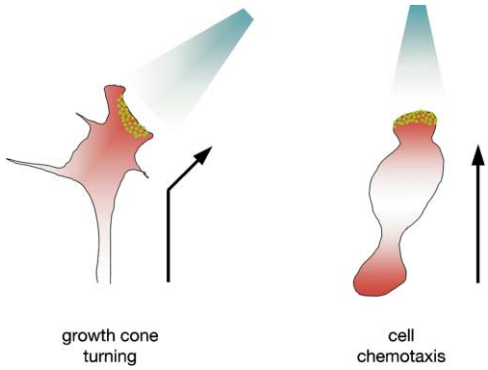

Figure 1. Spatial Organization of Signaling by Lipid Rafts

Lipid rafts (red) organize spatial signaling during growth cone guidance (left) and cell chemotaxis (right) by concentrating the gradient-sensing machinery (green dots) at the leading edge. Diffusible gradients are shown in blue.

and chemotaxis, but since the evidence for asymmetric raft distribution was obtained in fixed cells, it was not known whether rafts in fact redistribute during directional cell movement in living cells. In the new work, they used high-resolution confocal video microscopy to track raft-associated fluorescent GPI-anchored proteins during leukocyte chemotaxis in response to a diffusible gradient of the chemokine stromal cell-derived factor-1 (SDF-1). They found that chemoattractants induced a persistent redistribution of raft-associated GPI-anchored green fluorescent protein (GFP) to both cell edges during cell chemotaxis, while transmembrane, nonraft proteins were distributed homogeneously. In agreement with the results of Guirland et al., they also found that the chemokine receptor CCR5 accumulated in GM3-rich rafts at the leading edge. They also observed recruitment and activation of phosphatidylinositol-3 kinase γ (PI3Kγ) in leading edge rafts of migrating cells. As expected, cholesterol depletion prevented raft redistribution and asymmetric recruitment of PI3Kγ.

Together, the results of Guirland et al. and Gómez-Moutón et al. indicate that lipid rafts organize spatial signaling in moving cells and growth cones by concentrating the gradient-sensing machinery at the leading edge (Figure 1). In contrast, a recent study concluded that lipid raft proteins have a random distribution during focal activation of T cell receptors with coated beads in stationary T cells (Glebov and Nichols, 2004). Intriguingly, although these researchers did observe redistribution of fluorescent GPI-anchored proteins and G_{M1} gangliosides to the site of activation, in agreement with previous work in that field (Viola et al., 1999), they failed to detect significant changes in surface density of GPI-linked proteins using FRET (Glebov and Nichols, 2004). They therefore suggested that the apparent local concentration of lipid raft components seen in some experiments could be explained by convolution of the plasma membrane to generate an increase in fluorescence intensity. Although that could be the case of static cell membranes in direct contact with beads coated with stimulating substances, it would seem less likely in the case of a growth cone moving toward or away from a diffusible gradient of a chemotropic guidance cue. Moreover, as observed by Gómez-Moutón et al., the fact that nonraft transmembrane proteins distributed homogeneously in cells undergoing chemotaxis would argue in favor of an active mechanism of raft redistribution rather than membrane flow to the cell poles. A more exciting possibility suggested by the studies of Guirland et al. and Gómez-Moutón et al. is the idea that redistribution of lipid raft components may be specifically important for directional cell or growth cone movement and perhaps less so for interactions between stationary components. Thus, lipid raft mobilization and the ensuing localized downstream signaling may be part of an intrinsic three-dimensional cellular response to spatial cues, a sort of "subcellular patterning" that allows the cell to spatially integrate environmental cues coming from specific directions. This type of mechanism could be of importance in a number of other processes involving dynamic subcellular polarization of some sort, such as axonal branching and asymmetric cell division.

Carlos F. Ibáñez
Division of Molecular Neurobiology
Department of Neuroscience
Karolinska Institute
S-17177 Stockholm
Sweden

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Retina versus Cortex: Contrast Adaptation in Parallel Visual Pathways

Human vision adapts to the contrast of patterns by changing its sensitivity, but the origins of this perceptual adaptation have been disputed. In this issue of

***Neuron*, Solomon et al. show that contrast adaptation in the primate arises mostly in the retina for the magnocellular pathway and mostly in the cortex for the parvocellular pathway. It appears that adaptation arises most strongly at sites that pool over many inputs.**

Our visual system can detect changes in light intensity under many different visual conditions. For example, snow flakes against the background of a white sky present a much lower contrast environment than text on a printed page. The visual system adapts to these conditions of different contrast: it becomes less sensitive to variations in intensity when the contrast is high and more sensitive when the contrast is low.

Theories of efficient neural coding explain why contrast adaptation should occur. Neurons in the visual system have only a limited range of firing rates with which to encode the visual scene. As signals flow through the brain, each neuron faces the danger of saturation, where it remains pinned at its maximal or minimal firing rate, unable to signal variations in the stimulus. This saturation is avoided if the neuron adjusts its gain higher or lower depending on the recent history of the stimulus, allowing more efficient use of its dynamic range.

At the perceptual level, it has long been known that the human visual system adapts to contrast (Blakemore and Campbell, 1969). However, the search for the neural site of this adaptation has yielded conflicting results. Neurons in primary visual cortex already show the sensitivity changes consistent with perceptual contrast adaptation (Movshon and Lennie, 1979). Several studies reported that cells in the lateral geniculate nucleus (LGN) do not show contrast adaptation, which would place the phenomenon strictly into early visual cortex (Ohzawa et al., 1982, 1985). More recent results, however, showed clear contrast adaptation already in the retina (Baccus and Meister, 2002; Chander and Chichilnisky, 2001; Kim and Rieke, 2001; Rieke, 2001; Smirnakis et al., 1997). Furthermore, a reevaluation of adaptation in cortical neurons concluded that it occurs almost exclusively in that part of the visual pathway which is monocular (Truchard et al., 2000), again pointing to retina and LGN. Still, there has been some reluctance in the cortical vision community to consider that signals reaching the cortex are already normalized for contrast.

Solomon et al. (2004) now reveal that there is strong contrast adaptation in magnocellular neurons (M cells) of the primate LGN but much less in parvocellular neurons (P cells). In the presence of a high-contrast stimulus, M cells strongly decrease their gain, and during low contrast they recover sensitivity gradually over several seconds. This adaptation arises in the retina, because it can already be observed in afferents from retinal ganglion cells to the LGN. The authors then follow with an important analysis that places contrast adaptation in the context of neural information coding and demonstrates that this modulation of a neuron's sensitivity is indeed adaptive. At the level of firing in LGN neurons, contrast adaptation is found to increase the discriminability of similar stimuli. This result lays to rest speculation that retinal contrast adaptation is only a byproduct of some other function, such as metabolic conservation.

The difference between the gain changes in M cells ($\sim$250%) and P cells (30%–50%) is striking. Still, even changes of 30%–50% are not entirely insignificant and could have significant perceptual effects. For reference, synapses undergoing long-term potentiation often change their strength by this amount, and this is thought by some to underlie the mechanism of learning (references too numerous to cite). But why do the magnocellular and parvocellular pathways adapt so differently? Although the two pathways differ in their temporal and chromatic properties, it is not clear why these distinctions would matter. Instead, the important distinction might be in the spatial resolution of the two pathways. Magnocellular ganglion cells pool the signals of many more bipolar cells than do parvocellular ganglion cells. The parvocellular pathway does not pool many inputs together until the level of the cortex. A large convergence of neural inputs onto a target neuron presents a great potential for saturation and may require a mechanism to adjust the sensitivity. Thus, a neuron with many inputs and high enough gain to respond to any one input must adjust its gain to prevent saturation when all inputs are activated.

This suggests a unifying rule: contrast adaptation arises most strongly at sites where there is pooling over many inputs (Figure 1). Some support for this idea comes from prior work that dissected the phenomenon within the retina: photoreceptors do not adapt to contrast. Bipolar cells that pool over multiple photoreceptors show some modest change in gain, whereas ganglion cells have considerably more (Baccus and Meister, 2002; Chander and Chichilnisky, 2001; Kim and Rieke, 2001; Rieke, 2001). Not much additional adaptation occurs in LGN relay cells, which pool over only one or a few ganglion cell inputs (Solomon et al., 2004). In the visual cortex, additional pooling in the parvocellular pathway then coincides with additional adaptation.

The work of Solomon et al. (2004) also confirms and supports another general rule: contrast adaptation occurs over multiple time scales. One can distinguish a very rapid change in gain (complete within 0.1 s, also called "contrast gain control") from subsequent slow adaptation lasting several seconds (Baccus and Meister, 2002; Smirnakis et al., 1997; Victor, 1987). Interestingly, the two processes don't seem to separate: all sites in the visual system with fast contrast gain control also undergo the slow adaptation. These neural processes may be matched to different time scales in the ecology of vision. For example, eye movements can produce very rapid contrast changes within the retinal image, whereas movement of the animal from one environment to another elicits slower changes in the statistics of the visual scene.

Why was adaptation largely missed in previous recordings from the LGN? Some of the prior studies used changes in a neuron's firing rate as the measure of adaptation. However, as shown by Solomon et al. (2004), cells can shift their contrast sensitivity without substantially changing their firing rate, and a simple measurement of firing rate would ignore large changes in gain. Also, some earlier measurements used stimuli that activate cortex more strongly than LGN (Movshon and Lennie, 1979; Ohzawa et al., 1985). The authors here show directly that a strong adapting stimulus at one level of the

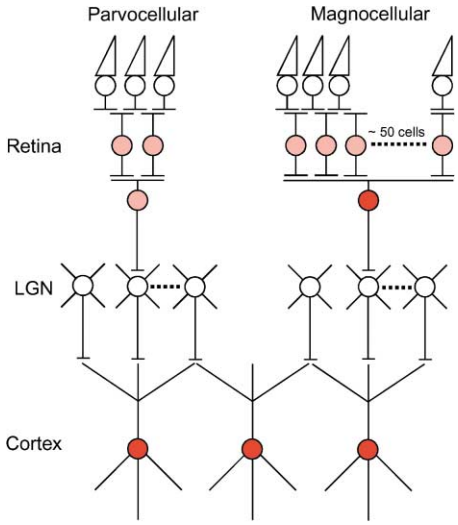

Figure 1. Sites of Pooling and Contrast Adaptation in Parallel Visual Pathways

Sites of strong pooling coincide with strong modulation in sensitivity to inputs (shading). At any given stage, the strength of contrast adaptation is the *cumulative* effect of modulation at preceding stages. Primate magnocellular input from Jacoby et al. (2000). Bipolar cell adaptation has been measured in other vertebrates.

visual system is not necessarily effective for another level.

A plausible hypothesis is that the mechanism for contrast adaptation is in fact available at every stage of the visual pathway, perhaps even in every synapse. Any given experiment will trigger adaptation most strongly in those neurons that—by virtue of convergence of their inputs and receptive field properties—experience the strongest stimulation. This process has the effect of maintaining a neuron's sensitivity to small inputs while avoiding saturation in the presence of large inputs (Chance et al., 2002). Of course, none of these arguments are specific to the visual system. One wonders whether these emerging principles of contrast adaptation will hold in other sensory systems and perhaps the nervous system in general.

Stephen A. Baccus and Markus Meister
Harvard University
Department of Molecular and Cellular Biology
Cambridge, Massachusetts 02138

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