus and Guido 2000). In such a case, wave activity in either eye conceivably leads to postsynaptic bursting (Mooney and others 1996), thus providing coincident pre- and postsynaptic activity (Fig. 6*B*). Note that unless the preferential strengthening of one group of synapses is somehow linked to a reduction in the strength of other synapses, this basic Hebbian principle will result in the strengthening of connections with both eyes.

Evidence for competitive interaction exists on the level of developmental plasticity. A selective blockade of retinal wave activity in one eye leads to a complete withdrawal of its retinal afferents from areas also innervated by the normally active eye (Penn and others 1998). Consistent with this, drugs that enhance retinal waves in one eye—by making them larger, faster, and more frequent (Stellwagen and others 1999)—lead to an expansion of the LGN area that it innervates, coupled with withdrawal of afferents from the other eye (Stellwagen and Shatz 2002). In comparison, increasing the activity in both eyes results in normal eye-segregation (Stellwagen and Shatz 2002), whereas blocking wave

activity in both eyes prevents eye segregation altogether (Sretavan and others 1988; Penn and others 1998).

Although this provides evidence for competition on the scale of developmental plasticity, direct evidence for competition at individual retinogeniculate synapses is less conclusive. In the frog's visual system, heterosynaptic depression—where stimulation of one set of inputs leads to depression at neighboring unstimulated inputs—has been observed (Tao and others 2000), suggesting a possible mechanism of competition. Heterosynaptic depression has recently been observed at the mammalian retinogeniculate synapse (Ziburkus and Guido 2000), though its induction was variable and it was only observed when tetanic stimulation was applied to the whole optic nerve. As a result, it is unclear whether such heterosynaptic depression plays a role in natural retinogeniculate refinement.

Alternatively, competition may also be mediated via homeostatic regulation of the postsynaptic neuron, which could counterbalance the increase in excitatory input caused by Hebbian learning by scaling the strength of all synapses down ("synaptic scaling") or through changes in intrinsic excitability of the postsynaptic neuron (Turrigiano and Nelson 2000). Unfortunately, evidence for homeostatic regulation has so far only been observed in culture.

A recently suggested method of mediating competition between inputs (Song and others 2000) is based on STDP (reviewed in Abbott and Nelson 2000). STDP, where precise time differences between pre- and postsynaptic spikes elicit varying degrees of potentiation and depression, has been seen during development in several related systems, including the developing visual system of *Xenopus* (Zhang and others 1998) and the developing mammalian somatosensory cortex (Feldman 2000). Implicit competition is mediated by STDP through the timing of the postsynaptic spikes: an input (or group of inputs) that drives a postsynaptic spike makes it less likely that other uncorrelated inputs drive a spike. As a result, because potentiation and depression are linked to causality, potentiation of the correlated inputs is simultaneous with a depression of uncorrelated inputs. This mechanism of competition tends to keep postsynaptic firing rate constant because a higher postsynaptic firing rate will implicitly depress most synapses because more inputs will become uncorrelated with postsynaptic spikes (Song and others 2000).

A Complete Set of Rules Governing Synaptic Changes?

With rules that specify competition and Hebbian learning, it is clear how retinal waves could drive refinement in the LGN. Referring back to Figure 6*B*, the eye that initially has a stronger connection (*red*) will have more coincident pre- and postsynaptic activity and will win out over the other eye (*blue*). Retinotopy could be refined in a similar way. A retinotopic bias would cause a postsynaptic neuron to preferentially burst when a retinal wave travels over the correct retinotopic location, leading to more coincident activity than during a wave traveling over another part of the retina (Fig. 6*C*). Initial retinotopic biases are formed through activity-independent processes: molecular gradients of ephrins present in the LGN interact with Eph receptors that are differentially expressed on RGC axons, resulting in repulsive signals that initially guide axons to their correct retinotopic location (Feldheim and others 1998).

It is interesting to note that the role of Hebbian mechanisms and competition is simply to sharpen—and maintain—preexisting biases. Several modeling studies have added local coupling among LGN neurons because it increases the ability of such mechanisms to establish initial biases and correct large errors in the initial projection (Haith and Heeger 1998; Eglen 1999; Elliott and Shadbolt 1999). The uniform success of achieving correct refinement provides a proof of principle that Hebbian-based refinement at the retinogeniculate synapse can be driven by retinal wave activity, though this success does not validate any particular developmental rules.

Although not applied to the retinogeniculate system, a recent theoretical study investigated map formation through STDP learning rules (Song and Abbott 2001). It demonstrated that—like the separate rules for Hebbian learning and competition investigated in the previously mentioned models—spike-based learning rules can use correlated input activity to sharpen and maintain preexisting biases. Yet, STDP does not require additional rules governing competition and the regulation of postsynaptic activity, because competition happens implicitly (as described above).

Unfortunately, the information content of retinal waves (discussed above) suggests that a spike-based learning rule could not take advantage of the information available to instruct retinogeniculate refinement (Butts and Rokhsar 2001). However, the self-regulating competition seen with STDP is neither contingent on particular units of pre- and postsynaptic firing (i.e., spikes versus bursts) nor on any particular time scale. Rather, it simply depends on a causal temporal window for potentiation, matched by a larger window for depression (Abbott and Nelson 2000). As a result, a burst-based learning rule, shown in Figure 7, might optimally extract the information provided by retinal waves, while mediating a self-regulating competition. Initial theoretical work has demonstrated that such a rule can drive retinogeniculate refinement using retinal wave input without additional assumptions (unpublished data). Observation of any of several aspects of the learning rule pictured in Figure 7 would be novel, including a dependence of the amount of potentiation or depression on the burst latencies, a window for depression, or a time scale of seconds. Because such a rule describes both how timing of realistic pre- and postsynaptic activity at a synapse would translate into changes in synaptic efficacy and additionally how competition would be implicitly mediated, it could offer a complete explanation of how retinal waves drive retinogeniculate development.

Spontaneous activity appears to be a nearly ubiquitous phenomenon in the developing brain (Yuste 1997; Feller

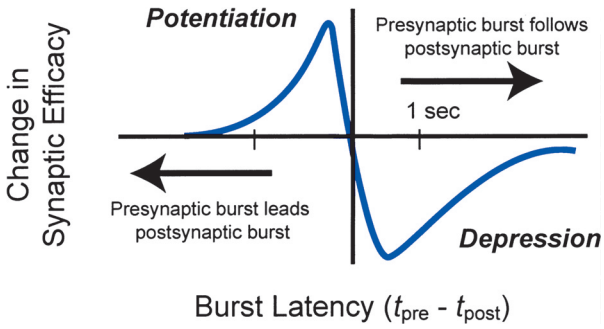

Fig. 7. A proposed learning rule operating at the retinogeniculate synapse. A presynaptic burst preceding a postsynaptic burst would result in potentiation, and lagging presynaptic firing would result in depression. Note the time scales on the order of 1 second. Such a rule would take advantage of the information provided by retinal waves and implicitly govern self-regulating competition.

1999; O'Donovan 1999). One example of such activity, retinal waves provide a unique opportunity to study synaptic learning rules in the context of their role in development. The analysis that can then be applied, discussed in this review, highlights the importance of using natural activity patterns as input in studies of synaptic learning rules and, more generally, suggests methods to discover rules of synaptic plasticity that are directly linked to developmental refinement.

References

Abbott LF, Nelson SB. 2000. Synaptic plasticity: taming the beast. Nat Neurosci 3(Suppl):1178–83.

Bansal A, Singer JH, Hwang BJ, Xu W, Beaudet A, Feller MB. 2000. Mice lacking specific nicotinic acetylcholine receptor subunits exhibit dramatically altered spontaneous activity patterns and reveal a limited role for retinal waves in forming ON and OFF circuits in the inner retina. J Neurosci 20:7672–81.

Berardi N, Maffei L. 1999. From visual experience to visual function: roles of neurotrophins. J Neurobiol 41, 119–26.

Boettiger CA, Doupe AJ. 2001. Developmentally restricted synaptic plasticity in a songbird nucleus required for song learning. Neuron 31:809–18.

Borst A, Theunissen FE. 1999. Information theory and neural coding. Nat Neurosci 2:947–57.

Butts DA, Feller MB, Shatz CJ, Rokhsar DS. 1999. Retinal waves are governed by collective network properties. J Neurosci 19:3580–93.

Butts DA, Rokhsar DS. 2001. The information content of spontaneous retinal waves. J Neurosci 21:961–73.

Catsicas M, Bonness V, Becker D, Mobbs P. 1998. Spontaneous Ca2+ transients and their transmission in the developing chick retina. Curr Biol 8:283–6.

Cover TM, Thomas JA. 1991. Elements of information theory. New York: John Wiley.

Crair MC. 1999. Neuronal activity during development: permissive or instructive? Curr Opin Neurobiol 9:88–93.

Cramer KS, Sur M. 1997. Blockade of afferent impulse activity disrupts on/off sublamination in the ferret lateral geniculate nucleus. Brain Res Dev Brain Res 98:287–90.

Eglen SJ. 1999. The role of retinal waves and synaptic normalization in retinogeniculate development. Philos Trans R Soc Lond B Biol Sci 354:497–506.

Elliott T, Shadbolt NR. 1999. A neurotrophic model of the development of the retinogeniculocortical pathway induced by spontaneous retinal waves. J Neurosci 19:7951–70.

Feldheim DA, Vanderhaeghen P, Hansen MJ, Frisen J, Lu Q, Barbacid M, and others. 1998. Topographic guidance labels in a sensory projection to the forebrain. Neuron 21:1303–13.

Feldman DE. 2000. Timing-based LTP and LTD at vertical inputs to layer II/III pyramidal cells in rat barrel cortex [In Process Citation]. Neuron 27:45–56.

Feller MB. 1999. Spontaneous correlated activity in developing neural circuits. Neuron 22:653–6.

Feller MB, Butts DA, Aaron HL, Rokhsar DS, Shatz CJ. 1997. Dynamic processes shape spatiotemporal properties of retinal waves. Neuron 19:293–306.

Feller MB, Wellis DP, Stellwagen D, Werblin FS, Shatz CJ. 1996. Requirement for cholinergic synaptic transmission in the propagation of spontaneous retinal waves. Science 272:1182–7.

Galli L, Maffei L. 1988. Spontaneous impulse activity of rat retinal ganglion cells in prenatal life. Science 242:90–1.

Gilbert CD, Sigman M, Crist RE. 2001. The neural basis of perceptual learning. Neuron 31:681–97.

Grzywacz NM, Sernagor E. 2000. Spontaneous activity in developing turtle retinal ganglion cells: statistical analysis. Vis Neurosci 17:229–41.

Hahm JO, Langdon RB, Sur M. 1991. Disruption of retinogeniculate afferent segregation by antagonists to NMDA receptors. Nature 351:568–70.

Haith GL, Heeger D. 1998. A computational model of retinogeniculate development. In: Bower JM, editor. Computational neuroscience: trends in research. New York: Plenum. p 35–40.

Holscher C. 1999. Synaptic plasticity and learning and memory: LTP and beyond. J Neurosci Res 58:62–75.

Katz LC, Shatz CJ. 1996. Synaptic activity and the construction of cortical circuits. Science 274:1133–8.

Linden DC, Guillery RW, Cucchiaro J. 1981. The dorsal lateral geniculate nucleus of the normal ferret and its postnatal development. J Comp Neurol 203:189–211.

Lisman JE. 1997. Bursts as a unit of neural information: making unreliable synapses reliable. Trends Neurosci 20:38–43.

Malenka RC, Nicoll RA. 1999. Long-term potentiation—a decade of progress? Science 285:1870–4.

Meister M, Wong RO, Baylor DA, Shatz CJ. 1991. Synchronous bursts of action potentials in ganglion cells of the developing mammalian retina. Science 252:939–43.

Mooney R, Madison DV, Shatz CJ. 1993. Enhancement of transmission at the developing retinogeniculate synapse. Neuron 10:815–25.

Mooney R, Penn AA, Gallego R, Shatz CJ. 1996. Thalamic relay of spontaneous retinal activity prior to vision. Neuron 17:863–74.

Nirenberg S, Carcieri SM, Jacobs AL, Latham PE. 2001. Retinal ganglion cells act largely as independent encoders. Nature 411:698–701.

O'Donovan MJ. 1999. The origin of spontaneous activity in developing networks of the vertebrate nervous system. Curr Opin Neurobiol 9:94–104.

Penn AA, Riquelme PA, Feller MB, Shatz CJ. 1998. Competition in retinogeniculate patterning driven by spontaneous activity. Science 279:2108–12.

Ramoa AS, McCormick DA. 1994a. Developmental changes in electrophysiological properties of LGNd neurons during reorganization of retinogeniculate connections. J Neurosci 14:2089–97.

Ramoa AS, McCormick DA. 1994b. Enhanced activation of NMDA receptor responses at the immature retinogeniculate synapse. J Neurosci 14:2098–105.

Reinagel P, Reid RC. 2000. Temporal coding of visual information in the thalamus. J Neurosci 20:5392–400.

Shatz CJ, Kirkwood PA. 1984. Prenatal development of functional connections in the cat's retinogeniculate pathway. J Neurosci 4:1378–97.

Shatz CJ, Stryker MP. 1988. Prenatal tetrodotoxin infusion blocks segregation of retinogeniculate afferents. Science 242:87–9.

Simon DK, Prusky GT, O'Leary DD, Constantine-Paton M. 1992. N-methyl-D-aspartate receptor antagonists disrupt the formation of a mammalian neural map. Proc Natl Acad Sci U S A 89:10593–7.

Song S, Abbott LF. 2001. Cortical development and remapping through spike timing-dependent plasticity. Neuron 32:339–50.

Song S, Miller KD, Abbott LF. 2000. Competitive Hebbian learning through spike-timing-dependent synaptic plasticity. Nat Neurosci 3:919–26.

Sretavan DW, Shatz CJ, Stryker MP. 1988. Modification of retinal ganglion cell axon morphology by prenatal infusion of tetrodotoxin. Nature 336:468–71.

Stellwagen D, Shatz CJ. 2002. An instructive role for retinal waves in the development of retinogeniculate connectivity. Neuron 33:357–67.
Stellwagen D, Shatz CJ, Feller MB. 1999. Dynamics of retinal waves are controlled by cyclic AMP. Neuron 24:673–85.
Tao H, Zhang LI, Bi G, Poo M. 2000. Selective presynaptic propagation of long-term potentiation in defined neural networks. J Neurosci 20:3233–43.
Tessier-Lavigne M, Goodman CS. 1996. The molecular biology of axon guidance. Science 274:1123–33.
Thompson I, Holt C. 1989. Effects of intraocular tetrodotoxin on the development of the retinocollicular pathway in the syrian-hamster. J Comp Neurol 282:371–88.
Turrigiano GG, Nelson SB. 2000. Hebb and homeostasis in neuronal plasticity. Curr Opin Neurobiol 10:358–64.
Weliky M. 2000. Correlated neuronal activity and visual cortical development. Neuron 27:427–30.
Wong RO. 1999. Retinal waves and visual system development. Annu Rev Neurosci 22:29–47.
Wong RO, Chernjavsky A, Smith SJ, Shatz CJ. 1995. Early functional neural networks in the developing retina. Nature 374:716–8.
Wong RO, Meister M, Shatz CJ. 1993. Transient period of correlated bursting activity during development of the mammalian retina. Neuron 11:923–38.
Wong RO, Oakley DM. 1996. Changing patterns of spontaneous bursting activity of on and off retinal ganglion cells during development. Neuron 16:1087–95.
Wong WT, Myhr KL, Miller ED, Wong RO. 2000. Developmental changes in the neurotransmitter regulation of correlated spontaneous retinal activity. J Neurosci 20:351–60.
Wong WT, Sanes JR, Wong RO. 1998. Developmentally regulated spontaneous activity in the embryonic chick retina. J Neurosci 18:8839–52.
Yuste R. 1997. Introduction: spontaneous activity in the developing central nervous system. Semin Cell Dev Biol 8:1–4.
Zhang LI, Tao HW, Holt CE, Harris WA, Poo M. 1998. A critical window for cooperation and competition among developing retinotectal synapses. Nature 395:37–44.
Zhou ZJ. 1998. Direct participation of starburst amacrine cells in spontaneous rhythmic activities in the developing mammalian retina. J Neurosci 18:4155–65.
Zhou ZJ, Zhao D. 2000. Coordinated transitions in neurotransmitter systems for the initiation and propagation of spontaneous retinal waves. J Neurosci 20:6570–7.
Ziburkus J, Guido W. 2000. Functional binocular connections in the developing lateral geniculate nucleus. New Orleans: Society for Neuroscience Abstracts.