Commentary
Limits of Reorganization in Cortical Circuits

John P. Donoghue

Department of Neuroscience, Brown University, Providence, RI 02912, USA

Since the earliest experimental enquiries into the function of the cerebral cortex, there has been a notion of plasticity of cortical representation patterns. Many early ideas related both to representation pattern and plasticity emerged from mapping studies of the motor cortex. One practical reason for this attention towards motor cortex was the ability to investigate its functional organization using electrical stimulation decades before the advent of the recording microelectrode. Sherrington, for example, wrote about the instability of cortical representations based on his investigations of monkey motor cortex, and concluded that 'the motor cortex is a labile organ' (Leyton and Sherrington, 1917, p. 144). Curiously, the converse idea – that the adult cortex was structurally fixed – seems to have ensconced itself roughly for the next 70 years after Sherrington's work (Leyton and Sherrington, 1917). By contrast, studies over the past 15 years have demonstrated the potential for reorganization throughout the adult cortex, either as a consequence of manipulation of sensory experience or with learning (see Garraghty and Kaas, 1992; Donoghue, 1995; Sanes and Donoghue, 1996 for more comprehensive discussion). The phenomenon appears to be general in cortex: reorganization occurs in primary sensory and motor areas as well as in non-primary regions. Despite extensive documentation of its existence in the past decade, the nature of the processes by which the plasticity of cortical representations occurs is only now beginning to be understood.

In this issue of *Cerebral Cortex*, Huntley (1996) uses a motor cortex model to advance our understanding of cortical plasticity. A key conclusion in this work is that existing intracortical connections provide a substrate for rapid restructuring of cortical representation patterns. The experiments follow up an earlier observation that cutting the motor nerve to the rat's whiskers commences a restructuring of the primary motor cortex (MI) map that appears within hours of the lesion (Donoghue *et al.*, 1990). As a consequence of this process, stimulation of a portion of MI initially related only to the whiskers now produces forelimb movements. The net result is an apparent expansion of the forelimb area into the former vibrissa territory. In this set of experiments Huntley not only confirms the potential for rapid reorganization of MI, but more importantly shows that the extent of this early reorganization follows from the pattern of intrinsic connections already present in motor cortex. Areas that reorganize immediately after the peripheral nerve lesion show extensive connections with the adjacent forelimb cortex, while other areas that remain unresponsive or 'silent' have only weak interconnections with the adjacent representations. This finding suggests that the route by which the stimulation eventually gains access to the forelimb depends upon these pathways.

The connections Huntley examined are those that spread tangentially along a cortical layer. The most extensive of these intracortical pathways travels through layers II–III and another system distributes within layer V. Because of their general trajectory, these fiber systems are often called 'horizontal' or sometimes lateral or reciprocal projections. Until recently the functions of horizontal connections in maintaining and organizing representation patterns anywhere in cortex have remained obscure. However, horizontal pathways are now attracting considerable attention because of their potential role not only in representation dynamics but also in many of the most complex functions of cortex such as perception, segmentation and object recognition (Singer, 1995; Gilbert *et al.*, 1996). The first strong evidence for a role of this fiber system in reshaping adult cortical maps came from a series of studies from Gilbert and his collaborators (see Gilbert *et al.*, 1996). They demonstrated that restructuring of cortical visual responsiveness after retinal lesions was a consequence of intracortical reorganization rather than a reorganization of subcortical circuitry. Further, the horizontal connections in visual cortex spread in precisely the manner appropriate to deliver the visual responses that emerged quickly in the deafferented cortical cells.

In the motor cortex there was considerable evidence to suspect that horizontal connections were important for shaping cortical maps. Long horizontal connections exist in MI and, under normal conditions, these fibers provide excitatory connections across wide regions of MI (Donoghue *et al.*, 1996). In rats individual horizontal fibers can span 1 mm or more, which is a considerable proportion of the rat's MI; ranges are greater in monkey MI (Huntley and Jones, 1991). Jacobs and Donoghue (1991) showed that focal blockade of inhibition in one part of MI could expose latent representations in other parts of MI; they suggested that this manipulation revealed existing excitatory horizontal connections that were masked by intracortical inhibition. These connections were capable immediately of supporting new MI representation patterns. The fact that shifts between some parts of the representation readily occurred, for example, between the forelimb and vibrissa representations, and others did not (e.g. hindlimb–forelimb) might be explained by Huntley's demonstration of regional variation in the expanse of horizontal projections. Other studies, employing slice preparations, confirm that horizontal connections form long-range excitatory connections in MI. Additionally they show that inhibition is situated in such a way to allow regulation of the effectiveness of horizontal intracortical interactions (see review in Donoghue *et al.*, 1996).

The horizontal pathways within a cortical area such as MI seem to be the essential scaffolding upon which restructuring of cortical representations can occur. Huntley's work shows that reorganization occurs quickly where the scaffolding is in place and fails to emerge when it is absent. Connections other than the horizontal systems may also contribute a reorganizational substrate; the thalamocortical fibers are one candidate. By

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typical extracellular recording methods, thalamic inputs appear to express their major functional influence over a fairly restricted region of cortex, but individual thalamocortical arbors spread widely (Rausell and Jones, 1995) so that these fibers actually influence broad regions of cortex. Alteration in the strength of thalamocortical connections has been proposed to explain plasticity of SI representations, although it has been alternatively argued that the potential for plastic changes is developmentally limited for these fibers (Singer, 1995).

Huntley's experiments do not explain how horizontal connections might invoke rapid reorganization of cortical maps. Several mechanisms are available to alter the efficacy of horizontal pathways. One, mentioned above, is to alter levels of inhibition. Inhibitory neurons and their receptors seem to respond to changes in sensory activity (Hendry *et al.*, 1994), indicating that inhibition is actively regulated. A second method is to adjust the efficacy of synapses formed by horizontal fiber systems. In motor cortex the strength of these interactions can be regulated up or down (via long-term potentiation and depression; LTP/LTD) depending upon the particular temporal activity patterns they experience – high levels of activity strengthen and low levels weaken the efficacy of horizontal connections within motor cortex (Donoghue, 1995). However, individual circuits also appear to require spatial summation or other specific circumstances in order for synaptic modification to occur (Hess *et al.*, 1996). These findings suggest that the cortical representation pattern is in a continual dynamic balance, regulated by ongoing adjustments in synaptic strength through activity-dependent processes and by adjustments in levels of inhibition, each constrained by the horizontal connectional lattice.

Does the connectional substrate completely constrain the extent of reorganization? Huntley's work is limited to the time immediately after a nerve lesion. Reorganization of MI and other cortical maps continues to occur over the days, weeks or months following a stimulus to reorganize. Shifts in the range of hundreds of micrometers occur in the early phases of reorganization. By contrast, shifts of many millimeters have been shown in somatic sensory cortex or visual cortex with long post-lesion survival times, although some cortex can remain silent (see Garraghty *et al.*, 1994). Because silent zones are not readily apparent in the motor cortex weeks after facial nerve lesions, additional reorganization must occur, but how this occurs is not clear. One explanation is that the modest collection of fibers that connected Huntley's silent cortex to adjacent areas increases its synaptic efficacy over time to reach a strength sufficient to express new outputs. Longer distance changes may also be relayed polysynaptically, by moving through several sets of horizontal connections. However, later changes might occur by other means; growth of new synaptic connections is one mechanism of interest.

There are indications that new connections can form in the adult brain. Visual cortical reorganization occurs over ensuing weeks after retinal lesions, during which time additional cortical neurons that have lost their normal visual input acquire new receptive fields from the intact retina. After these survival times, anatomical tracers reveal a projection from the surrounding cortex into the reorganized area, indicating that new fibers have grown into the 'blind' cortical region to provide new input. Further, in the motor cortex quantitative electron microscopic investigations find that synapse density increases after repeated electrical stimulation of the thalamus (Keller *et al.*, 1992). Thus under these somewhat extreme circumstances growth of new connections is possible. By contrast, synapses have been shown to increase in rat MI about 5 days after simply learning a motor skill (Kleim *et al.*, 1996); the source of these connections is not known. There are still many questions about newly generated connections in cortex. How extensively synaptogenesis occurs in cortex is not clear, and it is yet to be established that these new connections are fully functional. Subcortical sprouting may also influence the extent and form of reorganization reflected in cortical maps (Florence and Kaas, 1995). The occurrence of growth does not rule out the contribution of existing pathways to later phases of reorganization. Early phases of reorganization may only reveal initial changes in the efficacy of connections that already exist; continued modification of these pathways is likely in the face of altered activity arriving in cortex.

This body of evidence suggests that the existing connectional medium is the major arbiter by which new cell properties can be acquired and new representation patterns constructed in the cortex. The horizontal pathways possess a collection of properties that specifically link them to the process of shaping cortical representations: they spread in appropriate patterns, they participate in circuits with inhibitory neurons that allow for sensitive regulation of their efficacy, and they exhibit activity-dependent changes in strength. The precise pattern of intracortical connections also places some limits on the capacity for change, but, because the spread of these axonal systems is extensive, the potential for restructuring is immense. It will be essential to describe what limits are placed by particular patterns of existing connections or by restrictions to axonal outgrowth if we are to understand the dynamics of cortical representation.

Notes

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