Brain Architecture: Beyond Genes

Neuroscientists at a recent meeting highlighted how extragenetic factors—including neuronal activity, contact with other cells, radiation, and chemical factors—influence brain circuitry, especially during development

"EVEN if we knew all of the genes and what they coded for, we still could not predict in detail what kind of brain you would have," says Pasko Rakic of Yale University School of Medicine. Rakic's comments reflect a growing understanding that, although genes determine overall aspects of brain architecture and wiring patterns, factors outside the genome can modify details of the basic organization. Neuroscientists at a recent meeting in New York entitled "Brain Beyond Genes,"* analyzed what is known about such extragenetic factors and how they can influence neuronal circuitry.

Theories about the significance of genetic information versus the impact of experience on brain development and function have both had their heyday in neurobiology. But for a long time, the overriding conviction was that the physical layout of the brain, the positioning of nerve cells and the routes over which their fibers project to make synaptic contacts with other neurons, was rigidly controlled by genetic instructions.

During the last 20 years, this view has been changing. As Jean-Pierre Changeux, of the Pasteur Institute, Paris, graphically pointed out, "the human brain probably contains more than 10^{14} synapses, and there are simply not enough genes to account for this complexity." So, in recent years, neuroscientists have settled down to the business of determining experimentally to what extent various extragenetic factors can modify the pattern of synaptic connections in terms of their anatomy as well as physiology.

Major synaptic rearrangements occur normally during embryological and postnatal development, and many of these are genetically directed. Extragenetic factors also seem to exert their greatest influence early in development, although they can modify synaptic connections in the adult nervous system, too. The effects of various extragenetic factors on neuronal circuitry occur in a wide range of systems, from individual cells in tissue culture, to ganglia of the peripheral nervous system, the mammalian spinal cord, to the primate visual cortex, and all the way to the intact human brain.

Changeux uses chick nerve and muscle cells in tissue culture as a model system to show that "in addition to the importance of genes, there is a process of synapse selection that depends on activity." Motor neurons form synapses, or neuromuscular junctions, with individual muscle fibers. The junctions vary in number and location, depending on the amount of neuronal activity muscle fibers receive. In the developing brain, as in muscle, more synapses are established than will eventually be used, and many are eliminated. Neuronal activity tends to stabilize synapses, which may then persist.

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For many years neuroscientists have tested how a lack of activity affects brain function and behavior, by depriving animals of sensory input. Within the last 20 years, they have concentrated their efforts on a systematic study of the microanatomy of neuronal connections to and within the visual cortex after input from one or both eyes is blocked.

Like other areas of the cerebral cortex, the visual cortex is composed of several horizontal layers. The position of each neuron within the cortex determines the type of synapses it receives and the kind of neurotransmitter it releases to other neurons. But which normal extragenetic factors tell each neuron the position it should occupy in order to receive or send its information?

Part of the answer lies in the cell-to-cell contact that neurons have with nonneuronal cells. "Neurons in the visual cortex are generated within a 2- or 3-month period of intrauterine life in monkeys and humans," says Rakic. "However, none of these neurons is generated within the cortex itself. They all migrate there, from areas around the brain ventricles along columns of short-lived nonneuronal cells called radial glia."

If nerve cells in the cortex do not migrate at the proper time and along the correct pathway, synaptic organization can be disrupted. An extreme example can be seen in the postmortem brain of a 16-year-old boy who had been exposed as a fetus to atomic radiation from the Hiroshima blast. His brain contains nerve cells that never made it into the cortex because they were trapped in a zone of cell proliferation near the brain ventricles. In his case, radiation served as an abnormal extragenetic factor that prevented many nerve cells from migrating along their normal pathways during a critical stage of development. Smaller doses of radiation produce less dramatic effects on cell positioning that may result in mental retardation.

Visual experience, or the lack of it, can also affect the development of synaptic organization in the visual cortex. In new experiments with monkeys whose visual input from the eyes to the brain was eliminated at an early embryonic stage, Rakic finds that the lateral geniculate bodies (LGB's) in these animals as adults contain about one-third of the usual number of nerve cells. The LGB's lie in the thalamus, an area of gray matter under the cerebral cortex, and normally receive input from both eyes via the optic nerves. In turn, nerve fibers from the LGB's project to the visual cortex.

Interestingly, the visual cortex of an experimental animal shows a normal width, layering pattern, and density of synapses, although its surface area is about one-third smaller than normal. Rakic sees this as a cascade effect. "With no axons from the eyes to innervate them, the LGB's in the thalamus send fewer axons to the visual cortex. The reduced number of axons from the thalamus then seems to decrease the cortical surface area to some extent. So, within genetic constraints, extragenetic factors can

*"Brain Beyond Genes" was held in New York from 2 to 4 June 1986. The meeting was organized by Pasko Rakic and sponsored by the Institute for Child Development Research, 330 Madison Avenue, New York 10017.

influence the number and details of synaptic contacts in the cortex."

Torsten Wiesel, of the Rockefeller University in New York, reviewed evidence indicating that the extent and timing of an animal's visual experience during early postnatal development have a profound effect on brain circuitry. In studies during the 1960's and 1970's with David Hubel of Harvard, Wiesel showed that depriving an animal of visual input from one eye causes dramatic changes in the normal synaptic organization of the visual cortex. "We showed that you do not have to cut a nerve tract or make a lesion in order to change how the brain is wired," says Wiesel.

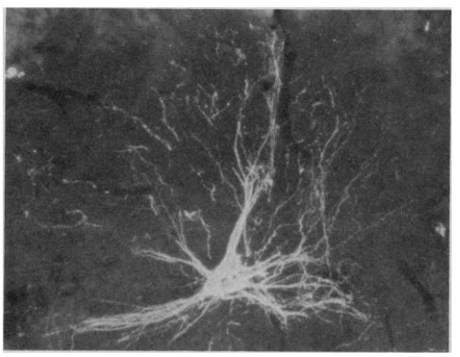
Wiesel and Hubel demonstrated that, in the normal adult monkey, there are vertical columns of nerve cells in the visual cortex that preferentially respond to incoming activity from either the right or the left eye. They named these patches of cortex ocular dominance columns and found that incoming activity from the lateral geniculate bodies dictated the size of each column. Normally, ocular dominance columns responding to the right and left eyes are the same width and contain equal numbers of responding neurons. But if one eye is closed early in an animal's postnatal development, the LGB innervated by optic nerve fibers from the good eye takes control over more of the visual cortex by expanding the area of its synaptic connections.

In experiments with monkeys that had one eye closed early in development, Wiesel and Hubel produced a "dramatic shift in the responding ocular dominance columns so that most of the responding cells were to the normal eye," says Wiesel. "What we thought was really exciting was that nerve fibers from the lateral geniculate nucleus rewired themselves so that about 80% of the neurons in the visual cortex responded to input from one eye. This is in great contrast to the normal situation in which 50% of the neurons in the visual cortex respond to one eye and 50% to the other."

The effect of depriving one eye was greatest within the first 6 weeks after the monkeys were born, and by 12 months of age the ocular dominance columns are formed and are resistant to change, says Wiesel.

Michael Stryker and his colleagues, at the University of California School of Medicine in San Francisco, find that in addition to activity from other neurons, spontaneous electrical activity within the embryonic brain also influences the development of ocular dominance columns in the visual cortex. For instance, with normal development and activity, an increasing number of cells in layer IV of the visual cortex is driven exclusively by one eye or the other, but not both. But, with all spontaneous activity blocked, the normal developmental pattern is arrested and layer IV contains largely binocularly driven cells.

Working entirely outside the visual system Edwin Furshpan, of Harvard University Medical School, and more recently Ira Black, of Cornell University Medical Center, showed that various chemical substances diffusing within the nervous system affect what kind of transmitter nerve cells will make. These substances have their most dramatic impact during development, but also seem to affect differentiated neurons in the adult nervous system.



Cluster of four androgen-sensitive motor neurons in the spinal cord (spinal nucleus of the bulbocavernosus) of a normal adult male rat. [*Courtesy of E. M. Kurz, D. R. Sengelaub, and A. P. Arnold*]

Furshpan and his collaborators, including Story Landis, also of Harvard, and Paul Patterson, now at the California Institute of Technology, challenged the classical notion that each neuron can make only one kind of neurotransmitter during its life. "An important question facing a young sympathetic ganglion neuron is one of character. What kind of neurotransmitter will it make? What kind of '-ergic' will it become?" says Furshpan. Furshpan and his co-workers found that even late in development, a diffusible glycoprotein from heart muscle can induce noradrenergic neurons that normally secrete norepinephrine as a transmitter to become cholinergic neurons that secrete acetylcholine.

Black and his colleagues find that when incoming nerve fibers release acetylcholine and stimulate sympathetic ganglion neurons, the sympathetic neurons increase their synthesis of norepinephrine and decrease synthesis of a peptide, substance P. Thus, the same extragenetic signal, termed "transsynaptic activity," has different effects on the same neurons.

Hormones are another kind of chemical factor that influence neuronal architecture. For instance, Arthur Arnold and his colleagues, at the University of California in Los Angeles, and Marc Breedlove, now at the University of California at Berkeley, find that androgens (male sex hormones manufactured in the testes) also influence neuronal development. Innervation of the levator ani and bulbocavernosus muscles in rats are sensitive to androgens. In response to input from motor neurons in the spinal cord, these muscles contract during copulation.

Male rats have many more of these spinal cord motor neurons than females. The reason, says Arnold, is "not because these cells are generated differently in males and females, but because androgens prevent cell death in males." Additionally, androgens increase the size of the cell bodies of these neurons, cause an increase in the length of their dendrites, and regulate the number of axons to individual muscle fibers of the levator ani. Arnold thinks that androgens might also influence the organization of inputs and outputs of spinal motor neurons.

A classic example of the influence of extragenetic factors on the human brain can be seen in the development of speech, an aspect of which Peter Eimas of Brown University in Rhode Island described. Eimas is interested in how the speech sounds heard in infancy act as extragenetic influences on a human being's ability to perceive those sounds later in life. Babies are born with the ability to hear a very large number of sounds and to speak any language. "But as adults, we do not hear the distinction among many sounds," said Eimas. "A good example is the inability of an adult raised in a Japanese-speaking home to distinguish between 'r' and 'l'. This is the result of having a parental language that doesn't include those sounds."

Between 6 and 12 months of age, infants begin "a selection process that seems to become fairly permanent at puberty," says Eimas. That is why adults find it difficult or perhaps impossible to learn to speak a new language without their original accent showing through.

"Our ability to adapt to an everchanging environment by changing our brains may be very positive," says Rakic. "But it could also have a negative effect. In our industrial society, many extragenetic factors—including drugs, toxins, radiation—could affect synaptic connections and brain chemistry adversely. These factors would mostly influence the developing brain, during both embryological and postnatal periods."

It is not only external factors that influence brain structure and function, but many normally occurring internal factors also act during development and into adulthood. Understanding the mechanisms by which extragenetic factors, whether internal or external, modify brain circuitry coded for in the genome is a future challenge. ■

DEBORAH M. BARNES