

Commentary

Transforming sensory experience into structural change

P. Read Montague

The Salk Institute, 10010 North Torrey Pines Road, La Jolla, CA 92037; and Division of Neuroscience, Baylor College of Medicine, Houston, TX 77030

Almost all biologically feasible theories of how neuronal networks perform any interesting learning use some variant of the notion that the efficacy of a connection from one cell to another can be modified based on its previous history. Using synaptic contacts, there are two obvious ways to change effective connection strength: modify the gain of the synapses in place or change the number and pattern of synaptic contacts onto the receiving cell. Recent work in both vertebrates and invertebrates suggests that experience-dependent changes in the effective drive from one neuron to another can depend upon alterations in synaptic structure, number, or pattern in a fashion similar to that seen in many developing nervous systems (1–3). Given this state of affairs, we must ask whether we think it plausible that changes in connection strengths in real or artificial networks are necessarily equivalent to modulating the gain of a synapse. If this were the case, then perhaps models of learning could for the most part ignore the deepest thickets of biological detail. Even if synapse number and pattern are routinely changed during learning and adaptation, it still remains an open question whether using such a mechanism necessarily makes a theoretical difference.

In one invertebrate model of learning, the habituation and sensitization of gill and siphon withdrawal in *Aplysia californica* (4, 5), both the modulation of synaptic efficacy and structural changes are thought to be underlying mechanisms. Work by Bailey and Chen (6) has shown that, for the connection in question, long-term habituation of gill withdrawal is associated with a significant decrease in the number of presynaptic varicosities and long-term sensitization is associated with a significant increase in the number of presynaptic varicosities. Although a number of well-studied nonstructural changes contribute to these modifications of behavior, only the changes in the number of presynaptic varicosities consistently correlated with the behavioral memory (7).

In the vertebrate, the retina is one system in which the relation between sensory experience and structural changes can be explored with a precision approaching that seen in the invertebrate. The neuroanatomy is well described, the response properties of all

major cell classes are known, and the stimulus domain, though rich, is both identifiable and manipulable (8), allowing the physiology of the retina to be related to perceptual phenomena (9).

Around 1980 (10, 11), data suggested that during light and dark adaptation in the teleost retina certain connections of horizontal cells undergo a dramatic structural reorganization that correlates with identifiable changes in their response properties to light. Horizontal cells are neurons of the outer retina that communicate information from photoreceptors to both bipolar cells and other photoreceptors (8, 12). These neurons give a graded response to a light stimulus (13) resulting from the cessation of glutamate release from photoreceptors. Like other parts of the vertebrate brain, glutamate is the main excitatory neurotransmitter in the retina. The receptive fields of horizontal cells are large and, depending on the species, can be >10 times larger than the extent of their dendritic arbors (14, 15) due to extensive low-resistance electrical coupling between neighboring cells (16). Horizontal cells confer a transient component to cone responses (15, 17–19), and there is strong evidence that their activity is the primary drive for the antagonistic surround responses of bipolar cells (12, 20, 21). Dopamine, supplied by cells of the inner nuclear layer, is known to significantly diminish the electrical coupling between horizontal cells that is critical for establishing their large receptive fields (22, 23). Furthermore, dopamine plays a role in the structural rearrangement alluded to above.

The dendrites of horizontal cells extend slender processes called spinules into the foot processes (pedicles) of cones and it is these anatomical profiles that undergo a dramatic daily reorganization (11, 24, 25). The spinules can be formed or retracted in ≈ 30 min; they are formed anew during light adaptation and retracted during dark adaptation with the attendant increase in glutamate release from the photoreceptors onto horizontal cell processes (25, 26). In teleosts, these changes are under a circadian influence and are anticipatory with spinules being made before dawn and degraded before dark (11, 24). The appearance of the spinules correlates with the appearance of color opponent responses in both hor-

izontal cells and retinal ganglion cells (10, 25). The well-defined retinal anatomy along with the characteristic appearance of spinules in an electron micrograph have made such correlations possible.

In their recent work on the subject, Weiler and Schultz (52) have now shown that stimulation of a particular class of glutamate receptor, the α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, is sufficient to cause the disappearance of the spinules. Moreover, other candidates for this role, the *N*-methyl-D-aspartate (NMDA) glutamate receptor and the metabotropic glutamate receptor, appear to have no influence on this structural change. This is significant since it is thought that NMDA receptor activation may play a critical role in the activity-dependent plasticity (27) and segregation (28–31) of synaptic contacts in vertebrates. The present work of Weiler and Schultz (52) adds to previous results that demonstrated that spinule formation requires dopamine (26, 32) and spinule retraction is induced by L-glutamate (26). This same group has also demonstrated that the initiation of new spinule formation requires the activation of protein kinase C, and this activation alone is sufficient for new spinule formation in a retina depleted of dopamine (33). For color processing, it is possible that during the day, the spinules function primarily to sharpen cone responses and antagonistic surround responses in color-opponent bipolar cells.

To summarize, we have an example of glutamate transmission through a particular receptor influencing a structural change that modifies the processing capabilities of a neural circuit. There are some important points to make as follows: (i) The making and remaking of spinules contributes to changing the processing capacities of the circuit. (ii) The process depends on glutamatergic transmission. (iii) The process is taking place in an adult vertebrate. (iv) There is currently no evidence for an associative component to the reorganization; e.g., it is not clear whether the pairing of normal light levels with dopamine release could act like the pairing of a sensory stimulus with an unconditioned stimulus in a classical conditioning experiment (34).

At first glance, changing the efficiency of a fixed synaptic junction appears to be a

reasonable adaptive mechanism to underlie learning or adaptation; however, structural rearrangement seems to be an inefficient method for changing the excitatory drive from one cell to another. Surely modification of synaptic structure, albeit potentially robust and fault-tolerant, is too costly a method to change the functional connectivity of a network. It is difficult to speculate on why the spinules are retracted at night rather than simply turned off in some fashion; however, recent theoretical work (35) suggests that, rather than being inefficient, spinule reorganization may be satisfying some internal homeostatic constraint such as the maintenance of internal calcium levels near some set point (36). In some vertebrate retinas, photoreceptors are mechanically reoriented so that photon catch is optimized and bleaching of the photopigment is minimized (37). In a system that has evolved such tricks, it is difficult to guess the most important constraints; likewise, it is also difficult to assume that the mechanisms employed are inefficient. In any case, the retinal results present a well-defined and identifiable structural rearrangement in an adult vertebrate potentially mediating an important information processing function. Such a situation is not as readily available in the vertebrate cortex where unambiguously establishing a connection between structural change and learning or adaptation has been more difficult. However, there is mounting evidence that structural rearrangement of synaptic contacts may be a general method for activity-dependent changes in vertebrates during both development and adult learning.

In the vertebrate nervous system, large-scale rearrangements of synaptic contacts is a theme that characterizes the activity-dependent phase of map formation in the tectum (38), thalamus (39, 40), and cortex (41). Here, mappings are refined because temporal contiguity in axonal firing is somehow translated into spatial contiguity of synaptic contacts. A number of experiments have demonstrated that this process depends on the temporal patterns of neural activity (41, 42) and may be Hebbian (43–46). In the adult rat, learning related synaptogenesis (47, 48) and changes in dendritic complexity (49) have been documented and the suggestion is that these changes may reflect some permanent record of learning (50). One possibility is that the developmental rules, used initially to refine mappings, account for some of the synaptic learning rules in the adult state. In the primate cortex, dramatic long-term functional rearrangements in cortical representations have been observed in response to perturbed sensory input (for review, see ref. 51). It is not a far leap to suppose that some portion of this plasticity is partially mediated by long-term

structural change; however, this is currently unknown.

Is there a computational principle(s) to be gleaned from the fact that making and breaking synapses may be one mechanism by which synapse-specific learning takes place in the vertebrate brain? Perhaps modulating the efficacy of a synapse is a process too susceptible to noise for long-term memory storage and so locally making and breaking connections is one solution. Alternatively, maybe the retinal results represent the tip of the iceberg for the possibilities in the cortex.

I thank Peter Dayan, Zach Mainen, and Terry Sejnowski for insightful comments and criticisms.

1. Udin, S. B. & Fawcett, J. W. (1988) *Annu. Rev. Neurosci.* **11**, 289–328.
2. Shatz, C. J. (1990) *Neuron* **5** (6), 745–756.
3. Stryker, M. P. (1991) in *Development of the Visual System*, eds. Lam, D. M. K. & Shatz, C. J. (MIT Press, Cambridge, MA), pp. 267–287.
4. Carew, T. J., Pinsker, H. M. & Kandel, E. R. (1972) *Science* **175**, 451–454.
5. Pinsker, H. M., Hening, W. A., Carew, T. J. & Kandel, E. R. (1973) *Science* **182**, 1039–1042.
6. Bailey, C. H. & Chen, M. (1988) *Proc. Natl. Acad. Sci. USA* **85**, 2373–2377.
7. Bailey, C. H. & Chen, M. (1989) *J. Neurosci.* **9**, 1774–1780.
8. Dowling, J. E. (1987) *The Retina* (Harvard Univ. Press, Cambridge, MA).
9. Daw, N. (1973) *Physiol. Rev.* **53**, 571–611.
10. Raynauld, J. P., Lavolette, J. R. & Wagner, H. J. (1979) *Science* **204**, 1436–1438.
11. Wagner, H.-J. (1980) *J. Neurocytol.* **9**, 575–590.
12. Naka, K.-I. (1972) *Vision Res.* **12**, 573–588.
13. Tomita, T. (1965) *Cold Spring Harbor Symp. Quant. Biol.* **30**, 559–566.
14. Naka, K.-I. & Rushton, W. A. H. (1967) *J. Physiol. (London)* **192**, 437–461.
15. Stell, W. K. & Lightfoot, D. O. (1975) *J. Comp. Neurol.* **159**, 473–502.
16. Kaneko, A. (1971) *J. Physiol. (London)* **213**, 95–105.
17. Baylor, D. A., Fuortes, M. G. F. & O'Brien, P. M. (1971) *J. Physiol. (London)* **214**, 265–294.
18. Fuortes, M. G. F., Schwartz, E. A. & Simon, E. J. (1973) *J. Physiol. (London)* **234**, 199–216.
19. Piccolino, M. & Gerschenfeld, H. M. (1980) *Proc. R. Soc. London B* **206**, 439–463.
20. Marchiafava, P. L. (1978) *Nature (London)* **275**, 141–142.
21. Toyoda, J. & Kujiraoka, T. (1982) *J. Gen. Physiol.* **79**, 131–145.
22. Mangel, S. C. & Dowling, J. E. (1985) *Science* **229**, 1107–1109.
23. DeVries, S. H. & Schwartz, E. A. (1989) *J. Physiol. (London)* **414**, 351–375.
24. Wagner, H.-J., Behrens, U. D., Zaunreiter, M. & Douglas, R. H. (1992) *Vision Neurosci.* **9**, 345–351.
25. Weiler, R. & Wagner, H.-J. (1984) *Brain Res.* **298**, 1–9.
26. Weiler, R., Kohler, K., Kirsch, M. & Wagner, H.-J. (1988) *Neurosci. Lett.* **87**, 205–209.
27. Bliss, T. V. P. & Lynch, M. A. (1988) in *Long-Term Potentiation: From Biophysics to Behavior*, eds. Landfield, P. & Deadwyler, S. (Liss, New York), pp. 3–72.
28. Kleinschmidt, A., Bear, M. F. & Singer, W. (1987) *Science* **238**, 355–358.
29. Scherer, W. J. & Udin, S. B. (1989) *J. Neurosci.* **9**, 3837–3843.
30. Cline, H. T. & Constantine-Paton, M. (1990) *Neuron* **3**, 413–426.
31. Simon, D. K., Prusky, G. T., O'Leary, D. D. & Constantine-Paton, M. (1992) *Proc. Natl. Acad. Sci. USA* **89**, 10593–10597.
32. Weiler, R., Kohler, K., Kobinger, W., Wolburg, H., Kurz-Isler, G. & Wagner, H.-J. (1988) *Neurosci. Res. Suppl.* **8**, S183–S196.
33. Weiler, R., Kohler, K. & Janssen, U. (1991) *Proc. Natl. Acad. Sci. USA* **88**, 3603–3607.
34. Alkon, D. L., Ikeno, H., Dworkin, J., McPhie, D. L., Olds, J. L., Lederhendler, I., Metzler, L., Schreurs, B. G., Kuzirian, A., Collin, C. & Yamoch, E. (1990) *Proc. Natl. Acad. Sci. USA* **87**, 1611–1614.
35. Bell, A. J. (1992) in *Advances in Neural and Information Processing Systems 4*, eds. Moody, J., Hanson, S. J. & Lippmann, R. (Morgan Kaufmann, San Mateo, CA), pp. 59–66.
36. LeMasson, G., Marder, E. & Abbott, L. F. (1993) *Science* **259**, 1915–1917.
37. Ali, M. A. (1975) *Vision in Fishes: New Approaches in Research*, ed. Ali, M. A. (Plenum, New York), pp. 313–355.
38. Meyer, R. L. (1982) *Science* **218**, 589–591.
39. Shatz, C. J. & Stryker, M. P. (1988) *Science* **242**, 87–89.
40. Garraghty, P. E., Shatz, C. J. & Sur, M. J. (1988) *Vision Neurosci.* **1**, 93–102.
41. Hubel, D. H., Wiesel, T. N. & LeVay, S. (1977) *Philos. Trans. R. Soc. London B* **278**, 377–409.
42. Stryker, M. P. & Harris, W. A. (1986) *J. Neurosci.* **6**, 2117–2133.
43. Hertz, J., Krogh, A. & Palmer, R. G. (1991) *Introduction to the Theory of Neural Computation* (Addison-Wesley, Redwood City, CA).
44. Rauschecker, J. P. & Singer, W. (1979) *Nature (London)* **280**, 58–60.
45. Reiter, H. O. & Stryker, M. P. (1988) *Proc. Natl. Acad. Sci. USA* **85**, 3623–3627.
46. Singer, W. (1990) *J. Exp. Biol.* **153**, 177–197.
47. Chang, F.-L. & Greenough, W. T. (1982) *Brain Res.* **232**, 283.
48. Black, J. E., Isaacs, K. R., Anderson, B. J., Alcantara, A. A. & Greenough, W. T. (1990) *Proc. Natl. Acad. Sci. USA* **87**, 5568–5572.
49. Greenough, W. T., Juraska, J. M. & Volkmar, F. R. (1979) *Behav. Neural Biol.* **26**, 287–297.
50. Greenough, W. T. & Bailey, C. H. (1988) *Trends Neurosci.* **11**, 142–147.
51. Merzenich, M. M. & Sameshima, K. (1993) *Curr. Opin. Neurobiol.* **3**, 187–196.
52. Weiler, R. & Schultz, K. (1993) *Proc. Natl. Acad. Sci. USA* **90**, 6533–6537.