

How the Timing and Quality of Early Experiences Influence the Development of Brain Architecture

Sharon E. Fox

*Harvard–MIT Division of Health Sciences
and Technology*

Pat Levitt

Vanderbilt University

Charles A. Nelson III

Children's Hospital Boston, Harvard Medical School

Early life events can exert a powerful influence on both the pattern of brain architecture and behavioral development. In this study a conceptual framework is provided for considering how the structure of early experience gets “under the skin.” The study begins with a description of the genetic framework that lays the foundation for brain development, and then proceeds to the ways experience interacts with and modifies the structures and functions of the developing brain. Much of the attention is focused on early experience and sensitive periods, although it is made clear that later experience also plays an important role in maintaining and elaborating this early wiring diagram, which is critical to establishing a solid footing for development beyond the early years.

Our current understanding of the role of experience in influencing the course of human development arises in large part from studies of atypical patterns and disorders of development, including disorders that arise due to adverse early experience. However, whereas studies of atypical development have done an excellent job of *describing* dimensional phenotypes that underlie disrupted development, it is imperative that we integrate these descriptive concepts with biological constructs of neurodevelopment in order to understand the relevant brain architecture and neurochemical constituents that determine responses to experience that ultimately lead to typical and atypical change (see Nelson & Jeste, 2008, for recent review). In this study we seek to elucidate the myriad ways the structure of experi-

ence weaves its way into the structure of the developing brain.

Background

The foundations of brain architecture are established early in life through a continuous series of dynamic interactions between genetic influences and environmental conditions and experiences (Friederici, 2006; Grossman, 2003; Hensch, 2005; Horn, 2004; Katz & Shatz, 1996; Majdan & Shatz, 2006; Singer, 1995). There is increasing evidence that environmental factors play a crucial role in coordinating the timing and pattern of gene expression, which in turn determines initial brain architecture. Because specific experiences potentiate or inhibit neural connectivity at key developmental stages, these time points are referred to as sensitive periods (Hess, 1973; Knudsen, 2004). Each one of our perceptual, cognitive, and emotional capabilities is built upon the scaffolding provided by early life experiences. Examples can be found in both the visual and auditory systems, where the foundation

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Correspondence concerning this article should be sent to Charles A. Nelson, Children's Hospital Boston, Harvard Medical School, 1 Autumn Street, 6th Floor, Mailbox #713, Au621, Boston, MA 02215-5365. Electronic mail may be sent to charles.nelson@childrens.harvard.edu.

for later cognitive architecture is laid down during sensitive periods for basic neural circuitry. The capacity to perceive stereoscopic depth requires early experience with binocular vision (Crawford, Pesch, & von Noorden, 1996), which at a later point in development may have implications for perceptual and cognitive development. Likewise, the capacity to perceive a range of tones requires variation in the tonal environment, and exposure to such variation later leads to language processing and proficiency (Kuhl, 2004; Newport, Bavelier, & Neville, 2001; Oyama, 1990; Weber-Fox & Neville, 2001). Just as a square house cannot be built on a round foundation, so must later refinements in adult perceptions reflect the architectural foundation developed through early experiences. Although early experiences are reflected in behavior, behavioral measures tend to underestimate (in part because of a lack of sensitivity and specificity) the magnitude and persistence of the effects of early neuronal development (Knudsen, 2004). In order to explore the role of timing and quality of early experiences on later cognitive function, we must therefore return to the genetic framework of the developing brain.

Genetics and Environment—The “Blueprint” for Neural Development

Refinements in the neural circuits that mediate sensory, emotional, and social behaviors are driven by experience (Feldman & Knudsen, 1998). Specifically, postnatal experiences drive a protracted process of maturation at the structural and functional level, but the very ability of such developmental processes to occur successfully is dependent in large part on the prenatal establishment of the fundamental brain architecture that provides the basis for receiving, interpreting, and acting on information from the world around us (Hammock & Levitt, 2006). While the term *blueprint* has been utilized in the past to describe a fixed set of genes with inflexible interactions, the term is used here as an analogy to a rough draft, or design—the framework from which a more defined structure will evolve. The emergence of the architecture in all vertebrate species begins early, when the fundamental cardinal axes are established in the neural plate by sets of different transcription factors that specify molecular differences, particularly growth factor signaling molecules (e.g., fibroblast growth factors, wnts) antero-posteriorly, medio-laterally, and dorso-ventrally; Puelles, 2001). In humans, this occurs within

the first 2 months postfertilization (Levitt, 2000, 2003). The initial focus of brain patterning was on the nature of specification of segmented regions of the nervous system, such as the brainstem and spinal cord, in which highly conserved homeobox-containing transcription factors control “downstream” gene networks that specify motor and sensory neuron types in each segment. It has become clear, however, that developmental gene networks are a highly conserved strategy for specifying the initial plan of the central nervous system. Thus, they are utilized even in the more complex, nonsegmented anterior regions of the brain that include the thalamus, hypothalamus, basal forebrain, and cerebral cortices (Sur & Rubenstein, 2005). The gene networks in large part encode transcription factors, proteins that control (through positive [enhancing] and negative [repressing] activity) the expression of genes downstream that mediate the major histogenic events that include progenitor cell proliferation, cell fate choices, cell migration, axon and dendritic growth, and synapse formation. Collectively, these highly structured events build the early plan for brain architecture. The genetic mechanisms are thought to be highly conserved because when examined, the networks are expressed in similar patterns across rodents and humans. Experimentally, however, the genetic mechanisms through which regional patterns and connections are established prenatally have been defined in animal models, primarily rodents and nonhuman primates (O’Leary, Chou, & Sahara, 2007; Rakic, 2006). In the context of understanding clinical disorders that have a prenatal origin, the challenge has been to extrapolate that information from different species in the context of the timing of human brain development, an exercise that has received considerable attention with new database tools (e.g., <http://www.translatingtime.net/>). The onset of histogenesis during prenatal development provides the cellular framework necessary for establishing and modifying later developing circuitry.

The cerebral cortex has garnered substantial attention in defining key developmental features across species. This is due in part to the technical advantages of studying a well-organized, layered structure, and the functional relevance of linking typical and atypical maturation of complex behaviors and neurodevelopment. The neocortex in all mammalian species comprises six layers of neurons, the architecture, connectivity, and chemistry of which are distinct depending upon their location. The neocortex is organized to receive information from the organism’s surrounding environment,

typically through connections with the thalamus. It does so by integrating information within and across architecturally distinct functional domains, and then relays this information to other brain centers that generate an appropriate functional response. There are two major organizing principles of the neocortex that are guided by gradients of expressed gene networks that establish an evolutionarily conserved design. First, the precursors of different functional areas emerge during the time period when neurons are produced and are displayed in the tangential domain (roughly the first and second trimesters of pregnancy in the human; see O'Leary et al., 2007; Sur & Rubenstein, 2005). Regional specification is not absolute but does involve transcriptional networks controlling the expression of axon guidance molecules that control the initial input and output wiring plan (see below). Expansion of the size of the neocortex during evolution (e.g., 1,000-fold between mouse and human) occurs mostly in this tangential domain (Rakic, 2005). Extending through the six-layered neocortex is the most fundamental of functional units, the radial column (Rakic, 2006). Each column of cells contains well-organized networks of local circuit and projection neurons, and are built in an orderly fashion in which the neurons destined to occupy deep layers are produced, or "born" first, followed by more superficially displaced neurons. Though there are some differences between rodents and primates, the projection neurons, which utilize the excitatory neurotransmitter glutamate, and the local circuit neurons, many of which use the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), arise in part from different regions of the forebrain (Wonders & Anderson, 2007). The regions of the forebrain proliferative zones from which glutamatergic and GABAergic neurons arise are specified genetically to give rise to the unique neuron types by different sets of transcription factors. For example, glutamatergic neurons arise from the dorsal pallium, the roof of the forebrain in which cells uniquely express transcription factors like *Emx1* and *Pax6*. GABAergic neurons destined for the cerebral cortex, joining their glutamatergic neuron partners, arise from the subpallium which also gives rise to the basal ganglia. This region expresses transcription factors in the *Dlx* and *Nkx* family. The genetic influence of these initial neurodevelopmental events is illustrated by experiments in which these different transcription factors are misexpressed in different regions will result in the anomalous production of projection or interneurons in the wrong location (Hebért & Fishell, 2008).

The "inside-out" pattern of neuron production and migration provides the basis for building essentially similar ontogenetic radial units across functional areas, with minor variations in the ratio of excitatory to inhibitory neurons in different regions. In fact, this conserved radial organization provides the framework for later developing refinement of circuits that are influenced extensively by patterns of physiological activity through experience-dependent mechanisms (see below). The tangential patterning of the neocortex into different functional domains that are prepared to receive specific thalamic input begins as soon as the first neurons are produced and is due largely to distinctive gradients of expression of transcription factors such as *emx1* and *2*, *pax6* and *lhx2*, which regulate the production of signaling molecules that include the fibroblast growth factors (*fgf*), bone morphogenetic proteins (*bmp*), and *wnt* proteins (O'Leary et al., 2007). Experiments in genetically manipulated mice demonstrate that by eliminating or altering the expression of just one transcription factor, the functional fate of cortical regions can be changed (Cholfin & Rubenstein, 2007). For example, *emx2* controls the expression of *fgf8* near the anterior end of the cerebrum. *Fgf8* alone is sufficient to specify the cortical regions that will eventually receive connections that are typical of frontal and somatosensory cortices (Fukuchi-Shimogori & Grove, 2001, 2003). This type of early genetic respecification is functionally relevant. For example, *Fgf17* is responsible for the initial patterning of different frontal cortex areas (Cholfin & Rubenstein, 2007). The early specification of the neocortex by genetic mechanisms is powerful because downstream from these signaling factors are axon guidance molecules that serve as the important chemical cues for getting axons to grow into their correct target region prior to beginning the extended process of synapse formation (e.g., see Alcamo et al., 2008). Gene regulatory networks also can influence the initial size of cortical areas by modulating the number of neurons that are produced. As noted above, key to the flexibility of this early architecture is the conserved nature of the radial organization. Thus, the long-distance circuit projections that help to define functional cortical areas, and even functional differences in superficial and deep projecting neurons, are altered when the disruption of early gene networks modifies guidance cues so that atypical connections are made. Though we tend to think that genetic mechanisms are immutable, it is important to stress that expression of early gene networks can be perturbed not only by catastrophic genetic mutations

that disrupt important regulatory genes but also by prenatal environmental influences, such as drugs, alcohol, toxins, and inflammatory responses. These may have less profound impacts on brain patterning but nonetheless can result in long-term disruption of cellular differentiation and behavioral development (Stanwood & Levitt, 2008).

In all mammalian species, this early period of specified patterning to generate a unique architecture is followed by an extended period of synapse formation, adjustment and pruning that typically extends from the last quarter of gestation through puberty (Bourgeois, Goldman-Rakic, & Rakic, 1999; Huttenlocher & Dabholkar, 1997). There is a unique relation that emerges between pre- and postsynaptic partners as physiological activity takes over from the activity-independent histogenic events to sculpt presynaptic terminals and postsynaptic dendrites and spines. Over the past decade, investigators have identified literally thousands of genes that encode proteins related to synapse formation, plasticity, and stabilization (Akins & Biederer, 2006; Sheng & Hoogenraad, 2007; Sudhof, 2008). While synapses can form under experimental conditions in the absence of physiological activity, experience is essential for the normally occurring regulation of the molecular basis for synapse formation. In this complex process, activity controls the expression of transcription factors that direct the downstream expression of structural proteins, receptors, and signaling molecules that are needed for synapses to function properly (Flavell et al., 2006; Majdan & Shatz, 2006; Paradis et al., 2007; Sugiyama et al., 2008). Moreover, activity regulates the distribution of key proteins within the synapse, making them available for the important task of information processing during sensitive and critical periods of development (Shepherd & Huganir, 2007).

Because of dramatic differences in brain size, the developmental timing of the histogenic events across mammalian species is unique. The process begins at about 56 days postconception and extends through the first years of life in humans. The events (e.g., cell type specification, axon guidance) that provide the initial brain blueprint, influenced by early genetic patterning, are completed early and relatively rapidly, by midgestation in the primates and the end of gestation in rodents (Levitt, 2003). The formation of neural connections, the development of unique cytoarchitecture (the structural correlate of functional areas), the growth of dendritic arbors, and the peak formation of synapses is a far more time-extensive process, extending through the second and third postnatal years in humans,

180 days in the macaque monkey, and at around weaning (21 days) in rodents. Thus, through a well-defined developmental process, the basic connectivity of local and long-distance neurons is set up to take advantage of a highly flexible organization that is both activity dependent and expectant postnatally. The continued growth of the neocortex occurs up to puberty by the addition of myelin, dendritic growth, non-neuronal cells, and a complex process of resculpting synapses whose numerical density across the entire neocortex is stable but may change in their laminar distribution. The mechanisms that control this latter event are not clear but are likely to be activity dependent. Recent studies of synaptic resculpting demonstrate that highly novel gene-environment regulatory mechanisms are at play, such as the activity-dependent movement of transcription factors from pre- to postsynaptic neurons to control maturation of neurons in a noncell autonomous fashion (Sugiyama et al., 2008).

Developmental Plasticity—Adjustments to the Architectural Plan

Although our genetic code provides an important foundation for early development, it must be understood as a framework upon which many environmental factors influence future structure and function. This can best be illustrated through studies of the sensory systems, which demonstrate the crucial role of environment in the early development and maintenance of the nervous system. Such work also demonstrates the need for patterned physiologic activity during development, as well as refinement and maintenance of detailed sensory maps. For example, supporting cells in the developing rat cochlea spontaneously release adenosine-5'-triphosphate (ATP), synchronizing the output of neighboring inner hair cells, which aids in the refinement of tonotopic maps. Spontaneous ATP-dependent signaling rapidly subsides after the onset of hearing, thereby preventing this experience-independent activity from interfering with the accurate encoding of sound. The initiation of electrical activity in auditory nerves before hearing suggests that peripheral, nonsensory cells may provide the necessary early environment for the development of central auditory pathways (Tritsch, Yi, Gale, Glowatski, & Bergles, 2007). In addition, auditory perception evolves according to the tonal rearing environment, with increased sensitivity to tones outside of those continuously experienced in

the environment (Hanm, Köver, Insanally, Semerdjian, & Bao, 2007).

Similarly, in the landmark studies of vision by Wiesel and Hubel (1963, 1965), it was demonstrated that kittens reared with normal visual experience resulted in each eye having sole access to alternating columns of neurons in layer IV of the striate cortex. At birth, however, both eyes synapse on *all* neurons in layer IV. In order to assure that a neuron is stimulated by experience coming from only one eye, a competitive process occurs in which activation and neighboring inhibition result in an alternating pattern of connectivity between columns of neurons in layer IV and each eye (Wiesel & Hubel, 1965). When kittens were reared with one eye closed for a period of time after birth, the occluded eye became essentially functionally blind. This blindness is due to the elimination of connections of the closed eye to layer IV and the lack of exposure to patterned activity. If occlusion extends beyond a certain time period, the typical pattern of ocular representation cannot be recovered despite the restoration of visual input to both eyes (Wiesel & Hubel, 1965). It has been hypothesized that the initial ingrowth of axons from the thalamus to ocular dominance columns in the visual cortex is governed by molecular cues (Crair, Horton, Antonini, & Stryker, 2001; Crowley & Katz, 2000). That is not to say, however, that an *atypical* or *plastic* change in visual representation is not achievable (Amedi et al., 2007; Antonini, Fagiolini, & Stryker, 1999; Flege, Munro, & MacKay, 1995; He, Ray, Dennis, & Quinlan, 2007; Miller, Keller, & Stryker, 1989). It has recently been shown, for example, that the decreased visual acuity seen in the adult rat suffering from chronic monocular deprivation is reversed if the adult rat is treated with dark exposure prior to removal of the occlusion (He et al., 2007). The increased plasticity induced by the dark environment may be due to a lack of input to the visual cortex through the functioning eye, and therefore a reduction in the strength of previously established connections. A similar restoration of visual acuity can also be induced with chronic administration of fluoxetine (Maya Vetencourt et al., 2008). Such dramatic changes in sensory system connectivity suggest that activity-dependent potentiation of these initial axons is required to maintain connections among cortical regions. In the case of the primary visual cortex, local circuit neurons have been implicated in activity-dependent plasticity through GABAergic inhibition over a wide range of neighboring axonal paths. (Fagiolini et al., 2004; Hensch & Stryker, 2004). An altered pattern of activity

through one circuit can thus radically change neighboring circuits through an increase or decrease in inhibition of mediating cells. Furthermore, visual deprivation has been shown to alter the formation of dendritic spines in the visual cortex once the pathways for normal vision have begun to potentiate (Oray, Majewska, & Sur, 2004; Trachtenberg & Stryker, 2001). Following deprivation, spines show increased structural motility—possibly allowing for plasticity of local connections—and later deterioration (Kim & Bonhoeffer, 1994; Mataga, Mizuguchi, & Hensch, 2004).

The early development of visual pathways may be likened to the laying of a foundation and scaffolding for a building. If the scaffolding pattern is changed, the building may not be constructed in its original form, though a functional alternative may be reached. Thus, irreversible changes at the synaptic level do not necessarily translate into irreversible changes in a complex behavior (Feldman & Knudsen, 1998). For example, we now understand that the sensitive period for visual representation reflects, predominantly, the critical period for thalamic input to layer IV (Antonini & Stryker, 1993; Miller et al., 1989; Pascual-Leone, Amedi, Fregni, & Merabet, 2005), but that plasticity of other sensory systems may allow a blind person to demonstrate normal—and possibly enhanced—spatial awareness (Amedi et al., 2007). Plasticity in higher regions involved in spatial awareness feeds back upon lower pathways, thus compensating for an abnormal visual representation.

Advanced perceptual processes are also dependent upon the normal development of basic visual systems. For example, early visual deprivation due to congenital cataracts can lead to subtle but persistent deficits in face processing, even when the cataracts are removed in the first months of life (Le Grand, Mondloch, Maurer, & Brent, 2001). Similarly, experience with specific faces, such as same versus different species, powerfully shapes subsequent face specialization. For example, monkeys deprived of viewing faces since birth are capable of discriminating both monkey and human faces following the selective restoration of faces in the visual environment, but *what kind* of faces determines whether that same monkey will be able to subsequently discriminate human or monkey faces—thus, monkeys selectively exposed to human faces can only discriminate human faces, not monkey faces, and monkeys selectively exposed to monkey faces can only discriminate monkey faces, not human faces (Sugita, 2008).

Sensitive Periods in the Early Development of Higher Cognitive Processes

Wiesel and Hubel's (1963, 1965) experiments involving visual deprivation brought about the concept of "sensitive" and "critical" periods in early cognitive development. "Sensitive" periods are defined as a time in development during which the brain is particularly responsive to experiences in the form of patterns of activity (Daw, 1997). Further, this time point may be termed a "critical" period if the presence or absence of an experience results in irreversible change (Newport et al., 2001; Trachtenberg & Stryker, 2001). Those factors that allow a circuit underlying cognition to be plastic—or render it unchangeable—are not yet well understood. In the area of speech and language, the maturational hypothesis predicts that native language proficiency cannot be obtained when learning begins after puberty (Bruer, 2001; Werker & Tees, 2005). Studies supporting this theory have correlated the degree of accent in a second language with age at the time of acquisition of that language (Birdsong & Molis, 2001; Johnson & Newport, 1989). Adults exposed to a second language in early childhood were found to have native-like accents and pattern of tone (Gordon, 2000; Long, 1990; Oyama, 1990; Stein et al., 2006). Other researchers have also found a negative correlation between age at acquisition and grammaticality judgments (Flege, MacKay, & Meador, 1999; Komarova & Nowak, 2001). These same studies, however, have failed to show any clear discontinuity in the relation between accent and age over the period from childhood to adulthood, thus suggesting that although a sensitive period may exist, a critical period for language acquisition is unlikely (Flege et al., 1999; Komarova & Nowak, 2001; Wartenburger et al., 2003; Weber-Fox & Neville, 2001). Many of these same investigators, however, argue that the decline in language-learning facility may be confounded by educational level and that involvement in a larger bilingual community may diminish the drive to find means for communication through a learned language (Flege et al., 1999; Hoff & Naigles, 2002; Komarova & Nowak, 2001). It has further been hypothesized that enhancements in nonlanguage cognitive systems, such as memory, may actually have deleterious effects on language learning (Newport, 1990; Newport et al., 2001). If this is the case, then the neural system responsible for language may in fact remain open, though difficult to access through adult cognitive processing or with only typical effort (the extent to which considerable

effort might force open the sensitive period can be found in training studies such as those focused on teaching native Japanese speakers to perceptually discriminate and correctly produce the R/L distinction (see Akahane-Yamada, Strange, Downs-Pruitt, & Masuda, 1998; Guion, Flege, Akahane-Yamada, & Downs-Pruitt, 1998; Guion, Flege, Akahane-Yamada, & Pruitt, 2000).

Several investigators have used the theory of neural networks, originally developed for vision research, to model the activity of individual neurons and/or groups of neurons in the brain during learning (Christiansen & Chater, 2001; Morton & Munakata, 2005). These neural network models are particularly useful for comparing the experience-independent and experience-based accounts of sensitive periods because the network can be kept constant with regard to features affected by maturation, motivation, and amount of exposure. Returning to the work of Wiesel and Hubel (1963, 1965), it is important to note that the loss of binocular function in the kitten did not arise simply because of the absence of input to the occluded eye. Occluding both eyes during the same time period of development was proved not to result in loss of binocular vision (Cynader & Mitchell, 1980). It is necessary for one eye to have access to layer IV of the visual cortex whereas the other eye is denied access, allowing exclusive connectivity of the unoccluded eye to striate cortex. The irreversible loss of binocular vision during development must therefore be due to a combination of environmental experience and cortical learning processes (Knudsen, 2004; Mataga et al., 2004). The fact that the existence of a sensitive period can depend upon occurrence of a particular environment suggests that in early development, portions of networks become perceptually biased, making future modifications more difficult. For example, in the literature on both speech and face perception, the perceptual window through which faces and speech is initially processed is broadly tuned, then narrows with experience. For example, Pascalis, de Haan, and Nelson (2002) demonstrated that 6- and 9-month-old infants and adults can readily discriminate two human faces, but only 6-month-old infants can discriminate two monkey faces. Similarly, 6-month-olds given 3 months of experience viewing monkey faces can readily discriminate monkey faces at 9 months of age, whereas 9-month-old infants not afforded such experience cannot (Pascalis et al., 2005).

As a rule, circuits that process lower level information mature earlier than those that process

higher level information (Burkhalter, Bernardo, & Charles, 1993; Scherf, Behrmann, Humphreys, & Luna, 2007). For example, in the neural hierarchy that analyzes visual information, low-level circuits that analyze the color, shape, or motion of stimuli are fully mature long before the high-level circuits that analyze or identify biologically important stimuli, such as faces, food, or frequently used objects (Burkhalter et al., 1993; Knudsen, 2004; Scherf et al., 2007). The process by which initial learning leads to a constraint on later learning is termed *entrenchment* and is equally apparent in the development of speech (Munakata & Pfaffly, 2004; Seidenberg & Zevin, 2006). Several studies have shown, for example, that adults are often better at discriminating nonnative phonetic contrasts when they differ substantially from phonemes of their native language (Best, McRoberts, & Sithole, 1988; Frieda, Walley, Flege, & Sloane, 1999; Guion et al., 2000; Kuhl, 2004). Adults are poorer at discriminating when the phonetic contrasts are similar to phonetic contrasts of their native language. This is akin to the nature of the developing auditory system, which as previously noted is more capable of discriminating tones outside of the tonal environment of rearing. At both the level of tone and of speech phonetic discrimination, there is evidence for a fixed bias of the neural network. As previously discussed in the case of visual networks, however, neurons may be constantly modifying connectivity, allowing learning from new environments to compete against already existing tendencies. This is well demonstrated in animals altered neonatally to receive retinal projections to the auditory portions of the thalamus (von Melchner, Pallas, & Sur, 2000). Such animals reveal that auditory cortex may be modified by extrinsic activity to develop retinotopic maps similar to those seen in the visual cortex. The role of environment and inputs to the brain may therefore be seen as critical in the bias of network formation during early life.

Altered patterns of enhancement and inactivity are thought to be the basis for neural plasticity and have been suggested in humans by studies of tactile and auditory perception in the blind, where such systems may even activate the “visual” cortex (Antonini & Stryker, 1993; Ellis & Lambon, 2000; Merabet, Rizzo, Amedi, Somers, & Pascual-Leone, 2005). It is likely that changes in experience have a greater impact on an untrained “young” network compared to the same experience on an “older” trained network. This biasing feature is suggested by studies on aphasia that show that words learned earlier in life are more resistant to loss and are

more easily accessed in naming tasks compared to words learned later (Greenough, Black, & Wallace, 1987).

It has been suggested that learning through experience leads to the capacity to understand specific environments and the responses needed for these environments (Anisman, Zaharia, Meaney, & Merali, 1998; Scarr & McCartney, 1983). Similarly, changes in the environment—particularly when they are dramatic and pervasive—may have the power to alter neural connectivity and cognitive processing between systems. Examples can be found in studies of sensory deprivation, such as blindfolding, as well as sensory enhancement through technology. In studies of deaf children receiving cochlear implants, it is clear that language learning improves with earlier correction (Tomblin, Barker, Spencer, Zhang, & Gantz, 2005). It remains to be determined, however, whether this effect upon learning is due to actual changes in cognitive capacity or changes in the learning environment brought about by the ability to interact with others through spoken language.

Global Development—Higher Level Functions Build on Lower Level Functions

The nature of our experiences, particularly during a time-limited period in early development, can profoundly affect the mental framework we use to understand the world around us. Sensitive periods in child development are of interest because they represent a time frame in which our capabilities can be modified and perhaps enhanced. The quality of experiences during such periods—be they adverse or enhancing—is also of importance in understanding why it may be difficult to restore normal function once development has been altered. While explanatory models for the timing of early experiences have generally been based at the genetic or neural circuit level, our direct observations of the effects of early environments are often made at the behavioral level. Through the study of sensitive periods, we are better able to understand the impact that early experience may have upon development. To cite but one example, it has recently been demonstrated that otherwise typically developing young children institutionalized at birth have intelligence quotients (IQs) in the low 70s. However, placing such children in high-quality foster care *before the age of 2 years* leads to a dramatic increase in IQ (Nelson et al., 2007). A similar trend also occurs for language (Windsor, Glaze, Koga, &

the BEIP Core Group, 2007) and the development of the EEG (Marshall, Reeb, Fox, & the BEIP Core Group, 2008), although in the case of the former, the sensitive period occurs around 16–18 months.

It is important to note recent work suggesting that the brain retains the capacity to adapt and change throughout the lifespan (Crawford et al., 1996; Jones, 2000; Keuroghlian & Knudsen, 2007). However, the foundation of brain architecture must lie in the early developmental years, and the influence of childhood environment is much more salient in such basic cognitive processes as sensory perception (Amedi et al., 2007; Antonini & Stryker, 1993; Grossman et al., 2003; Hensch, 2005; Hess, 1973; Karmarkar & Dan, 2006; Knudsen, 2004; Pascual-Leone et al., 2005). Each sensory and cognitive system reaches a unique sensitive period (Daw, 1997), and thus identical environmental conditions will result in very different cognitive and emotional experiences for a child, depending upon his or her age (Amedi et al., 2007; Jones, 2000; Trachtenberg & Stryker, 2001; Tritsch et al., 2007; for reference, see Bailey, Bruer, Symons, & Lichtman, 2001).

Behavioral analysis can demonstrate the value of early experiences in the development of the brain. It must be remembered, however, that information is processed in a series of networks, each reflecting the effects of environment at varying time points. Higher level processing may mask modifications in lower level networks (Daw, 1997; Feldman & Knudsen, 1998; Trachtenberg & Stryker, 2001). Thus, behavioral outcomes may be shaped by later experience, even though circuits at the lowest levels in a pathway remain irreversibly altered. In addition, studies of the plasticity of sensory processing reveal that similar information can be derived from alternative pathways (Akins & Biederer, 2006; Antonini & Stryker, 1993; Ellis & Lambon, 2000; von Melchner et al., 2000; Pascual-Leone et al., 2005). For example, when using sound devices to assess space, blind individuals have been shown to activate the lateral occipital cortex in the same manner as sighted individuals do through vision (Amedi et al., 2007). It has been suggested that loss sensory input—such as occurs in late blindness—may in fact lead to the unmasking and strengthening of alternative pathways stemming from multisensory integration regions of the brain (Pascual-Leone et al., 2005). These pathways may not only substitute for the original sensory inputs but may also enhance previously existing capabilities. This form of sensory enhancement can often be seen in the highly tuned auditory and tactile perception of blind.

High-level neural circuits that carry out sophisticated mental functions depend on the quality of the information that is provided to them by lower level circuits. Low-level circuits whose architecture was shaped by healthy experiences early in life provide high-level circuits with precise, high-quality information. High-quality information, combined with sophisticated experience later in life, allows the architecture of circuits involved in higher functions to take full advantage of their genetic potential. Thus, early learning lays the foundation for later learning and is essential (though not sufficient) for the development of optimized brain architecture. Stated simply, rich early experience must be followed by rich and more sophisticated experience later in life, when high-level circuits are maturing, in order for full potential to be achieved (DeBello & Knudsen, 2004; Karmarkar & Dan, 2006; Nelson, de Haan, & Thomas, 2006; Sabatini et al., 2007).

Concluding Comments

Although studies of the adverse effects of deprivation on brain development are powerful and compelling, they tell us little about the benefits of enrichment. Much of what we know about the impact of early experience on brain architecture comes from animal or human studies of deprivation. As we work to clarify further the patterns of genetic expression required for normal neural structure, we have also recognized that an optimal level of environmental input or “expectable” environment must exist in parallel. Increasing evidence suggests that this “expectable environment” of early development requires not only the variation in light necessary for vision, or the tones heard in a spoken language, but also the emotional support and familiarity of a caregiver (Nelson et al., 2007; Sánchez, Ladd, & Plotsky, 2001). It is important to emphasize that the well-documented negative impacts of deprivation on brain circuitry do not mean that *excessive* enrichment produces measurable enhancements in brain function. A small number of case reports exist in which neglected children with very little language experience in early childhood were given enriched language exposure in a protective environment (Curtiss, 1977; Itard, 1801/1932; Zingg, 1940). Longitudinal follow-up studies of these children demonstrated that after several years of language exposure, they were unable to achieve adult-level native language abilities. In animal models, rat pups deprived of maternal care were shown to have reduced hippocampal volume compared to pups with “enriched”

maternal care (Bredy, Humpartzoomian, Cain, & Meaney, 2003). Placement of deprived pups into an “enriched care” environment resulted in learning and memory aptitude similar to high-care pups; however, hippocampal volume did not change, suggesting that plastic mechanisms early in life allow for alternative pathways to form typical behavior despite lasting structural deficits. Most recently, early intervention to correct a deeply impoverished early environment has been shown to greatly improve cognitive, linguistic, and emotional capabilities in humans (Ghera et al., 2009; Nelson et al., 2007; Windsor et al., 2007). Activity-dependent mechanisms of network formation, as described earlier, may be responsible for such changes when children are placed into a stimulating environment for learning and exploration. With continued research into the modification of sensitive periods, as well as the factors influencing cortical plasticity throughout life, we may remain optimistic about the possibility of recovery from early deprivation. This in turn may provide hope for children who lack the biological framework or necessary environment required for optimal neural and cognitive growth.

Finally, the possibility of cognitive and neural rehabilitation leads to theories of enrichment beyond the norm to a level of *enhanced* development. Educational and environmental enrichment of preschool children from impoverished economic settings has been shown to improve cognitive measures through early adulthood (Campbell, Pungello, Miller-Johnson, Burchinal, & Ramey, 2001; Martin, Ramey, & Ramey, 1990; see Farran, 2000, for review). Cognitive capabilities, however, may follow a pattern similar to the growth curve of the human body; that is, although it is possible to enhance the environment of a child to assume the pattern of the normal curve, it is not possible to exceed the predicted trajectory to a significant extent without causing some potential harm. This is suggested by large studies of children from varying socioeconomic status, which demonstrated an improvement in cognitive performance only in those born to a low socioeconomic class, with no significant difference between those of middle-class and high-income families (Jeffaris, Power, & Hertzman, 2002). If the possibility for enhancement exists, it is perhaps related to forms of enrichment that lie outside access to unlimited resources—that is, beyond the expectable environment. Creativity, for example, is a key component to enhanced cognitive functioning, yet we have not been able to define the neural processes or environmental attributes that can enrich this aspect of cognition, nor

are there sure-fire ways of boosting creativity among the population at large. Similarly, exposure to art or music or great literature or horseback riding may not confer any evolutionary advantage (i.e., reproductive success), yet these activities may confer some advantage among certain strata of society. Thus, perhaps it would be useful to draw a distinction between *enrichment* as applied to those experiencing downward deviations from the expectable environment (such as those reared in situations of neglect or deprivation) and *enhanced enrichment* applied to those reared in typical (expectable) environments. Enrichment may lead to a restoration of typical development whereas enhanced enrichment may lead to exceeding the typical environment. Of course, a challenge here lies in accounting for individual differences, as some individuals have greater potential to benefit from art or music lessons than others. Individual heterogeneity may be under control of Gene \times Gene, Gene \times Environment, and Environment \times Environment factors. For example, animal studies show that epigenetic mechanisms—whereby environmental factors and experiences early in life can permanently alter the genome of an individual through chemical modification—will impact long-term cognitive and social-emotional functioning (Szyf, McGowan, & Meaney, 2008). The field awaits translation of this type of mechanism into human experiences. Finally, how might the field of developmental psychology benefit from advances being made in developmental neuroscience? First, given that our genome contains many fewer genes than we surmised even a decade ago (approximately 20,000), and given advances being made in the field of epigenetics, renewed attention should be paid to the origins and elaboration of complex human behaviors. Second, those working in the field of intervention should take stock in what is now known about neural plasticity; for example, it is quite possible that we could witness a revolution in new treatment approaches based on what we know about the malleability of the human brain. Finally, for the millions of children around the world who begin their lives in adverse circumstances, we should be mindful of what is known about sensitive periods and act with alacrity to improve the lives of these children before neural circuits become well established and, thus, difficult to modify. To borrow an analogy from economics, by investing early and well in our children’s development, we increase the rate of return later in life and in so doing improve not only the lives of individuals but of societies as well.

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