A new slant on the development of orientation selectivity

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High-resolution analysis of immature receptive fields in lateral geniculate neurons suggests that transient oriented receptive fields in the thalamus may contribute to the development of orientation selectivity in visual cortex.

Hubel and Wiesel opened the modern era of visual neuroscience four decades ago with their finding that visual cortical neurons are selective for the orientation of elongated visual stimuli, even though their inputs from the lateral geniculate nucleus of the thalamus have no such orientation selectivity[1]. Two questions have dominated research in this area ever since: what is the underlying neuronal substrate for orientation selectivity, and how does it develop? The first question gave rise to years of debate and controversy, but a consensus has now emerged in favor of Hubel and Wiesel's original hypothesis, namely that orientation selectivity arises from a 'feedforward' process in which a few unoriented geniculate cells with receptive fields arranged along one axis converge onto a cortical cell (**Fig. 1a**).

In this issue, Tavazoie and Reid[2] offer a surprising partial answer to the second question. It is not a complete account, because it does not explain the development of orientation columns (in which neighboring neurons have similar orientation preferences), nor does it explain why some cells with orientation selectivity are present[3–5] before the postnatal period studied by these authors. Nevertheless, Tavazoie and Reid have proposed a plausible mechanism that may be involved in the formation of oriented receptive fields. Their proposal is surprising because, whereas most ideas about the development and establishment of orientation selectivity have concentrated on processes within visual cortex itself or the retina[6,7], the new model points to the neglected lateral geniculate nucleus as a critical locus for the emergence of cortical orientation selectivity. Moreover, because visual pathways are considered an excellent model system for the study of brain development, particularly thalamocortical relationships, these ideas may be widely applicable.

Tavazoie and Reid[2] followed the postnatal development of neuronal receptive field properties in the lateral geniculate nucleus of ferrets. The visual pathways of ferrets seem to be organized and develop essentially like those of the better-studied cat, but they have the advantage for developmental studies that they are born 'prematurely', after only 6 weeks of gestation; this is equivalent to about two thirds of the way through gestation for cats[3].

The authors used a sophisticated, quantitative technique to analyze these immature receptive fields, thereby revealing their properties at a higher resolution than earlier studies. They recorded from single geniculate neurons while stimulating them visually with a sequence of small spots that appeared pseudorandomly throughout the neuron's receptive field, then used a reverse-correlation technique to determine the latency and spatial position of each spot that excited or inhibited the neuron. This extra resolution allowed them to correlate geniculate cell development with the development of cortical orientation selectivity.

In adult animals, one retinal axon dominates the input to each geniculate neuron, so the receptive fields of geniculate cells resemble those of their retinal inputs (**Fig. 1b**). Both receptive fields are roughly a degree in diameter with a circular central region surrounded by an annulus. These center and surround regions have opposite responses to visual stimulation (for instance, a center excited by light spots and inhibited by dark ones, and a surround inhibited by light and excited by dark). This configuration can be effectively modeled by the differential sensitivity of two Gaussian functions—one for the center and another for the surround—so Tavazoie and Reid were able to determine the number of such configurations that best fit their geniculate receptive field maps, and thereby estimate the number of convergent retinal axons innervating each geniculate cell.

Consistent with other studies[8], Tavazoie and Reid[2] found a general decrease in receptive field size with age that seems to result from reduced convergence of retinal afferents. In young animals, it appears that several axons innervate each geniculate neuron; the adult pattern emerges when these inputs compete for dominance in a 'winner take all' process, in which unsuccessful suitors are pruned away. The authors' key additional observation is that some odd-shaped receptive fields in young animals are best explained as resulting from a haphazard assortment of retinal inputs converging onto single geniculate cells. Later, during the 'critical period' when

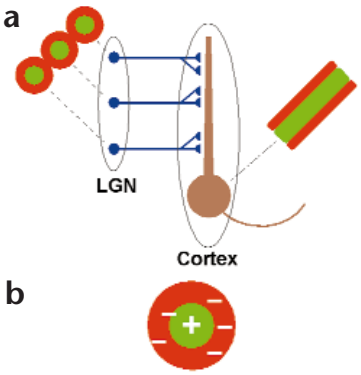

Fig. 1. Receptive fields of cells of lateral geniculate nucleus and visual cortex. The center/surround receptive fields of 3 geniculate cells are aligned so that when output axons of these cells converge onto a cortical cell in layer 4, the receptive field of the cortical cell has an elongated shape with orientation selectivity (**a**). Retinal and geniculate cells have similar receptive fields (**b**). The central, circular region is excited by bright spots and inhibited by dark spots (+), and a surrounding annular region is excited by dark spots and inhibited by bright spots (–). Other retinal and geniculate cells have the mirror-image receptive field with a center excited by dark and surround excited by light.

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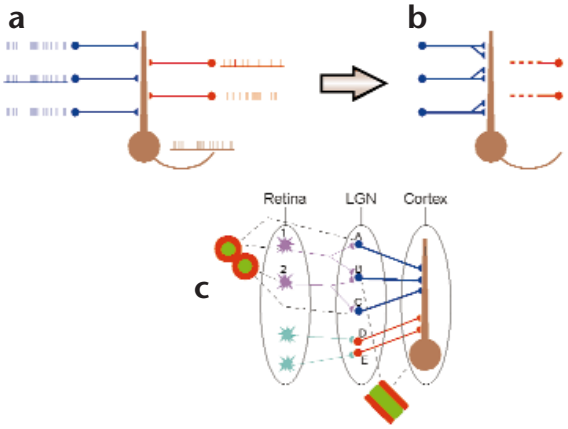

Fig. 2. Hebbian plasticity and the development of receptive fields. Early in development (**a**), a lateral geniculate neuron receives input from five retinal axons. The three on the left have correlated activity, whereas the two on the right are uncorrelated. Through a Hebbian process, correlated inputs are strengthened and uncorrelated inputs withdrawn to form the adult pattern (**b**). (**c**) Immature lateral geniculate receptive fields influence the development of cortical orientation selectivity. See text for details.

orientation selectivity is being sharpened and many connections are especially susceptible to visual deprivation[3], many of these converging retinal inputs are lost, but some geniculate neurons still have at least two strong retinal afferents with slightly offset receptive fields. This gives the geniculate neuron an elongated, indeed oriented, receptive field, a feature that has not been emphasized in previous developmental studies.

Before considering how this observation might explain the establishment of cortical orientation selectivity, it is worth taking a brief detour to see how converging retinal afferents to a geniculate cell are pruned by competition to a single survivor. Most students of brain development, including Tavazoie and Reid, attribute this process to a 'Hebbian' mechanism (**Fig. 2a** and **b**), named after Donald Hebb, who proposed the idea in 1949 (ref. 9). The Hebbian model proposes that a strong correlation between the firing of a presynaptic axon and its postsynaptic partner causes the intervening synapses to be strengthened; if the correlations are weak or nonexistent, synapses are weakened and may eventually be lost (see ref. 10 for details).

Hebb's rule is a theoretical framework that can explain many features of neural development (but see below), but there is no explicit demonstration that it applies to development of retinogeniculate or geniculocortical connections. This would be technically very difficult, because it would require simultaneous recording of a cell and its presynaptic inputs to show that high correlations between input and output strengthen synapses and that poor correlations weaken them. The closest finding to such a demonstration is that high-frequency electrical stimulation of the retinogeniculate input *in vitro* can strengthen retinogeniculate synapses when inhibition is blocked[11].

Nonetheless, this Hebbian mechanism for synaptic strengthening is central to the hypothesis of Tavazoie and Reid[2] regarding the significance of immature geniculate neurons with elongated receptive fields. In the example of Fig. 2c, one geniculate neuron (cell B) with an elongated receptive field is near two cells (A and C) with mature circular, center/surround receptive fields. These receptive fields result from cells A and C receiving input via a single retinal axon from cells 1 and 2 respectively, and cell B receiving convergent input from both cells 1 and 2. Because geniculate cells A and B receive the same pattern of synaptic activation from retinal cell 1, they would tend to have correlated activity. Likewise, cell 2 would tend to synchronize the outputs of geniculate cells B and C.

Over time, then, if cells A, B and C converge onto a single cortical target neuron, all three have an advantage in establishing connections via a Hebbian process over other inputs whose firing is not correlated (such as cells D and E). Eventually a similar Hebbian process will reduce the receptive field of geniculate cell B to the adult, circular pattern as retinal cell 1 or 2 wins the battle to dominate its inputs. The net result is that the cells A, B and C dominate the geniculate inputs to the cortical cell, leading to an innervation pattern (**Fig. 1a**) that produces orientation selectivity in the cortical cell. Notice that this process does not require that cells A and C be correlated with each other, only that each is correlated with cell B early in development.

Two caveats are worth mentioning. First, the arrangement in Fig. 2c accounts for the alignment of only two center/surround receptive fields in inputs to a cortical cell because, after its own Hebbian development, cell B must end up with a receptive field identical to either cell A or cell C. However, this may not be a serious problem, as Tavazoie and Reid only propose that this process participates in establishing orientation selectivity and do not suggest that it is the entire story. Moreover, the average length of the receptive field of a first-order cortical cell in layer 4 is approximately equal to two geniculate receptive field centers, consistent with their model[12].

The second caveat does not relate specifically to the Tavazoie and Reid paper, but is rather a comment on the generality of Hebbian rules for establishing connections. Assuming that they apply in this system (despite the lack of direct evidence noted above), Hebbian rules can in principle account for many aspects of retinogeniculate synapse formation. One reason is that retinal inputs strongly activate geniculate cells, a necessary condition for correlation of pre- and postsynaptic responses. However, retinal inputs account for only 5–10% of the synapses onto geniculate cells projecting to cortex; the vast majority derive instead from local inhibitory cells, from visual cortex feedback projections and from brainstem inputs[13]. Functionally, retinal inputs act as drivers, which carry the main information to be relayed to cortex and strongly control the firing of lateral geniculate neurons, whereas nonretinal inputs modulate the response of the geniculate cells to their driving inputs[14]. In the adult, at least, firing in various modulatory inputs does not seem to produce much correlated firing in geniculate cells. If this is also true during development, it is hard to see how Hebbian mechanisms can affect these inputs. In other words, Hebbian mechanisms may apply only to strong inputs, leaving many inputs without a clear developmental mechanism. This may be true for the cortex as well; geniculate input accounts for only about 5–10% of the synapses onto cortical cells[14], raising the possibility that many intracortical connections may also develop without Hebbian rules.

In any case, Tavazoie and Reid have made a strong argument that a key property of cortical neurons—orientation selectivity—develops, at least in part, through dynamic changes at the thalamic level. The thalamus has had bad

press until recently, being seen as an uninteresting, immutable relayer of information to cortex. This view is now changing, as it becomes clear that the thalamus provides a dynamic, changeable relay that can alter the extent and format of information relayed in functionally important ways. The new findings suggest that the thalamus may also be important in development, especially if the lessons drawn from the lateral geniculate nucleus are also relevant to other thalamic nuclei.

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AMPA receptors jump the synaptic cleft

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Satake *et al.* show that glutamate release in the cerebellum causes heterosynaptic depression of GABA release and that AMPA receptors act presynaptically to mediate this phenomenon.

Synaptic communication between neurons involves conversion of a presynaptic electrical signal, the action potential, into a chemical signal, the neurotransmitter, and then back into an electrical signal, the postsynaptic potential. However, this communication is much richer than simply relaying a signal from one neuron to another, because it is well established that neurotransmitters, in addition to their actions on the postsynaptic cell, can also act presynaptically to alter the amount of transmitter released in response to the incoming action potential. Little is known about the mechanisms underlying this regulation, or which transmitters can lead to presynaptic effects when activated endogenously. In the present issue of *Nature Neuroscience*[1], a very persuasive study shows that this neuromodulatory action is mediated *in situ* by heterosynaptic activation of excitatory (glutamatergic) AMPA receptors on presynaptic terminals of inhibitory GABAergic synapses in the cerebellum.

The first, and still the best characterized, examples of presynaptic control of transmitter release are the actions of GABA at the crustacean neuromuscular junction[2] and on the spinal primary afferent terminals[3]. At these synapses, activation of presynaptic $GABA_A$ receptor-coupled chloride channels at GABAergic axo-axonic synapses inhibits glutamate release. However, with the subsequent discovery of numerous presynaptic metabotropic receptors for many transmitters, which can inhibit neurotransmitter release through G-protein-coupled biochemical cascades, the idea that ionotropic receptors could regulate transmitter release was largely forgotten.

Many recent studies have re-awakened interest in the possibility that the presynaptic regulation of transmitter release by ionotropic receptors may be more general than previously thought[4]. More specifically, the ionotropic glutamate receptors of the kainate[5–9], AMPA[10] and NMDA[11] subtypes have all been proposed to regulate neurotransmitter release. Physiological studies have focused primarily on kainate receptors, which inhibit both excitatory[5,6] and inhibitory[7–9] transmission. However, these receptors may inhibit release through a G-protein-coupled metabotropic action, independent of their ionotropic action[8,9]. Moreover, the location of these 'presynaptic' receptors on inhibitory neurons is debated[8,9,12], and it is unclear whether these receptors mediate their effects directly on the terminal.

Satake and colleagues now show convincingly that AMPA receptors, located on the presynaptic terminal, can inhibit neurotransmitter release[1]. These authors take advantage of the simple cellular architecture of the cerebellum, where the single output neurons of the cerebellar cortex, the Purkinje cells, receive inputs from a number of sources including excitatory climbing fibers and inhibitory basket cells. They show that repetitive activation of climbing fibers, which form a one-to-one contact with Purkinje cells, inhibits GABA release from basket cells to Purkinje cells. This heterosynaptic effect of the climbing fiber is confined to the Purkinje cell on which it synapses. A number of tests (discussed below) indicated that the depression is presynaptic and direct, and that the climbing fiber synapses release a transmitter that spreads to the basket cell synapses.

A series of pharmacological experiments indicate that the transmitter mediating this presynaptic inhibition is likely to be glutamate acting on presynaptic AMPA receptors. The effect is mimicked by the application of AMPA and is blocked by the AMPA receptor-selective antagonist GYKI 53655. The effect can also be enhanced by cyclothiazide, a drug that selectively blocks desensitization of AMPA receptors. Where are these AMPA receptors located? The experiments of Satake *et al.* suggest that they are located in the terminals themselves. Dual recordings of synaptically coupled basket cell–Purkinje cell pairs showed that changes at the basket cell soma cannot explain the effect. Moreover, there is a tight correlation between depression of GABA release and the activation of single climbing fibers. This argues against the possibility that the depression results from circuit effects downstream of activation of a population of climb-

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