

Visual cortex: **Fatigue and adaptation**

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Prolonged exposure to a visual pattern perturbs visual perception, affecting the appearance of subsequently viewed patterns. Recent results demonstrate that this visual adaptation is explained partly by a cellular mechanism acting in individual cortical neurons.

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The visual system is endowed with a number of self-calibration mechanisms that are continuously at work. As with football referees, we tend to notice these mechanisms only when they appear to misbehave. This happens, for example, during visual adaptation, induced when the visual system is exposed to the same stimulus for a prolonged time (seconds to minutes). The calibration mechanisms adapt the visual system according to the prevailing statistics in the stimulus. When the stimulus is turned off, the calibration mechanisms are caught off-guard, and visual perception is briefly perturbed.

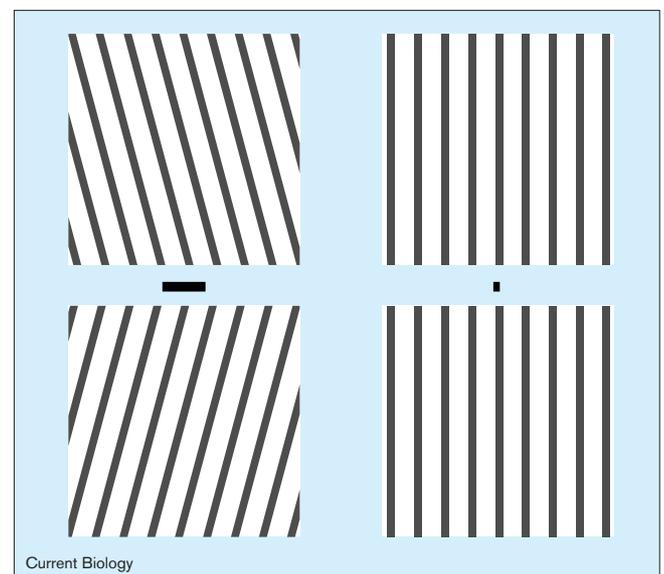
Adaptation involves a variety of visual attributes and stages of visual processing [1]. The early stages in the retina adapt to mean light intensity: the incoming light intensity signals are divided by their recent mean value, effectively computing contrast [2]. Adaptation at the level of the cerebral cortex involves more complex attributes. Striking effects are observed with visual motion [3], but there are also clear effects involving attributes such as orientation and contrast [4]. An example of such effects is illustrated in Figure 1, with a stimulus consisting of two grating patterns, one slightly oblique and the other vertical. After staring at the oblique grating for 30 seconds or so, the vertical one appears briefly as if it were tilted in the opposite direction (pattern adaptation). Similarly, prolonged exposure to high contrasts reduces the perceived contrast of subsequent stimuli (contrast adaptation).

A simple explanation for these perceptual effects is based on the assumption that prolonged stimulation with a visual pattern ‘fatigues’ the neurons that respond most strongly [4,5]. The fatigued neurons are assumed to respond less than they normally would, so that perception is biased away from the adapting pattern. This fatigue hypothesis is supported by the finding [6] that, after a few seconds of stimulation with a high-contrast stimulus, neurons in the primary visual cortex (V1) of the cat give a weaker

response than they otherwise would to a subsequent low-contrast stimulus. Research in the 1980s showed that this adaptation is to some extent a form of input gain control, which increases the amount of contrast needed to obtain a given firing rate (Figure 2a) [7,8]. Because an adapting stimulus in one eye affects the responses to stimuli presented to the other eye (and only cortical neurons are binocular), and because the responses of subcortical neurons adapt only very weakly [6,7], contrast adaptation is thought to originate in the cortex, not in the retina or in the thalamus.

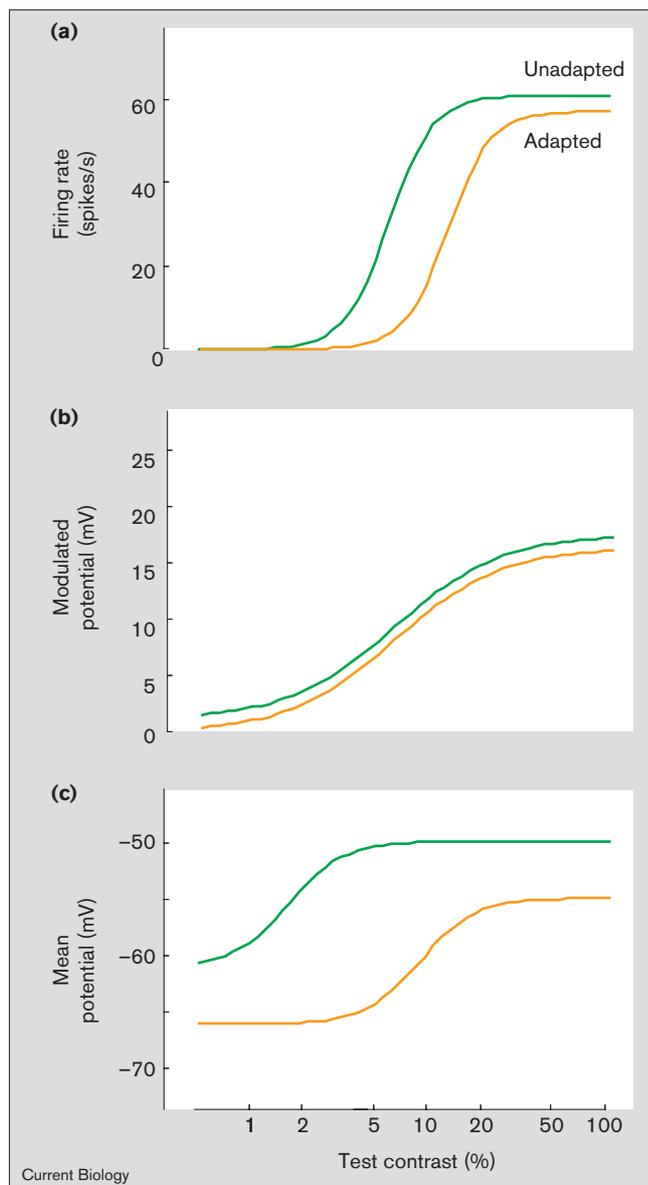
But what is the mechanism underlying this uniquely cortical form of fatigue? A recent pair of elegant papers by Sanchez-Vives, Nowak and McCormick [9,10] has made a strong case that the mechanism is cellular. Their combined approach, involving intracellular recordings made both *in vivo* and *in vitro*, points to a novel type of current as a biophysical substrate of neural fatigue and visual adaptation. This discovery helps to settle a debate that originated with the publication of two earlier intracellular *in vivo* studies of visual adaptation [11,12], one of which [11] I was directly involved in.

Figure 1



A classical demonstration of after-effect in the orientation domain, derived from [19]. For at least 30 seconds, look at the line between the two gratings on the left, while moving your eyes from one end to the other (to avoid the formation of retinal after-images). Then, look at the dot between the two gratings on the right. They should briefly appear tilted in the opposite orientations to the two gratings on the left.

Figure 2



A schematic illustration of contrast responses measured intracellularly in the cat primary visual cortex, derived from the data in [11]. The responses obtained with adaptation to a blank screen are illustrated in green, whereas those obtained with adaptation to a high-contrast adapting stimulus are shown in red. The value in the abscissa is the contrast of a test stimulus presented after the adapting stimulus.

(a) The firing rate responses. **(b)** The first harmonic component of the membrane potential (V_{F1}) — that is, the size of the membrane potential modulations caused by the passage of each bar of the grating over the cell's receptive field. **(c)** The mean membrane potential of the cell (V_{DC}).

In 1997, Ferster and I [11] reported on the effects of visual adaptation on the membrane potential responses of simple cells to drifting grating stimuli. We measured the size of the membrane potential modulations caused by the passage of each bar of the grating over the cell's receptive

field. We termed this component the V_{F1} , and found it to be unaffected by adaptation (Figure 2b). We also measured the mean membrane potential, which we termed V_{DC} , and found that it was substantially reduced by visual adaptation (Figure 2c). This hyperpolarization was large (5–10 mV) and long-lasting (10–20 seconds). The resulting shift in the curve of mean potential against contrast leads in turn to the rightward shift in the curve of firing rate against contrast shown in Figure 2a [13]. The interpretation of our results, however, was soon made difficult by a study [12] that did not observe any hyperpolarization.

The *in vivo* study of Sanchez-Vives and colleagues [9] confirms that adaptation does indeed involve the hyperpolarization of cortical neurons. Using established methods of visual stimulation [6] and data analysis [11], Sanchez-Vives and colleagues [9] found that adaptation makes V_{DC} more negative by 1–12 mV. Moreover, they have confirmed our [11] other findings that visual adaptation does not affect the stimulus-induced modulation in membrane potential — the V_{F1} — and that the generation of spikes during exposure to the adapting stimulus is not a necessary condition for the subsequent hyperpolarization [11]. But what causes the hyperpolarization? This could potentially involve changes in the activity of other neurons in the network or in the efficacy of synapses, or the action of some intrinsic cellular mechanism.

To tease apart these possible contributions, Sanchez-Vives and colleagues measured membrane conductance changes associated with hyperpolarization, and found average increases of 22%. Ferster and I had found no such changes in conductance [11], but it seems likely that our measurements were flawed [14]. Sanchez-Vives and colleagues also compared the adaptation effects of high-contrast visual stimulation, on the one hand, and of steady current injection of similar duration (presumably eliciting a similar number of spikes), on the other. The effects of these two types of stimulus were in many respects similar, suggesting that intrinsic membrane mechanisms might account for at least some of the adaptation observed with high-contrast visual stimulation.

Given that adaptation increases membrane conductance, it becomes natural to ask whether it involves the opening of any ion channels. The second study [10] addressed this issue with recordings from slices of ferret visual cortex *in vitro*. The authors found that current injection alone caused in most neurons a slow reduction in firing rate, and was followed by a long after-hyperpolarization, similar to that observed *in vivo*. This cortical after-hyperpolarization is much longer — about 30 seconds — than those described previously [15], and is largely absent in thalamic neurons. Sanchez-Vives *et al.* [10] argue that the after-hyperpolarization is caused by a K^+ current. Using a hybrid current clamp–voltage clamp protocol, they found

reversal potentials of -109 mV, which depolarized as the external K^+ concentration was increased. This current is not Ca^{2+} -sensitive, as neither blocking transmembrane Ca^{2+} nor introduction of a Ca^{2+} chelator could block the after-hyperpolarization. Because reducing the external Na^+ concentration reduced the after-hyperpolarization, the authors argue that the current is Na^+ -dependent. Sanchez-Vives and colleagues [10] have thus discovered a new slow after-hyperpolarization in cortical neurons, mediated by a current that is most likely permeable to K^+ and probably sensitive to Na^+ .

There are, however, reasons to doubt that this newly discovered slow after-hyperpolarization explains all of the effects of visual adaptation on the membrane potential. Firstly, the slow after-hyperpolarization disappears when action potentials are blocked with the Na^+ channel blocker tetrodotoxin — presumably because less Na^+ is entering the cell — whereas the intracellular effects of visual adaptation are seen also when the cell is prevented from firing [9,11]. Secondly, the reduction in firing rate during adaptation to a visual stimulus is much larger (58%) than during steady current injection (13%), indicating that not all the effects of visual adaptation are a consequence of current entering the cells [9].

But even if the slow after-hyperpolarization were the final explanation of neural fatigue in cortical cells, there are indications that there is more than just fatigue to adaptation. Fatigue should affect the responses to all stimuli equally, without knowledge of the visual stimulus that is being shown after the adapting stimulus. The effects of visual adaptation, instead, are somewhat specific, being strongest when the adapting and test patterns are identical [8,16]. The missing pieces that are needed to explain adaptation are thus probably to be found in the network [12] or in the synapses [17,18].

The recent studies of Sanchez-Vives *et al.* [9,10] have thus provided key evidence for the effects of visual adaptation at the cellular level. Moreover, they point to the existence of a novel current that is likely to operate constantly to control the responsivity of cortical cells. Given the field's enthusiasm for *in vitro* methods, it may help to point out that the process that led to these discoveries originated from experiments *in vivo* [9,11,12]. Indeed, the reports of Sanchez-Vives *et al.* [9,10] are a particularly happy outcome of the increasingly frequent mating of systems neuroscience with cellular neuroscience. In particular, the hybrid methods of current injection and natural stimulation that they introduce are likely to become standard in the investigation of a variety of sensory structures.

Acknowledgements

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