Correlated Neuronal Activity and Visual Cortical Development

Minireview

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The mechanisms by which highly organized neural circuits develop within the mammalian central nervous system are poorly understood. These circuits emerge during brain development through the establishment of precise synaptic connections among many thousands of neurons. During early stages of circuit development, genetically specified molecular signals appear to guide such processes as axonal outgrowth and targeting. However, these early connections are typically diffuse and imprecise. Adult patterns of connectivity subsequently emerge by a process of refinement, elimination, and remodeling of this initial scaffold. In the visual system, neuronal activity has been shown to play a crucial role in this process. While early studies demonstrated that blocking neural activity dramatically disrupts the normal development of the lateral geniculate nucleus (LGN) and visual cortex (Wiesel and Hubel, 1963; reviewed in Katz and Shatz, 1996), recent work reveals that severe disruptions of visual cortical development can also be produced by manipulating the finer scale correlational structure of neuronal activity (Weliky and Katz, 1997; Chapman and Gödecke, 2000).

Building upon the work of Hubel and Wiesel, who first demonstrated the crucial role of sensory experience in cat visual cortical development (Wiesel and Hubel, 1963), recent work in the ferret utilizes novel pharmacological and electrophysiological methods to directly manipulate and record patterns of neuronal activity within the developing visual pathway and to demonstrate the presence of highly organized spatiotemporal patterns of correlated neuronal activity within different levels of the developing visual pathway before eye opening. In separate experiments, manipulations of the specific correlational structure of neural activity have also been shown to disrupt the normal development of neuronal response properties such as orientation tuning and ocular dominance in visual cortex.

Current concepts of how activity shapes the development of neural circuits are based upon a model in which axons compete against one another to establish synaptic contacts onto target neurons (Shatz, 1990). In this model, initially diffuse patterns of connectivity are refined by a process in which simultaneously active inputs strengthen their connections onto common postsynaptic neurons at the expense of inputs that are weakly or nonsynchronously active (Figure 1). As a result of this process, synchronously firing neurons innervate common postsynaptic target cells, while nonsynchronously active neurons are weakened and eliminated.

Much of our current knowledge of geniculocortical

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connectivity derives from studies in the cat (Figure 2). Visual input is first processed by the retina and LGN before being passed on to the visual cortex. Light entering the eye is transformed within the retina into patterns of nerve impulses that are conveyed to higher visual processing stages by retinal ganglion cells. Retinal ganglion cells have circular receptive fields that respond best to small spots of light. Their receptive fields are grouped into two main classes: ON-center cells that respond best to a spot of light shone onto the center of their receptive field and OFF-center cells that are inhibited when the central area of the receptive field is illuminated but fire strongly when the light is turned off. Retinal ganglion cells project their axons via the optic nerve to the LGN. Cells within the LGN are organized into functionally specific layers. Layers A and A1 receive input from the contra- and ipsi-lateral retinas respectively. ON- and OFF-center LGN cells, which have functionally similar receptive properties as their ON and OFF retinal ganglion cell counterparts, are intermixed within each layer (in the ferret each layer is divided into ON and OFF sublaminae as shown in Figure 2). LGN neurons make synaptic connections with layer IV simple cells in primary visual cortex. The receptive fields of simple cells contain elongated ON and OFF subregions that are formed by the spatial segregation of LGN ON and OFF cell inputs. The parallel arrangement of these subregions endows simple cells with the property of orientation tuning, in which cells preferentially respond to bars or edges oriented at a particular angle. Cells with the same orientation preference are arranged in a columnar manner across the different cortical layers. Orientation preference smoothly shifts between neighboring columns across the cortex. Alternating bands of ocular dominance columns, within which cells are preferentially driven by one eye or the other, are also jointly mapped together with orientation preference across visual cortex.

Recent experiments have tested whether patterns of neural activity carried in the separate ON- and OFF-center pathways are necessary for the development of orientation selectivity in visual cortex. Pharmacological methods were used to selectively manipulate the activity of the ON-center pathway within the visual system of the ferret while leaving the OFF-center pathway intact. In this experiment, the activity of ON-center retinal ganglion cells was selectively blocked by daily intravitreal injections of the mGluR6 glutamate receptor agonist DL-2-amino-4-phosponobutyric acid (APB) into both eyes (Chapman and Gödecke, 2000). The specificity of the block was demonstrated in the LGN where ON responses were absent while OFF responses remained normal. The result of this manipulation was that orientation-selective responses and optically imaged orientation maps did not develop in the visual cortex. This indicates that normal patterns of activity within both ON- and OFF-center pathways must be present for the proper development of visual cortical orientation tuning.

This work fits well with theoretical predictions that activity-dependent interactions between the ON- and
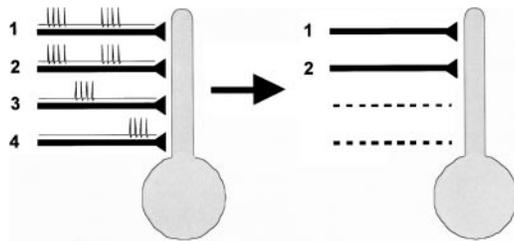
Figure 1. Modification of Neuronal Connections by Correlated Firing of Presynaptic Inputs to a Neuron

Inputs 1 and 2 fire synchronous bursts of action potentials, resulting in the strong depolarization of the postsynaptic cell. Inputs 3 and 4 fire asynchronously, producing weak postsynaptic depolarization. A mechanism, such as the NMDA receptor coupled with the activity-dependent release of a molecular signal, detects coincident pre- and postsynaptic activity and drives the selective stabilization and strengthening of inputs 1 and 2 onto the postsynaptic cell. Weak postsynaptic activation by inputs 3 and 4 results in their elimination.
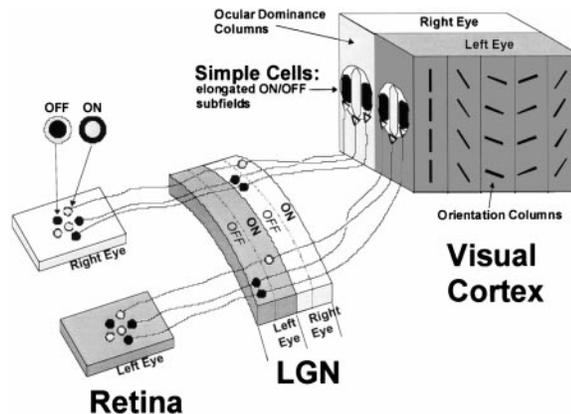

Figure 2. Anatomical and Functional Organization of the Early Stages of the Visual Pathway

In the retina, ganglion cells have ON-center and OFF-center circular receptive fields. Ganglion cell axons project to eye- and center-type specific functional layers within the LGN. In the ferret, each eye projects to a separate functional LGN layer, and these layers are divided into ON and OFF sublaminae, which receive input from ON-center and OFF-center retinal ganglion cells, respectively. Receptive fields of LGN cells are similar to those of retinal ganglion cells. Cells within the LGN form synaptic contacts with layer IV simple cells in visual cortex. Simple cell receptive fields consist of alternating ON and OFF subregions that are formed by the spatial segregation of LGN ON and OFF cell inputs. This receptive field organization endows simple cells with the property of orientation tuning. Cells within the visual cortex are functionally organized into orientation and ocular dominance columns that are jointly mapped across the cortex.

OFF-center pathways drive the development of visual cortical simple cell receptive fields (Miller et al., 1999). Analytical results and computer simulations show that the process of simple cell ON/OFF subfield segregation requires specific patterns of correlated activity among LGN ON and OFF inputs. In this model, like center-type inputs (either ON-center or OFF-center) should tend to be more coactive than opposite center-type inputs at small retinotopic distances. This relationship should reverse at larger retinotopic distances such that opposite center-type inputs should tend to be more coactive than like center-types. These correlations induce ON and OFF LGN inputs to sort themselves out such that they form spatially segregated, adjacent bands across the simple cell receptive field, an arrangement that endows the cell with orientation selectivity. As predicted by this model, a manipulation (such as ABP injection) that alters the correlational structure of this activity should disrupt receptive field development. While this interpretation of the experimental results is enticing, it should be viewed with appropriate caveats. First, there are some subtle differences between the ferret and cat visual system that may bear on the interpretation of results. In the ferret, only 40% of layer IV cells are orientation selective (as opposed to 85% or more in the cat), and we do not know to what extent those cells have simple cell receptive fields with segregated ON/OFF regions as in the cat. Second, while it is likely that APB injections disrupted not only visually driven ON-center responses but also ON-center spontaneous activity, it is unclear to what extent APB affected OFF-center spontaneous activity. This is an important point since the initial development of orientation selectivity occurs independently of visual experience and may depend upon spontaneous activity (Crair et al., 1998). If APB suppressed or disrupted OFF-center spontaneous activity, then this could have played a critical role in preventing the development of orientation selectivity.

Direct electrical stimulation of the visual pathway has also been utilized to study how altered patterns of correlated activity affect the development of orientation selectivity. The development of orientation tuning has been shown to be disrupted following the introduction of artifi- cially correlated activity into the developing visual pathway of the ferret through chronic electrical stimulation of the optic nerve (Weliky and Katz, 1997). Periodic bursts of pulses, applied through a cuff electrode implanted around the optic nerve, synchronously activated retinal ganglion cell axons. In this experiment, the degree of correlated activity between ON and OFF ganglion cells was increased above normal. In stimulated animals, the orientation selectivity of visual cortical cells was significantly reduced but not abolished. While the amplitude of optically imaged differential iso-orientation maps was also significantly reduced compared to unstimulated controls, the spatial organization of orientation maps was normal. ON and OFF responses of cells within the LGN were unaffected, indicating that the site of the disruption was within the visual cortex. These results directly demonstrate that altering the correlational structure of neuronal activity within the visual pathway disrupts the development of visual cortical orientation tuning. This may occur by a process in which abnormally high correlated activity between ON and OFF LGN inputs to the visual cortex disrupt simple cell subfield segregation as theoretically predicted (Miller et al., 1999) or by a disruption of the intracortical circuitry responsible for sharpening orientation tuning within different cortical lamina. One possible reason why orientation selectivity was not completely eliminated, nor was the spatial structure of orientation maps affected, is that the visual pathway was only stimulated for 10% of the time. In this way, the activity present during the remaining 90% of the time between bursts could have contributed to normal cortical development. Results

from the electrical stimulation experiments directly support the Hebbian proposal of correlation-based growth and refinement of synaptic connections in which synchronously firing inputs are stabilized onto common postsynaptic target neurons, while nonsynchronous inputs are destabilized. The synchronous activation of neurons by chronic stimulation adds "noise" to the information contained within neuronal firing patterns, thus obscuring the natural pattern of correlations and leading to the growth and stabilization of inappropriate synaptic connections and a reduced specificity of orientation selective responses.

If correlations in cell firing drive the refinement of LGN inputs onto neurons within the visual cortex, then ordered patterns of correlated neuronal activity should be present within lower stages of the developing visual pathway including the LGN and retina. Correlated patterns of spontaneous activity have been observed in the developing retina of the ferret in vitro consisting of synchronized bursts of ganglion cell spike firing that sweep across the retina as waves of cell activity (Meister et al., 1991). Retinal spontaneous activity is crucial for the normal development and maintenance of LGN eye-specific layers. Pharmacological blockade of retinal spontaneous activity during the first postnatal week (P0–P7 to P9) prevents the normal segregation of LGN eye-specific layers (Penn et al., 1998; Cook et. al, 1999). Surprisingly, animals that have been treated for longer periods of time (P0–P14) also show incomplete but further eye-specific segregation than animals treated for only the first 7 days, suggesting a more premissive role for activity (Cook et. al, 1999). Furthermore, blocking retinal activity in older animals after eye-specific segregation is complete causes desegregation to occur (Chapman, 2000). While these experiments demonstrate that activity-dependent mechanisms are necessary for establishing and maintaining LGN eye-specific layers, it is unclear whether retinal activity plays a permissive role in these processes or whether patterns of correlated retinal activity play a more instructive role in patterning these connections.

While much is known about the spatial and temporal structure of retinal spontaneous activity, the properties of in vivo spontaneous neural activity within the next stage of the developing visual pathway, the LGN, have remained unknown. Multielectrode recordings obtained from awake behaving ferrets (P24–P27) prior to eye opening reveal synchronous bursts of action potentials produced within all LGN layers (Weliky and Katz, 1999). At this time in development, retinal waves are still present but are gradually disappearing by P30 (Wong et al., 1993). In addition, only weak orientation selectivity is present in visual cortical neurons (Chapman and Stryker, 1993), and it is several days before orientation preference maps can first be detected using optical imaging at P32–P34 (Chapman et al., 1996). Thus, orientation preference maps and orientation selectivity appear to be initially emerging during this stage of visual system development.

Cross-correlation analysis revealed systematic differences in correlated firing between different ON/OFF and eye-specific layers: neurons within the same eye-specific and center-type layer were most highly correlated, neurons within the same eye-specific but opposite center-type layer were more weakly correlated, while neurons within different eye-specific layers had the weakest, but still significant, correlations. If each retina independently generates spontaneous bursts of activity, there should be essentially no correlation between the patterns of spontaneous activity within the two LGN eye-specific layers. The observed binocular correlations could be generated by a number of mechanisms including intrinsic LGN circuitry or thalamo-cortical feedback interactions. To study the circuits underlying this correlated activity, retinal and cortical inputs were selectively removed. Removal of all retinal input revealed the presence of intrinsic oscillatory LGN bursting, which was substantially correlated across all layers. This activity was abolished following subsequent removal of cortical feedback. However, removal of cortical feedback did not appreciably change the pattern of LGN activity when retinal input was intact, but did abolish binocular correlations between the two eyes. Thus, cortico-thalamic feedback plays a crucial role in generating correlated activity between the eye-specific LGN layers. These results also suggest that cortical feedback may trigger intrinsic LGN oscillatory activity across different layers to generate the binocular correlations. The correlational structure of LGN spontaneous activity also differed from the predictions of in vitro retinal recordings. In vitro recordings, carried out in retinas obtained from similar age animals as used in the LGN recordings, reveal that ON and OFF retinal ganglion cells burst at different frequencies (Wong and Oakley, 1996). However, bursts within ON and OFF LGN layers occurred synchronously and at the same frequency. Taken together, these results demonstrate how the coupling of multiple mechanisms, including endogenous network oscillations and feedback connections, produce emergent patterns of spontaneous activity within the LGN. In this way, the LGN does not simply relay patterns of retinal activity to the cortex, but rather this activity is reshaped and transformed by corticothalamic interactions.

Many features of the experimentally observed correlational structure of LGN spontaneous activity are consistent with the predictions of correlation-based models of cortical map and receptive field development (Erwin and Miller, 1998). For example, ocular dominance maps, as well as binocularly matched orientation maps, develop before animals have had any visual experience (Crair et al., 1998). If the development of these maps is guided by neuronal activity, then spontaneous activity within the developing visual pathway must carry instructive information for the construction of early cortical circuits. Correlation-based models demonstrate that the independent development of orientation preference and ocular dominance maps have competing requirements in terms of the correlational structure of LGN spontaneous activity: ocular dominance maps require locally asynchronous activity within different eye-specific layers, while binocularly matched orientation maps require synchronous activity. Locally asynchronous activity induces inputs from the two eyes to segregate into separate ocular dominance bands, while synchronous activity yields local alignment of preferred orientations between the two eyes. Joint ocular dominance and orientation maps will form only under specific conditions. Under these conditions, there must not only be differ-

ences in correlated firing between ON/OFF cells, but a bias must exist such that local within-eye activity is more highly correlated than between-eye activity. This is what was experimentally observed in the LGN (Weliky and Katz, 1999). Since the retinotopic location of recorded LGN neurons was not determined, these experimental observations cannot test the more detailed model predictions in which like center-type inputs (either ON-center or OFF-center) should tend to be more coactive than opposite center-type inputs at small retinotopic distances and that this relationship should reverse at larger retinotopic distances.

Another mechanism by which correlated neuronal activity may contribute to the development of orientation selectivity is suggested by experiments demonstrating that receptive fields in the immature LGN have diverse receptive field shapes: some are concentric, elongated, or have "hot spots" of high retinal input (Tavazoie and Reid, 2000). These receptive fields are larger than those in the adult LGN and arise by the convergence of synaptic inputs from multiple retinal ganglion cells onto each LGN neuron. Many of these synapses are eliminated during development such that one retinal ganglion axon dominates the input to each LGN neuron in the adult, resulting in circular symmetric LGN receptive fields (Figure 2). In concert with Hebbian mechanisms of synaptic plasticity, early elongated LGN receptive fields could act as a scaffold to guide the emergence of visual cortical orientation selectivity. In this scenario, the convergence of several ganglion cells onto neighboring LGN neurons will induce correlated firing among these LGN neurons. If one of the LGN neurons' receptive fields is elongated and overlaps with colinearly arranged concentric receptive fields of its neighbors, correlated firing among these neurons will cause their connections to increase onto a common cortical cell. Later, as LGN receptive fields shrink to their adult size and shape, these LGN neurons will retain their synaptic connections to the common cortical cell and their colinear arrangement will endow the cortical cell with orientation tuning.

Recent experiments have challenged the notion that correlations in spontaneous neuronal activity drive the patterning of early synaptic connections in visual cortex. These experiments demonstrate that bilateral enucleation during early ferret development does not affect ocular dominance column formation (Crowley and Katz, 1999) nor the clustering of horizontal connections (Ruthazer and Stryker, 1996). While these results would seem to suggest that retinal activity is not absolutely required for formation of ocular dominance columns, they do not rule out a role for activity in general. Following binocular enucleation, overall levels of correlated activity actually increase between all LGN layers, although they do not increase uniformly between all layers (Weliky and Katz, 1999). Variations in correlated activity that are still present between the different eye-specific LGN layers could be sufficient to drive the segregation of thalamic afferents into ocular dominance columns within the visual cortex (Erwin and Miller, 1998). While patterns of spontaneous activity within the visual cortex are not yet known, it is also possible that appropriate spatiotemporal activity patterns within visual cortex are present both before and after binocular enucleation and act to guide the clustering of horizontal connections

and the formation of cortical columns. By utilizing new methods to manipulate and record neuronal activity patterns directly within the developing visual pathway, the mechanisms by which activity shapes and refines neural circuits within the visual cortex are becoming better understood. These studies are revealing that highly organized patterns of correlated neuronal activity are present within different stages of the developing visual system and that the fine scale manipulation of these patterns can dramatically disrupt the normal development of visual cortical structure and function. While these results provide evidence that neuronal activity plays an instructive role in shaping cortical circuits during development, it is likely that neuronal activity plays a more complex and subtle role that may be both instructive and permissive under different circumstances. Thus, a complete understanding of early neuronal circuit formation may not be achieved until we unravel the intricate interplay between neuronal activity, molecular guidance cues, and gene expression.

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