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Although developmental psychology and developmental neuroscience share interests in common problems (e.g., the nature of thought, emotion, consciousness), there has been little cross-fertilization between these disciplines. To facilitate such communication, we discuss 2 major advances in the developmental brain sciences that have potentially profound implications for understanding behavioral development. The first concerns neuroimaging, and the second concerns the molecular and cellular events that give rise to the developing brain and the myriad ways in which the brain is modified by both positive and negative life experiences. Recurring themes are that (1) critical, new knowledge of behavioral development can be achieved by considering the neurobiological mechanisms that guide and influence child development, and (2) these neurobiological mechanisms are in turn influenced by behavior.

INTRODUCTION

Although our understanding of child development has increased exponentially over the last 25 years, knowledge of the neurobiological forces that shape, and that are shaped by, behavioral development remains primitive. That this is so can in part be attributed to the fact that developmental psychology and the neurosciences, each rapidly moving autonomous sciences, typically seek answers to questions that lie at different points on a continuum of knowledge (e.g., the cellular basis of memory versus the behavioral expression of memory). Furthermore, each science requires different levels of analysis (e.g., single-cell structural, functional, or chemical analyses versus description of naturally occurring behavior). Without a doubt, a greater awareness of the neurobiological mechanisms that underlie behavior would improve our understanding both of behavioral and of biological development. It is our goal in this article to examine a number of empirical and theoretical advances in the brain sciences that have implications for understanding child development.

We have selected two key areas from the neurosciences to illustrate recent progress in developmental research. We begin our discussion by considering advances in neuroimaging that permit detailed examination of both the structure and function of the brain. Here we focus on complementary sets of tools: those that permit inferences about the brain based on behavior; those that permit direct visualization of the brain and that provide excellent resolution in the spatial domain (e.g., functional Magnetic Resonance Imaging); and those that permit direct visualization of the brain and provide comparable resolution in the temporal domain (e.g., Event-Related Potentials, Magnetic Source Imaging). This section is designed to introduce the reader to the insight that these tools have brought to our understanding of the brain and, as well, to provide a tutorial on how these methods can be used in developmental research. In the second part of this article, we discuss new findings about the molecular events that give rise to the developing brain, as well as the environmental circumstances that can modify the brain. Here we capitalize on progress in the field of molecular genetics and cell biology and describe, for example, how regulatory genes sculpt the brain and how gene expression can be modified both by intrinsic and by extrinsic events. Having established that even the earliest stages of neural development can be altered by experience, we then turn our attention more specifically to the issue of neural plasticity. Here we provide examples of both adverse (e.g., the effects of early maternal stress on the brain of the immature animal) and adaptive outcomes (e.g., neural reorganization following injury, such as amputation, or following training, such as practice with a musical instrument) that can occur both early and late in the lifespan. An important theme emerges here: Within certain limits, forms of neural plasticity remain possible throughout the lifespan, and may not be limited to early development.

FUNCTIONAL NEUROIMAGING

The term *neuroimaging* is typically taken to mean the ability to examine the structure and/or function of the brain. Many such tools exist, and it is our intent

to review only those that lend themselves to the study of human development and that are not restricted to clinical populations. Thus, for example, we avoid discussion of the use of intracranial recording of evoked potentials, as this tool is generally restricted to neurosurgical cases. It should be borne in mind that advantages and disadvantages go with each tool. As a result, the question under investigation determines which tool should be used (e.g., Does one wish to examine the *rate* at which information is transmitted through the brain or *where* in the brain a particular function is taking place?). Moreover, it may well be that some tools can only be used with others, such as Magnetic Resonance Imaging (MRI) with *functional* Magnetic Resonance Imaging.

Neuropsychological Tools

Few would argue with the premise that the ultimate instantiation of a neural process is behavior. It should therefore come as no surprise that predating all other neuroimaging methods is the use of behavioral tools to infer brain function. The ideal strategy here is to generate a hypothesis about which area of the brain is involved in a particular behavior, and then develop a behavioral litmus test to evaluate this hypothesis. Examples of such a test might be the Serial Reaction Time Task used to evaluate implicit memory, or the Delayed Non-Match-to-Sample Task used to evaluate explicit memory. The neuropsychological method typically must be applied using a cluster of tasks to observe dissociations in function, and often involves testing both normative and clinical populations.

There are numerous examples of this approach. Perhaps of historical importance would be the case of patient H.M., who suffered from medically intractable epilepsy (i.e., his seizures could not be controlled by medication). To avoid the potentially life-threatening complications that would result if his seizures were not brought under control, H.M. underwent experimental neurosurgery. Because his seizures originated in the medial temporal lobe, H.M. underwent a bilateral resection (removal) of both temporal lobes. H.M. benefited from this surgery in that his seizures were brought under control; on the other hand, H.M. was also left without the ability to form new memories (for a recent lay description of this case, see Hilts, 1995).

The cases of H.M. and others like him have been extensively reported in the literature and have been instrumental in informing us about the relation between brain structure and brain function. Based on extensive neuropsychological testing of H.M., for example, the hypothesis has been confirmed that portions of the medial temporal lobe, such as the hippocampus, play a critical role in memory (for more recent examples with other patients, see Bechara et al., 1995); it is also believed that this region of the brain does not play a role in other forms of memory, such as procedural learning (for discussion, see Salmon & Butters, 1995; Schacter, 1987). The use of neuropsychological tools can easily be applied to the developing human, particularly if the investigator can draw on either the human adult or animal literature to generate hypotheses. For example, Diamond has employed a set of behavioral tasks with infants and young children (e.g., the Piagetian A-not-B task; the barrier detour task) that has led to the proposal that the prefrontal cortex plays a critical role in spatial working memory (see Diamond, 1990; Diamond & Doar, 1989; Diamond & Goldman-Rakic, 1989; Diamond, Zola-Morgan, & Squire, 1989). Similarly, Bachevalier (with respect to the monkey) and Nelson (with respect to the human) have utilized a set of tools (e.g., visual paired comparison; the "oddball" paradigm using Event-Related Potentials) that have resulted in the proposal that the medial temporal lobe structures that support some forms of explicit memory develop in the first year of life (see Bachevalier, 1992; Bachevalier, Brickson, & Hagger, 1993; Bachevalier, Hagger, & Mishkin, 1991; Nelson, 1994, 1995, 1996, 1997).

There are four noteworthy advantages to the use of neuropsychological tools. First, they are completely noninvasive. Second, they can be used across the lifespan. Third, parallel studies can be conducted across species (such as the human and the monkey). Finally, they can provide insight into specific behaviors (e.g., the limits of working memory). Alas, there are also a number of shortcomings to this approach that must be acknowledged. First, these tools only indirectly couple brain structure and function, and thus may lack precision with regard to this relation. Second, when adopting such tools from the animal literature, it is important to consider whether both humans and nonhumans are responding to the tasks in the same way (of course, this problem can also apply within species, when, for example, adults are compared to infants). Third, caution must be exercised when generalizing from clinical to normative samples. Finally, when used with the lesion method (i.e., the population under study suffers from some discrete neural insult), it is important to be aware that the mapping of specific lesion to specific function may not be one to one (e.g., How does one know that

it is a lesion of the hippocampus proper that results in poorer performance on a given task rather than the surrounding rhinal cortex that is often damaged when lesioning the hippocampus?).

Collectively, neuropsychological tools have contributed a great deal to understanding brain function, although they do possess certain limitations. As will be clear in the following sections, this criticism is not unique to neuropsychology; rather, each tool that we discuss has its own unique set of limitations.

Metabolic Procedures

Positron Emission Tomography. Procedures such as Positron Emission Tomography and functional Magnetic Resonance Imaging typically involve the coupling of some element of metabolism (e.g., changes in blood oxygenation levels, the uptake of glucose) with ongoing cognitive activity. The first metabolic tool we will discuss is Positron Emission Tomography (PET). This procedure typically involves the injection of a radioactive substance such as oxygen or glucose. Such substances are fuels for the brain, and thus whatever region of the brain is performing a particular function will require more fuel. As the radioactive substance decays, positrons are emitted. A positron detector can analyze these emissions and then reconstruct their point of origin. As a result, PET is able to localize where in the brain activity is taking place.

Using radioactive glucose, Chugani and colleagues have conducted an extensive series of studies with infants and children that has shed light on the development of brain metabolism and, by inference, the development of synapses (i.e., synapse formation requires energy, and thus glucose can be used as an indirect marker for synaptogenesis; see Chugani, 1994; Chugani & Phelps, 1986; Chugani, Phelps, & Mazziotta, 1987). There are a number of significant shortcomings with PET that must be acknowledged, however. First, although the levels of radioactivity used in this work have declined over the past 10 years, ethical constraints prevent large samples of normally developing children from being evaluated. Second, the spatial resolution of PET is typically confined to relatively large voxels (cubic centimeters of tissue), and thus it is difficult to pinpoint the locus of neural activity much beyond the centimeter range. Third, the temporal resolution of PET is on the order of minutes, and thus little useful information can be obtained about *when* brain activity is taking place. Finally, because a cyclotron is required to make the radioactive agents, PET studies are an expensive endeavor.

Functional Magnetic Resonance Imaging. Functional Magnetic Resonance Imaging (fMRI) is one of the most rapidly growing methods by which it is possible to image the living brain. The technique is based on the principle that deoxygenated hemoglobin is paramagnetic (paramagnetism refers to the ability of a normally nonmagnetic material to become magnetic), and thus can be detected using conventional magnetic resonance technology (for tutorial, see Brown & Semelka, 1995). When a particular brain region is called upon to perform some task (e.g., attend to a visual stimulus or move a finger), that region receives increased blood flow and, as a by-product, increased oxygen. Subtle increases and decreases in oxygen are then tracked on a moment-by-moment basis. The MRI scanner, by taking consecutive slices of the brain in various orientations, is able to reconstruct where in the brain the greatest areas of activation occur. By comparing activation patterns under task versus no-task (e.g., control) conditions, it is possible to tease apart those brain regions that are selectively active from those that are not, given whatever it is the individual is doing at a particular point in time. The procedure is noninvasive, does not require exposure to ionizing radiation, and can be performed in a relatively short period of time. Importantly, the spatial resolution of fMRI is comparable to conventional MRI, and thus can provide detailed anatomic images along the lines of a few millimeters. An example of both structural and functional MRI scans is provided in Figure 1.

The use of fMRI has already shed light on a number of fundamental problems of sensation, perception, and cognition. For example, the human visual system has now been mapped in detail (e.g., Belliveau et al., 1991; Sereno et al., 1995), essentially confirming the long-held suspicion that the human visual cortex bears remarkable resemblance to that of the monkey. Cohen and colleagues (e.g., Cohen et al., 1994) have described the neuroarchitecture of nonspatial working memory, elucidating the role of the middle and inferior frontal gyri, and extending previous nonhuman primate studies to the human. Ugurbil, Georgopoulos, and colleagues have demonstrated that portions of the cerebellum (i.e., dentate nucleus) may play an important role in learning and problem solving (Kim, Ugurbil, & Strick, 1994). Finally, this same group has revealed that, for left-handed individuals, the left and right motor cortices are activated when the left hand is used. This is in contrast to right-handed individuals, in whom the more commonly reported contralateral activation is observed (Kim et al., 1993). These findings are important in that they bring into question the popular view

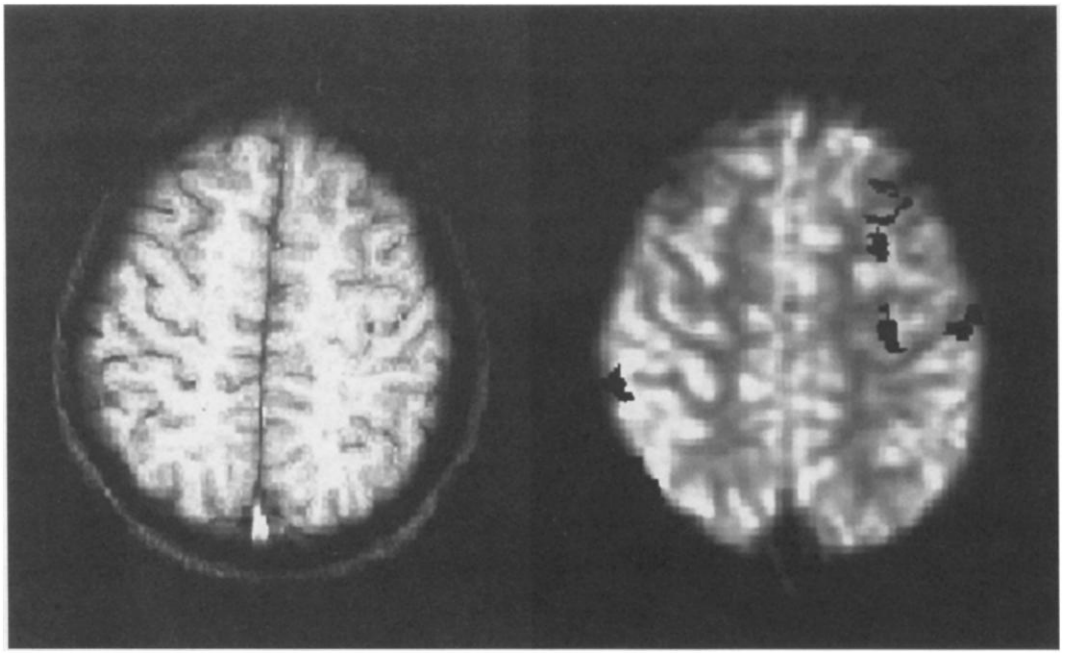

Figure 1 The image on the left side of the figure represents an anatomic (structural) view of the brain of a normal, healthy 10-year-old girl; the right side represents the functional image superimposed on the structural image. By "functional" we mean the areas of the brain that show activation (increases in oxygen consumption). Here we see regions of the motor strip (specifically the hand—see middle right portion of functional image) lighting up, as well as areas of the prefrontal cortex (see upper right portion of functional image). The former is activated because the child was pushing a button during the task, whereas the latter was activated because the task involved spatial working memory, a higher cognitive function involving the prefrontal cortex.

in neurology that each side of the body is controlled by the contralateral hemisphere *for both left- and right-handed individuals.* They also open the door to examining other differences in asymmetrical cerebral organization between left- and right-handed people.

Collectively, tremendous insight has been gained into the relation between brain structure and function using fMRI in the adult. The superb spatial resolution, coupled with its noninvasive nature, would seemingly make this method suitable to the study of children. Indeed, Casey and colleagues (e.g., Casey et al., 1995), as well as Truwit et al. (1996), have explored the use of fMRI in normally developing children as young as 6 years. For example, Casey et al. revealed that in 9- to 11-year-old children, the middle and inferior frontal gyri are activated in a task of nonspatial working memory, the same pattern as observed in adults (Cohen et al., 1994). In collaboration with this group, we (Truwit et al., 1996) have observed activation of areas of the prefrontal cortex in a task of spatial working memory in 8- to 10-year-old children (see Figure 1), a finding consistent with the nonhuman primate literature.

Admittedly stringent requirements are placed on participants tested in a fMRI study. They must, for example, sit very still so as to keep motion artifacts to a minimum. In addition, they must be able to tolerate a somewhat high (e.g., 90 dB) level of noise (although participants use ear plugs) and a confining environment. However, experience thus far suggests that children over the age of 7 to 8 years are remarkably tolerant of these constraints (more so than adults) and are remarkably easy to test (see Figure 2). We therefore expect that this procedure will become more widespread in the coming years.

In summary, both PET and, in particular, fMRI lend themselves to the study of developing brain function. Unfortunately, neither PET nor fMRI provides much useful information about the chronometry of mental events. If we wish to examine this dimension of mentation (i.e., *when* thinking is occurring versus *where* it is occurring), we must turn to a different class of procedures.

Electrophysiologic Procedures

Electroencephalogram. Whereas metabolic procedures reflect the fuel (e.g., oxygen, glucose) requirements of neural activity, electrophysiological procedures reflect the by-product of synaptic activity. Here the goal is to link this electrical activity with ongoing mentation or emotion (e.g., During a particular cog-

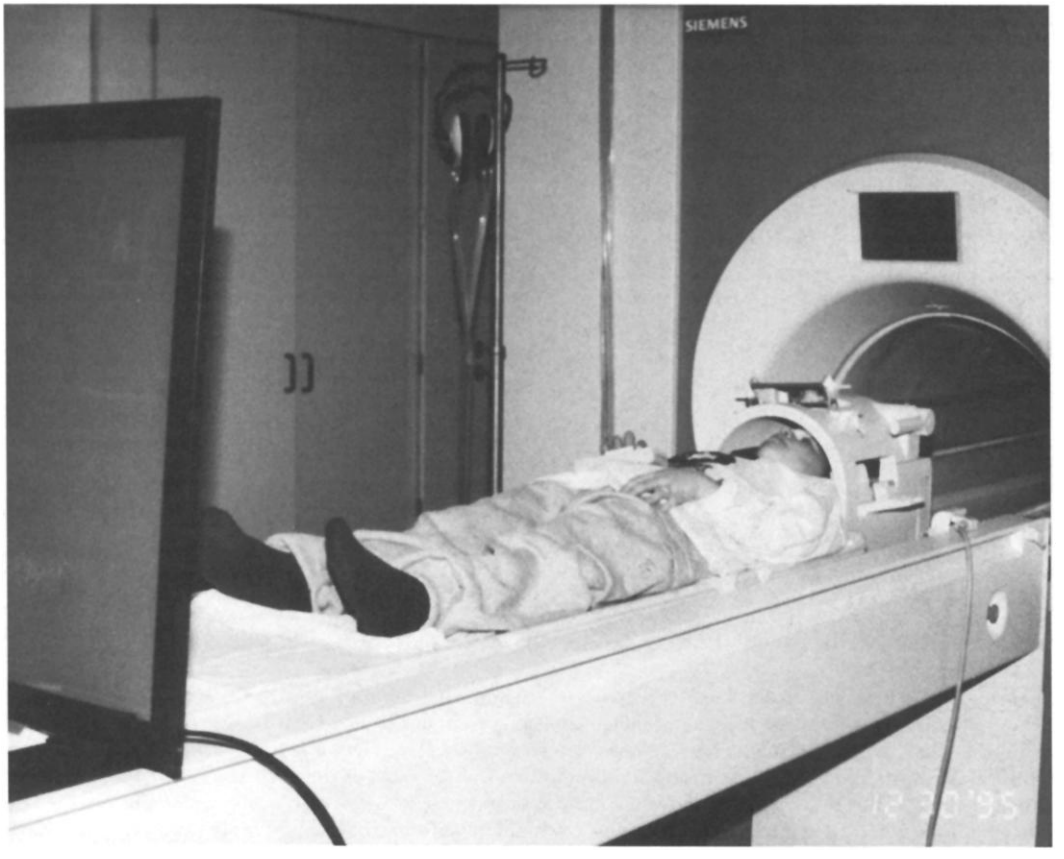

Figure 2 A 10-year-old normal, healthy child about to be tested in a study of working memory involving functional Magnetic Resonance Imaging (fMRI). An overhead projector (not seen) projects visual images onto a screen at the foot of the table. A mirror directly above the child's head allows these images to be seen by the child. The child has a button box (containing nonmagnetic material) in his hand and, during the study (when the child will be in the scanner itself), will push buttons that correspond to task demands (e.g., push a button that corresponds to a position of a light on the screen).

nitive task, in which region of the brain is most synaptic activity taking place, and on what time frame?). The two most widely used electrophysiological methods include the recording of the electroencephalogram (EEG) and the event-related potential (ERP). Because these methods have been fruitfully employed for a number of years in the study of both cognitive and emotional development, only a cursory review will be provided.

The EEG reflects the background electrical activity that is a by-product of neuronal communication. It is generated throughout the brain, can be recorded from electrodes placed on the scalp surface, and is ideally suited to study behaviors that are distributed in time, such as the experience and expression of emotion. For example, Fox (e.g., 1991) has demonstrated that individual differences in left versus right frontal EEG activation map onto individual differences in emotionality (e.g., fearful or inhibited children show greater relative right than left activation). Similarly, Dawson and colleagues (e.g., Dawson, Klinger, Panagiotides, Hill, & Speiker, 1992) reported that infants born to depressed mothers show greater relative right versus left EEG activation, raising the possibility of predicting which individuals are predisposed to internalizing disorders such as depression.

The EEG procedure is noninvasive and relatively inexpensive. It is very sensitive to state changes, and perhaps underlying changes in emotionality, and thus lends itself to the study of social and emotional development. However, because the EEG has relatively poor temporal resolution (because events are not time-locked to discretely presented stimuli) and poor spatial resolution, it is not particularly suited to the study of cognitive processes. However, a close relative of the EEG is the ERP, which does lend itself to the study of cognition.

Event-Related Potentials. Like the EEG, the ERP is recorded by attaching electrodes to the scalp, and the

electrical activity detected by these electrodes is amplified, filtered, and recorded (for tutorial, see Coles & Rugg, 1995). One key difference between these methods, however, is that the ERP is time-locked to some discretely presented event (e.g., a briefly flashed visual stimulus), and thus provides superb temporal resolution (e.g., it resolves time on the order of milliseconds). In addition, because of the ease with which ERPs can be recorded (e.g., hundreds of trials can be presented in a matter of minutes, and the participant need not be required to respond verbally or motorically), this method has proven extremely useful in examining a number of cognitive abilities in infancy (for review, see Nelson, 1994, 1996) as well as later in childhood (for review, see Friedman, 1991). For example, different components of the ERP have been used to examine attention (e.g., N200), memory (e.g., P300), and language comprehension (e.g., N400) in the adult (for review, see Rugg & Coles, 1995), as well as in the infant. (Figure 3 illustrates several components of the infant ERP that are thought to reflect different aspects of attention and memory.) The ERP has also been used increasingly in clinical contexts, such as in the study of autism, dyslexia, and language disorders (for review, see Nelson & Luciana, in press). For example, Kraus et al. (1996) have used a component of the ERP—the Match-Mismatch Negativity (MMn)—to examine the proposition that difficulty in segmenting the speech train may underlie some forms of language-learning impairments (LLIs). The MMn response is thought to reflect an auditory attentional mechanism mediated by auditory thalamocortical pathways. The authors reported that the amplitude of the MMn was smaller in those children showing the greatest degree of impairment in discriminating rapid speech contrasts (e.g., /da/ versus /ga/). This observation is consistent with the proposition that the neurophysiological basis of certain LLIs lies within regions of the auditory thalamocortical pathway (for elaboration of this point, see subsequent discussion of work by Tallal).

Overall, the ERP has yielded valuable information

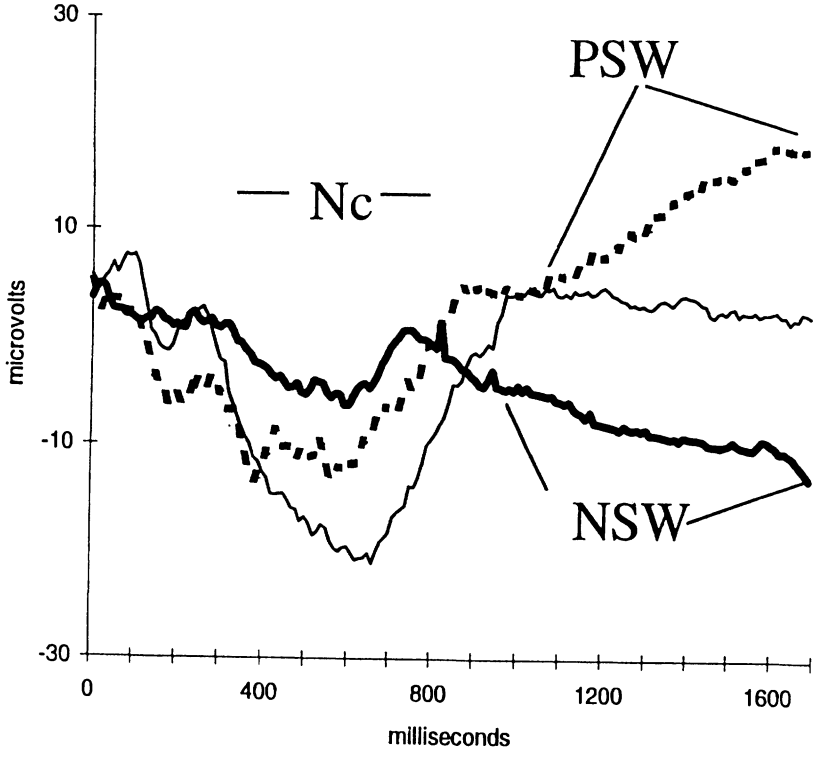

Figure 3 The major components that have been observed in the infant event-related potential (ERP) waveform. The negative component thought to reflect an obligatory aspect of attention can be seen most clearly in the thin, solid line, peaking between 400 and 800 ms after stimulus onset. As depicted by this same curve (thin, solid line), this negative peak resolves to baseline. This baseline response is thought to reflect the process underlying fully encoding a stimulus. In contrast, if the stimulus is partially encoded into memory, but must be updated, the negative peak shifts positive, and becomes a positive slow wave (illustrated by the dashed line). Finally, if the infant attends to the stimulus (determined by observer ratings), but merely detects its presence against a background of recurring other events, the negative peak shifts further negative, manifesting itself in a negative slow wave (thick, solid line). (From Nelson, 1996, Figure 3; reprinted with permission.)

about cognitive development. Although conventional ERP recordings made with a (relatively) small number of electrodes (e.g., 8–16) can only approximate where in the brain events are taking place, new methods are being developed that permit much greater scalp coverage, perhaps by using as many as 128 electrodes. This advance will prove critical to improving the spatial resolution of both ERPs and EEG, as there is a strong correlation between the density of electrodes placed on the scalp and the identification of the neural dipoles generating the scalp-recorded responses. A problem that remains to be resolved concerns the relatively high rate of obtaining artifactual data due to muscle or eye movement (which in turn results in the loss of individual trials or, in some instances, entire cases).

Magnetic Procedures

Magnetic Source Imaging. The EEG and ERP methods reflect the electrical activity associated with some brain process. In contrast, the key principle of magnetic recording arises from the small magnetic fields developed with every bioelectric signal that a neuron generates. According to the rules of physics, the magnetic field develops at right angles to the flow of bioelectric signals. Given that the major sources of axial currents in the human cortex are the apical and basal dendrites of the pyramidal neurons, neurons in the sulci of the brain would be expected to generate magnetic potentials that can be detected from the surface of the brain at those locations. Because the current generated by even 10,000 neurons is relatively weak, accurate detection of the resulting magnetic fields requires a sensitive magnetometer and a test chamber that has a very high shield against the earth and any moving metal objects in the vicinity. High-gain magnetometers have been devised from Superconducting QUantum Interference Devices (so called SQUIDs) that operate while chilled in liquid helium. Magnetic Encephalography (MEG) localizations of the centers of functional activity (sensory and motor activity have been especially useful) can be modeled as single equivalent current dipoles. Those localizations can now be combined with MRI to provide the combination of structure and function known as Magnetic Source Imaging.

Magnetic Source Imaging, or MSI, is a new technology that has both temporal and spatial resolution adequate to detect neuronal activation and to detect the bioelectric consequences of neuronal activity. For certain types of phasic neuronal responses, MSI can resolve time on the order of milliseconds and resolve space along the lines of millimeters. With the development of large-array magnetic detector systems that can completely monitor the entire cortical surface (e.g., 70–100 detector arrays), and the development of software that integrates the magnetic recordings with the participant's own magnetic resonance image, researchers have been able to apply the technology to large-scale clinical and normative samples.

Like ERPs, MSI is completely noninvasive. When large arrays of detectors are used, it is also possible to map out relatively expansive regions of the cortex in brief amounts of time. However, because MEG/MSI is limited to localizing dipoles near the surface of the brain, it is less useful for imaging deeper structures such as those that might be involved in emotion (e.g., the amygdala) or some aspects of cognition (e.g., rhinal cortex). There have been no large scalp studies done using MEG/MSI with children.

Implications and Future Directions

It could be argued that what will drive our ability to understand the neural basis of human behavior will be improvements in the methods of imaging the living brain. Such improvements may have a secondary benefit beyond linking behavior with biology; the methods of neuroimaging may also make it possible to make more accurate diagnoses and to determine the efficacy of a given treatment. Regarding the latter, it has recently been demonstrated that both a behavioral treatment for obsessive-compulsive disorder and a pharmacological treatment yielded identical behavioral outcomes; as importantly, PET revealed that the changes that occurred in the brain under both treatment conditions were also identical (Baxter et al., 1992; Schwartz, Stoessel, Baxter, Martin, & Phelps, 1996). The use of PET as an outcome measure permitted the investigators to determine that both treatments were not only efficacious, but that the neural mechanisms mediating such changes were likely similar in both cases.

A second area of potential future application will be to examine the validity of various theories of behavior. For example, much has been written about the concepts of infantile amnesia and so-called repressed memories. Examining the neural basis of such phenomena would surely help to address (1) the underlying mechanisms of early amnesia and (2) whether memory repression legitimately exists. With regard to repressed memories, for example, Schacter and colleagues have recently demonstrated (through PET) that the brain encodes false memories (i.e., memory for information that did not really exist) differently than true memories (for discussion, see Schacter, Koutstaal, & Norman, 1996). Although it

would be unlikely for tools such as PET or fMRI to examine the memories themselves (memory, after all, is a behavioral phenomenon), the technology can be used to examine how the brain forms memories and how it retains and retrieves information.

Having described how the living, developing brain can be studied, it would now be useful to take a step back and describe the events that actually result in the formation of the human brain. We begin our discussion at the molecular level by describing the genes and gene products involved in brain development. Because even these early molecular events can to some degree be altered by a variety of intrinsic and extrinsic factors, this section lays the groundwork for the expanded discussion of neural plasticity that will follow. Here we focus specifically on the malleability of the brain across the lifespan. Our goal is to make clear that experience plays a critical role in shaping many aspects of brain development; moreover, experience can also alter the structure and function of the "mature" brain.

DEVELOPMENT AND NEURAL PLASTICITY

Molecular Biology of Brain Development

The tools reviewed in the previous section have in many respects revolutionized our ability to examine both the structure and function of the developing brain. Equally impressive have been the advances in our understanding of the series of molecular and cellular events by which the embryonic sheet of rapidly dividing cells is transformed into a fully formed and properly constructed brain. Indeed, the processes by which these events unfold is recognized as one of the most complex phenomena of biology, perhaps as extraordinary as the brain's production of the higher-order mental processes we attribute willingly to human beings. Yet for decades it has been recognized that all vertebrates share the basic macromorphological steps by which the primitive brain emerges: Neuroepithelium forms a primitive neural tube that quickly folds into the intact central nervous system, with the five upper vesicles that become the forebrain (with telencephalon and diencephalon), midbrain, and hindbrain (with medulla and cerebellum). These vesicles are illustrated in Figure 4.

Although these phenomena could be readily observed and experimentally manipulated in chick and amphibian embryos, the nature of the genes and gene products involved in brain ontogeny seemed beyond the reach of scientific discovery until recently. In the past decade, this situation has yielded to powerful new methods devised to detect and chemically identify the genes and gene products involved in many aspects of brain development. Furthermore, equally powerful means have appeared to identify the microscopic steps of neural development, with highly sensitive tools for defining (1) the time and location of a neuron's final cell divisions, (2) the migration of such cells to their final location within the developing neuroaxis, and (3) the selection of the major targets for its efferent connections. These techniques have now combined to achieve an exciting glimpse into nervous system development. These events are no longer depicted in terms of macroscopic phases, but rather in terms of key sequences of expressions of specific genes and the elicitation of subsequent series of genes and their products.

To illustrate the rules that govern the development of the human nervous system, we draw on research using very small invertebrate embryos such as those of the fruit fly *drosophila* and the flatworm *C. elegans*. (Despite dramatic differences in complexity between humans and invertebrates, the rules we describe appear to be the same across species.) From such research it appears that the development of major body components is under the control of a series of master genes, the *homeotic* genes. The representation of these genes along the chromosomal units of the genome aligns precisely to the linear sequences of the components whose development they control. Manipulation of these gene segments can thus convert limbs into wings or antennae, or abdominal segments into additional thoraces. The homeotic gene products are proteins that act to regulate the expression of other genes by binding to the DNA. These master genes lead to the expression of submaster genes, then to the expression of genes that specify which cells and supporting structures are needed to make all of the cellular elements of, for example, an eye. A major advance in the field of developmental neurobiology emerged when it was recognized that families of homeotic genes have been very well conserved throughout evolution, such that, with significant expansions and duplications, the same general principles of gene action apply across mammalian development in relatively precise detail. For example, the master control gene for the drosophila eye, recognized through analysis of an eyeless fruit fly (see Halder, Callaerts, & Gehring, 1995a, 1995b), is so similar to the gene whose mutation leads to the *small eye* mouse that the mouse gene can be substituted for the fly gene. Moreover, both genes bear strong resemblance to the gene held to be responsible for the human birth defect *aniridia* (a defect in which the iris of the eye fails to develop).

As reviewed by McConnell (1995), the three major

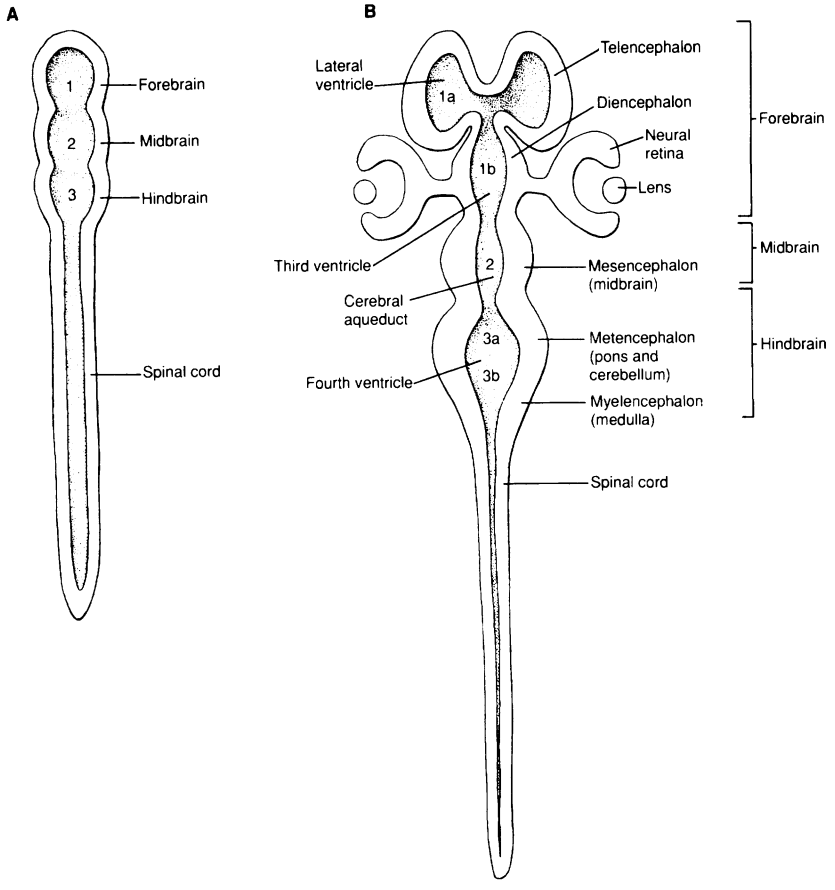

Figure 4 The neural tube is derived from the ectodermal (outer) layer of the embryo. From the sheet of epithelial cells that lines the ectoderm, a pear-shaped neural plate emerges. The neural plate gradually thickens and folds over onto itself. The rostral ("toward the head") end of the tube begins to close at about day 24 of gestation, followed by the caudal ("toward the tail") end 2 days later. The conversion of neural plate to neural tube is called "neurulation," and is the first external sign of the development of a bilaterally symmetrical craniocaudal axis. Early in this stage of development, the neural tube is composed of three vesicles (forebrain, midbrain, and hindbrain; see upper left panel, *A*). With greater differentiation, the forebrain gives rise to two additional vesicles (telencephalon and diencephalon; see upper right panel, *B*). The former will become the cortex and cerebral hemispheres, and the latter will become the thalamus and hypothalamus. (From Kandel, Schwartz, & Jessell, 1991, Figure 21-2; reprinted with permission.)

steps to vertebrate nervous system development—induction of the neural tube, cell proliferation and migration, and cell differentiation—are now profiting from the application of these and other technological refinements. For example, from such tools it is now known that the growth factor known as "transforming growth factor beta" acts on stable cells and transforms them into dividing, undifferentiated cells that must be bound to each other to have activity. In addition, an area of particularly intense activity in vertebrate nervous system development is the cerebral cortex. More than 20 years ago, Rakic was able to identify the fundamental principle that the cortex forms itself "inside-out" (see Figure 5). Through a series of studies, Rakic (1971, 1972, 1974) demonstrated that the earliest differentiating neurons to leave the proliferative zones surrounding the primitive ventricular system take up permanent locations in the deepest layers of cortex. The later differentiating neurons and macroglia, on the other hand, pursue final locations at progressively more superficial cortical layers. More recent advances have now identified the early gene markers that specify cortical versus subcortical regions, as well as the specific genes that define the earliest neurons to emerge from the proliferative zones.

The cellular-biological tools that permit the observation of axonal outgrowth have also allowed insight into the manner by which fibers that innervate the cortex define their target neurons. Within at least specific sensory systems, such selections depend on intracortical events and on a class of neurons (the sub-

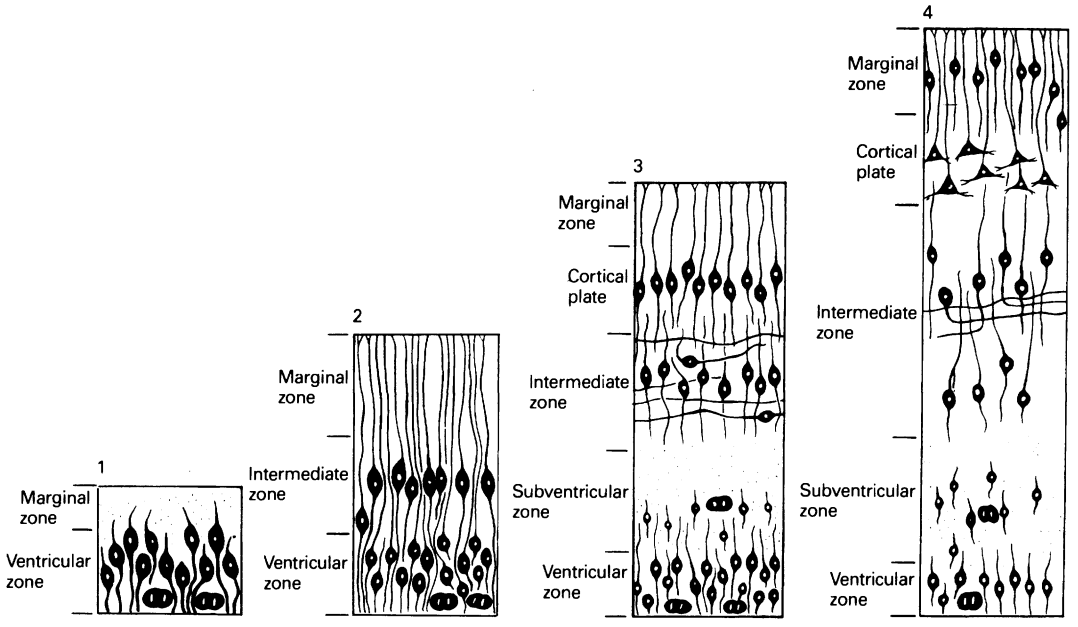

Figure 5 This figure illustrates the inside-out pattern of development that occurs with the formation of the cerebral cortex (the cerebellum, in contrast, forms in an outside-in pattern, although similar molecular principles apply). At the earliest stage of development (see frame 1), a simple epithelium is present, in which the *ventricular zone* contains the cell bodies (soma) and the *marginal zone* contains only outer cell processes (i.e., axons, dendrites). When some of the cells withdraw from the mitotic cycle (after losing their capacity for synthesizing DNA), they form a second layer, the *intermediate zone* (see frame 2). In the forebrain (see Figure 1), the cells that pass through this zone aggregate to form the cortical plate, the region in which the various layers of the cerebral cortex will develop (see frame 3). The cortical cell layers develop in an inverted fashion, so that cells in the deeper layers of the cortex (e.g., layer VI) develop first. The cells in the superficial layers (those closest to the surface of the brain) must migrate past older cells to reach their final destination. At the latest stage (see frame 4), the original ventricular zone remains as the lining of the ventricles (from which is eventually produced cerebral spinal fluid), and the relatively cell-free region between this lining and the cortex becomes the subcortical white matter, through which myelinated nerve fibers enter and leave the cortex. The subventricular zone also represents a second proliferative region in which many glial cells are generated. (From Kandel & Schwartz, 1985, Figure 55-7; reprinted with permission.)

cortical plate neurons) that appear relatively early in cortical development and then basically disappear. If these evanescent neurons are experimentally destroyed, or if the incoming sensory fibers fail to evoke functional responses from the intended targets, then appropriate connections are not established and cortical function (e.g., binocular vision) never achieves its potential.

Collectively, students of brain development can now view what once appeared to be a hopelessly complicated series of events as a definable, sequential, and functionally determined process. It is through this process that the brain assembles, refines, and matures, and in which the role of ongoing activity is a necessary element in shaping subsequent development of neural circuits.

The present momentum in developmental neurosciences points to two major applications that may be realistically envisioned. First, more precise specifications of growth factors and other gene products that regulate the complex chain of events underlying the brain's self-assembly may pave the way to understanding environmental factors (viruses, drugs, or atmospheric contaminants) that may cause congenital abnormalities. Second, more sophisticated knowledge of the rules and molecular signaling by which neurons form, strengthen, or eliminate synaptic connections could help scientists engineer ways for the brain to improve its capacity for self-repair.

Neural and Behavioral Plasticity

An unfortunate misconception of developmental neurobiology is that most aspects of brain development during the pre- and immediate postnatal periods reflect rigidly deterministic, genetic programs that are implemented at different points in time. In the preceding section, we made clear that this view is inappropriate for even the very earliest stages of brain development. In this section, we amplify this perspective by describing the critical role of experience in postnatal development. Moreover, we draw

on recent research in neural plasticity to point up the remarkable ability of even the adult brain to be modified by experience.

The view that many aspects of brain development depend on experience is best illustrated in the models of brain-environment interactions offered by Greenough and colleagues (for review, see Greenough & Black, 1992). These investigators have proposed two major mechanisms whereby new neural connections (synapses) are driven by experience. *Experience-expectant synaptogenesis* refers to processes by which synapses form after some minimal experience has been obtained. A good example is the development of stereoscopic depth perception. Normal visual input is necessary for ocular dominance columns to develop (the connections between each eye and layer IV of the visual cortex). If the muscles in one eye are weak, preventing the eye from aligning properly with the other in converging on a distant target, then the ocular dominance columns supporting normal stereoscopic depth perception will develop abnormally (or not at all). If this condition is not corrected by the time the absolute number of synapses begins to reach adult values (generally the end of the preschool or early elementary school period), the child will not develop normal stereoscopic vision. In contrast to this mechanism, *experience-dependent synaptogenesis* optimizes the child's adaptation to specific and possibly unique features of the environment. A good example is the information acquired by learning. Depending on a child's learning history, different information will be obtained and stored for use at a later time, giving rise to individual differences in knowledge base, memory skills, and so forth.

In general, Greenough has proposed that the structural substrate of "expectation" is the unpatterned, temporary overproduction of synapses dispersed within a relatively wide area of the brain during a sensitive period, with a subsequent pruning back of synapses that have not yet formed connections (or, presumably, that have formed abnormal connections; for an excellent tutorial on sensitive periods in general, see Bornstein, 1989). The expected experience produces patterned activity of neurons, presumably targeting those synapses that will be selected for preservation. The assumption is that synaptic contacts are initially transient and require some type of confirmation, perhaps by use, for their continued survival. If synapses are not confirmed or stabilized, they regress according to a developmental schedule or due to competition from confirmed synapses. Support for this model can be found in both human beings (e.g., Huttenlocher, 1994) and monkeys (e.g., Rakic et al., 1986), where it has been reported that the brain massively overproduces synapses early in life, only to be followed postnatally by selective elimination of these exuberant connections. Presumably, the purpose of overproducing synapses is to "prepare" the nervous system for experience by proliferation of connections on a sensory-system-wide basis. Experience-related neural activity can then select a functionally appropriate subset of the abundant synaptic connections. This period of excessive synaptogenesis is also correlated with a burst of brain metabolism and, at least in the monkey, with the onset of social interactions (after 3 months; see Jacobs et al., 1995, for discussion).

Neural Plasticity in the Developing Organism

Numerous demonstrations, in a variety of species, now show that positive or negative early life experiences can alter both the structure and function of the brain. For example, rats raised in enriched laboratory environments perform certain cognitive tasks better than rats raised in isolation (e.g., the former make fewer errors on tasks of spatial cognition). At the cellular level, some of the changes observed among rats raised in enriched environments include the following: (1) Several regions of the dorsal neocortex are heavier, thicker, and have more synapses per neuron; (2) synaptic connections improve; (3) dendritic spines and branching patterns increase in number and length; (4) the amount of glia (a second major class of brain cell, which generally provide support functions for neurons, and which outnumber neurons by a factor of 10 to 1) increases; and (5) there is increased capillary branching, thereby augmenting provisions of blood and oxygen (for examples, see Black, Sirevaag, Wallace, Savin, & Greenough, 1989; Greenough & Black, 1992; Greenough, Juraska, & Volkmar, 1979; Greenough, Madden, & Fleischmann, 1972). In the monkey, it is known that maternal exposure to loud sounds presented unpredictably during mid to late gestation results in offspring with neurobehavioral dysfunction (e.g., they are jittery) and neurochemical abnormalities (e.g., elevated levels of circulating catecholamines; see Schneider, 1992). In addition, monkeys raised from birth in social isolation manifest behavioral symptoms of emotional dysregulation (e.g., stereotypies) and neuroanatomical abnormalities of brain regions that contribute to emotional and/or cognitive behavior (e.g., portions of the hippocampal formation are deficient in numbers of certain neurons; see Ginsberg, Hof, McKinney, & Morrison, 1993a, 1993b; Siegel et al., 1993). Similarly, rats raised in social isolation make more errors than socially raised rats in the initial phase of learning to

discriminate two stimuli (i.e., conditioned discrimination response), although they reach a level of accurate performance that is comparable to that of socially raised rats. However, discrimination performance in isolates relative to peer-raised rats is less disrupted by manipulations of task requirements. (For a tutorial on the role of stress and cognitive function, see McEwen & Sapolsy, 1995.) Furthermore, rats raised in isolation exhibit neurochemical and behavioral abnormalities suggestive of hyperactivity in mesolimbic dopamine (DA) systems; isolation-raised animals are also initially hyperreactive to auditory startle probes. The deficit in sensorimotor gating exhibited by isolation-raised animals may be normalized by the administration of the DA antagonist, raclopride. This, in turn, suggests that isolation rearing may provide a nonpharmacological means of inducing in rats a sensorimotor gating deficit exhibited by schizophrenic humans, and that has been attributed to one of the key transmitter systems (i.e., dopamine) affected in schizophrenics (for elaboration of these points, see Geyer, Wilkinson, Humby, & Robbins, 1993; Jones, Hernandez, Kendall, Marsden, & Robbins, 1992; Jones, Marsden, & Robbins, 1990, 1991; Phillips, Howes, Whitelaw, Robbins, & Everitt, 1994; Phillips, Howes, Whitelaw, Wilkinson, Robbins, & Everitt, 1994). Finally, Levine and colleagues have demonstrated that brief maternal deprivation in the rat pup permanently alters the sensitivity of the hypothalamic pituitary axis (see Rots et al., 1995; Suchecki, Mozaffarian, Gross, Rosenfeld, & Levine, 1993). Presumably, the modification of this axis results in long-term abnormalities in mediating stress responses. This hypothesis is currently being examined in humans, by studying children who have been removed from maternal care early in life and placed in orphanages (e.g., Earls, 1996).

Neural Plasticity in the Mature Organism

For many years it was assumed that large-scale neural reorganization following injury was limited to the infancy period, with only modest reorganization possible in the older child and adult. This assumption was based on the observation that greater sparing (preservation of function) was evident when neural injury occurred during the infancy period. For example, Merzenich and colleagues (e.g., Merzenich, 1983, 1984) demonstrated that the somatosensory cortex (the region of the cortex involved in the reception of tactile stimuli) of adult animals was capable of undergoing only modest (e.g., 1.0–2.0 mm^2) reorganization after manipulations of the peripheral nerves (i.e., the area of the brain that originally received input from one part of a limb could only expand slightly to occupy the neighboring region that occupied the adjacent region of the limb). This reorganization occurs within 2 months after injury. In follow-up studies, the limit of 1–2 mm^2 of cortical reorganization was confirmed (e.g., Calford & Tweedale, 1990), suggesting that the expansion was mediated by arborizations of axons from the thalamus to the cortex (i.e., thalamocortical axons) that cannot extend beyond approximately 1 mm. This limit is quite different in the infant animal, where rather massive reorganization has been observed (e.g., Sherman & Spear, 1982).

Within the past few years, this model of restricted adult neural plasticity has been reexamined. Precipitating this reexamination was the work of Pons and colleagues (Pons et al., 1991), who reported on a group of cynomolgus monkeys that 12 years earlier had received deafferentations of an upper limb (i.e., the afferent fibers connecting the limb to somatosensory cortex had been severed, resulting in the animal having no sensation from that limb). After an experimental perturbation of unanticipated length due to continued legal interventions (these animals became known as the "Silver Spring Monkeys"), the investigators eventually examined the response of the brain to the loss of limb sensations. Neuronal responses were elicited from area SI, the region of somatosensory cortex that would normally correspond to the deafferented portion of the limb, including the fingers, palm, and adjacent areas. Surprisingly, this region of the brain now responded to stimulation in an area of the face. Not coincidentally, this region of facial sensation would normally border the cortical region innervated by the deafferented limb. For the face now to occupy the region previously represented by the limb suggested a reorganization of somatosensory cortex along the lines of 10–14 mm.

This report, and others that followed (see Pons, 1995, for discussion), was impressive in demonstrating that large-scale cortical reorganization can occur following injury even in the mature primate. Equally impressive were subsequent reports of comparable findings in the adult human. For example, based on the monkey studies, Ramachandran, Rogers-Ramachandran, and Stewart (1992) reasoned that an individual who had experienced a limb amputation (e.g., of a forearm) should show sensitivity on the area of the body represented by the area of the brain adjacent to the amputated limb. To test this prediction, Ramachandran began examining adults who had experienced various forms of amputation. In one such patient, the left arm was amputated several centimeters above the elbow. This individual, similar to others in his situation, experienced sensation in the

limb that had, in fact, been amputated (i.e., "phantom limb phenomenon"). Ramachandran also examined this patient's sensitivity to tactile stimulation along the regions of the face known to innervate the somatosensory cortex adjacent to the area previously innervated by the missing limb. When this region of the face was lightly stimulated, the patient reported sensation in both the face and the missing limb. By carefully mapping out the stimulated area, Ramachandran was able to determine the degree to which the cortical surface had been reorganized to subsume the area previously occupied by the missing limb. This report was subsequently replicated in other patients (for discussion, see Ramachandran, 1995) and by other groups (e.g., Flor et al., 1995).

One limitation of the Ramachandran studies is that the index of cortical reorganization reported by the investigators was indirect; that is, changes at the neural level were not observed directly, but rather were inferred from overt behavior. However, recent work using MEG in combination with MSI (see previous discussion) has confirmed Ramachandran's interpretation of the findings. Separate groups of investigators have now mapped the somatosensory cortex in normal, intact individuals using MEG (e.g., Yang, Gallen, Schwartz, & Bloom, 1993; Yang, Gallen, Schwartz, et al., 1994; Yang, Gallen, Ramachandran, et al., 1994) and in adult human amputees (e.g., Elbert et al., 1994). These observations confirm that the region of the brain previously representing the missing limb expands to subsume the area adjacent to the limb, such as the cheek in the case of forearm amputation.

In summary, there is now strong evidence for cortical reorganization following peripheral nervous system injury in the adult human. One question that must be addressed is whether similar reorganization can be observed in nonadverse situations. In other words, might there be something unique about the brain's organizational response to injury (e.g., diminished neuronal activity) that differs from its response to normal experience? This question has recently been addressed by examining normal adults with and without specific, selective experiences. The model tested by these investigations was conceptually similar to that already described in the case of limb injury: Specifically, would an individual with extensive motor experience involving the hand show a different pattern of cortical organization and activity compared to (1) the other hand and (2) individuals not having this experience?

In a study reported by Elbert, Pantev, Wienbruch, Rockstroh, and Taub (1995), the somatosensory cortex of adults with and without experience playing a stringed instrument (e.g., violin) was mapped using MEG. Consistent with reports of monkeys and adult human amputees, the investigators reported that the area of the somatosensory cortex representing the fingers of the left hand (the hand used on the fingerboard) was larger than that in the contralateral hemisphere (i.e., the area representing the right hand, which was used to bow) and larger than the corresponding area in nonmusicians. Although the sample size was small, there was a trend toward the effect to be larger (i.e., greater cortical representation) in individuals who had begun musical training before the age of 10. Whether this was an effect of age (i.e., a sensitive period) and/or extensive experience could not be ascertained.

This work suggests that the brain of the adult human can reorganize in response to positive experiences in the environment as well as to negative ones (e.g., injury). To extend this finding to the nonmotor and nonsensory domain, consider a recent study on cortical reorganization in the language domain following training. Tallal and colleagues (Tallal et al., 1996) have speculated that children with language-learning impairments (LLI) have difficulty in segmenting phonetic elements embedded in ongoing speech, particularly when these elements are presented rapidly. This deficit results in difficulty discriminating speech sounds, which may lie at the heart of the LLI. In earlier work, Tallal reported that children's performance could be improved if the rate of change in phonetic transitions was slowed (e.g., Tallal & Piercy, 1973). Tallal and colleagues (Tallal et al., 1996) and Merzenich and colleagues (Merzenich et al., 1996) later reported that when LLI children were given 4 weeks of intensive training in speech processing, significant improvements (e.g., a gain of 2 years) in both speech discrimination and language comprehension were noted. In one study, these gains were reported to persist 6 weeks beyond the training period (Tallal et al., 1996). Although direct examination of the structural or physiological changes in the brains of the study children was not performed (previous studies have documented baseline anatomical differences in the brains of LLI and normal children; see Jernigan, Hesselink, Sowell, & Tallal, 1991), presumably such changes were responsible for the improved performance. Indeed, in earlier studies, Merzenich and colleagues have reported that adult monkeys markedly improve performance in making fine temporal or spectral discriminations following intensive behavioral training, and that these changes are accompanied by electrophysiological alterations

in the cortex (e.g., Merzenich & Jenkins, 1994, 1995; Recanzone, Merzenich, & Jenkins, 1992; Recanzone, Merzenich, & Schreiner, 1992).

Collectively, then, it appears that reorganization of cortical pathways is possible in both the older child and adult brain. Although initial reports suggested that such changes were limited to motor or sensory pathways, more recent work suggests that cognitive systems (e.g., language) can also be affected. In this context it may be useful to question the simplistic view that the brain becomes unbendable and increasingly difficult to modify beyond the first few years of life. Although clearly much of brain development occurs late in gestation through the first years of postnatal life, the brain is far from set in its trajectory, even at the completion of adolescence. There is now strong evidence that at least some regions of the brain under some conditions are able to incorporate the structure of experience into the structure of the brain throughout much of the human lifespan.

Implications and Future Directions

Neural plasticity is clearly not confined to the infancy period. This is not to say, however, that there are not temporal constraints on plasticity. For example, it seems likely that there is limited modifiability to sensory systems once such systems have fully matured. In addition, the neuropathology that accompanies normal aging will likely limit the modifiability of neural circuits that are embedded in pathological tissue (e.g., the tangles that form in the hippocampal region due to amyloid protein deposits such as occur in Alzheimer's disease). However, the adult nervous system appears considerably more open to change than previously thought.

There are many important implications of the work on neural plasticity for the field of child development. We mention only two. First, these observations should be of particular interest to those conducting intervention studies (for elaboration, see Nelson, in press). The long- and short-term success or failure of any intervention for intellectual (e.g., Head Start) or psychotherapeutic (e.g., treatment of depression) purposes depends in part on the ability to modify the brain at the cellular, physiologic, and possibly microanatomic levels. Investigating the neural mechanisms that underlie an intervention is useful in its own right, but the methods that permit such investigation could ultimately be used as a "marker" variable to evaluate the intervention itself. A second implication concerns the development of the tens of thousands of infants who are born prematurely each year. In a 28-week preterm infant, for example, many important milestones of brain development (e.g., laying down of myelin and the formation of synapses) occur in postnatal rather than intrauterine life. Given the vast differences between the extrauterine and intrauterine environments, it would seem useful to examine how these different experiences result in different patterns of brain development.

CONCLUSIONS

In this article we selectively targeted areas of experimental and clinical neuroscience that have achieved dramatic progress in recent years and that have important implications for child development. Clearly we have neglected a number of important and relevant areas of knowledge, such as the questions surrounding events that contribute to cell fate, how migrating neurons identify the regions of the cortex to occupy, how neurotransmitter signaling and response mechanisms are determined, and how neuronal activity-dependent equilibria are established. We believe that closer alliances between studies of behavior and brain development are warranted, and that such collaborations could shed new and revealing light on the biological bases of behavior. In so doing, it may be possible to blend biological with behavioral views of development and thus achieve a synthetic view that illuminates the growth of the whole child.

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