An eye-opening experience

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Many aspects of visual development are known to depend on activity. Two recent reports of rapid rewiring of connections in visual cortex and superior colliculus make clear that eye opening is an important event in the maturation of the visual system.

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Plasticity in the postnatal development of the visual system has been studied extensively by manipulations that disrupt normal visual experience, such as eyelid suture or strabismus. But eye opening, a natural, timed event in the course of development, has generally been neglected. Two recent reports[1,2], however, give us insight into how eye opening guides the maturation of the visual cortex and superior colliculus.

There are strong reasons to believe that eye opening may be important to cortical maturation. Around the time the eyes open, the primary visual cortex (V1) is undergoing considerable synaptogenesis[3]. Reflecting this new synapse growth, the input layer of V1 shows a rapid rise in the frequency of spontaneous excitatory synaptic events[4]. Just as ocular dominance plasticity turns on the cAMP-responsive element (CRE) transcription factor—a molecule that coordinates activity-dependent synaptic rearrangement—in cortex[5], so does eye opening[6]. Also, PSD-95, a postsynaptic scaffolding protein, relocates to cortical dendrites within hours of eye opening[7]. Are these molecular and functional indicators of synaptic reorganization actually stimulated by opening the eyes, however, or are they merely coincident with it?

A report in last month's issue of *Nature Neuroscience* may shed new light on the cortical consequences of eye opening[1]. Maffei *et al.* kept one eye closed in young rats while allowing the other eye to open naturally. Because one hemisphere's monocular V1 receives visual input from the open eye and the other from the closed eye, this manipulation provides a nice internal control. Taking slices of each hemisphere and assaying them in a medium that enhanced excitability, the authors recorded the spontaneous discharge of cells in the input layer. Excitatory pyramidal cells that had experienced visual stimulation through the open eye were 20 times less spontaneously active than their counterparts that had not. The authors went on to show that cell type–specific changes in local synaptic connectivity within the input layer were driving the spontaneous discharge.

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Layer IV in the closed eye's V1 had stronger feedback excitation and weaker inhibition than in the open eye's V1. Such circuit changes, like those found in cultures[8], were interpreted to act homeostatically to create similar amounts of activity on the two sides *in vivo*.

The authors interpret these cortical changes in the context of experiments on monocular visual deprivation[9]. Indeed, the enhanced cortical response to one eye when it is opened after prolonged dark-rearing has been interpreted as an extension of the critical period of susceptibility to monocular deprivation[10]. But an alternative explanation of all these experiments seems even more likely. Could it be that eye opening rather than visual deprivation of the closed eye caused the change in layer IV's local wiring? Part of the answer will have to come from contrasting the author's results with recordings to be taken before normal eye opening (**Fig. 1a**). Even then, to be certain that opening or closing the eye is sufficient for the rewiring effect discovered by Maffei *et al.*, it will be necessary to separate eye opening from other developmental programs whose timing may coincide with it.

Variability in the timing of eye opening (1–2 d) has posed a serious impediment to studying its effects. Martha Constantine-Paton's laboratory has eliminated this variability by closing the eyelids of littermates bilaterally and then opening the eyes synchronously at the age desired. One can then measure the time series of changes in the visual system in littermates at varying intervals from the synchronized opening. Yoshii *et al.* used this synchronization procedure to show convincingly that PSD-95 relocates to cortical and collicular dendrites within hours of eye opening[7]. Using synchronization, the same group showed that opening

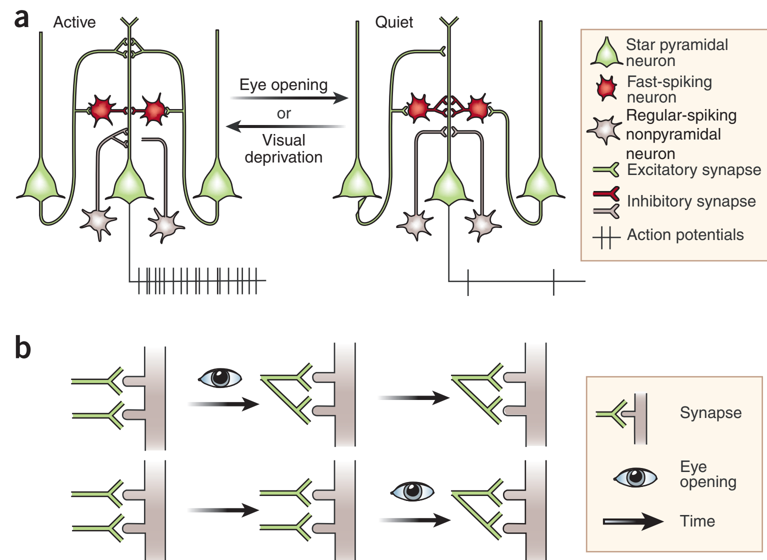

Figure 1 Does eye opening or its deprivation cause the change in layer IV spontaneous activity? (**a**) Maffei *et al.*[1] observed that spontaneous activity of layer IV pyramidal cells bathed in an excitatory medium is 20-fold higher than normal in a visual cortex that gets its input from an eye that has been prevented from opening. Underlying the increase is a local rewiring that favors recurrent excitation over recurrent and feedforward inhibition. The state of layer IV excitability before the eyes open is unknown. Does it resemble the active (closed-eye) or quiet (open-eye) state? Opening the eyes may silence spontaneous activity or else visual deprivation may amplify layer IV excitability. (**b**) Synchronization protocol controls timing of eye opening and distinguishes it from other timed developmental programs. Schematic simplifies the results of Lu and Constantine-Paton[2]. Eye opening rapidly increases the specificity of inputs to superior colliculus neurons by boosting the number of connections per input and paring down the number of inputs. Synchronizing eye-opening between animals and testing at different ages unambiguously connects this rewiring event to eye opening.

the eyes stimulated prompt synaptic changes that strengthened the specificity of collicular inputs[2] (**Fig. 1b**). Applying this synchronization procedure to the experimental design of Maffei *et al.* would nail down whether eye opening (or its deprivation) is sufficient to reorganize layer IV or whether instead a developmental program independent of patterned vision also participates.

Would the huge changes in spontaneous activity measured by Maffei *et al.* in cortical slice be detectable in the intact brain? Extracellular recordings like those done[11] in layer IV will be required to address this question. One can imagine combining the clever designs of the two new papers[1,2] to evaluate local connectivity and activity in whole-cell recordings from layer IV in animals with one eye open and the other closed.

Cortex and superior colliculus are not the only structures in the visual pathway that eye opening might reorganize. Retinal ganglion cells were long believed to be immune to activity-dependent modification. Yet we now know that a week of patterned vision stimulates the segregation of ganglion cell dendrites into on- and off-response specific layers[12] and increases the rate of spontaneous synaptic events[13]. Retinogeniculate connections are refined throughout this period, but we do not know to what extent the reorganization is driven by eye opening[14]. Synchronization experiments may tease out other prompt effects of eye opening on visual system maturation.

Though patterned vision through the opened eyes seems to trigger a maturation of the visual pathway, the effects of eye opening may be mediated instead or in addition by factors other than a change in activity. For example, the neurotrophic molecule BDNF is produced in the retina upon eye opening[15]. Transneuronal transport of BDNF injected into a visually deprived eye occludes the ocular dominance plasticity that would normally shift cortical responses toward the non-deprived eye (Mandolesi, G. *et al.*, *Soc. Neurosci. Abstr.* 66.6, 2004**.** Neurotrophins may be an important prerequisite for allowing activity to mature the visual pathway.

It is gratifying to see that a dramatic event in development like eye opening has such striking effects on the visual system. Using spontaneous firing as a readout of rapid changes in local connectivity[1] and synchronizing eye opening to measure prompt biochemical and synaptic changes[2] seem like ideas too good to have taken this long to appear. But maybe really good ideas always seem obvious once our eyes have been opened to them.

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Bridging the gap: coupling single-cell oscillators in the suprachiasmatic nucleus

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Neurons in the mammalian master clock can maintain circadian rhythms in isolation, but must synchronize to function as a time-keeping system. A new study finds that gap junctions between neurons promote synchronous electrical activity and rhythmic behavior.

From daily sleep cycles to dinnertime, the circadian system is responsible for the timing of behavior and physiology. In mammals, the conductor of this multifaceted timing system can be localized to a pair of structures in the hypothalamus known as the suprachiasmatic nucleus (SCN)[1]. Individual SCN neurons in isolation have the capacity to generate circadian oscillations in electrical activity, secretion and gene expression, but the cells drift out of phase with each other[2]. Understanding how individual oscillators remain synchronized in the intact SCN has been a fundamental gap in our knowledge of SCN function. In this issue, Long *et al.*[3] unambiguously demonstrate that SCN neurons are electrically coupled and that this coupling not only promotes synchronization of neural activity, but also is required for the maintenance of circadian rhythms in behavior.

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The authors made intracellular recordings from pairs of neighboring SCN neurons. They found that about 25% of the neurons were electrically coupled and that these coupled cells showed synchronized spiking activity. The coupling strength and biophysical properties were similar to those measured in other types of coupled neurons[4]. Gap-junction channels are formed by a family of proteins called connexins. Connexin 36 (Cx36) is a major component of gap-junction-mediated electrical coupling in neurons[4], and this seems to be the case in the SCN. Long *et al.* found that the electrical coupling between SCN neurons was lost in Cx36 knockout mice[3]. As compared to regions like the inferior olive, the new study found that the percentage of coupled cells in the SCN was relatively low [3]. This lower coupling frequency between SCN neurons seems to be consistent with our knowledge of SCN physiology. These clock cells do not show absolutely synchronized action potential generation; instead the population has coordinated firing rates that are high during the day and low during the night. However, it may be that some cell populations within the SCN are highly coupled and others not at all.

To determine whether gap-junction-mediated electrical coupling may also be involved in behavioral rhythmicity, the authors turned to the best-characterized behavioral output of the circadian system—namely, the wonderfully precise rhythms in wheel-running activity. In a light:dark cycle, both wild-type and *Cx36* knockout mice synchronized to the