

Cortical Plasticity: Time For A Change Dispatch

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Two recent studies have tested whether synaptic learning rules, inferred earlier from work on cell cultures and brain slices, apply in intact brains. The evidence indicates that they do, and reveals interesting implications for brain development and perceptual learning.

An important and difficult task in neuroscience is to integrate knowledge of the rules governing the behavior of single neurons studied in reduced systems into our understanding of the behaviors of networks of neurons in an intact brain. From work on reduced preparations, such as cultured neurons and brain slices, numerous forms of synaptic plasticity have been described and their properties characterized. In recent years, rules for changing synaptic efficacy based on the precise timing of presynaptic and postsynaptic activity, on the scale of tens of milliseconds, have been revealed at several synapses in the central nervous system (CNS). This spike-timing-dependent plasticity has several properties which are desirable, on theoretical grounds, for transforming changes in environmental inputs into changes in neural representations. The implementation of such a 'learning rule' in functional neural circuits has been largely limited to theoretical work, because of the technical difficulty of observing and controlling synaptic activity in the intact brain at an adequate spatial and temporal resolution. Whether spike-timing-dependent plasticity is instantiated *in vivo* has been unclear, but now two studies [1,2] have cleverly demonstrated its role in the intact cortex using similar, but complementary, approaches.

Experiments in a number of systems have shown that the strength of synaptic transmission can be modified up or down depending on the precise timing of presynaptic and postsynaptic activity [3,4]. When presynaptic activity repeatedly precedes postsynaptic activity by 5–20 milliseconds, a synapse will undergo a long-lasting (~30–60 minute) increase in strength; when the temporal order of pairing is reversed, a long-lasting depression of synaptic strength ensues. The functional consequence of this 'learning rule' is that synapses from a presynaptic neuron which contribute to the firing of the postsynaptic neuron will be strengthened, whereas synapses which are uncorrelated or anti-paired with postsynaptic spike times will tend to be weakened. Such a rule for the modification of synaptic weights expands current thinking about 'Hebbian rules' governing the development of sensory cortex and its plasticity in the mature brain (for an interesting computational analysis of how

spike-timing-dependent rules can explain synaptic plasticity and cortical maps, see [5,6]).

The primary visual cortex (V1) of the mammalian brain has been a rich proving ground for work on the experience-dependent development and plasticity of functional cortical circuits. The responses of V1 neurons are selective for the orientation of lines presented in their receptive fields [7]. V1 contains a map of orientation preference, such that neurons sharing the same orientation preference are grouped together, with the preferred orientation changing gradually across expanses of the cortex [8]. This selectivity presumably arises from the specific arrangement of thalamic and cortical synaptic inputs a neuron receives [9,10]. By selectively manipulating these inputs, either pharmacologically [11] or by altering the visual inputs to developing or adult brains, one can change the selectivity of the responses of neurons and the structure of the orientation map [12–14]. But what are the rules that govern the synaptic modifications that underlie these changes?

Schuett *et al.* [1] and Yao and Dan [2] both tested whether patterns of inputs to neurons in V1, which from slice experiments would be expected to induce spike-timing-dependent synaptic plasticity, can induce changes apparent in the selectivity of the responses of V1 neurons. By pairing electrical stimulation of the cortex with visual stimuli that selectively activate isolated patches of the cortex (gratings of a particular orientation), Schuett *et al.* [1] were able to manipulate the temporal order of two sources of inputs to a subset of neurons in the cortical map. To control the two inputs temporally, they had to first calibrate the time it takes for visual inputs to flow through the visual system — from the retina through the thalamus to the neurons from which they recorded. They found that, on average, neurons responded to a flashed stimulus with a latency of ~47 milliseconds. Thus, by applying the electrical stimulus either 65 or 35 milliseconds after the visual stimulus, they were able to produce a situation in which the inputs arising from the visual stimulus arrived at the neurons in visual cortex either 18 milliseconds before (pairing), or 12 milliseconds after (anti-pairing), the inputs arriving from the electrical stimulus.

Using optical imaging of intrinsic signals to map the cortical response, Schuett *et al.* [1] demonstrated that the responses of neurons in V1 were shifted towards the paired orientation, or away from the anti-paired orientation. This was manifested as an increase in the signal strength in response to the paired orientation, and in an increase in cortical area which preferred the paired orientation. Using extracellular recording from individual neurons, they further demonstrated that this plasticity was prominent in the supra- and infragranular layers, where inputs from other cortical cells predominate, but not in layer 4, where input from the thalamus is prominent. Thus, they concluded that the synaptic inputs responsible for generating the responses to the paired orientation were of cortical origin and were enhanced (or suppressed in the case

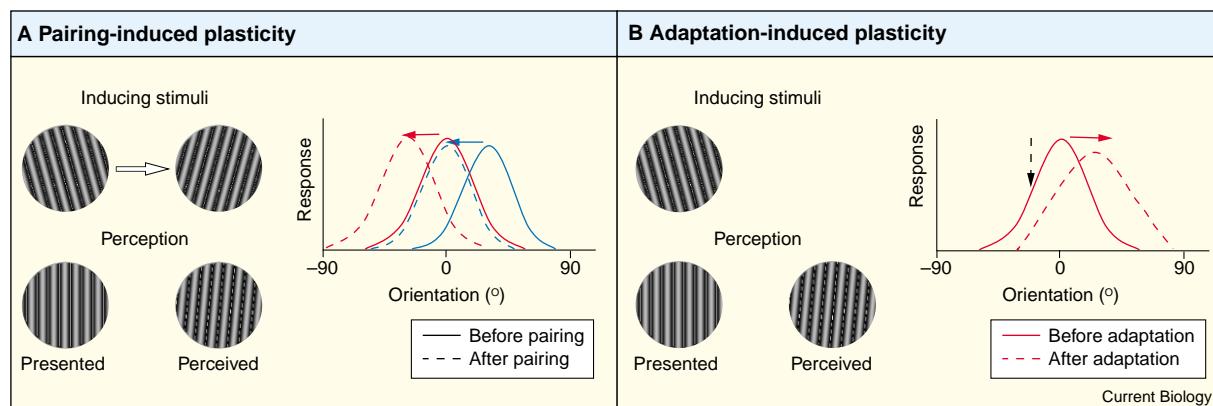


Figure 1. Two kinds of plasticity in V1 of the adult brain that lead to transient changes in the orientation tuning of neurons and to changes in visual perception.

(A) Pairing-induced plasticity [1,2]. This is induced in cortical neurons and human observers by repeated presentation of a grating stimulus at one orientation followed within a brief interval by a grating of a different orientation. A typical paired stimulus (top left) is a grating tilted counterclockwise from the vertical followed by a grating tilted clockwise. Orientation tuning curves of two neurons, before and after many such episodes of pairing, are shown on the right: the preferred orientations shift counterclockwise, towards the first stimulus. Perceptual changes induced by paired stimulation are illustrated bottom left. Following repeated presentations of the stimuli shown above, a vertical grating is perceived as tilted clockwise. The neuronal basis for this percept is likely to be the altered orientation preference of neurons illustrated on the right. (B) Adaptation-induced plasticity [14]. This is induced by presenting a single grating (top left) for a short period of time to a neuron or to an observer. The tuning curves of a neuron before and after adaptation are illustrated on the right; the adapting orientation is marked by the black dashed arrow. When the adapting grating is close in orientation to a cell's preferred orientation, it causes the neuron's preferred orientation to shift away, together with a decrease in response at the adapting orientation and a broadening of the tuning curve. After such adaptation, a vertical grating is perceived as tilted clockwise [17,19]. This tilt aftereffect is likely to be caused by the combination of changes in neuronal tuning curves that accompany adaptation. (We thank Christine Waite for help in preparing this figure.)

of anti-pairing) causing the tuning curves to be shifted towards the paired orientation.

Yao and Dan [2] took a similar approach, but instead of electrical stimulation used a second grating as the other half of the stimulus pair. They found that flashing a grating tilted 15° away from a cell's preferred orientation 8–40 milliseconds before a grating at the preferred orientation caused the cell to shift its preferred orientation towards the first grating. Flashing the gratings in the opposite order caused the preferred orientation to shift away from the tilted grating. These changes in preferred orientation are short-lasting, on the time scale of minutes, and are most likely due to short-term changes in the strength of synapses the recorded cells receive from other cortical cells. The control of the timing of inputs in the intact brain is not as precise as in slice experiments, but it appears to be adequate to induce such changes in synaptic strength. This is because, on average, more pairing between presynaptic activity and postsynaptic firing has occurred for the paired orientation than for an unpaired, or anti-paired, orientation. This is an important point, because it is extremely unlikely that anywhere in the intact brain will the timing of activity be as precise as in the well-controlled experiments performed in slices.

The two papers [1,2] describe existing synaptic mechanisms by which cortical neurons change their responses as a result of the timing of stimulation. But each paper also contains an interesting sidelight that is equally significant for the field of visual cortex plasticity. First, how might plasticity of V1 responses influence vision? Second, are there specific locations

in V1 that might be privileged places for plasticity? Both questions suggest the field is ready for a major change in the way it regards the role of visual cortex networks in general, and networks for creating orientation selectivity in particular.

While the role of V1 in conscious vision has been debated [15,16], it would be puzzling indeed if changes in V1 responses do not relate to changes in visual perception. Yao and Dan [2] describe an intriguing psychophysical experiment in which they repeatedly flashed two gratings in succession, each tilted to one side or the other of the vertical, and then asked subjects to judge the orientation of a vertical grating. Thus, flashing a grating oriented at -2° (counterclockwise from the vertical) followed by a grating at $+2^{\circ}$ (clockwise from the vertical) altered orientation perception so that a vertical grating was perceived as slightly tilted clockwise (Figure 1A). Conversely, the reverse sequence of training caused a vertical grating to be perceived as tilted counterclockwise. Importantly, the timing between the training flashes that produced this perceptual effect was roughly the same as that required to change the physiological responses of V1 cells.

The translation of physiological responses to a percept requires a 'readout' of cellular responses. The most obvious proposal is that a cell is a labeled line for a stimulus: its firing is synonymous with presence of its preferred stimulus in the visual field. Thus, vertical contours in a visual scene are signaled when cells that prefer vertical orientations fire. Pairing-induced plasticity transiently changes the physiological orientation selectivity of cells. When a stimulus oriented at

-2° is repeatedly followed by a stimulus at $+2^\circ$, the rules of spike-timing-dependent plasticity cause the preferred orientation of cells to shift counterclockwise. Thus, a cell that used to prefer, say, $+0.5^\circ$ now prefers 0° (vertical), so that a vertical contour now activates this cell maximally (Figure 1A). The perceptual consequence is that a vertical contour is judged to be of orientation $+0.5^\circ$ — tilted clockwise from the vertical — in an opposite orientation from the physiological tilt.

There are few natural situations where strict timing relations between stimuli of the sort used to define such perceptual tilts would occur. A much more common situation involves the perceptual tilts caused by the recent history of visual stimulation — the 'tilt aftereffect' (Figure 1B). Here, viewing a tilted contour even briefly causes the perceived orientation of a subsequently viewed contour to be tilted away from the adapting contour [17]. Recently, it has been shown that such viewing transiently reduces the responses of V1 cells at the adapting orientation [18], broadens orientation selectivity and shifts the preferred orientation of cells away from the adapting orientation [14]. The tilt aftereffect cannot be explained simply by a shift in the preferred orientation of cells. Indeed, the physiological tilt of orientation selectivity away from the adapting orientation would, by itself, act to alter orientation perception in the opposite way. Rather, the combination of response reduction and broadening of orientation selectivity [19], together with the shift in orientation, cause the population of V1 neurons to signal a perceived orientation tilt.

The adaptation-induced effects are maximal at specific locations within V1 called pinwheel centers, where neurons that prefer different orientations are represented in close proximity [20]. Schuett *et al.* [1] briefly describe results showing that pairing-induced plasticity of orientation tuning is *minimal* at pinwheel centers. But adaptation-induced plasticity of orientation tuning involves pooling of inputs from neurons that prefer different orientations, and such pooling is highly effective at pinwheel centers. More generally, convergence of inputs is critical for inducing changes that rely on altering the strength of inputs. This is the essence of plasticity in the adult brain.

There is much that remains to be discovered about the creation and maintenance of a fundamental emergent property such as orientation selectivity in visual cortex. It is clear, however, that spike-timing-dependent plasticity is an important mechanism for altering synaptic strength, particularly between cortical neurons. The preferred orientation of a cortical cell is shaped during development and remains only transiently malleable in the adult brain. Nevertheless, the short-duration changes have consequences for visual physiology and perception, as demonstrated by the two recent papers [1,2] and in earlier psychophysical and physiological experiments on the tilt aftereffect and pattern adaptation. These descriptions of orientation plasticity demonstrate that multiple aspects of neuronal responses, at specific cortical locations, can be altered by stimulus history or timing, and that these changes together influence visual perception.

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