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The Importance of Brain Development for Psychology

THIS BOOK BEGAN with a discussion of the psychological debate over the origins of knowledge. Central to that debate is the definition of the concept of innateness. Nativists define innate concepts as those that are acquired or available in the absence of learning. Recent constructivist accounts have attempted to define a level of innate representation that might plausibly emerge in the absence of input and rely entirely on organism-intrinsic factors. The difficulty with both of these accounts lies in the failure to provide a biologically feasible account of precisely what it means for something to be innate. One argument that has been voiced by some psychologists is that defining biological feasibility of an innate factor is the job of the biologist. Psychological models provide characterizations of sensory, motor, perceptual, cognitive, and social abilities, and although they assume that biological systems underpin behavior, the job of the psychologist is ultimately to explain behavior, not biology. It is true that the proper focus of the psychologist is psychology. However, the essential link between all behaviors and the biological systems that mediate and support them demands a more rigorous definition of the concept that is both central to psychological thought and inextricably rooted in biology. Psychology does not benefit from an impoverished or underspecified definition of what it means for something to be innate. The psychological concept of innateness might plausibly benefit from stronger and more fully articulated links to the biological systems that support it.

A central question raised in this book is, how do biologists think about the question of innateness, and can those ideas inform the

psychological debate? The biological concept of innateness is focused on questions of inheritance and on explaining both intergenerational constancy and variation. What is inherited is genetic material and the cellular mechanisms for making use of the information contained in the genes. Thus, from the beginning, the biological concept of inheritance, of innateness, involves a process, specifically, a process for translating and making use of the information contained in the genes. It is that process that drives all the subsequent development and functioning of the organism. The biological view of innateness also stresses the inseparability of inherited factors and experience acting in concert to direct the development of the organism. Thus it is ultimately a concept about the process of development itself.

This chapter will explore the biological perspective on innateness and development and will consider how these ideas may be important for psychologists. It will begin with a discussion of the historical roots of the biological concept of innateness, drawing largely from topics considered in Chapter 2 in the discussion of the emergence of the concept of the gene. Next, the chapter will attempt to place the recent, dramatic advances in our understanding of brain development—the content of much of this book—into the perspective of the biological view of innateness. From the early embryonic period through the postnatal period, development entails the complex interaction of intrinsic signaling cascades coupled with extrinsic signaling. In this chapter, examples taken from earlier chapters of the book will be used to elaborate specifically on the interactive nature of neural development and to illustrate how the basic processes that drive brain development exemplify the biological view of innateness.

Development can also be construed as a series of events and processes that unfold over time. The next sections of the chapter will consider the multiple ways in which the timing of the biological events that constitute brain development serves to constrain and direct development. Over time, the influence of any particular factor is variable such that, for example, a factor that has little effect on early development may play a critical role in shaping neural organization later in life, and vice versa. Thus a complete account of the factors that influence and contribute to brain development must consider the effects of both the timing and the sequence of developmental events. In the

postnatal period, the concept of the "critical period" has played an important role in thinking about the development of the sensory, perceptual, and conceptual systems. Critical or sensitive periods are temporally defined periods during which input from the environment is required to establish a particular behavior. Changing ideas about the nature and functions of critical or sensitive periods will be considered. The chapter concludes with a discussion of constancy and variability in brain development and how the model of brain development presented in this chapter can accommodate the essential demands of constancy during typical development and still allow for the degree of flexibility observed when the experience of the organism demands adaptation.

Biological Perspectives on the Concept of Innateness

As discussed in Chapter 2, the biological concept of innateness has historically been linked to questions about the intergenerational transmission of information, that is, inheritance. How is the intergenerational transfer of information explained, what is the source of variation, and how is the competition between the opposing pulls of constancy and variability reconciled in a single account of inheritance? The history of change in these central ideas is captured in the search for the material nature of inheritance, in the quest for what became known as the gene. That history contains the press to define a source of constancy by specifying the nature and location of particulate matter that carries intergenerational information, combined with the puzzle of variation. How is constancy ensured when variation is allowed? The key to the conundrum posed by these seemingly opposing forces lies in the modern ideas about gene expression.

Genes provide the material code for the development and functioning of all biological structures and processes, but the code is neither prescriptive nor singular. Gene expression is a process, and the triggers for expression of any given gene are external to the nucleotide sequences that make up the coded genetic material. Gene expression requires the interaction of multiple factors within the environment of the cell, and cellular environments are, in turn, influenced by factors external to the cell. The layers of environments extend from the molecular to the world outside the organism. Further, the interactive

influences are multidirectional. The expression of a gene initiates a cascade of events that influence and direct other processes that alter the organization or functions of the organism. Each change in the system influences other processes. In addition, the developmental and functional state of the organism at any given time constrains which factors can exert an influence. Thus sound originating in the external environment is unlikely to affect the migration of neurons, but maternal ingestion of particular drugs or alcohol during precise moments in development can interfere with migration and disrupt the laminar organization of the cortex. Similarly, a defective gene may impair development, but its effects are specific to those developmental processes that depend on the normal production of the particular proteins coded by the gene. In short, a first principle of the biological concept of inheritance is the inseparability of inherited and environmental factors. It is the orchestrated and constrained interaction of intrinsic and extrinsic factors—broadly construed—that defines and drives development.

The view of biological development as the product of the inseparable influences of inherited and environmental factors has been bolstered by recent work suggesting that environmental factors can be transmitted across generations. Work on epigenetic marking suggests that regional modification of the nuclear chromatin (via DNA methylation or histone acetylation) influences the level of specific gene expression. Modifications in the chromatin can be induced by dietary or other external environmental factors. Importantly, those externally induced modifications are transmissible to the offspring. Thus it is not just the DNA that is inherited, but also changes in the state of chromatin originating in the parent that are transmitted to the offspring. At an even more basic level, it is critical to remember that DNA is never transmitted in isolation. As Keller (2001) has emphasized, transmission of genetic material is always accompanied by transmission of the cellular machinery necessary for gene expression. What is inherited are both the genetic material and the cellular environment that gives the organism the capacity to transform the information in the coded nucleotide sequences into the active agents of biological development and function. Thus for every organism, the inseparability of inherited and environmental factors begins at conception.

Inseparability of Inherited and Environmental Factors

The processes that underlie and guide brain development provide a particularly rich example of the interplay of inherited and environmental factors. At each period of neural development, organism-intrinsic factors interact with environmental cues to shape the increasingly complex and elaborate structures and functions of the brain. During the embryonic period, the interactive processes play out largely at the level of cell-cell interactions where one population of cells generates molecular signals that alter the developmental course of another population of cells. However, even during this earliest period, interactions involving factors in the external environment also play essential roles in the development of the embryonic brain. During the fetal and postnatal periods, organism-intrinsic factors continue to play a critical role in development, but during this extended period a wide array of factors in the external world play increasingly prominent roles in shaping and directing the course of brain development.

Embryonic Brain Development

The embryonic period is a time of rapid and dramatic change. In a matter of a few weeks, the embryo acquires the cell lines necessary to generate all the organ systems of the body; it undergoes rapid growth and develops its characteristic shape. Even during this very early period, interactive processes are essential for directing the developmental course of the organism. Within the developing nervous system, the neural progenitor cell line is specified during gastrulation. As discussed in Chapter 3, the fate of particular progenitor cells is the product of complex molecular signaling cascades that occur along well-defined spatial and temporal trajectories. Many of the cues that signal the fate of particular cells are organism intrinsic, but they reflect interactive processes occurring both within cells and, most important, among cells. The migrating cells of the organizer, for example, send out molecular signals that block the production of a specific protein (BMP4) as they pass through particular regions of the developing embryo. Those signals are critical for the normal differentiation of the ectodermal cells that overlie the migratory pathway of the organizer cells. Absent the signaling from the organizer cells, the particular small population of ectodermal cells located along the midline of the

embryo would fail to differentiate into neural progenitor cells, and the entire process of neural development would be interrupted. Thus it is the interaction among cells that directs the early development of this critical cell population. But the early development of the neural progenitor cell line is even more complex in that the particular fate of an individual neural progenitor cell reflects its spatial position within the embryonic nervous system. For example, some neural progenitors produce cells specific to anterior brain regions, while others produce cells that will form the hindbrain and the spinal column. The cues for anterior-posterior neural-fate specification come from regionally specific signaling cascades arising from the mesendodermal organizer cells that underlie the newly specified neural progenitor cell population. Thus whether a particular neural progenitor produces cells appropriate for the forebrain or the hindbrain is determined by the signals it receives from other nonneural cells in the local embryonic environment.

The role of interactive cell-cell signaling in early brain development is further illustrated by the morphogenic signaling cascades that give rise to different cell types. During morphogenic signaling, concentration gradients of one or more secreted molecules determine the fate of particular cells within the gradient distribution. Within the developing spinal column, for example (see Chapter 5), the genes *SHH* and members of the *TGFB* superfamily (e.g., *BMP4, BMP7*) are expressed in opposing ventral-dorsal and dorsal-ventral gradients, respectively. SHH is produced by cells of the notochord and the floor plate that are located in the most ventral region of the spinal cord, while TGFBs are produced by roof-plate cells in the most dorsal regions. The interaction of these two diffusing gradients induces the expression of different transcription factors in cells at different levels of the neural tube. The specific transcription factor expressed at a given level, in turn, activates cell-intrinsic programs that cause the local neuron populations to adopt specific cell fates. Within ventral regions, different concentration gradients give rise to a range of different motor-neuron populations, and within dorsal regions, specific classes of interneurons arise. Morphogenic signaling provides a dramatic example of the importance of the interaction among cells in the development of the central nervous system (CNS). Here the cell populations of the roof and floor plates produce opposing gradients

of secreted molecules that systematically alter the fate of a large number of spinal column neurons, thus creating the layered subpopulations of cells that define the dorsal-ventral organization of the spinal column.

Factors external to the organism also play an important role in the development of the embryonic brain. In some cases, the effects of environmental factors can be damaging to the developing embryo. For example, a wide range of substances that can be introduced into the embryo from the external world are known to have teratogenic effects on the developing brain. Alcohol, drugs, lead, and radiation are just a few of the many factors that have documented pathological effects on brain development. But the developing embryo also relies on factors derived from the external world for its development. The maternal system provides many factors that are essential for the normal development of the embryo. One clear example of the importance of an externally derived factor for typical brain development is retinoic acid (RA; see Chapter 5). RA is a substance that is critical for the normal development of the hindbrain, but it cannot be produced in animal cells. Rather, it is typically derived from vitamin A available from environmental sources. For the embryo, the availability of RA depends on maternal ingestion of vitamin A. The role of RA in hindbrain development involves control of *HOX* gene expression. *HOX* genes are an important and highly conserved family of genes that control the segmental organization of the hindbrain and the spinal column. They are expressed in a nested sequence along the rostral-caudal extent of the hindbrain and the spinal column. The expression of different subsets of *HOX* genes is confined to specific and highly localized regions (i.e., rhombomeres or spinal-cord segments), and this specific targeting of gene expression produces the characteristic segmental organization of the hindbrain and the spinal cord. Importantly, *HOX* gene expression is regulated by RA in a dose-dependent manner. Either too much or too little RA can disrupt the segmental organization of the posterior nervous system and compromise the viability of the embryo. The example of RA illustrates the range of interactive processes that are essential for embryonic development. Although organism-intrinsic factors are crucial, factors in the external environment are also essential for the normal development of the embryo.

Fetal Brain Development

Both the increasing complexity of interactions among cell populations and the influence of environmental factors in shaping and directing brain organization and function become more prominent during the later stages of development. Molecular signaling continues to play an important role, but the range of signaling within the developing nervous system expands to include a wider range of functions, such as those involved in mediation of neuronal migration, myelination, cell adhesion, and axonal guidance. Furthermore, neuronal activity becomes an important factor influencing processes such as apoptosis and synaptic stabilization that are essential for the establishment of the neural pathways and networks. The dynamic and interactive nature of later brain development is observed in a wide array of developmental processes. This section considers examples that illustrate both the increasing complexity in the range of cellular interaction and the growing prominence of environmental input.

During the embryonic period, interactions among cell populations played an important role in the differentiation of cell types. Furthermore, the specific patterns of regional interactions defined cell types that served to establish the initial spatial organization of the embryo along the anterior-posterior, dorsal-ventral, and right-left axes. Later in development, the range of cellular interactions becomes more varied. Although cellular differentiation continues to play a role (for example, in defining the different cell types that compose the different cortical layers), interactions among cell populations also serve other functions. The two examples that follow, illustrate the role of interactions between neurons and specific classes of cells whose signaling serves to regulate the organization of neuron populations.

First, Cajal-Retzius (C-R) cells are class of cells produced early that are involved in establishing the laminar organization of the neocortex (see Chapter 7). They are among the first cells to migrate to the newly developing cortical preplate, and they remain in the marginal zone (MZ) after the cortical plate splits the preplate into the separate MZ and subplate layers. C-R cells produce the protein reelin that provides a critical signal for neurons to stop migrating and take up their positions within the developing cortical plate.

The second example involves subplate neurons that play a critical early role in establishing the major sensory pathways, the thalamocor-

tical (TC) and corticothalamic (CT) pathways (see Chapter 8). In the mature brain, neurons from the thalamus project axons to the sensory input layer (layer 4) of the neocortex, forming the TC pathway; and cortical neurons project to the thalamus, forming the CT pathway. Early in development, before the arrival of thalamic axons to the cortex or cortical projections to the thalamus, subplate neurons establish connections with both layer 4 neurons and the thalamus. The role of these early, transient subplate connections appears to be to prepare the developing input layers of the cortex for future connections with the thalamus (Kostovic et al. 2002). Both C-R and subplate cells engage in neuronal signaling, but rather than inducing cellular differentiation in the target neuronal population, the signals produced by each of these cell populations affect aspects of the organization of neuronal populations.

C-R cells are critical for the laminar organization of the cortex, while subplate neurons act as pioneers in setting up the major sensory relay pathways. Importantly, both the C-R and the subplate cell populations are transient. Each is present early, plays an important and specific role in the development of the brain, and then dies off via apoptosis when the particular aspects of neural organization it directs are complete (Kostovic and Rakic 1990; Soriano and Del Rio 2005). The functions of both cell populations provide striking examples of the kinds of interactive processes that are essential for establishing fundamental aspects of neural organization.

Postnatal Brain Development

In the postnatal period, the role of experience in defining patterns of brain organization and connectivity becomes more pronounced (see Chapter 9). Indeed, Greenough has described the early postnatal period as a time of experience-expectant learning, suggesting that the neurobehavioral system "expects" or depends upon certain kinds of input from the world to develop normally. These kinds of effects are clearly demonstrated in the seminal work of Hubel and Wiesel on the developing visual system (Hubel, Wiesel, and LeVay 1977; Wiesel and Hubel 1963a, 1963b, 1965). The mature primary visual cortex (PVC) is organized into ocular dominance columns that reflect the segregation of input from the two eyes. Monocular deprivation early in postnatal development alters this typical pattern of organization. PVC neurons

responsive to the nondeprived eye increase in number, while neurons responsive to the deprived eye decrease. The magnitude, duration, and permanence of these effects depend on the timing of deprivation onset, the duration of deprivation, and the postdeprivation interventions that are imposed. These findings suggest that during a period after birth, the specific visual experience of the organism significantly affects the emerging organization of the neural system that supports vision.

Studies examining the effects of early brain injury also support the idea that experience can affect brain organization. Goldman-Rakic's (Goldman 1974; Goldman and Galkin 1978; Goldman and Rosvold 1972; Goldman, Rosvold, and Mishkin 1970), Bachevalier and Mishkin's (1994), and Kolb's (Kolb 1987; Kolb and Elliott 1987; Kolb, Holmes, and Whishaw 1987; Kolb and Tomie 1988) studies of the effects of early circumscribed cortical injury on the development of memory and problem-solving abilities clearly demonstrate that, unlike the mature brain, the developing brain has the capacity to organize differently to support functions that would normally have been supported by injured brain areas (see Chapter 9). For example, Bachevalier examined the effects of specific temporal-lobe lesions experimentally introduced in either adult or infant monkeys. In the adult monkeys, the lesions compromised performance on a simple memory task. However, the performance of infant monkeys was nearly comparable with that of normal controls. Furthermore, follow-up suggested that the abilities acquired early were retained into adulthood. The studies suggest that when injury occurs early in life, the initially exuberant connectivity within the temporal lobe can be exploited to preserve function. In the young animal, normally transient connections within the temporal lobe stabilize, providing an alternative neural network that supports memory function. Kolb's work provides evidence of the limits of plasticity by demonstrating that bilateral injury results in more pronounced impairment than injury confined to a single cerebral hemisphere. That work also illustrates that the effects of the timing of the injury depend on the nature of the injury. In unilateral cases, outcomes following early injury are better than outcomes following later injury, while in cases of bilateral injury, the opposite pattern is observed. Importantly, Kolb has also demonstrated that environmental enrichment following early injury can significantly reduce the level of impairment even in cases of early bilateral injury.

Findings such as those from the work on the effects of deprivation on early visual system development or the effects of early lesions on the development of memory and problem solving document both the responsiveness of the neural system to such factors as variation in input or injury and the limits on the capacity of the neural system for adaptation. These examples, which reflect a much larger body of work, illustrate what has been described as the plasticity of the developing brain. Plasticity here refers to the capacity of the developing brain to respond adaptively and to adjust patterns of neural organization and connectivity to meet the demands of the specific experience of the organism. When input is altered or diminished, the neural system adjusts to maximize remaining input. When portions of the neural system are damaged, the remaining system organizes differently to support functions that would normally have been mediated by injured brain areas. The mechanisms thought to support neural plasticity in the postnatal period are principally those associated with the exuberant production of neural connections and their subsequent elimination (see Chapter 9). The studies of deprivation or experimental injury suggest that the capacity for plastic adaptation early in development is considerable, but it is important to emphasize that although the developing system exhibits considerable plasticity, there are also limits. For example, in Bachevalier's study, it is notable that although performance in the early lesioned monkeys was good, it never fully reached the level of controls either during infancy or in the adult follow-up study. Further, there is ample evidence that not all neural systems exhibit the level of plasticity observed in the cortical-lesion studies. For example, in Goldman-Rakic's studies, while monkeys with early cortical lesions performed nearly as well as controls, performance was compromised in infant monkeys with lesions to subcortical pathways. Kolb's studies of bilateral versus unilateral injury also document variation in the capacity to compensate for injury.

Finally, the effects of experience are temporally constrained. In the visual deprivation studies, one important moderating factor was the timing of the onset of deprivation. The greatest effects were associated with very early alteration of input. When deprivation onset was delayed by even a few weeks, the effects on cortical organization were diminished. These kinds of findings are important because they place the construct of plasticity within the developmental context. The developing

brain does appear to be responsive to input and to retain the capacity to organize adaptively. In that sense, plasticity of the developing brain in the postnatal period provides a very good example of the interaction between intrinsic factors and experience. However, the limits on plasticity highlight the fact that the developmental process is one of continuing change within the context of increasing specification. Development happens over time, and the timing of events and experience matters. The next section will consider some of the multiple levels at which time affects and constrains the development of the emerging organization of the CNS.

Time as an Organizing Factor in Brain Development

Development is a complex, multilevel process that unfolds over time. At the macro level, brain development appears to be a simple, additive process, and in some respects it is. Cells differentiate, multiply, and congregate in appropriate regions of the brain in increasing numbers. Connections among cells are formed both locally and over long distances. Thus at a global level, the neural system becomes more complex over time because more and more elements are incorporated into the system. But this simple additive model fails to take account of both the dependencies among the accumulating neural elements and the effects of experience, and thus masks much of the complexity of brain development.

A more nuanced view reveals multiple levels of change that, over time, are all driven by the interactions among the emerging and constantly changing complement of elements that compose the developing neural system. Across the entire period of brain development, the neural system depends upon the availability of the right neural elements appearing at the appropriate moment in developmental time for its integrity, stability, and growth. Often the emergence of a new element depends upon developmental events that immediately precede its appearance. All of this may seem a formula for chaos, but developmental changes appear to be orderly and follow regular patterns over time. At all levels of the neural system, from the cell to the neural pathways, progressive differentiation of specific elements and structures, coupled with progressive commitment of those elements to functional systems, appear to be the governing principles of brain development.

The timescales for differentiation and commitment vary both at different levels of the system and across subsystems within a neural level. The coordination and integration of these multiple levels of change happening on multiple timescales are essential elements of brain development. The sections that follow will examine the complementary processes of progressive differentiation and commitment for different levels of the neural system. The importance of the timing of interactive processes for the orchestrated development of the neural system is illustrated with examples drawn from the morphological, cellular, and neural pathway levels.

Progressive Differentiation

Progressive differentiation of neural elements is observed at all levels of the neural system, from basic morphology to cells to neural pathways. Differentiation is probably most obvious at the level of basic morphology, particularly during the embryonic period, when the shape of the primitive nervous system changes dramatically over a relatively short period of time (see Chapter 4). At the onset of neurulation, the embryonic disc elongates as the neural tube begins to form. By the end of neurulation (E28), three primary subdivisions of the embryo can be discerned, and by E50 the embryo has differentiated into five distinct subregions, each of which will give rise to a different part of the developing CNS. Further, rates of growth across the subregions are not uniform. During this early period, the rate of growth in the most rostral regions of the embryonic nervous system far outpaces that in more caudal regions, setting the stage for the emergence of the critical structures of the telencephalon. Within more caudal regions, the compartments that define the segmented organization of the hindbrain and the spinal cord begin to emerge. The formation of rhombencephalic compartments is achieved by a simple but elegant difference in the timing of cellular element production within alternating rhombomeres. During the embryonic period, failure of differentiation of any of the major morphological divisions results in serious deformation or death of the embryo. Later in development, telencephalic development continues to be the most prominent morphological feature of the mammalian, and particularly the primate, brain. The size of the brain increases dramatically, and as size outpaces cranial capacity, the

characteristic patterns of gyral and sulcal folding begin to appear. Sulci appear in a regular sequence, beginning with the primary sulci, which mark the major divisions of the developing neocortex, followed by the secondary and finally the tertiary sulci. Differences in gray- and white-matter compartments become increasingly evident.

Progressive differentiation at the cellular level begins within the CNS with the differentiation of the neural progenitor cells (see Chapter 6). As discussed earlier, differentiation depends upon signaling from migrating organizer cells. The additional differentiation of neural progenitor cells into those that produce cells appropriate to anterior or posterior neural regions is also signaled by nonneural mesendodermal cells. By the end of neurulation, neural progenitors begin to divide. Initially, the cells divide symmetrically, producing clones of themselves and thus increasing the pool of neural progenitor cells. By about E42, a subset of progenitor cells begins to divide asymmetrically, producing a new type of daughter cell, a neuron. Across the period of cortical development, the type of neuron produced by the neural progenitors changes repeatedly, and the timing of those changes is critical for the laminar organization of the neocortex. Specifically, signals thought to arise in part from neurons generated earlier induce the progenitor cells in the ventricular zone to produce neurons appropriate for the cortical layer currently being generated. Thus at the level of cellular differentiation, signaling between neural and nonneural cell populations initially defines the progenitor cell lines that will give rise to the brain and the CNS. Later those cells receive other signals that instruct them to produce a variety of neuronal subtypes. Further, the timing of the neuronal subtype production is carefully orchestrated to ensure that the correct cell types are generated and migrate to the appropriate cortical layers. Finally, at the end of neurogenesis, progenitors begin to produce the support cells of the brain, specifically, the astrocytes and myelin-producing oligodendrocytes and Schwann cells.

There are many examples of progressive differentiation of cortical pathways, which often take the form of increasing specification of the patterns of input and output. Some of the original work documenting the progressive specialization of connectivity within the primate neocortex came from Rakic and colleagues (Zecevic, Bourgeois, and Rakic 1989). In that work, they documented the early exuberance and later

pruning of synapses within motor, visual, and frontal cortices in rhesus monkeys (see Chapter 8). For all three systems, they reported initial widespread and distributed patterns of connectivity that were replaced over time with more selective patterns of connectivity. Huttenlocher (1990; Huttenlocher and Dabholkar 1997) reported similar patterns of synaptic exuberance and pruning for humans. Unlike the monkey studies, however, Huttenlocher reported different timescales for overproduction and loss within different brain areas. Specifically, the temporal course within primary sensory areas was earlier than that in frontal regions in both the timing of peak production and the rates of both initial exuberance and later pruning. The refinement and stabilization of cortical pathways during the postnatal period are thought to be influenced by the experience of the organism.

Progressive Commitment

As differentiation proceeds, the complementary processes involved in progressive commitment unfold to produce the orderly emergence of neural structures and functions. The functional commitment of neural elements to specific networks and pathways serves to organize and constrain the developing neural system. Morphological differentiation of the embryo establishes the structural basis for regional differences in function. For example, the segmental differentiation of the hindbrain and the spinal cord is morphologically suited to the functional organization of the peripheral nervous system, while the early rapid expansion of the telencephalon provides a mechanism for generating the complex and intricate neocortex. Progressive commitment is also observed at the cellular level (see Chapter 6). For example, the neural stem cells that will form the principal neocortical progenitor population are initially multipotent neurepithelial cells that transform into radial glial cells (Merkle and Alvarez-Buylla 2006). At the onset of neurogenesis, radial glial cells are capable of producing the full range of cortical neurons. However, with development their production range becomes progressively more constrained (Desai and McConnell 2000; Frantz and McConnell 1996; McConnell and Kaznowski 1991). Once production of the neurons appropriate for the first cortical layers is complete and the progenitor has begun to generate a different type of neuron for a subsequent layer, the progenitor is no longer capable of

generating the initial neuron type. Later in corticogenesis, radial glial cells produce oligodendrocytes and astrocytes. Finally, there is evidence that radial glial cells eventually exit the mitotic cycle and transform into astrocytes (Merkle and Alvarez-Buylla 2006).

The progressive commitment of neural resources is probably most evident in the formation of neural pathways. In early postnatal development, pathway formation is both exuberant and flexible. As the studies of visual deprivation and early injury suggest, brain organization adapts to meet the contingencies of experience. However, as pathways stabilize and exuberant connections are eliminated, the neural system becomes increasingly committed and the capacity for flexible reorganization becomes limited. The commitment of resources is gradual and progressive and, as Huttenlocher and Dabholkar's (1997) data suggest, operates on different timescales for different neural systems. Sensory and motor pathways stabilize earliest, while pathways that mediate higher cognitive and social functions show different and more protracted patterns of commitment. Finally, the capacity for change and reorganization, while increasingly constrained over development, is never completely lost. Work documenting at least limited plasticity in the adult brain (Buonomano and Merzenich 1998; Kaas 1991; Kaas, Merzenich, and Killackey 1983) demonstrates the continuing capability for neural pathway modification. Further, the capacity for lifelong learning must be mediated by the formation of new neural circuits and pathways.

Changing Influences across Development

As the structural and functional organization of the emerging system changes over time, the factors that are most central to the ongoing process of development also change. As discussed previously, early in development, organism-intrinsic signaling dominates the developmental process, inducing cellular differentiation and establishing the primitive spatial organization of the embryo. Organism-extrinsic factors influence early development, but play a less central role than later in development. As the neural system becomes more complex, the range of factors that direct and influence development also expands. The increasing variety of structural elements (some permanent, some transient) creates diversity in the kinds of interactions that can be en-

gaged in the complex signaling cascades that structure the developing brain. For example, by midgestation, populations of cells have emerged that direct the movement of neurons into organized structures. In this same period, other groups of cells act to guide the advance of neuronal processes to appropriate locations within the brain where they can establish functional connections with other cells. The activity of the emerging neural circuits creates another kind of signaling that has a significant impact on brain organization. For example, in the prenatal period, a cell's survival can depend on whether it becomes integrated within active neural circuits (see Chapter 8). Cells that make connections with other cells survive, while those that fail to make connections are subject to apoptotic cell death. The establishment of sensory input systems and motor circuits creates yet another avenue for neural signaling and expands the influence of the external world on the development of the neural system.

Developmental periods are often characterized by the particular "superordinate" event that is most prominent and defines the major structural change of the period. Embryonic events include such processes as gastrulation or neurulation; later events include corticogenesis or thalamocortical pathway formation. But each of these major developmental events is composed of many smaller epochs of change, each with its own unique and well-defined spatial distribution and temporal window. It is the combination of these many smaller developmental processes unfolding over time and interacting with other temporally convergent events that constitutes the larger "superordinate" processes. Thus, although the most obvious changes may appear to be the superordinate events, they are really the product of many smaller developmental processes, each of which contributes an essential element to the larger developmental event. An example from the embryonic period illustrates this point.

Early in development, this kind of temporally convergent network of changes serves to organize the embryonic proliferative zone. Initially, spatially specific expression of BMP4 and the BMP4 antagonists noggin, chordin, and follistatin define the neural progenitor population (Chapter 3). Soon after, posteriorizing agents such as WNTs are expressed. They induce cells in posterior regions of the embryonic brain to a posterior fate but are blocked by the concurrent expression of WNT antagonists, such as Cerberus and Dickkopf, in more anterior

regions. Still later in embryonic development, the regionally specific expression of the transcription factors EMX2 and PAX6 plays an important role in establishing anterior-posterior patterning within the developing neocortex, while the temporally and spatially specific expression of *HOX* family genes defines the anterior-posterior axis in the hindbrain and the spinal cord (see Chapter 5). All the signals described for these early embryonic events are single, organism-intrinsic events; they are the products of specific gene expression. But no single gene product can independently define spatial organization of the embryonic nervous system. Rather, each constitutes a small developmental event that contributes an essential element to the larger, more complex signaling cascade. Each contribution is unique in terms of the signal content, its spatial distribution, and its temporal onset and duration. But it is the combination of many small developmental events interacting in larger signaling cascades that serves to establish the structural and functional organization of the embryonic nervous system.

"Critical Periods" in Postnatal Development

The term *critical period* has been used to describe the temporally circumscribed periods of postnatal development when specific input is required to establish a particular behavior, presumably because the input plays a central role in the establishment of the neural system that supports the behavior (Knudsen 2004). The early definitions of the critical period came from ethologists studying animal behavior. Lorenz's (1957) early work with chicks and goslings examined imprinting behaviors in which young birds establish filial relations with a moving object encountered early. Contingencies in the natural environment make it likely that the mother will be the first object encountered, but Lorenz's work suggested that the young birds would imprint on any moving visual stimulus available in a critical period after hatching. The early definitions of the critical period made very strong claims about intrinsic control of the time window during which experience could affect development. Later work on the role of early experience in the emergence of birdsong (Marler 1970) and maternal attachment (Harlow and Harlow 1965) provided support for a strong version of a critical period. The concept was also applied to studies of

humans. Bowlby (1969) introduced the concept of the critical period to the study of human attachment behaviors, and Lenneberg (1967) extended the idea to explain observations of declining capacities in language learning with age.

Despite the prevalence of the critical period concept as an explanatory construct for a wide range of early-learned behaviors, subsequent work suggested that revision of the original definition of the term was necessary. A substantial body of evidence demonstrated that there was greater flexibility in both the onset and the termination of the critical period for many behaviors. Other data suggested that critical period effects could be modified or in some cases even reversed by variations in experimental conditions (Michel and Tyler 2005). These kinds of findings led to a revision of the initial concept and the introduction of the term *sensitive period* as a more moderate alternative (Johnson 2005; Knudsen 2004; Michel and Tyler 2005). The sensitive period terminology acknowledges the well-documented findings based on data from a range of behavioral domains that experience has a greater effect on particular behaviors during specific developmental windows. But the sensitive period account does not require the narrowly conceived ideas about either developmental timing or maturational mechanism that are often associated with the critical period. Indeed, the conceptual shift appears to reflect a change in basic questions that were being asked about these important early developmental events. While critical period studies focused on documenting the existence of behavior-specific developmental windows and the timing of their onset and offset, studies of sensitive period events focus more on identifying the underlying mechanism for a particular event, as well as the complement of factors that might affect the timing and plasticity of learning for the event. As Michel and Tyler (2005) noted, "Replacing 'critical' with 'sensitive' marked the recognition that once the 'what' of development was discovered, timing alone would not be critical for manipulating the developmental outcome" (p. 160).

The construct of the postnatal sensitive period fits well with the dynamic, interactive model of brain development presented here. Throughout the prenatal period, both organism-intrinsic and extrinsic factors play important roles in brain development. With development, as the range of both structural elements and neural circuits expands, extrinsic factors play an increasingly prominent role. By the early

postnatal period, the importance of input in developing brain and behavioral systems is well documented and indeed is the substance of the critical-period then sensitive-period debates. The importance of experience on a wide range of systems from sensory and motor to social, affective, cognitive, and linguistic is well established. Greenough used the term *experience-expectant* to refer to those aspects of early postnatal development that appear to expect or require particular input. But not all behaviors manifest this developmental pattern. For many aspects of learning, the timing of a particular input is not critical to acquisition. Greenough referred to this kind of learning as "experience-dependent." The challenge is to define more specifically why some aspects of learning appear to manifest a sensitive period while others do not.

Johnson (2001, 2005) has offered three competing accounts of sensitive period effects: maturational, skill learning, and interactive specialization. By the maturational view, sensitive periods are defined by the physical development of the brain. As brain regions mature, they assume specific, well-defined functions but require specific input to achieve full functionality. Thus physical maturation sets the limits on the sensitive period. The skill learning view presents a very different perspective on sensitive period effects, suggesting that the apparent insensitivity to new learning after the close of the "sensitive period" actually reflects the stabilization of a particular neural system as specific expertise in a skill area is acquired. Thus stabilization constrains plasticity within the system and indirectly limits sensitivity to novel input. Interactive specialization focuses on processes involved in organizing and integrating interactions among brain regions and suggests that the response properties of a region are dependent on its connections with other brain regions. As learning proceeds, patterns of connectivity sharpen and functions within a region become more specifically defined. Thus the end of the sensitive period is associated with the learning process itself.

The maturational view most closely approximates a strong critical period view in that it emphasizes the temporal constraints of brain maturation as central to the opening and closing of the development window. For both skill learning and interactive specialization, the sensitive period appears to be an epiphenomenon of the underlying developmental processes associated with learning. Learning-associated

input shapes the patterns of connectivity and refines the neural systems. It is quite possible that, depending on the specific system, maturational factors also contribute significantly to the stabilization of the neural system. The models offered by the skill learning and interactive specialization views differ in the scope of learning they define and in their account of the interactions among neural systems. However, both take a dynamic view of the effects of learning (i.e., input and its effects) on the developing neural system, suggesting that multiple factors interacting in a dynamic fashion direct the course of brain and behavioral development. Thus in these views, the principles that appear to drive prenatal brain development continue during the postnatal period. The postnatal brain is a significantly more complex structure than the prenatal brain, and the range of inputs and outputs far exceeds that of the prenatal period. But the principles of progressive differentiation and, in particular, of progressive commitment of neural resources to functional systems continue into the postnatal period. Learning itself appears to become an important factor in the postnatal commitment of neural systems to particular patterns of organization.

Temporal Constraints on Brain Development

The view of brain development presented here is dynamic, interactive, and adaptive. Complex signaling cascades direct the formation and fate of cell populations, specify the migratory pathways and final destinations of new neurons, direct the formation of connections, and even signal cell death in targeted populations. The developmental process can adjust to contingencies and even to direct insult to brain structure. Yet there does not appear to be a blueprint, an executive, or even a homunculus directing the continuous changes in the complex array of elements, systems, and processes that emerge, expand, change, and sometimes just disappear across the period of development. How can a process with apparently so many degrees of freedom succeed so regularly in the real world of pre- and postnatal brain development?

Part of the answer lies in the fact that biological development is a process that unfolds over time. Thus at any point in time, there are limitations on how development can proceed. Therefore, at any point in time, the developing organism has both a state and a history. The

history is the sum of all the events that contributed to the current state of the organism. The state represents both the current structure and the functional capacity of the organism, as well as its potential for further change. In short, development does not happen all at once; rather, it builds upon itself, often creating as it goes the tools necessary for each successive step in the developmental process.

In addition to time, there are other constraints on the process of development. It is first constrained by inheritance, that is, by the species- and parent-specific genetic material passed on at conception, coupled with the cellular machinery necessary to make use of the information in the genes. The information in the genes is very specific; it provides the coded nucleotide sequence information necessary for producing the protein products that are the active agents in development. Many genes, particularly developmental genes, have a long evolutionary history that shaped their functional role both historically and within the developing individual organism. Environment, broadly construed, also constrains development. Cells reside in a nested set of environments, and each environment has the potential to influence change in the cell either directly or through signaling cascades. Some aspects of the environment are the product of the developmental process, as in the case of newly generated cell populations whose function is to direct some other aspect of development. But many environmental factors are external to the organism. Nutrients provided by the maternal system, teratogens introduced into the fetus via ingestion by or infection of the mother, gravity, light, temperature, and sensory input are all factors that affect and constrain the development of the organism. The developmental state of the organism in turn influences whether or not it can be affected by environmental factors. For example, teratogens that have a specific effect on neuronal migration can affect development only during a very specific temporal window, and even within that window, early versus late exposure affects cells migrating to different cortical layers, thus inducing very different kinds of disorders in the developing organism.

An important part of the account of why brain development is so consistently successful lies in the process of development itself. Neural system development is constrained by both inherited and environmental factors, but the process of development also introduces its own temporal and structural constraints. Early in development, the set of

available structures and the range of possible processes are comparatively limited. Interactions are governed by intrinsic signaling cascades that function to define primary cell lines and the primitive spatial organization of the embryo. Later in development, the system is structurally more complex, but the developmental process has produced greater compartmentalization and regionalization of systems, as well as increasing commitment of neural elements to specific structures with particular functions. Thus the process of development introduces levels of structure and function that constrain the range of possible developmental trajectories for the organism. In that sense, development is, in part, a self-organizing process. The idea of development as a self-organizing process is not new. It has a long and varied history in disciplines as diverse as evolutionary biology, psychology, anthropology, and computational modeling. The principle as applied to brain development is important and consonant with the growing body of evidence on the basics of brain development emerging from developmental neurobiology. There are constraints on brain development that derive from both genetics and the environment, but neither genes nor the environment can specify the complex set of events that must occur for a brain to develop normally. The particular temporal dynamics of the developmental process introduce the additional constraints necessary to account for the continuity and robustness of brain development.

The idea that brain development is a process is also important for understanding what happens when things go wrong. Some early pathological events are devastating and lethal to the organism. More often, specific factors, such as a genetic anomaly, introduction of a pathogen, hypoxia, or frank brain injury, affect the course of brain development but are not fatal to the child. One important and basic set of questions raised by such early events is how they will affect the cognitive and social abilities of the affected children (Uylings 2006). Considerable work in developmental neuropsychology has over many years attempted to address these kinds of questions for a range of disorders. The models used for studying these questions draw from studies of adult-onset disorders in that they attempt to link a specific pathology with a particular behavioral outcome. However, more recently this model has been challenged as inadequate for the study of child populations because it fails to take account of the fact that the

neuropathological event occurred within a developmental context (Karmiloff-Smith et al. 1998; Thomas and Karmiloff-Smith 2002). If brain development is a dynamic and progressive event, any nonlethal neuropathological event will become one of the many factors that affect brain development because it is part of the biological experience of the individual child. It will become part of the developmental history of the child and thus part of the developmental process itself.

The effects of neural insult on the developing brain and cognitive system are illustrated by a rare condition that affects approximately 1 in 4,000 children, perinatal stroke (Nelson and Lynch 2004). Perinatal strokes typically happen during the last trimester of pregnancy and are often associated with motor-system weakness on the contralesional side of the body. Studies of the effects of these early strokes on linguistic and cognitive development suggest that although children have deficits in a range of areas, they are typically mild compared with deficits observed among adults with comparable injury (Bates et al. 1997, 2001; de Schonen et al. 2005; Levine 1993; Levine et al. 1987, 2005; Reilly et al. 2004, in press; Reilly, Bates, and Marchman 1998; Reilly and Wulfeck 2004; Stiles et al. 2005, in press; Stiles, Paul, and Hesselink 2006). Further, there appear to be differences in the magnitude of deficit across behavioral domains (de Schonen et al. 2005; Stiles et al. 2005, in press). Children usually develop normal language skills but have persistent subtle deficits in visuospatial and affect processing. Recent functional imaging data suggest that the brain systems that mediate both language and visuospatial function in these children differ from those observed in typically developing children, suggesting that alternative patterns of brain organization emerged in the wake of early injury, and these alternative patterns of neural connectivity are capable of supporting a range of cognitive and linguistic functions at normal or near-normal levels (Raja et al. 2006; Saccuman et al. 2006; Stiles et al. 2003; Stiles, Paul, and Hesselink 2006). Data of these kind suggest that although neural insult is never a good thing, when it occurs in a child, it is, by definition, part of a developmental profile and thus part of a larger developmental process. In the case of children with perinatal stroke, the process of brain development supports the emergence of an alternative pattern of neural organization that in turn supports relatively high levels of behavioral functioning. Because developing systems emerge over time, the final functional organiza-

tion of the brain in a child with early brain injury reflects an alternative developmental pathway, a variant of the typical pathway, which is itself developmentally constructed. From the moment of the stroke, both the state of the neural system and the developmental history of the child diverge from those of a typically developing child. Subsequent steps in brain development must incorporate both the neuropathology and the cognitive and neural consequences of that pathology into an ongoing developmental process that is unique to that individual. Nonetheless, the developmental pathway has much in common with that of a typical child—the genetics have not changed, mechanisms for neuronal differentiation and axon guidance are the same, and the laminar organization of the cortex and the organization of major pathways within unaffected areas are intact. But the injury affects both the state of the neural system at the moment of injury and the subsequent developmental trajectory. This perturbation of the developmental process has specific effects that give rise to the patterns of deficit, adaptation, and compensation that are the hallmark of development in this population of children.

Brain Development as a Dynamic Process

The model of brain development presented here is dynamic and adaptive. It is a temporally defined process that is constrained by both inherited factors and experience, as well as by the process of development itself. It is a model that allows for adaptation, that is, for divergence from the "typical" pathway, but adaptation is also limited and must fit within the constraints of the developmental process. Development involves production of new elements and functions via processes of progressive differentiation but also imposes limits in the form of commitment of elements to particular structures and functions. Timing is critical both for the moment-to-moment process of development and for the longer-term emergence of stable structures and functions, as well as for any influence external factors might have on development trajectories. The model of brain development presented here differs significantly from older maturational models in which systems emerge in a linear fashion. But this more dynamic model fits the growing body of data on brain development from the early embryonic period through postnatal development.

The concept of brain development as a constrained and temporally bound but flexible and adaptive process has significant implications for psychologists. First, on the question of innateness, within this model of biological brain development, innate factors, that is, inherited factors, are inextricably linked to experience, and together inheritance and experience define and direct the developmental process. This presents a very different view of what it means for something to be innate than is typically presented in psychological models. In this view, everything that develops has an innate aspect. It must because all developmental processes rely, fundamentally, on the information encoded in the genes and on the cellular mechanisms that provide access to that information. Genes themselves do not participate in developmental processes; rather, it is the products of gene expression, the proteins, that are the active agents in development. But gene products do not by themselves create neural structures or functions. Rather, they participate in complex signaling cascades that over time serve to direct the fate of cells, the organization of systems, and the establishment of signaling pathways. Indeed, the same gene product can have markedly different effects depending on the developmental context in which it is expressed. When *BMP4* is expressed during gastrulation, its gene product directs the epidermal fate of ectodermal cells (Chapter 3). However, later in development, *BMP4* expression within the spinal column contributes to defining the dorsal-ventral axis of organization within the neural tube by directing the induction of specific types of interneurons (Chapter 5). Thus development depends equally on processes that decode the information in the genes and on the ever-expanding levels of environments that arise, in part, as the product of development itself.

This is a very different way of thinking about what it means for something to be innate. It renders any attempt to classify things as innate or learned moot. By this model, the neural structures and functions are the products of developmental processes that rely upon, but are distinct from, the inherited and contextual factors that interact to create them. Innate factors and environmental context act in concert to direct the processes that generate the developing neural system. The question, by this model, becomes, what is the nature of the developmental process that gives rise to a particular biological structure, neural function, learning mechanism, or concept? It is the under-

standing of development, both biological and psychological, that becomes central in this model of brain and behavioral development.

This approach to thinking about brain and behavioral development raises interesting and important questions for psychologists who study the typical development of children. Specifically, to what extent can our growing understanding of the basic processes of brain development be used to inform our understanding of social and cognitive development in typical populations of children? Ideas about neural flexibility and adaptation within developmentally constrained systems should inform the way we think about how children learn or interact socially. The very old questions about whether there are "optimal" ways for children to learn new material may be informed by data that allow us to capitalize on information about the state of the neural system at particular points in development. It may also help address questions about individual differences and the extent to which performance differences among children reflect different states of readiness or flexibility at a neural level. Evidence for the effects of experience or for progressive commitment of neural systems should be reflected in how children learn. Will learning in some domains "stabilize" and become less adaptable earlier than others? What is the effect of "enriching" a child's environment? Do we know enough about the relationship between input and brain development to define, beyond cases of extreme deprivation, what it means to enrich a child's world? These are precisely the kinds of questions that motivated this book. They are questions that suggest that knowledge of the developing neural system is important for understanding cognitive and social development more generally. The goal of this book is to make accessible this important body of information to nonbiological investigators whose work might be informed by it.

Chapter Summary

- The biological concept of inheritance stresses the inseparability of inherited and environmental factors. It is the interaction of intrinsic and extrinsic factors that defines and drives development.
- During the embryonic period, the interactive processes are principally observed at the level of cell-cell interactions where one

population of cells generates molecular signals that alter the developmental course of another population of cells, but external factors also play an important role. Later in development, intrinsic factors continue to play a critical role, but extrinsic factors play increasingly prominent roles in shaping and directing the course of brain development.

- Development is a process that unfolds over time. Thus the timing of developmental events is critical. There are multiple levels of timing, and each plays an important role in shaping the developing brain.
- At all levels of the neural system, progressive differentiation of specific elements and structures, coupled with progressive commitment of those elements to functional systems, are governing principles of brain development.
- A critical period is a time in postnatal development when specific input is required to establish a particular behavior. The onset and offset of the critical period are thought to be sharp and controlled by intrinsic factors. A more moderate conceptualization of the critical period is the sensitive period. The construct of a sensitive period focuses on the importance of experience during specific developmental windows but does not require the narrowly conceived ideas about either developmental timing or maturational mechanism.
- Brain development is constrained by both inherited and environmental factors, but the process of development also introduces its own temporal and structural constraints.
- Everything that develops has an innate aspect because developmental processes rely on the information encoded in the genes and the cellular machinery that allows access to that information. Brain structure and function are the products of developmental processes that rely upon, but are distinct from, the inherited and environmental factors that interact to create them.

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