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Commentary

Is most of neural plasticity in the thalamus cortical?

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We now have 20 years or more of rapidly accumulating evidence that sensory-perceptual systems, especially at the cortical level, are highly plastic, even in mature mammals (1–3). Much of the evidence comes from deprivation studies where part of the sensory input to a system is removed and the deactivated neurons in the brain stem and cortex recover responsiveness to remaining inputs. The recoveries can be immediate, but they also can have slowly developing components. The rapid reorganizations generally are attributed to a rebalancing of excititory and inhibitory factors within a dynamically maintained system.

For various reasons, the major research emphasis has been on reorganizations in cortical sensory representations. Evidence for subcortical plasticity has been much more limited, and it sometimes is questioned. Nicolelis and coworkers (4, 5) have provided some of the most convincing recent evidence for subcortical changes in the receptive fields of neurons in the somatosensory thalamus, and in this issue of the *Proceedings* they now provide results indicating that the rapid adjustments are partially mediated by feedback inputs from cortex (6). Thus, not only do changes in the sources of activation occur for neurons in the thalamus, but most surprisingly, many of the changes depend on the poorly understood network of feedback connections that descend rather than ascend the hierarchy of processing levels in the somatosensory system.

Sensory-perceptual systems consist of subcortical nuclei and cortical areas that are connected in a complex manner, with enough serial components that it is possible to assign hierarchical levels to structures (7). One of the basic features of these systems is that nuclei and areas that project to structures at higher levels nearly always receive projections back from these targets. Connections between the thalamus and cortex and between cortical areas are, with few exceptions, reciprocal. Projections to a higher level are called feed-forward; those to a lower level are feedback. The functions of feed-forward connections are, by far, better understood. The general premise has been that transformations in response properties mediated by local circuits of neurons at one level are relayed for further processing by neurons at the next level. Thus, the response properties of neurons become increasingly complex at higher and higher levels. This simple formulation of sensory processing postulates no clear role for the ubiquitous feedback connections. In a like manner, the general assumption in plasticity experiments has been that changes that occur in the receptive field properties of neurons at one level of the system have been created at that level or have accumulated in relays of information from lower levels. The report of Krupa *et al.* (6) is important in that it demonstrates that much of the plasticity that is observed at the thalamic level depends on feedback connections from the cortex. This finding challenges us to consider sensory-perceptual systems in the full richness of their connectivity and include the possible roles of feedback connections in our thinking.

Krupa *et al.* (6) used a relatively new and powerful approach to obtain their convincing evidence for a role in thalamic plasticity for cortical feedback. They implanted microwire electrodes in the ventroposterior nucleus of the somatosensory thalamus, and its cortical target, primary somatosensory cortex (S1) of the same rats. These electrodes allowed the responses of many different single neurons in each structure to be simultaneously recorded during sensory stimulation over long periods of time. The receptive field locations and response properties of neurons in both structures were quantitatively evaluated, both before and after a peripheral sensory loss produced thalamic and cortical plasticity, and after a sensory loss was combined with cortical deactivation. By these means, thalamic plasticity was evaluated with and without feedback from somatosensory cortex. When a local anesthetic, lidocaine, was injected to reversibly block inputs from a region of skin and cortical feedback was intact, neurons in both the ventroposterior nucleus and S1 cortex that were previously responsive to touch on the anesthetized skin rapidly became responsive to inputs from the surrounding normal skin. This type of rapid plasticity has been described as the "unmasking" of previously "silent" or ineffective synapses (8). The typical interpretation of such results is that afferents from a restricted region of skin not only drive a group of brainstem neurons that relay to a group of neurons in the thalamus that relay in turn to cortex, but they also activate inhibitory neurons at each level that connect laterally to suppress activity produced by an outer fringe of weak excititory projections. Blocking or removing a region of sensory input from the skin not only removes the effective drive of a group of relay neurons, but also the drive of inhibitory local circuit neurons that keep weak, fringe inputs from other regions of skin from being effective. Now, Krupa *et al.* (6) show us that this "feed-forward only" view of plasticity is too simple, because feedback from cortex contributes to the plasticity of thalamic neurons. If the responses of neurons in the corresponding parts of S1 of somatosensory cortex were blocked by a drug at the same time as plasticity was induced by anesthetizing the skin, the unmasking of new receptive fields and response properties in neurons of the ventroposterior nucleus was reduced to about half. Thus, feedback from the cortex creates or potentiates thalamic plasticity in some way.

Anatomically and functionally, feedback connections are quite different from feed-forward connections. Although the feedback connections are often much more numerous than the feed-forward connections between the same structures (9, 10), individual feedback connections mediate less powerful effects. Feed-forward axons generally have more densely branching, compact terminal arbors with many synapses located on the proximal dendrites of target neurons where synapses are most effective. Feedback axons generally have more sparsely branching, widespread arbors, with fewer, less effective, synapses largely on distal dendrites (11–13). Feedback connections are also less precisely focused within a sensory representation, reaching a larger proportion of the representation (11, 14, 15). Overall, feedback connections seem better designed to weakly stimulate larger groups of neurons and modulate ongoing activity, whereas feed-forward connections create activity in smaller groups of neurons.

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Although a number of intriguing functional roles have been proposed for feedback connections (9, 11, 16, 17), including that of comparing the past with the present (18), the physiological consequences of activating feedback connections are perhaps best understood for inputs from visual cortex to the visual lateral geniculate nucleus of the thalamus (e.g., refs. 19 and 20). When a restricted visual stimulus activates a cluster of thalamic neurons that relay to cortex, the responding feedback projections from cortex appear to reinforce the core of the thalamic activity by densely focusing on the most active relay neurons while indirectly inhibiting a fringe of surrounding thalamic neurons. This feedback narrows the thalamic responsive zone, restricts receptive field sizes, and alters neuron response properties. This role of corticothalamic feedback appears to be general. The blocking of somatosensory cortex in monkeys recently has been shown to greatly increase the sizes of receptive fields of neurons in the ventroposterior nucleus (21). The necessary inhibition is partly mediated by a population of inhibitory neurons that are scattered within the larger focus of neurons in the ventroposterior nucleus that are activated by the feedback connections. In addition, the feedback connections activate γ-aminobutyric acid (GABA)-ergic inhibitory neurons in the adjacent thalamic reticular nucleus, which in turn project into the ventroposterior nucleus to inhibit neurons (22, 23). The ventroposterior nucleus of rats is unusual in that it does not contain inhibitory neurons (24), but instead depends completely on inhibitory inputs from the thalamic reticular nucleus.

Although feedback connections clearly have an important role in the processing of sensory information, and they function in both rapid (6) and more slowly emerging forms (see ref. 21) of thalamic plasticity, the full extent of cortical plasticity is not always reflected in the thalamus. Small lesions of the retina, for example, may produce zones of deactivated neurons in the thalamus that are only partly reactivated; whereas the deactivated neurons in cortex are fully reactivated (25). Similar observations have been made in the somatosensory system (26). These more extensive cortical reorganizations may depend in part on the activation of the widespread network of horizontally connecting axons within areas of cortex, a feature missing from subcortical nuclei. The more extensive thalamic and cortical reorganizations that emerge slowly over weeks to months of time after sensory loss also may depend, in part at least, on the growth of new connections (27).

By perturbing a balanced system, studies of short-term or immediate plasticity tell us much about the normal functions of the processing machinery. Results from such studies also have implications for how sensory networks mediate other types of rapid changes, such as in use-dependent plasticity and learning. Finally, we should now seriously begin to consider the possible role in cortical plasticity of the feedback connections of higher cortical areas to lower, primary areas.

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