NEUROSCIENCE

Growth through learning

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CONNECTIONS between neurons in the brain are thought to be made, broken and adjusted in strength both during learning[1] in adult life and during development[2,3]. Specific cellular changes called long-term potentiation and depression (LTP and LTD) seem to be responsible, at least in large part, for an important form of learning[4,5]. Are similar mechanisms involved in the refinement of neural connections in development? Papers on pages 325 and 328 of this issue[6,7] provide correlative evidence that they are.

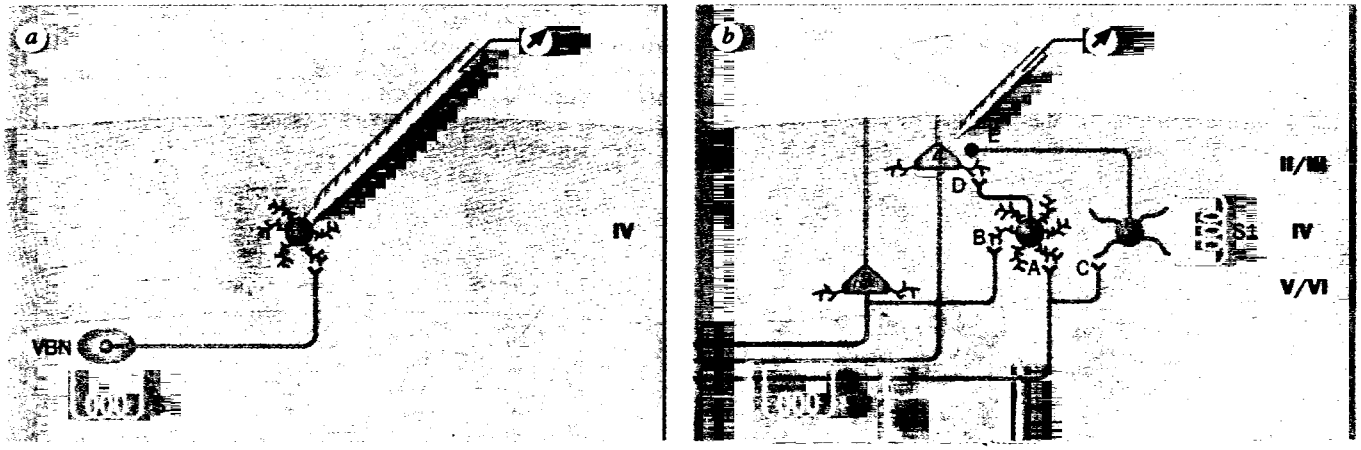
Unlike a computer, in which a circuit diagram specifies the connections in advance, the brain must wire itself. At least in primary sensory cortical areas, the brain refines its connections to a state of high precision during a critical period in early life, in a form of unsupervised learning[8]. During this critical period, but not before or after, synaptic connections between neurons are highly plastic and respond dramatically to alterations in the pattern of neural activity[9–11].

Cellular mechanisms of neural plasticity have been worked out in greatest detail in the hippocampus[5,12], where the study of LTP and LTD has become a growth industry. The use of the slice preparation allows a specific class of synapse to be manipulated and studied directly *in vitro*, and a great deal has been learned about the cellular events that underlie the changes in the strength of these synapses. The question, again, is whether plasticity in cortical synapses during the critical period is carried out by the same cellular machinery responsible for LTP in the hippocampus. Many features of the synapses are similar, and the same neurotransmitters and receptors seem to be involved. If we were confident that the mechanisms were indeed the same, then work on cortical development could piggy-back on the hippocampal story.

One way of tackling the question is to look for correlations between the occurrence of LTP and manipulations known to affect developmental cortical plasticity *in vivo*. The most prominent feature of such plasticity is the critical period. Crair and Malenka[6] and Kirkwood *et al.*[7] take advantage of it by comparing LTP in slices from animals of different ages, and both find forms of LTP during the critical period that are smaller or absent thereafter. In addition, Kirkwood *et al.* raise animals in darkness, which appears to extend the critical period *in vivo*[13], and they find that susceptibility to one sort of LTP is also extended. The findings are consistent with the notion that LTP *in vitro* involves the same mechanisms that organize neuronal connections in development.

An understanding in cellular and molecular terms of the mechanisms responsible for properly connecting up neurons in the cortex would not only be tremendously satisfying on intellectual grounds, it would also have valuable implications for further experiments and for attempts at therapy. The power of studies of LTP *in vitro* is that, unlike most experiments that can be carried out on development *in vivo*, the particular synapses that change can be identified, and their properties can be made susceptible to pharmacological and biochemical analysis. Crair and Malenka's study on somatic sensory cortex realizes this promise. Their slice preparation allows them to find the synapse (at the earliest or input stage of cortical processing) at which changes take place, and further cellular studies of this synapse in this system can only enrich our understanding of the mechanisms that control cortical plasticity in development.

Kirkwood and colleagues' findings on visual cortex present a more complicated picture. These authors study the aggregate activity produced in the upper layers (which constitute the second stage of cortical processing) by the whole visual cortical circuit, monitored by extracellular recordings. They find that one form of LTP, evoked by stimulation of layer IV (electrode S1 in the figure), is of similar magnitude no matter what the age of the slice; while a second form of LTP, evoked by stimulation of white matter (electrode S2), disappears after the critical period (confirming earlier findings). Because of the complex nature of the circuitry activated by S2, the change in synaptic efficacy responsible for the plasticity during the critical period could occur at any of synapses A–E shown in the figure. The disappearance of plasticity after the end of the critical period could equally result not from a loss of plasticity at the originally plastic site but from compensatory changes at any of these loci. Indeed, the authors' hypothesis to explain the end of the plasticity *in vitro* is an increase in inhibition produced by cells such as cell 2 in the figure, rather than some decrement in a synaptic mechanism of plasticity. This



a, The thalamocortical slice experiment of Crair and Malenka[6], showing the synapse from the thalamic relay neuron (in ventrobasal nucleus, VBN, near stimulating electrode S) onto the layer IV cortical that becomes stronger after LTP during the first week but not later in life. Whole-cell, patch-electrode records voltage response to and current through this particular synapse. *b*, Experimental arrangements of Kirkwood *et al.*[7], showing some of the synapses (A, B, C, D, E) at which long-term changes may have taken place after tetanic stimulation at stimulating electrodes S1 or S2. Neurons 1, 3 and 4 are excitatory, and neuron 2 is inhibitory. S2 will activate all the neurons and synapses indicated. S1 will activate all the synapses illustrated and will activate at least neurons 1 and 2 directly and neuron 3 synaptically. Extracellular electrode records small voltage changes in the fluid outside the cells due to aggregate activity at many synapses like those illustrated. Increases in these voltage changes are interpreted as increases in the synaptic activation of cells such as neuron 3, produced by either an increase in the efficacy or activity of excitatory synapses (D for example) or a decrease in the efficacy or activity of inhibitory synapses (E for example). Selected cortical layers are indicated by roman numerals.

Erratum: The position of the stimulating electrode S2 was corrected on this copy.

explanation may well be correct, but it is not clear what we have gained in simplicity by taking the system *in vitro*. It is certainly not yet clear from these findings whether changes in the actual cellular mechanisms of plasticity at the input synapse could account for the end of the critical period in rodent visual cortex, as Crair and Malenka have now shown evidence for in somatic sensory cortex.

'Long-term potentiation' is often taken to refer to a cellular mechanism. But it actually denotes a wide variety of phenomena, for only a few of which is there any understanding in cellular terms. One hopes that the unity of biology will triumph in the end and that common mechanisms will be found to operate in all neocortical areas as well as in hippocampus. For now, however cognizant we may be of the promise of a cellular understanding of visual cortical plasticity, we must continue to seek it. □

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