Previews

Mapping by Waves: Patterned Spontaneous Activity Regulates Retinotopic Map Refinement

A role for spontaneous spiking activity in shaping neuronal circuits has frequently been debated. Analyses of retinotopy in mutant mice with reduced correlated firing among neighboring retinal cells by Grubb et al. and McLaughlin et al. in this issue of *Neuron* indicate the importance of patterned spontaneous activity for retinotopic map refinement in subcortical visual targets.

Retinotopic maps that relay orderly representations of visual space from the retina to the brain are a universal feature of the visual system of vertebrates. Both molecular guidance cues and neural activity are thought to be essential for establishing precise retinotopic projections (Debski and Cline, 2002). Although it is apparent that molecular guidance cues set up a coarse, initial retinotopic map, how activity contributes to the refinement of this map remains unclear. One possibility is that activity plays a permissive role whereby it is simply needed for axons to read out molecular cues (Katz and Crowley, 2002). Alternatively, activity may play an instructive role where the precise, relative timing of spikes among afferent neurons is important (Willshaw and von der Malsburg, 1976).

The discovery of waves of spontaneous activity that correlate the firing of neighboring ganglion cells in the developing retina raised the possibility that patterned activity guides the development of retinotopic maps (Wong, 1999). However, experimentally reducing these correlations in firing between nearby ganglion cells without eliminating activity altogether has been challenging. The availability of mouse mutants in which retinal activity is altered in specific ways during development has spurred investigations into how neural activity shapes retinotopy. In addition, studying map development in mice is ideal, because retinotopic maps emerge relatively late, during the first postnatal week (Simon and O'Leary, 1992) when spontaneous retinal activity is patterned (Bansal et al., 2000).

Two papers in this issue of *Neuron* (McLaughlin et al. [2003] and Grubb et al. [2003]) provide considerable new insight into a role for patterned retinal activity in retinotopic map development. Both studies assessed the organization of retinotopic maps in subcortical visual targets of the β2 nicotinic receptor subunit knockout (β2 KO) mouse. In the first postnatal week, retinal waves in wild-type mice require cholinergic transmission (Bansal et al., 2000), and so the β2 KO mouse is a useful model for assessing the role of patterned activity in visual system development. Of particular importance is that retinal ganglion cells remain spontaneously active in β2 KO animals although retinal waves are absent during the first postnatal week (McLaughlin et al., 2003). By using multielectrode recording and calcium imaging methods, McLaughlin et al. discovered that, during the first postnatal week, correlated firing between neighboring retinal ganglion cells was lowered in the β2 KO mice and did not depend significantly upon intercell distance. In contrast, the degree of correlated firing in pairs of retinal ganglion cells from wild-type mice decreased systematically as the distance between the cells increased. Such distance-dependent correlations can help the target cells, acting as coincidence detectors, to ascertain whether afferent retinal ganglion cells are firing at the same time and thus likely to be neighbors (see Figure 1). The reduction in the level of correlated firing between neighboring cells in the β2 KO mouse thus presents a unique opportunity for assessing whether activity plays a permissive or instructive role in the refinement of retinal projections (Cohen-Cory, 2002).

Both McLaughlin et al. and Grubb et al. elegantly demonstrate that the mere presence of retinal activity in the β2 KO animal is insufficient for creating a precise retinotopic map. Their anatomical tracing studies reveal that the terminal arborizations of retinal axons in the dorsal lateral geniculate nucleus (dLGN) and superior colliculus (SC) are more diffusely spread across the target compared to their wild-type counterparts. Furthermore, Grubb et al. performed impressive electrophysiological recordings in vivo to show decisively that the perturbation in organization is not only structural but, importantly, functional. It is worthwhile to note that the terminal arbors of retinal ganglion cells in the β2 KO mouse still undergo some refinement during the first postnatal week when waves are absent. Thus, the current findings underscore a requirement for patterned retinal activity not for the formation of retinotopic maps, but rather in their refinement with maturation.

In addition to this central finding, there are several observations in the β2 KO mice that are intriguing. The first is that waves resume in the second postnatal week in the KO. Unlike the first postnatal week, the later-emerging waves require glutamatergic transmission (Bansal et al., 2000). Despite the reemergence of correlated activity by propagating waves, the retinotopic map of the β2 KO animal is less precise compared to that of wild-type animals at 3–4 weeks after birth. McLaughlin et al. suggest that this reveals a critical period for retinotopic map refinement. If so, this would imply that another feature of the mammalian visual system (maps) apart from dLGN eye-specific layers (Huberman et al., 2002) or cortical columns (Hubel and Wiesel, 1963) is shaped by interactions restricted to a particular window of development. However, because retinal circuits themselves are not fully mature until about a month after birth, it remains to be elucidated whether map refinement in the β2 KO animal is severely retarded, such that more tightly focused axonal terminal zones might be found in animals several months of age. Nevertheless, that glutamatergic waves cannot rapidly reverse the perturbation in axonal terminal organization by loss of cholinergic wave activity does suggest that there may be cues
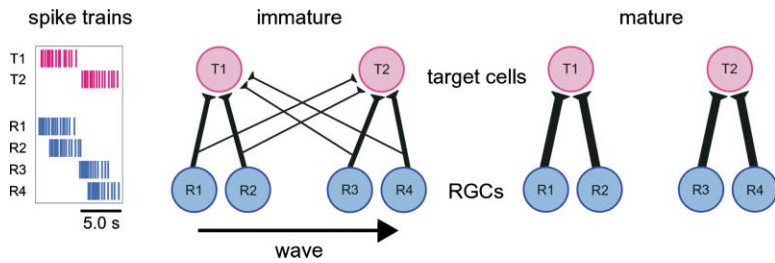
Figure 1. How Waves Might Refine Retinotopic Maps

Immature retinal ganglion cells (RGCs, R1-4) have diffuse axonal arbors and form supernumerary connections in the developing visual system; however, molecular cues generate a retinotopic bias in connectivity (e.g., R2 is more strongly connected to T1 than T2). The synaptic strength between cells is proportional to the line width. As waves propagate in the immature retina, spike trains from nearest neighbor RGC pairs (R1 and R2; R3 and R4) are better synchronized than spike trains of RGCs separated by a greater distance (e.g., R2 and R3). Coincident firing between RGCs and their target cells result in the strengthening of retinotopically appropriate connections (e.g., R3 to T2). In contrast, RGCs that fire when the target cell is inactive result in the weakening of retinotopically inappropriate connections (e.g., R3 to T1). This hypothesis has been proposed and verified in computer models (Willshaw and von der Malsburg, 1976).

present only early in development that establish the fine structure of retinotopic maps.

Another curious feature of the retinal projections in the β2 KO animals reported by Grubb et al. is that, in the dLGN, the dorsoventral map is not as affected as the nasotemporal map. Why might this be so? The authors suggest that this biased effect may be because there is an order in the initial ingrowth of retinal axons to subcortical targets (Simon and O'Leary, 1992). The β2 KO mouse may therefore provide renewed opportunities for elucidating the importance of temporal order in the ingrowth of axons in generating biases in spatial organization of the projections, including eye-specific layer and column formation. The electrophysiological analyses of Grubb et al. also highlighted the preservation of key aspects of retinal connectivity with the dLGN at the level of the target neurons. In the adult β2 KO mouse, dLGN neurons are monocular and are stimulated by increased (on) or decreased (off) illumination, as in wild-type animals. Preventing the occurrence of early cholinergic waves in both eyes is thus unlikely to determine the physiological phenotype of an individual geniculate neuron.

Although it would be satisfying to conclude from the current studies that retinal waves indeed underlie refinement of retinotopic maps, several issues still require consideration. The first is that the β2 nicotinic receptor subunit is genetically removed throughout the animal, including the target structures examined. The authors argue that this caveat is not problematic because of previous studies in which in vivo application of nicotinic receptor antagonists over the subcortical targets did not affect retinotopic map refinement in the SC (Simon et al., 1992) or ocular lamination in the dLGN (Penn et al., 1998). Because it is often difficult to assess how effectively pharmacological agents act over the long term in vivo, there remains a possibility that the aberrant projections observed in the β2 KO mouse may be a combination of effects on retinal activity patterns and transmission within the targets. With more selective mouse KOs being generated and available, it is likely that this issue will be resolved in the near future.

Also, despite the usefulness of the β2 KO animal, a more ideal situation would be to maintain the firing rates of retinal ganglion cells while disrupting their correlated firing. Spike rates of ganglion cells in the β2 KO animals are about 50% higher than those at equivalent ages in wild-type mice. Because it is generally thought that increased activity enhances production and action of neurotrophins (Cohen-Cory, 2002), the widespread distribution of retinal axonal arbors in the β2 KO may reflect increased axonal elaboration rather than decreased branch elimination. It will therefore be important not only to examine the arbors of individual mouse retinal ganglion cells in the future but also to image their dynamic behavior in living animals over the time course of map refinement, such as has been performed in the tectum of frogs (Cohen-Cory, 2002; Ruthazer et al., 2003). Such in vivo imaging studies in mice will be facilitated by the generation of transgenic animals in which single retinal axons express green fluorescent protein from birth.

The work of McLaughlin et al. and Grubb et al. will fuel renewed interest in the mechanisms by which patterned retinal activity leads to refinement of visual projections. Undoubtedly, among possible future directions are studies aimed at comparing the behaviors of active versus inactive axons. Also, we have yet to understand the cellular mechanisms underlying how correlations in spiking of neighboring retinal ganglion cells regulate map refinement. Another level of investigation is likely to encompass studies on how activity-driven refinement interacts with molecular guidance cues during the period of map refinement. Can molecular cues substitute for activity cues and vice versa? Future studies are likely to make use of conditional knockout animals in which either expression of specific guidance molecules or activity patterns may be selectively perturbed over a chosen period of development.

The final stages of retinotopic refinement are likely to take place after eye opening, as waves disappear and vision begins. Dissecting the relative contributions of spontaneous activity and visually evoked activity during this period is important. Indeed, studies in the frog tectum suggest that growth and elaboration of retinal axon terminals are modified by visual activity (Ruthazer et al., 2003). It would thus be interesting to ascertain whether vision is altered in significant ways in the β2 KO mice, even though the receptive fields of the dLGN neurons appear normal by adulthood. Regardless, the use of transgenic animals in which endogenous activity patterns are altered has enabled McLaughlin et al. and Grubb et al. to lend new insight on the question of how neural activity sculpts connectivity in the CNS. Their findings are certain to keep the debate on this controversial area in the forefront.

Stephen J. Eglen,[1] Jay Demas,[2]
and Rachel O.L. Wong[2]
[1]Institute for Adaptive and
   Neural Computation
School of Informatics
University of Edinburgh
5 Forrest Hill
Edinburgh EH1 2QL
Scotland
[2]Department of Anatomy and Neurobiology
Washington University School of Medicine
St. Louis, Missouri 63110

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Episodic Memory Signals
in the Rat Hippocampus

How does the hippocampus signal memory for episodes? In this issue of *Neuron*, Ferbinteanu and Shapiro show that classic place cell activity in the rat hippocampus together with robust retrospective and prospective memory signals reflects the sequence of past, present, and future events that make up an episode.

Ever since Scoville and Milner (1957) hypothesized that damage to the hippocampus may underlie the profound memory deficit exhibited by patient H.M., intense research has focused on understanding the specific contributions of this structure to memory function. The discovery of place cells in the rat hippocampus by O'Keefe and Dostrovsky (1971) suggested that an understanding of the neurophysiological correlates of memory was within reach. However, the early emphasis on the idea

that hippocampal place cells constitute a spatial map of the environment (cognitive map theory; O'Keefe and Nadel, 1978) led many researchers to focus on the spatial firing properties rather than on the memory correlates of hippocampal cells. Moreover, the view endorsed by the cognitive map theory, that the rat hippocampus is involved exclusively in spatial processing, was difficult to integrate with the classic findings that humans with medial temporal lobe damage exhibit long-lasting, multimodal memory impairments for facts and events.

More recently, a growing number of groups have started to examine the mnemonic correlates of rat hippocampal cell activity as animals perform various memory-demanding tasks. These studies clearly demonstrate that both spatial as well as nonspatial memory signals are observed in the rodent hippocampus. For example, Wood et al. (1999) recorded in the hippocampus as rats performed an olfactory delayed nonmatching to sample task. This study reported that more than half of the task-related activity was associated with nonspatial variables including olfactory-selective responses, as well as recognition memory signals. Other studies showed that place cell activity could be modulated by behavioral context including information about past or future behavior (Frank et al., 2000; Wood et al., 2000). These findings together with others led to the idea that the hippocampus signals a running record of the ongoing events in an episode irrespective of whether the information is spatial or nonspatial (memory space theory; Eichenbaum et al., 1999). However, none of the above-mentioned studies verified that task performance was dependent on intact hippocampal function or separated the influence of memory context from spatial trajectory.

To test the role of the hippocampus in signaling the on-going events in an episode, Ferbinteanu and Shapiro (2003) examined the mnemonic signals of hippocampal cells during the performance of a + maze alternation task impaired by fornix damage in rats. In this task, animals could start from either the north or south arm of the + maze and performed alternating blocks of trials where either the east or west arm was rewarded. Hippocampal activity was recorded as animals executed four possible journeys: north-east, north-west, south-east, or south-west (Figure 1). Between each trial, the animal was placed in a holding area, making the beginning and end of each journey distinct. Two major patterns of task-related activity were reported. The first was classic hippocampal place cell activity, which they term "journey-independent" spatial activity. These cells fired in a given location in the maze, irrespective of the journey taken on that trial (Figure 1B). The second major pattern of activity was termed "journey-dependent" spatial activity. Cells exhibiting this pattern of activity fired in a particular location on the maze only during a specific journey (i.e., activity on the north arm only during the north-east journey, but not during the north-west journey). Two different kinds of journey-dependent activity were described. The first type of journey-dependent activity was observed on the goal arm and was dependent on the identity of the start arm visited on that trial (Figure 1A). Thus, these cells signaled information about the previously visited place (retrospective signal). The second type of journey-dependent activity was observed