The Plastic Brain

Adapted from a Presentation by Martha Constantine-Paton

Departments of Biology and Brain and Cognitive Sciences, Massachusetts Institute of Technology, 77 Massachusetts Ave., Cambridge, Massachusetts 02139-4301

Developmental plasticity is the term used to describe the developing brain's ability to organize its circuitry and subsequent function based on the activity patterns it receives. This form of plasticity decreases as the brain matures, providing both advantages and disadvantages to the organism. On the one hand, brain circuitry that must remain relatively invariant to maximize functional efficacy throughout later life can be optimally "tuned" to the environment during a relatively protected childhood period. Also, younger brains are able to functionally recover from injury much more readily than older brains. Unfortunately, on the other hand, this pronounced early plasticity and its downregulation with maturity also render young brains much more susceptible than older brains to long-term disruptive effects from abnormal or "deprived" environments. Thus, understanding the mechanisms underlying early brain plasticity and its downregulation would enable the development of treatments to selectively reactivate it in mature brain, to facilitate recovery from a wide-range of neurological dysfunction.

During the Decade of the Brain, neuroscientists have studied plasticity at behavioral, cellular, and molecular levels (see Fig. 1). At the behavioral level, cognitive scientists have documented many instances where early disruptions of normal function produce permanent functional impairment. Developmental neurobiologists have described likely cellular correlates of such change in the organization of circuitry that controls and coordinates our behavior. Molecular biologists have supplied ever-growing lists of molecules that change in the brain as it matures. Current research attempts to develop preparations in which scientists at multiple levels can work together to understand how molecular changes control cellular and behavioral changes, to intelligently and adaptively reactivate plasticity in maturity.

BEHAVIORAL STUDIES OF PLASTICITY

One of the ways in which a scientist goes about studying plasticity at the behavioral level is by using animal models with specialized sensory capabilities. One important study involves the use of barn owls. These birds can use vision to localize prey, yet the majority of their hunting is done at night, when they can use auditory spatial cues to localize their prey in the complete absence of visual input. Researchers know that in the brains of these animals, as well as in humans, there are both an auditory map and a visual "map of space." In all normal individuals, those maps overlap. For example, in Fig. 2, a prey object sitting at the vertical meridian would stimulate the same region of the brain through both the auditory sensory modality and the visual sensory modality. However, when the young owls are fitted with prisms that deflect the visual image, as the figure shows, the image moves $-23°$ off the vertical meridian. The sound, however, in these birds still comes from directly in front. The prisms misalign the visual and auditory maps of space in the brain. If these young birds are placed back in their aviary and allowed to hunt normally, they very rapidly adapt to the prisms and become, for all intents and purposes, like normal birds. When these animals are studied physiologically and behaviorally, it becomes apparent that the auditory map of space actually shifts within the brain, to maintain registration of auditory prey stimuli with visual prey stimuli. The young barn owl's brain uses convergence in the patterns of activity to influence its effective wiring.

This ability to realign what is a very major aspect of auditory organization is age dependent. Birds up to about 125 to 150 days of age realign their maps very, very readily. But older birds, and in particular adults, are never able to adjust to this abnormal sensory environment.
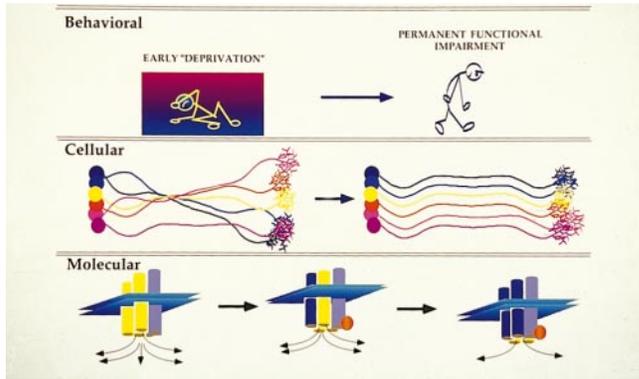
FIG. 1. Brain plasticity occurs at the behavioral, cellular, and molecular levels.

CORTICAL PLASTICITY IN THE DEVELOPING HUMAN BRAIN

Developing children change their behavior as a result of their experience, frequently, rapidly, and in irreversible ways. Scientists learned that this can produce permanent functional impairment by studying children who experienced a variety of very early deprivations, but it is important to recognize that this plasticity can also be of great benefit. Observations using noninvasive imaging techniques, such as functional magnetic resonance imaging (fMRI), on human subjects illustrate the extent to which the patterned
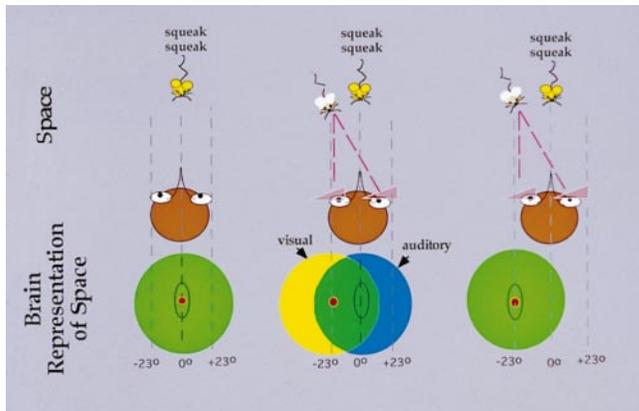

FIG. 2. The brain uses correlations in activity to bring auditory and visual space maps into register. Adapted from Brainaird, M.S., Knudsen, E. Experience-dependent plasticity in the inferior colliculus. A sight for visual calibration of the neurorepresentation of auditory space in the Barn Owl, *Journal of Neuroscience* **13**, 4589–4608.
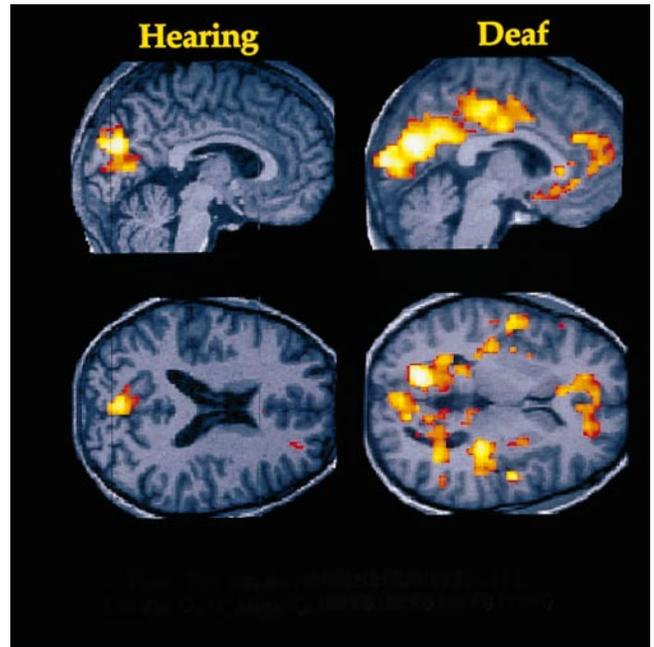

FIG. 3. Neural response to visual motion. Reprinted with permission from Toman, A., Mitchell, T., Nevilla, H. J., Corina, D., Hutton, C., Liu, G., Bavelier, D. (1998).

activity of early life can produce adaptive changes in the circuitry of the developing human brain. For example, the images in Fig. 3 show the brain patterns of a hearing individual and an individual deaf since childhood, who grew up using American Sign Language as a native language. The hearing individual, when shown a visual moving image, displayed a bright locus of activation in the posterior or visual region of the cerebral cortex. The same visual stimulus, given to the native signer, stimulated not just the visual region of the cerebral cortex, but, in fact, large regions of the cortex normally involved in auditory function and regions of frontal cortex normally involved with interpretation and emotion. fMRI shows that in the brain, the visual sensory modality of such an individual takes over many of the perceptual tasks normally performed by the auditory system. Activity patterns within both auditory and visual regions of the cortex have been changed dramatically following this altered early experience. Evidence of such extensive reorganization is not seen in individuals who learn sign language as adults. It is a plastic change in the organization and the function of the cortex that occurs early in development and thereafter appears to be relatively turned off.

Similarly, in deaf users of sign language since childhood, the brain region normally reserved for language recognition has been found to be responsive to "signed" words. When the long unused ascending auditory pathway is artificially stimulated using auditory prostheses, the artificially induced auditory signal for the word has no effect on this language recognition region; only signed words activate this region.

Obviously, as technology improves to a point where we can replace defective sensory organs, we also have to develop treatments that allow those sensory pathways to recapture the cognitive functions of brain regions with which they would have normally established connections during childhood. To accomplish this, scientists have to unravel the activity-dependent mechanisms of the brain "wiring" as it sequentially unfolds and becomes established during normal development.

PLASTICITY AT THE CELLULAR LEVEL

The development of the nervous system occurs according to a basic rule, "neurons that fire together, wire together," or more whimsically, "neurons that play together, stay together." In other words, neurons that fire action potentials or nerve impulses in unison onto target cells tend to stay connected to those targets into adulthood, whereas other inputs that may be just as electrically active in isolation are actually lost.

The upper three panels of Fig. 4 show the refinement of a visual map in the brain. For example, in the retina of the eye, neighboring retinal ganglion cells tend to fire very highly correlated patterns of nerve impulses, whereas the activity of more distantly positioned retinal ganglion cells is not synchronized. The "rule" of maintaining and preserving cells that are firing together plays a significant role in the development and refinement of the nervous system's visual map of space. Figure 4 shows one of the major visual centers of a young rat pup. A small part of the projection of ganglion cells from the retina has been labeled with a dye, making it appear white in the picture. Over the first week and a half of life, this initially very diffuse projection refines to a very precise position within the visual target region of the brain. In fact, other regions of the visual map are refining back to one particular place within the target region at the same time. Development proceeds from a very diffuse map of the retinal surface within the target region to a very highly refined map that can register, with high
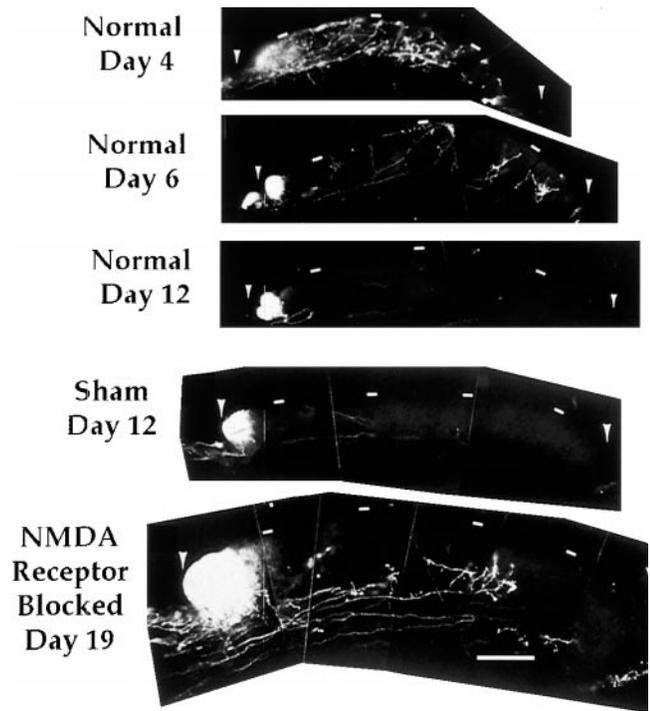

FIG. 4. NMDA receptor in visual map refinement. Reprinted with permission from Simon, D. & O'Leary. (1992) Development of topographic order in the mammalian retinocollicular projection, *Journal of Neuroscience* **12,** 1212–1232; and Simon, D. Pruski, G. O'Leary, Constantine-Paton, M. (1992) N-Methol-D-Asparatate Receptor Antagonists Disrupt the Formation of A Mammalian Neural Map *Proc. Nat'l. Acad. Sci. USA* **89,** 10593–10597.

spatial resolution, the visual image stimulating the retina.

PLASTICITY AT THE MOLECULAR LEVEL

What is the mechanism for this developmental process? The major central nervous pathways can reorganize their connections to refine initially diffuse low-resolution projections of visual space, or to bring projections of auditory and visual space in register by means of sets of receptors for the neurotransmitter glutamate. Glutamate binds to the receptive surfaces of target neurons in the brain, and is the dominant excitatory transmitter in our brains. It is the major "go" signal. Other major transmitters, such as serotonin and dopamine, though very potent factors in behavior, usually work by modulating the ongoing glu-

tamatergic transmission in the brain. As a result of work in this Decade of the Brain, scientists know a tremendous amount about the glutamate receptors. For instance, there are major classes or receptors that are essentially glutamate-activated ion pores or channels. One major class of glutamate receptors predominant in the young brain is called the *N*-methyl d-aspartate (NMDA) receptor. This receptor is unusual in that it activates neurons uniquely well when the various inputs from other neurons stimulating the neurons on which the NMDA receptors sit are correlated in time. With new DNA technology scientists can destroy the genes that make this receptor in mice, so-called *knockout mice.* When this receptor is knocked out completely in mice, they die within a day or two of birth. In the experiment mentioned earlier, the refinement of the retinal map within a visual target region of young rats can be disrupted by using drugs to block the NMDA receptor from the day of birth. Rather than experiencing a steady refinement of their visual maps, these pups are left with a very disorganized map of visual space. In the barn owl a similar blockade of the NMDA receptor was carried out. Those animals with blocked NMDA receptors were unable to realign auditory with their visual map of space. From these and numerous other studies in this Decade of the Brain we know that the NMDA receptor molecule is important for the normal communication between nerve cells and for the normal developmental organization of the brain's response to the world within which it must operate.

The NMDA receptor is unique among the ion permeable receptors because to function it requires not only the presence of the neurotransmitter glutamate but also a depolarization of the cell membrane in which it sits. The depolarization results from a very recent activation of the same cell. Thus, NMDA receptors function maximally when many of a young neuron's inputs are active at nearly the same time. The NMDA receptor is also unique among ion-passing receptors because it allows an unusually large amount of the important ion calcium (Ca^{2+}) into young neurons, and, once inside, this Ca^{2+} activates mechanisms that retain, as a physical form of memory, the inputs that initiated the Ca^{2+} entry. Thus, the NMDA receptor serves as a fundamentally important key to the early function and development of the nervous system.

In the mature brain functional cooperation between two classes of glutamate receptors, the α-amino-3-hydroxy-5-methylisoxazoleproprionic acid (AMPA) and NMDA receptors, has been repeatedly implicated in learning. A very unexpected discovery in recent years has been that at very young synapses, NMDA receptors are present and functioning in the absence of AMPA receptors. At these young neuronal communication points, the neurotransmitter γ-aminobutryric acid (GABA), which is critical to the inhibition of excitation in the mature brain, can serve in place of the AMPA receptor, to help depolarize and excite baby neurons. Consequently, in the young brain, very much unlike the adult brain, GABA receptors and NMDA receptors cooperate to get Ca^{2+} as a secondary signal or "second messenger" into neurons.

Too much intracellular Ca^{2+} however, can be disastrous for young neurons. It can become neurotoxic and lead to the breakdown of cell structure and, sometimes, to neuron death. The early robust function of the NMDA receptor must be tightly controlled as brain circuits mature. Too little NMDA function and optimal activity-dependent tuning of circuitry cannot occur, whereas too much NMDA function leads to seizures and excitotoxic cell death. This dichotomy dictates a robust and occasionally very rapid down-regulation of NMDA receptor function in the maturing brain that has been closely associated with greatly decreased potential for adaptive brain rewiring.

In short, the adult brain that has developed with the constructive and destructive potential of the NMDA/Ca^{2+} system under control has been optimized to the environmental signals it received. It has managed to sequester the remaining potential for plasticity to regions that readily incorporate incoming patterns of neural activity into meaningful, ongoing behavior, and for learning and memory. But what about a brain that, because of illness, trauma, genetic defects, or neglect, has not experienced the necessary stimulation during the developmental periods when NMDA receptor function allows adaptive wiring to occur? What is the hope for locally reactivating developmental plasticity in selected regions in the mature brain?

REACTIVATING PLASTICITY IN THE MATURE BRAIN

The answer to these questions lies in what scientists have learned about the factors controlling the developmental regulation of the NMDA receptor and Ca^{2+} influx into cells. Three discoveries are particularly significant. First, researchers now know that the genes that code for the NMDA receptor change during de-

velopment so that the receptor actually lets less Ca^{2+} into neurons as the brain matures. They know which genes are responsible for this control and can potentially express the appropriate ones in targeted regions of the mature brain. Second, scientists have now identified Ca^{2+} sensitive enzymes that sit at synapses and can decrease the NMDA receptor's function when Ca^{2+} levels are too high. They can potentially turn down the activity of these enzymes in targeted brain regions to reactivate developmental plasticity. Finally, researchers now understand many of the changes in the GABA neurotransmitter systems within developing central nervous system circuits that allow GABA to switch from excitatory to inhibitory function and thus prevent overactivation as excitation matures and tuned circuits begin to arise. They can potentially develop drugs that target these mechanisms and thus control whether GABA synapses work to facilitate or dampen NMDA receptor function and Ca^{2+} influx in particular brain regions.

Translating this promise into reality rests on a rapidly emerging technology for targeting genes selectively to small subsets of neurons in the brain and bringing this gene expression under precise control. It also rests on progress in a parallel, explosive area of research that is defining the biological pathways that actively control cell death. Neurons with high NMDA receptor function in the mature brain are going to be not only more plastic, but also much more vulnerable to excitotoxic death. Work in worms and fruit flies now indicates that cell death pathways can be selectively turned off in ways that allow other functions of the neurons to occur normally. It seems likely that we will soon be able to accomplish this in vertebrate cells as well. Finally, realizing the promise of selectively reactivating plasticity in the mature brain rests on obtaining more basic developmental information to define the brain pathways and regions that alter their plasticity at particular stages of childhood development. It is only through this developmental description and cataloguing of these events in humans, coupled with coordinated experiments in animal models, that researchers will know which regions must be targeted for the amelioration of any particular activity-dependent dysfunction.

Obtaining this essential information will be the most difficult task of all. It requires cooperation and much dialogue among neurologists, psychiatrists, educators, developmental psychologists, and neuroscientists who work to translate the complex world of human behavior into the functioning of identifiable brain circuits. It also requires patience and continuous financial public and private support from individuals and institutions that must understand that effectively documenting the still mysterious unfolding of human brain circuits will take time.

Once such information is available, the scientists, clinicians, and technicians of the 21st century will be able to selectively reactivate the powerful mechanism of adaptive brain wiring in maturity. This will bring true sensory perception to individuals afflicted by sensory deprivation early in life. It can also facilitate a return to the full range of normal movement capabilities in individuals paralyzed by brain or spinal cord trauma. Furthermore, it can bring about normal cognitive function in individuals handicapped by genetic or environmental aberrations that deprived their brains of the normal patterns of stimulation as children.